Sunday 20 October **0900-1030**
HSANZ Symposium 1: Lymphoproliferative Disorders I **Auditorium (Arena B)**

Primary CNS Lymphoma

Andrés JM Ferreri
Unit of Lymphoid Malignancies, Department of Onco-Hematology, San Raffaele Scientific Institute, Milan, Italy

Primary central nervous system lymphoma (PCNSL) is a highly aggressive malignancy, potentially curable with chemotherapy and radiation therapy however the level of scientific evidence supporting the therapeutic choices in this disease is very low and molecular and biological knowledge limited.
Treatment with a primary chemotherapy combination containing high-dose methotrexate (dose ‡ 1 g/m^2) as main drug, followed by consolidation with whole-brain irradiation (WBRT) yields a remission rate near 60%, with a 5-year overall survival (OS) of ~30%. Importantly, this combined approach is associated with a treatment-related mortality (TRM) of 8-10% and an increased risk of severe late neurotoxicity, mostly among patients older than 60 years.
Recently, our Group concluded and reported the first worldwide randomized trial in this field (IELSG #20 trial), which has furnished the highest level of evidence in this field, and, importantly, has stimulated other Collaborative Groups to concentrate their efforts to design and conduct other randomized trials. The IELSG #20 trial has demonstrated that the addition of high-dose cytarabine (HD-araC) to HD-MTX is associated with significantly better outcome with respect to HD-MTX alone. Thus, this MTX-araC combination followed by WBRT should be considered as the standard treatment for patients †75 years old with PCNSL and the control arm for future randomized trials.
Several potential strategies to improve the overall therapeutic efficacy, including the identification of more active drugs and reduction of iatrogenic neurotoxicity, have been included in the next IELSG randomized trial on PCNSL. This trial, named IELSG #32, consists of a factorial double randomization.
In the first randomization, the impact of the addition of rituximab ± thiotepa to the standard MTX-araC combination will be investigated. Patients who achieve an objective response to one of the three chemoimmunotherapy combinations will undergo a second randomization to receive WBRT (control arm) or high-dose chemotherapy supported by autologous stem-cell transplant (HDC/ASCT – experimental arm). The randomized comparison between WBRT and HDC/ASCT in the IELSG #32 trial will allow us to establish the most effective and better tolerated strategy to consolidate response obtained with primary chemotherapy and prospective assessment of neuropsychological functions through validated tests will define the real impact of these strategies and hopefully result in a significant improvement in the fight against this orphan and dismal malignancy.
Keywords Primary CNS Lymphoma

Sunday 20 October **0900-1030**
HSANZ Symposium 1: Lymphoproliferative Disorders I **Auditorium (Arena B)**

Small Molecule Inhibitors in CLL

Jennifer R Brown
CLL Center, Dana-Farber Cancer Institute & Harvard Medical School, Boston, USA

The last several years have witnessed an explosion of novel small molecule therapies for CLL, focusing particularly on the inhibitors of the B cell receptor pathway but also including BCL-2 inhibitors. Although mutational activation of the B cell receptor pathway is relatively rare in CLL, the pathway is constitutively activated, likely related to chronic stimulation from the microenvironment. Targeting this pathway results in an unusual pattern of clinical activity, with shrinkage of lymphadenopathy concomitant with an initial increase in lymphocytosis which is of variable duration depending on the drug and the patient population. Over time this lymphocytosis often resolves. The depth and stability of remissions induced by inhibitors of this pathway in CLL is marked, with the BTK inhibitor ibrutinib the most active single agent described to date in CLL. Inhibitors of the delta isoform of PI3 kinase are also showing great promise in ongoing clinical trials. This talk will briefly review the clinical data to date with these drugs and discuss the upcoming implications for CLL therapy as well as the many questions still to be answered about how best to use these drugs.

Keywords Ibrutinib, BTK, BCR pathway inhibitors
Conflict of interest Dr Brown has served as a consultant for Pharmacyclics, Celgene, Novartis, Vertex, Genentech, Sanofi, Onyx and Emergent, and has received research funding from Sanofi.

Sunday 20 October **0900-1030**
HSANZ Symposium 1: Lymphoproliferative Disorders I **Auditorium (Arena B)**

PET in Lymphoma: Certainties and Uncertainties

Judith Trotman
Concord Hospital, University of Sydney, NSW, Australia

There is increasing evidence for the central role of PET-CT (PET) scanning in the staging and response assessment of FDG-avid lymphoma. The accuracy of PET staging in Hodgkin Lymphoma (HL) and Diffuse Large B Cell Lymphoma (DLBCL) is challenging the need for bone marrow biopsy in staging of these histologies. The poor prognosis observed in patients remaining PET positive after two cycles of ABVD in HL has driven studies of interim PET (iPET) directed therapy. Similarly, the poor prognosis of patients with DLBCL with positive end of treatment PET (ePET) is driving studies of iPET scanning and an iPET directed treatment approach. Interpretation of early results from DLBCL studies in the Rituximab era are hampered by uncertainty over the optimal timing of iPET and definition of PET positivity, (visual vs. semi-quantitative SUV analysis).

Clinical trials are providing better clarity on PET quality assurance and standardised response assessment criteria applying the reproducible 5 Point Scale (previously referred to as the Deauville Criteria) referencing tumour FDG uptake with uptake in the mediastinum and liver. In addition to examining the role of SUVmax in DLBCL the use of PET-based quantitative assessment with metabolic tumour volume (MTV) and total lesion glycolysis (TLG = MTV x SUVmax) is also being explored.

Finally, previous International Harmonization Project guidelines integrating PET into the revised staging and response criteria for lymphoma (2007) focused principally on DLBCL and HL. Emerging data suggests the importance of PET in both staging and response assessment of Follicular Lymphoma where observational studies demonstrate increased staging sensitivity and correlation of ePET status with both Progression Free and Overall survival.

The above issues have been addressed at the ICML and International PET in Lymphoma workshops and revised consensus guidelines for staging and response assessment of lymphoma are in development.

Keywords PET-CT, Lymphoma,
Conflict of interest No

Sunday 20 October **0900-1030**
ANZSBT/ISBT Academy: A Global Perspective **Central Hall A**

Transfusion in Sub-Saharan Africa

Jean-Pierre Allain[1] & Shirley Owusu-Ofori[2]
[1] *Dept Haematology, University of Cambridge, Cambridge, UK*
[2] *Transfusion Medicine Unit, Komfo Anokye Teaching Hospital, Kumasi, Ghana*

Transfusion in sub-Saharan Africa (SSA) is dependent on two main factors: emergency indication for severe anaemia related to bleeding or massive haemolysis and lack of resources. These circumstances radically distinguish transfusion in SSA from transfusion in developed affluent countries.
Indications of transfusion in SSA are acute malaria in young children (20-40%), massive bleeding peri-partum or in surgery (40%) and severe anaemia related to haemoglobinopathies. For most of these emergency circumstances, whole blood (WB) is indicated, particularly fresh WB (<1 week of storage). RCC are indicated for elective and paediatric transfusion. FFP and Platelet concentrates are in limited demand.
70% WB is collected from family/acquaintances donors (FAD) and 30% from volunteer, non-remunerated, donors (VNRD) mostly recruited in secondary schools from 16-19 year old students. Although paid donors are banned in nearly all SSA countries, family/acquaintance donors being unavailable, some paid donors might be used. Solid evidence showed that FADs are as safe as first-time VNRDs and that they are willing to repeat donation and become VNRD. Contrary to WHO, PEPFAR, CDC and AABB recommendation, blood collection from FAD should not be discouraged but indispensable to achieving sufficient blood supply. FADs are volunteer, unpaid and not coerced, meeting the current definition of VNRD.
Health expenditure in SSA (except South Africa) ranges between $23 and $283 (median $55.3). The cost of a blood unit ranges between $20 and $100 (median $52). The main reasons for differences in cost are recruiting VNRDs, centralisation, automation, expensive equipment and tests and systematic component preparation. Most of these expenses have been introduced or imposed by international organisations and blood systems funded by affluent countries. Assumptions such as lower infectious risk of VNRD, improved supply from centralisation and clinical necessity of components have not been supported by evidence in SSA. These imported concepts are largely inadequate and not affordable if sustained. Re-assessment of external aid is necessary and urgent.
There is no universal solution to reaching sufficient supply of safe blood. Small hospital transfusion services as well as larger units collecting from FADs and VNRDs are adapted to local circumstances but need to improve. Progress by little steps according to local resources on the basis of local evidence proved more successful than adopting affluent countries models.
Key words developing countries, whole blood, blood supply, economic
Conflict of interest: none

Sunday 20 October **0900-1030**
ANZSBT/ISBT Academy Symposium: A Global Perspective **Central Hall A**

Approaches to Transfusion Development in the Asia/Pacific Region

Neil Waters
Australian Red Cross, Carlton, VIC, Australia

The availability of safe blood tor transfusion is an essential component of any well functioning and effective health system. Yet many countries in the Asia Pacific region face significant challenges achieving and maintaining a safe and sufficient supply of blood.

Australian Red Cross has for many years held a focus on emergency and development programs in Asia and the Pacific. In 2009 the Australian Red Cross and the Australian Red Cross Blood Service jointly developed an International Humanitarian Blood Strategy which utilises respective niche expertise in international development and blood service delivery. The Strategy is focused on improving the capacity of international blood services to safely collect, screen, supply and use blood products and thereby improve outcomes for transfusion recipients, blood donors and communities.

Australian Red Cross manages a number of different projects across the region utilising the technical expertise of the Australian Red Cross Blood Service. Projects focus on a range of transfusion related issues from volunteer blood donor recruitment and community motivation through to clinical education, regional networks and leadership.

The expectations of funders, in-country partners' organisational goals and country context all influence the way projects are designed and delivered.

Keywords **i**nternational development transfusion
Conflict of interest None

Sunday 20 October **0900-1030**
ANZSBT/ISBT Academy: A Global Perspective **Central Hall A**

Emerging Infectious Risks of Transfusion

Peter Flanagan
New Zealand Blood Service, Auckland, New Zealand

The safety profile of blood components with respect to infectious agents in developed countries has improved considerably during the last 20 years. This is particularly the case for major blood borne viruses such as HIV and hepatitis B and C. Ongoing vigilance is necessary to assure this safety profile is maintained.

Emerging risks to the blood supply arise in a number of ways. Firstly the epidemiology of agents already known to pose a risk to the blood supply can change. This can occur for several reasons including globalisation of commerce, population migration and climate change. The recent emergence of West Nile Virus (WNV) in a number of European countries, malaria in Greece and Trypanasoma Cruzi in the United States and Spain are good examples. It is interesting to note that these are all arthropod borne infections. Secondly, concerns might arise that known agents might be transmissible by transfusion. Examples include Dengue and hepatitis E. Outbreaks of Dengue in northern Queensland have been a particular concern for the ARCBS. Finally truly new infectious agents with characteristics suggestive of transfusion transmissibility might emerge. The recent discovery of a novel coronavirus (MERS-coronavirus) in the Middle East is a good example.

Blood Services need to develop effective monitoring systems to ensure that emerging risks are identified at an early stage. Risk assessment systems and, where appropriate, the introduction of measures to reduce the risk will need to be developed and maintained.

Blood Services have a limited repertoire for managing emerging risks. Conventional solutions have comprised exclusion of donors deemed ‘at risk’ usually as a consequence of overseas travel. The alternative has been introduction of additional screening tests, often on a selective basis, linked to travel history. Whilst effective these approaches can have a significant impact on donor availability and are prone to error. An alternative approach, recently implemented in the Netherlands, is to a general deferral of any donors who have travelled overseas in the preceding four weeks. This is seen as easier to implement and avoids a requirement for regular changes to ‘at risk countries’. There is a potential trade-off between ease of application and the level of donor loss. There is increasing interest in the application of pathogen reduction systems to manage these risks. Currently however this is limited by the absence of systems for treatment of red cells.

Keywords Infection, arthropod, travel**Conflict of interest** None.

Sunday 20 October **0900-1030**
ASTH Symposium 1: Controversies in VTE **Central Hall C**

Duration of Anticoagulation for Venous Thromboembolism (VTE)

David Keeling
Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, United Kingdom

Initial anticoagulation to treat an acute proximal DVT or PE is needed for three months. After that in theory therapy should be continued if the risk from recurrence on stopping treatment is greater than the risk from anticoagulant-related bleeding. The risk of recurrence is low (0.7% p.a.) after proximal DVT or PE following surgery, moderate (4.2% p.a.) following non-surgical transient risk factors (such as plaster cast, combined oral contraception) and high (7.4% p.a.) after unprovoked events. The difficult clinical question is which patients should receive long-term anticoagulation after a single unprovoked proximal DVT or PE?

Recurrences after unprovoked VTE are more likely in males and in those with raised D-dimers after completing anticoagulation. Age, post-thrombotic syndrome and residual vein thrombosis have also been examined as possible risk factors. Prediction scores such as HER DOO2 and DASH have been proposed. A further consideration is that patients with an initial unprovoked PE are 3 to 4 times more likely to suffer recurrence as PE compared with patients with an initial DVT.

This talk will examine our ability to predict the risk of recurrence and discuss how in conjunction with patients we decide who should have long-term anticoagulation.

Keywords anticoagulation, venous thrombosis
Conflict of interest none for this presentation

Sunday 20 October **0900-1030**
ASTH Symposium 1: Controversies in VTE **Central Hall C**

IVC filters

Andrew McCann
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Abstract not available at time of going to print

Sunday 20 October **1400-1530**
Nurses Symposium 1: Focus on Management of the Haematology Patient in the Home
Meeting Rooms 5/6

Shared Care Pathway's Intervention to Reduce Chemotherapy Outpatients' Unplanned Presentations to Hospital

Kate White
Cancer Nursing Research Unit, Royal Prince Alfred Hospital, Sydney, NSW, Australia

Abstract not available at time of going to print

Sunday 20 October **1400-1530**
Nurses Symposium 1: Focus on Management of the Haematology Patient in the Home
Meeting Rooms 5/6

Viewing Health Care Differently: Changing the Way Patients Are Treated to Improve Outcomes

Julie Wilkes
Chemo@home. Perth, WA, Australia

Abstract not available at time of going to print

Sunday 20 October **1400-1530**
Nurses Symposium 1: Focus on Management of the Haematology Patient in the Home
Meeting Rooms 5/6

The Townsville Telenursing Model of Care for Rural Hospitals

Susan Price, Sandra Roberts, Amy Bloomfield
Townsville Cancer Centre, Townsville Hospital, Townsville, QLD, Australia

Background
One-third of Australians diagnosed with cancer live outside metropolitan areas in which tertiary cancer centre cares are located. Rural patients face many challenges in accessing care provided by centres utilising traditional models of care. The aim of this model of care is to build capacity within a rural hospital service to provide local access to low-risk chemotherapy/biotherapy treatments for patients.
Method
Senior management and relevant stakeholders from the tertiary centre and rural hospital formed a working party to consult on the patient cohort, chemotherapy/biotherapy protocols and educational framework in order to commence a pilot project. After clinical placement at the tertiary cancer centre, attainment of oncology competencies and completion of education modules, rural nursing staff will be able to administer chemotherapy at the local hospital under the remote supervision via videoconference of a specialist cancer nurse from the tertiary centre.
Results
This model of care is underway with education and assessment processes established. It is now implemented in two rural areas.
Conclusions
Patients no longer have to relocate for low-risk chemotherapy treatment. Nursing staff in rural hospitals have gained skills and knowledge in cancer care and service delivery. The processes used in this model is providing a template for other rural hospitals to provide selected cancer services.

Keywords Telenursing, Rural, Chemotherapy
Conflict of interest No

Sunday 20 October **0900-1030**
BMTSAA Symposium: Current Status of Cord Blood Transplantation in Australia 1
Meeting Room 7

Unrelated Cord Blood Banking in Australia

Robyn Rodwell
Queensland Cord Blood Bank at the Mater, Brisbane, QLD, Australia

Abstract not available at time of going to print

Sunday 20 October **0900-1030**
BMTSAA Symposium: Current Status of Cord Blood Transplantation in Australia 1
Meeting Room 7

Family Cord Blood Banking – Current Status and Future Prospects

Mark Kirkland
Cell Care Australia Pty Ltd, Melbourne & Deakin University Geelong, Vic, Australia

Umbilical cord blood (UCB) is a recognised source of haemopoietic stem cells (HSCs) and has been used for HSC transplant for almost 25 years. For almost as long, it has also been recognised as a potential source of therapeutic cells for a wide range of other diseases. Other cells of interest in UCB include MSCs, undifferentiated stem cells and regulatory T-cells (Tregs). In vitro studies have demonstrated differentiation of UCB stem cells along multiple lineages, notably neural. For this reason, a large number of preclinical studies have been undertaken using human UCB in animal models of brain and spinal cord injury. Almost uniformly these studies have demonstrated improved repair or reduced tissue damage from a range of different insults, though the evidence suggests that UCB acts indirectly through dampening inflammation and cell death, enhancing repair and recruiting endogenous stem cells to the site of injury rather than by direct differentiation.
The anti-inflammatory and immunomodulatory effects of UCB are now being tested in human clinical studies. A recent randomized controlled study of UCB in children with cerebral palsy (CP) demonstrated significant benefit on all measures (motor, cognitive and social). Further studies are underway around the world in CP, as well as in other neurological disorders. One of the key questions being asked is “how could UCB have effect in established brain injury, such as CP?” A possible mechanism of action will be discussed.
The Tregs in UCB are naïve and potent immunosuppressors, suggesting a possible therapeutic role in autoimmune disease. A world first study is being undertaken at Children’s Hospital Westmead exploring the potential for autologous UCB to forestall the development of type 1 diabetes in children at high risk (as measured by the presence of multiple autoantibodies to beta cell antigens).
The use of autologous or sibling UCB for HSCT through to adulthood is also under intensive investigation, with a number of groups developing ex vivo expansion technologies. Successful expansion (of Tregs as well as HSCs) promises to make a lifelong therapeutic resource for individuals and families

Keywords Cord blood
Conflict of interest Medical Director, Cell Care Australia

Sunday 20 October **0900-1030**
BMTSAA Symposium: Current Status of Cord Blood Transplantation in Australia 1
Meeting Room 7

Directed Cord Blood Collection, Processing, Storage and Transplant

CJ Hutchins
Cellular Therapy / BMT Laboratory, Cancer Care Services, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia

The collection, processing, cryopreservation and infusion of directed cord blood units (CBU) presents several challenges for scientific staff in a cell processing facility. In contrast to public cord blood banking, an intended recipient with a haematological malignancy or a non-malignant disease has been identified prior to the cord blood collection. In some instances, pre-implantation diagnosis and HLA typing have been performed at considerable expense. Therefore it is essential that the collection of cord blood is optimised as the CBU cannot be discarded due to insufficient nucleated cell count or microbial contamination.
Most directed CBU are collected in non-fixed collection sites unlike the fixed collection sites associated with public cord blood banking. This necessitates the preparation and distribution of cord blood collection kits to facilitate the collection. The kit components and the collected CBU require temperature monitoring during storage at the collection facility and transport between the collection and processing facilities. Training materials for collection staff are provided with each cord blood collection kit as dedicated collection staff are not available with different obstetricians or midwives performing each collection.
Between 1992 and 2013, the Cellular Therapy / BMT Laboratory has banked 211 directed CBU. Since 2004, most CBU have been red cell and plasma reduced using the low volume cord blood protocol (UCB-LBC) on the Biosafe Sepax. This results in a post processing volume of 8.5 to 10mL and a final volume post cryopreservation of 13 to 15mL. Between 2011 and 2013, the median volume reduction was 90.3%, the median recovery of nucleated cells was 57.6% and the median recovery of CD34+ cells was 76.2%.
Five directed CBU have been infused, one in combination with allogeneic bone marrow. Four CBU were red cell replete. One CBU had been processed on the Biosafe Sepax. The recipient of the UCB-LBC Sepax processed CBU received 3.8 x 10^7 NC/kg and 1.6 x 10^5 viable CD34+ cells/kg. Neutrophils (ANC > 0.5 x 10^9/L) and platelets (Plt > 20 x 10^9/L) engrafted on days 19 and 29 respectively.
The banking of directed CBU provides an alternative source of haemopoietic progenitor cells for allogeneic transplantation although time consuming and specialised laboratory procedures are required to maintain the program.

Keywords Cord blood, Processing, Cryopreservation
Conflict of interest No

Sunday 20 October **1100-1200**
HSANZ/BMTSAA Combined Symposium: BMT **Auditorium (Arena B)**

Allo-transplantation for Lymphoma

Stephen Mackinnon
University College London, UK

Historically, high levels of treatment-related mortality restricted the use of standard myeloablative allogeneic stem-cell transplantation to a minority of young and fit patients with lymphoma. Over the last decade, increasing numbers of patients with lymphoma have undergone allogeneic stem-cell transplantation using reduced-intensity protocols that are associated with lower toxicity and reduced transplantation-related mortality. Graft-versus-lymphoma effects contribute to the therapeutic effect in patients with indolent or Hodgkin's lymphoma. However, definitive evidence for efficacy of this strategy is lacking because most patients undergoing transplantation do so after failure of several lines of treatment, leaving no obvious comparator arm for randomised controlled studies. Nevertheless, encouraging results have been reported for selected patients for most lymphoma subtypes, with pretransplantation disease status emerging as the most important predictor of outcome. The major long-term toxicity is chronic graft-versus-host disease that contributes to ill health in a significant minority of survivors. In the future, risk-adapted trials that evaluate reduced intensity allogeneic transplantation in patients with predicted poor outcomes with immunochemotherapy or autologous transplantation will be important in determining the role of this treatment.

Keywords Allogeneic transplantation, lymphoma, conditioning regimens
Conflict of interest No

Sunday 20 October **1100-1200**
HSANZ/BMTSAA Combined Symposium: BMT **Auditorium (Arena B)**

Cytokine and Cellular Modulation in Stem Cell Transplantation

Geoff Hill
The Queensland Institute of Medical Research & The Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Graft versus host disease (GVHD) remains a major problem after allogeneic stem cell transplantation and improvements to standard calcineurin inhibitor and methotrexate based prophylaxis have been difficult to realize. The coordination of GVHD is now recognized to involve complex cellular and cytokine based networks that appear to operate differentially in GVHD target organs. Recently the Th17/Tc17 differentiation has been shown to play a dominant role in skin and lung GVHD particularly in their chronic forms where regulatory T cell deficiency is a cardinal feature. We have undertaken a number of preclinical studies of IL-17 and related cytokines in order to more fully understand disease pathophysiology. These studies have resulted in the choice of logical lead targets and IL-6 in particular, with translation to phase II therapeutic trials with very encouraging results. The treatment of established chronic GVHD is a more difficult proposition and preclinical studies suggest that redressing the defect in cellular regulation will be a prerequisite for success. The ability to infuse sufficiently large numbers of phenotypically and genotypically stable regulatory T cells in this patient group represents a significant technical hurdle. Studies addressing these issues of safety, stability and the parameters determining therapeutic efficacy of regulatory T cell adoptive transfer will be presented together with novel approaches to genetically modify cells to allow their rapid deletion if deleterious effects ensure following their transfer into patients.

Keywords Bone Marrow Transplantation, Cytokines, Regulatory T cells
Conflict of interest None

Sunday 20 October **1100-1200**
ANZSBT/ASTH Combined Symposium **Central Hall A**

Fibrinogen Concentrates/Transfusion Support in Major Bleeding

Sibylle Kozek-Langenecker
Department of Anaesthesia and Intensive Care, Evangelical Hospital Vienna, Austria

1) Fibrinogen is coagulation factor 1 and plays a pivotal role in haemostasis.
2) Fibrinogen levels correlate inversely with postoperative bleeding in cardiovascular surgery (up to r=-0.897). Fibrinogen is useful in protecting against bleeding.
3) Decreased fibrin polymerization occurs among other pathomechanisms in the complex perioperative coagulopathy. This may result in decreased resistance against fibrinolysis, platelet aggregation, adsportion of factors IIa and Xa with potential clinical correlates of increased fibrinolysis, platelet dysfunction and thrombosis.
4) Fibrinogen is antithrombin 1. Accordingly, fibrinogen is useful in protecting against thromboembolism.
5) Fibrinogen is affected by other confounders which may occur during major surgery. Acidosis increases fibrin(ogen) breakdown, hypothermia decreases fibrinogen synthesis. During progressive bleeding fibrinogen levels deteriorate critically before other coagulation factors.
6) Fibrinogen can be substituted by administration of fibrinogen concentrate, fresh frozen plasma, cryoprecipitate - differences in efficacy and safety exist.
7) Scientific evidence including prospective RCTs show that goal-directed substitution with fibrinogen concentrate according to predefined target values (of fibrinogen function) decrease bleeding, transfusion requirements, re-exploration rates, critical adverse events, thrombosis, costs, lactate levels, postoperative duration of mechanical ventilation, and mortality. Accordingly, procoagulant therapy with fibrinogen concentrate among other goal-directed interventions according to an algorithm is useful in improving patient outcome and patient safety.
8) Evidence-based guideline of the European Society of Anesthesiology ESA on the management of severe perioperative bleeding recommends treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen levels or function (GRADE 1C). Plasma fibrinogen levels < 1.5-2.0 g l-1 or ROTEM/TEG signs of functional fibrinogen deficit are recommended as triggers for fibrinogen substitution (GRADE 1C).

Keywords fibrinogen concentrate, severe bleeding, guidelines
Conflict of interest honoraria for lectures and travel reimbursement from CSL Behring

Sunday 20 October **1100-1200**
ANZSBT/ASTH Combined Symposium **Central Hall A**

Management of ECLS

Leonardo Brandao
The Hospital for Sick Children, Toronto, Canada

Abstract not available at time of going to print

Sunday 20 October **1100-1200**
Nurses Free Communications 1: Focus on Support **Meeting Rooms 5/6**
O001 **1100**

Evaluating Mindfulness Based Stress Reduction as a Psycho-Social Support Intervention for Haematology Patients

Rebecca Weeks
Leukaemia & Blood Cancer New Zealand, Auckland, New Zealand

Background
The effectiveness of Mindfulness Based Stress Reduction (MBSR) for people living with and beyond cancer has been established. Randomised controlled trials have demonstrated that MBSR can help manage the psychological sequelae of a cancer diagnosis. The majority of research has focused on breast cancer patients, and little is known of the effectiveness of MBSR on those living with a blood cancer.
Aim
To pilot a MBSR program to ascertain its practicality and effectiveness for people affected by blood cancers.
Method
An 8 week MBSR program facilitated by a clinical psychologist, was set up based on the program developed by Jon Kabat-Zinn and modified for people living with cancer by Carlson and Speca. The program consisted of weekly 2 hour classes and one full day introducing mindfulness, and guided participants through meditation, relaxation and gentle yoga exercises. Participants were encouraged to practice mindfulness in between classes. Participants completed the Profile of Mood States (POMS) assessment, Calgary Symptoms of Stress Inventory (C-SOSI) and the Post Traumatic Growth Inventory (PTGI) at the beginning and end of the program. Course evaluations were completed.
Results
The course was completed by 7 participants (4 patients and 3 carers). Four different haematological malignancies were represented among the group. A reduction in stress was experienced by 6 out of 7 participants (C-SOSI) and 6 out of 7 experienced personal growth (PTGI). POMS assessments are currently being analysed. Improved sleep, increased ability to enjoy sensory experiences and manage every day stress, increased perception of calm and acceptance with decreased worry and bitterness were evidenced. All participants rated the usefulness of the course as 9 or 10 out of 10, and all said they had gained lasting value from participating in the programme. Specific findings regarding the practical aspects of running this type of program will be shared.
Conclusion
MBSR appears to be an effective program for addressing the psycho-social consequences of a blood cancer diagnosis. Larger studies and RCT's would be necessary for the purposes of confirming the value of MBSR in this patient group.
Key Words: MBSR, haematology, psychosocial. **Conflict of interest:** None

Sunday 20 October **1100-1200**
Nurses Free Communications 1: Focus on Support **Meeting Rooms 5/6**
O002 **1115**

National Myelodysplastic Syndrome (MDS) Impact Survey to Improve Service Delivery

Rebecca Dring
Leukaemia Foundation of Australia, Preston, VIC, Australia

Aim/Background
Myelodysplastic Syndrome (MDS) is a rare type of malignancy of the bone marrow; it is incurable other than with a bone marrow transplant, with an estimated 1300 Australians will be diagnosed this year. It is more commonly a disease of the elderly and more prevalent in men. Other than a bone marrow transplant the only PBS listed treatment, azacitidine, is not suitable for all MDS subtypes. The current treatment regimens aim to control the symptoms of the disease and slow its progression. Treatment of MDS can be complex as it is a group of diseases and each sub type has its own treatment. Treatment can vary; watch and wait, supportive care, chemotherapy and azacitidine (Vidaza). The effects from the disease and some of the treatments can be debilitating and have a detrimental impact physical and psychologically. The aim of this survey was to gain an understanding of the impact of having MDS has on the lives of Australians.
Methods
The Leukaemia Foundation, with the support of a range of health professionals, consumers and international MDS groups, developed a mostly quantitative National MDS survey which was conducted in 2013. Ethics approval was granted by South Eastern Sydney Local Health District- Northern Sector in January 2013. Themes ranged from: diagnosis; treatment options (including access to clinical trials); services available at treatment centres; transport and accommodation issues for regional patients; patient's perception of wellbeing; financial implications and complementary and alternative medicines. 212 people with MDS participated in the survey
Results
The findings were collated and analysed by Sweeney Research and are presented as part of this presentation.
Conclusion
MDS is predominately a disease of the elderly and is incurable other than with a bone marrow transplant. Disease symptoms and treatment side effects impact on a person's sense of wellbeing. It is a disease where people often require significant support to help improve their quality of life. Having an improved understanding of the issues confronting people living with MDS, will allow multidisciplinary teams to improve services to meet the needs of this vulnerable patient population.
Keywords Myelodysplastic Syndrome (MDS), Impact Survey, Service Delivery

Sunday 20 October **1100-1200**
Nurses Free Communications 1: Focus on Support **Meeting Rooms 5/6**
O003 **1130**

Targeted Support Needs for People Affected by a Myeloproliferative Neoplasm

Samantha Soggee
Leukaemia Foundation of Australia, Preston, Victoria, Australia

Aim/Background
This review is aimed at identifying the specific support needs of people affected by an MPN, unique to their disease type and symptomology. Myeloproliferative Neoplasms (MPN) are rare diseases with only 3 in every 100,000 people diagnosed each year. These diseases include Polycythaemia Vera, Essential Thrombocythaemia, Myelofibrosis, Mastocytosis, Chronic Eosinophilic Leukaemia/Hypereosinophilic Syndrome, and Chronic Neutrophilic Leukaemia. There are no support services targeting the needs of people affected by an MPN in Australia. The Leukaemia Foundation aims to develop support services addressing the supportive requirements of this community.
Methods
A review of the literature has been conducted using Proquest Central, Medline, CINAHL and Google Scholar Databases. Key words included polycythaemia vera, essential thrombocythaemia, mastocytosis, hypereosinophilic syndrome, chronic Neutrophilic leukaemia, quality of life, symptoms, support needs, support, needs, itch, anaphylaxis, clots, clotting, bleeding, bone pain, spleenomegaly, weight loss, satiety, constitutional symptoms, fatigue.
Results
The findings of this literature review will be presented. Discussion will focus around the specific support needs of people affected by an MPN as identified in the literature. The Leukaemia Foundations development of support services targeting the identified needs will be discussed. Services include information, education and support in regards to management of itch, spontaneous anaphylaxis, satiety, spleenomegaly, contact with water, temperature changes, on-going fatigue, bleeding and clotting and incessant bone pain.
Conclusion
The literature suggests that support needs of people diagnosed with Myeloproliferative Neoplasms are unique. Therefore, support services need to be specifically targeted towards each subset of the MPN population.
Keywords Myeloproliferative Neoplasms, support needs, support services
Conflict of interest None

Sunday 20 October **1100-1200**
Nurses Free Communications 1: Focus on Support **Meeting Rooms 5/6**
O004 **1145**

Young Adult Cancer Patients' Communication Needs: What Do Online Narratives Tell Us?

B Kim[1], D Gillam[2], P Patterson[3], K White [1]
[1]Cancer Nursing Research Unit, Sydney Nursing School, University of Sydney, Sydney, NSW, Australia. [2]Flinders University, Bedford Park, SA. [3]CANTeen

Background
Young adults diagnosed with cancer are often faced with complex and multiple challenges. These can include interruption to education or career preparation, impact on relationships, employment, housing, and emotional development. Many young people have no experience of illness or the health care system prior to their diagnosis, nor life skills in managing competing priorities at this time in their life.
Aim
The overarching objective for this research is to improve the delivery of supportive care for young people diagnosed with cancer. There are three components to the work 1) Systematic review of the literature 2) Exploration of experiences and gain a better understanding of young adults affected by cancer (YAACs) by examining their online narratives (also known as Web logs or blogs) (this paper). The final component will examine both supportive care and information expectations from perspective of both YAACs and health care professionals.
Methods
Drawing on established procedures for reviewing Websites, inclusion and exclusion criteria were used to identify eligible Web sites. Blog content generated in 2011 was collected, authored by a 34 female and 12 male writers and included 136 (by female) and 28 (by male) blog entries. Researchers conducted a descriptive qualitative examination of blogs to explore YAACs' experiences during/after cancer.
Results
Ten main themes were identified: physical burdens, future prospects, isolation (physical and psychological), guilt, mortality, images of cancer, creating a positive attitude, healthcare, online social interaction, and cancer survivorship. The Internet provides young cancer patients with a space in which to express themselves and to share experiences with those who are of similar age and in similar situations.
Conclusions
While blogs can be particularly helpful when patients are isolated or physically unable to interact with other people because of treatment requirements or physical deterioration, there exist confusion about the role of health professional, in particular haematology nurses. These results, combined with the literature review, have informed the development of the next phase of the research, which will examine supportive communication between YAAC and health professionals.
Keywords Young adults, cancer experience, haematology nursing.**COI** None

Sunday 20 October **1200-1300**
ASTH: Barry Firkin Oration **Auditorium (Arena B)**

What a Difference Thirty Years Makes

Alison Street
Department of Pathology and Immunology, Monash University, Prahran, Vic, Australia

Barry Firkin was an ideal mentor; knowledgeable, enthusiastic, curious and generous. His own mentor, Professor Ruthven Blackburn, had introduced him to haemophilia in Sydney in 1955. Barry's pioneering coagulation studies of FVIII and VWF with Margaret Howard, from the early seventies, complemented a career-long interest in the welfare of patients with bleeding and thrombotic disorders.

In 1984, Australians were confronted by HIV transmitted by transfusion, clinicians were challenged and the haemophilia community devastated. There was widespread fear and loss of confidence in the health system. Haemophilia treatment centres, where they had arisen "ad hoc," were poorly resourced to cope with the epidemic. There was added frustration because of severe and continuous supply constraints of plasma derived replacement factors and then there was HCV.

Barry encouraged me to enter this (mine)field of medicine and provided much appreciated support until his death.

Nearly thirty years later the ground has completely changed. Australian and New Zealand patients have access to and availability of recombinant products in plentiful amounts. Haemophilia Centres have become multi-disciplinary clinics, with funder and clinician subscription to the principles of chronic disease management and measurement of patient related outcomes. Now commonplace, Haemostasis-Thrombosis Units offer recognised value to medical institutions and excitement to bright young clinical researchers.

In describing the journey and lessons from then to now I am mindful that we all need to learn from our histories' documentation and from our mentors

Key Words haemophilia, management, mentors
Conflicts of Interest none

Sunday 20 October **1400-1530**
HSANZ/Nurses Combined Symposium: Myeloproliferative Disorders Auditorium (Arena B)

Practical Tips on Using JAK Inhibitors as Therapy for Myelofibrosis

Srdan Verstovsek
Department of Leukemia, The University of MD Anderson Cancer Center, Houston, Texas, USA

The discovery in 2005 of the JAK2V617F mutation in 50-60% of patients with myelofibrosis (MF), led to the clinical development of ten JAK inhibitors, which have completely changed the treatment paradigm for this debilitating disease. Ruxolitinib, an oral JAK1/JAK2 inhibitor is the first and so far the only JAK inhibitors to be approved by the United States Food and Drug Administration and the European Medicines Agency for treatment of MF. Patients with MF generally present with symptomatic organomegaly, disease-related constitutional symptoms, and anemia, all of which lead to very poor quality of life. Ruxolitinib has been shown to reduce spleen size and greatly improve quality of life in patients with or without the JAK2V617F mutation. It also improves quality of life in patients without splenomegaly, and may also decrease hepatomegaly. Despite the myelosuppressive effects of ruxolitinib, which can worsen anemia in some patients, after dose adjustments almost all patients can be treated safely with it. Adding another agent, such as danazol, erythropoietin, or low-dose thalidomide, to manage the anemia can be helpful in many cases. For patients with significant anemia or thrombocytopenia, starting at a lower dose (5 mg BID) and increasing to 10 15 mg BID during the first 3 months on treatment can be an effective and safe strategy. Even in cases where ruxolitinib worsens anemia to the point of transfusion dependence, patients often opt to remain on treatment, as the improvements in spleen and symptoms significantly out-weigh the risk of transfusion dependence. It is important to maintain patients on therapy as much as possible, and proactively adjust the dose if needed, as interruption or discontinuation of ruxolitinib leads to a return of constitutional symptoms within 7-10 days, which can leave patients feeling very badly within a short period of time. Tapering of ruxolitinib is suggested in such instances and reasons for discontinuation should be seriously considered. While 5 mg BID dose can be used transiently in case of myelosuppression, 10 mg BID or higher has been shown to be effective long-term maintenance dose. Finally, recently published data suggest that ruxolitinib may improve survival and even reduce bone marrow fibrosis after long-term treatment, suggesting that ruxolitinib should not be reserved only for patients with high-risk disease.

Keywords myelofibrosis, JAK inhibitors, JAK2 V617F
Conflict of interest Research support from Incyte Corporation, Astrazeneca, Lilly Oncology, Roche, Geron, NS Pharma, Bristol Myers Squibb, Celgene, Infinity Pharmaceuticals, YM Biosciences, Gilead, Promedior, SBio.

Sunday 20 October **1400-1530**
HSANZ/Nurses Combined Symposium: Myeloproliferative Disorders Auditorium (Arena B)

New Insights into CML Heterogeneity – Are We Ready for Customised Therapy?

Timothy Hughes
SA Pathology and SAHMRI, Adelaide, SA, Australia

Clinicians in many countries now have three TKIs approved for frontline therapy. This leads to a treatment dilemma - what is the best therapeutic approach for a particular patient given the excellent therapies available? Assuming that all three tyrosine kinase inhibitors (TKIs) are locally approved, it is unlikely and probably undesirable that the clinician would select the same drug in every case. While in many cases it makes good sense to use the TKI that the clinician is most familiar with, there is emerging evidence that in certain circumstances one TKI may be a better choice for a particular patient. Detailed knowledge of the safety profile and efficacy of each TKI, the patient's comorbidities, and clarity about the therapeutic goals will assist drug selection. Since none of the 3 available TKIs have shown a clear survival advantage, they all represent reasonable choices. However in individual patients the case may be stronger for a particular TKI. In the younger patient where the prospect of eventually achieving treatment free remission is likely to be of greatest importance, dasatinib or nilotinib may be preferred, although their advantage over imatinib in this setting remains to be proven. Additionally in patients with a higher risk of transformation, currently based on prognostic scoring, the more potent TKIs may be preferred because they appear to be more effective at reducing the risk of transformation to blast crisis. However, imatinib still represents an excellent choice for many CML patients. All of these considerations need to be made in the context of the patient's comorbidities which may lead to one or more TKI being ruled out of contention. Whatever first choice of TKI is made, treatment failure or intolerance must be recognized early because a prompt switch to another TKI likely provides the best chance of achieving optimal response. Before deciding on the best therapeutic approach for a newly diagnosed CP-CML patient it is important to be clear about the goals of therapy in each case. For elderly patients with substantial co-morbidities the main focus of CML therapy is likely to be prolonging survival by reducing the risk of progression. Furthermore, for the frail elderly patient who tolerates TKI therapy poorly, maintaining reasonable quality of life may become a higher priority than prolonging survival. For younger patients, maximizing the prospects of survival remains the main goal of therapy but improving the prospect of treatment free remission should now be considered as an additional goal. While imatinib appears to be a safe drug over the course of 10-15 years of exposure, significant organ toxicities may be revealed with life-long exposure. Young women who wish to start a family would also value the achievement of treatment free remission very highly.

Keywords Treatment-free-remission, CML heterogeneity, customised therapy.
Conflict of interest Research funding and honoraria from Novartis, BMS & Ariad

Sunday 20 October **1400-1530**
HSANZ/Nurses Combined Symposium: Myeloproliferative Disorders **Auditorium (Arena B)**

Adherence to Oral Chemotherapy – What Are the Challenges?

Monica Fliedner
University Center for Palliative Care, Department of Oncology, University Hospital Bern, Switzerland

The treatment with oral anti-tumour drugs in patients with cancer started in the early 1940's when chlorambucil was successfully used for the treatment of lymphoma. Since then the treatment modalities developed rapidly and the introduction of imatinib around the change of the century initiated a new era of treatment options for various types of cancer.
For many patients the treatment of a potentially lethal disease with oral drugs offered more independence from hospital-based medical care shifting to outpatient clinics with minimal scheduled contacts with the professional team but more options for a relative normal lifestyle.
Adherence in taking these drugs for successful treatment was not thought to be an obstacle because it was assumed that patients with a life-threatening disease would take the drug as being advised. We know that complying to long-term oral medication is a challenge worldwide – also in patients with cancer (WHO 2003). Several tumour-specific studies presented data on adherence rates ranging between 16% and 100%, depending on the individual therapy, the complexity of treatment and measurement method used.
The assessment of risk factors for non-adherence should guide multifacetted interprofessional prolonged individualized interventions that are needed to support the patient and his family in the long-term challenge to comply to the agreed upon treatment against cancer.
The presentation will reflect on the challenge of adherence in patients with haematological malignancies and different ways to measure adherence. It will also critically discuss potential interventions and educational strategies to support these patients in their daily life to reach and maintain successful therapy management and to answer the question whether oral anti-tumour therapies are an asset or an obstacle.

Keywords adherence / compliance, patient education, oral therapy
Conflict of interest No conflict of interest

Sunday 20 October **1400-1530**
ANZSBT/ISBT Academy: TRALI **Central Hall A**

TRALI and TACO: Pulmonary Consequences of Transfusion

Mark A Popovsky
Haemonetics Corporation & Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, USA

Transfusion-related acute lung injury (TRALI) & Transfusion-associated circulatory overload (TACO) are the 2 most frequent causes of mortality from transfusion. The mortality rates are 10% & 4%, respectively. The mechanisms of each complication are increasingly well understood. Anti-leukocyte and anti-HNA antibodies are implicated in both “one-hit” and “two-hit” TRALI. There may be other pathways but these are the most important. The incidence of TRALI is decreasing due to segregation of female plasma from production of FFP, but fatal cases due to RBC and platelet transfusions persist. The profile of the high risk patient for TRALI is not well defined. TRALI’s presentation consists of acute respiratory distress, hypoxemia, acute pulmonary edema and hypotension within 6 hours of transfusion. TRALI & TACO may occur concurrently. The published incidence of TACO is 1-8% but is most certainly underreported. It occurs in any age group but most patients are greater than 70 years. The mean RBC volume is 2.11 units and frequently involves only 1 RBC. FFP infusion is an important cause of TACO. Risk factors include history of congestive failure, vasopressors, fluid imbalance, left ventricular dysfunction, female gender and extreme age. Dyspnea (77%), hypertension (43%) and hypoxemia (36%) are the most common presenting features of TACO. Elevated brain natriuretic peptide has a positive predictive value in 74-78% of TACO cases. TACO is a preventable complication of hemotherapy. For patients at high risk, slowing the rate of transfusion to less than 2-4 ml/min and administration of pre-transfusion diuretics are appropriate.

Key words TRALI, TACO
Conflict of interest None

Sunday 20 October **1400-1530**
ANZSBT/ISBT Academy: TRALI **Central Hall A**

The Pivotal Role of Neutrophils in the Pathology and Investigation of TRALI

Lin Fung
Critical Care Research Group, The Prince Charles Hospital and the University of Queensland, Brisbane, QLD, Australia

TRALI events are clinically diagnosed and laboratory investigations act to support the diagnosis. The two event or priming TRALI hypothesis proposes that the patient's underlying illness induces activation of the pulmonary endothelium leading to the sequestration of primed neutrophils. Leukocyte antibodies or biological response modifiers (BRMs) in the transfused blood product activate the primed neutrophil producing an augmented respiratory burst response which causes injury to the microvasculature, resulting in the symptoms of ALI[1]. Hence neutrophils are a key effector cell in this pathology[2]. Current laboratory investigations are predominantly focussed on the antibody mediated TRALI. Both human neutrophil antigens (HNA) and human leukocyte antigens (HLA) have been associated and implicated in TRALI events. The combination of the granulocyte immunofluorescence tests (GIFT) and granulocyte agglutination test (GAT) have been recommended for the screening and detection of neutrophil reactive antibodies (i.e. HNA and HLA class I antibodies)[3]. HLA class II antibodies also have been implicated in severe TRALI, but HLA assays are needed to detect them[4]. Cross-matching of recipient neutrophils with donor sera by GIFT and GAT provide a useful means of confirming if an antibody is implicated. Otherwise only an association can be assumed. Although tedious and often protracted the laboratory investigation of TRALI events is needed so that blood donors with "risky" antibodies can be identified and removed from therapeutic use. There is not accepted method for investigating non-antibody mediated TRALI. The Granulocyte Immunobiology Working Party of the International Society of Blood Transfusion (ISBT) is a collective of the world's granulocyte experts. They advice the ISBT on granulocyte immunobiology matters, have a granulocyte nomenclature sub-committee, conduct annual granulocyte immunobiology workshops and have made recommendations on TRALI investigations[3]. And thus are a useful resource for TRALI investigations.

Keywords transfusion-related acute lung injury, neutrophils, antibodies
Conflict of interest No conflict of interest to disclose.

1. Silliman CC, Fung YL, Ball BB, Khan SY. Blood reviews 2009;23(6):245-55.
2. Fung YL, Silliman CC. Transfusion Medicine Reviews 2009;23(4):266-83.
3. Bierling P et al. Vox Sang 2009;96(3):266-9.
4. Reil A et al Vox Sang 2008;95 313-7.

Keywords Neutrophils, TRALI, Laboratory Investigation
Conflict of interest None

Sunday 20 October 1400-1530
ANZSBT/ISBT Academy: TRALI **Central Hall A**

Animal Models of Transfusion-Related Acute Lung Injury (TRALI)

John-Paul Tung[1,2]
[1]*Research and Development, Australian Red Cross Blood Service, Brisbane, QLD*
[2]*Critical Care Research Group, the Prince Charles Hospital and the University of Queensland, Brisbane, QLD, Australia*

Patients with transfusion-related acute lung injury (TRALI) develop hypoxaemia and pulmonary oedema during or soon after transfusion. Despite TRALI being a significant cause of transfusion-related morbidity and mortality, the underlying mechanisms remain to be fully elucidated. Patient and blood product factors appear to interact in a two-event threshold mechanism. The blood product factors could be antibodies directed against class I or class II human leucocyte antigens (HLA) or human neutrophil antigens (HNA), or biological response modifiers (BRMs), some of which accumulate in blood products during routine storage.

Animal models have been, and will continue to be, crucial to developing an understanding of the underlying mechanisms of TRALI pathogenesis. Initial models were *ex vivo* lung perfusion circuits using rabbits or rats, and provided evidence of both antibody and non-antibody mediated TRALI. These *ex vivo* models were followed by *in vivo* small animal TRALI models: in mice where either a major histocompatibility complex (MHC) class I monoclonal antibody or trauma-haemorrhage followed by stored syngeneic packed red blood cell (PRBC) transfusion were employed; and in rats where either of 2 MHC class I monoclonal antibodies or supernatant from stored human or rat blood products were used. To complement these models, our team developed the first *in vivo* large animal model of TRALI using sheep. In this model, LPS-infusion followed by transfusion with pooled supernatant from either stored human PRBCs or stored human buffy coat platelet concentrates precipitated the development of TRALI. Notable in the ovine model was the detailed haemodynamic and respiratory monitoring which revealed that blood product type (i.e. PRBC vs. platelets) also contributed to severity of injury. Also, for the first time in an animal model, TRALI was defined by the development of hypoxaemia as well as pulmonary oedema, aligning experimental TRALI more closely with the clinical definition. Animal research into TRALI pathogenesis has been further enriched by the subsequent report of an *in vivo* porcine model of TRALI. An overview of TRALI animal models, and a detailed discussion of the ovine model, and its continued development, will be presented.

Keywords transfusion-related acute lung injury, animal models, stored blood
Conflict of interest No conflict of interest to disclose.

Sunday 20 October **1400-1530**
ASTH Symposium 2:Rare Bleeding Disorders **Central Hall C**

Factor XI Deficiency

Simon McRae
Department of Haematology SA Pathology. Royal Adelaide Hospital, Adelaide, SA, Australia

Factor XI deficiency in many countries is the commonest of the rare bleeding disorders. It has been recently recognized that a central role of factor XI is the generation of sufficient thrombin to allow sufficient adequate generation of thrombin activatable fibrinolysis inhibitor (TAFI). Inadequate factor XI activity results in increased susceptibility of thrombus to fibrinolysis. Patients with factor XI deficiency therefore appear to be particularly at risk of bleeding at sites with active fibrinolysis. This talk will examine methods, both clinical and laboratory based, to predict bleeding risk in patients with factor XI deficiency. Management of surgery in patients, including the options of observation alone, anti-fibrinolytic therapy, and factor replacement will be discussed. A national registry of factor XI deficient patient including clinical and laboratory data will be proposed.

Keywords Factor XI, fibrinolysis
Conflict of interest None

Sunday 20 October **1400-1530**
ASTH Symposium 2:Rare Bleeding Disorders **Central Hall C**

Rare Bleeding Disorders

John Rowell
Royal Brisbane and Women's Hospital, Pathology Queensland, Brisbane, QLD, Australia

The rare bleeding disorders (RBD) can be defined by an incidence of less than 1 in 500,000, are usually autosomal recessive and constitute up to 3-5% of all inherited bleeding disorders. RBDs include inherited deficiencies of fibrinogen, factor II, V, VII, X,XI, XIII, combined FVIII/FV and combined deficiency of VKORC associated proteins. The incidence may be greater in cultures with high rates of consanguinity and with greater migration from such countries may be seen with greater frequency in Australia. RBDs are challenging due to less available quantitative diagnostic assays, poorer correlation of symptoms with factor level, less experience with managing these disorders and less availability of recombinant factor concentrates specific for each disorder. Some treatments have been associated with thromboembolism arguing for a cautious approach to replacement therapy. Genetic diagnosis and counselling can be challenging considering the poorer correlation of factor level with severity and lack of genetic diagnostic testing in Australia. Several case studies will be presented outlining clinical and management issues of RBDs.

Keywords RBDs
Conflict of interest None

Sunday 20 October **1400-1530**
BMTSAA Symposium: Current Status of Cord Blood Transplantation in Australia 2
Meeting Room 7

Receipt, Testing and Preparation of Unrelated Cord Blood Units for Infusion

Vicki Antonenas
The Blood and Marrow Transplant Laboratory, Westmead Hospital, part of Sydney Cellular Therapies Laboratory, Sydney, NSW

Cord Blood (CB) is an alternative haematopietic stem cell source for paediatric and adult patients with haematological and non- haematological diseases. More than 600,000 cord blood units are available and are stored world wide in CB banks and more than 30,000 unrelated CB transplants have been performed. Although there are several publications on the optimum method for CB collection and processing before cryopreservation, there is no consistent or best methodology for the transplant centre to follow in the handling and treating of the CB units after thaw in preparation for infusion. Transplant centres are using cord blood units that have been processed and stored by many CB banks with a variety of methods. Since the TNC and CD34 dose are important parameters for CB engraftment and cell dose is often a log lower than marrow and apheresis, it is critical that the receiving laboratory of the transplant centre is able to be familiar with the receipt, testing of the frozen CB units, and be familiar with few procedures available for CB infusion including the thaw and dilution method or the thaw and wash method. In all cases, it is important the lab staff are familiar with procedure for CB infusion with minimum cell loss and provide a safe graft for hematological recovery. The experience of the BMT Laboratory at Westmead Hospital in the receipt and preparation of more than 100 unrelated CB units for paediatrics and adults will be presented and discussed.

Keywords cord blood, transplantation
Conflict of interest No

Sunday 20 October **1400-1530**
BMTSAA Symposium: Current Status of Cord Blood Transplantation in Australia 2
Meeting Room 7

Outcomes of Paediatric Cord Blood Transplantation in Australia

Christopher J Fraser
Department of Haematology-Oncology, Royal Children's Hospital, Brisbane, QLD, Australia

This presentation will focus on the history of umbilical cord blood transplantation (UCBT) in Australia and address issues including indications for UCBT in the paediatric population, advances in donor cord blood unit selection and expected outcomes following UCBT.

Keywords Cord blood transplant
Conflict of interest No

Sunday 20 October **1400-1530**
BMTSAA Symposium: Current Status of Cord Blood Transplantation in Australia 2
Meeting Room 7

Outcome of Adult Cord Blood Transplantation in Australia

Glen Kennedy
BMT / Clinical Haematology, Cancer Care Services, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia

Abstract not available at time of going to print

Sunday 20 October **1600-1730**
HSANZ Symposium 2: Lymphoproliferative Disorders II **Auditorium (Arena B)**

Treatment of B-precursor Acute Lymphoblastic Leukemia with Blinatumomab

Max S Topp
Department of Internal Medicine at the University of Würzburg, Germany

Blinatumomab is a T-cell engaging antibody construct that binds both CD19 on healthy and malignant B- cells and CD3 on the T-cells. This interaction results in lysis of the B-cells and activation of T-cells.

Twenty one B-precursor ALL patients were recruited in a phase II trial and treated with a continuous i.v. infusion of Blinatumomab for 28 days followed by a two week break with the primary endpoint of MRD conversion. Responders could receive up to 5 cycles. Twenty patients were available for assessment of the primary endpoint of converting from MRD positivity into MRD negativity. This was achieved by sixteen out of twenty patients resulting in 80% MRD response rate. Furthermore, at a median follow-up of 33 months, the haematologic relapse-free survival was 61%.

Relapsed/refractory B-precursor ALL in adults has a dismal prognosis with only 35-40% of patients reaching a haematological complete remission (CR) with a median overall survival rate of 4-6 months. A phase II trial was conducted in this patient population with blinatumomab with the primary endpoint of reaching a complete remission. Thirty six patients were treated; 25 out of 36 of them (69%) achieved a haematological CR. Twenty two out of 25 responders also achieved a molecular response within the first two cycles. Thirteen responders proceeded to allogeneic HSCT in CR after their blinatumomab treatment. The median survival for all 36 treated patients is 9.0 months with a median follow-up time for OS of 10.7 months. For patients who achieved a CR/CRh*, the median survival is 14.1 months.

Full clinically reversible adverse drug events of the CNS leading to treatment interruption were observed at a frequency of 17% in the relapsed ALL cohort. After the symptoms were clinically resolved, all patients were re-exposed to blinatumomab at lower doses and two thirds could then successfully be treated with blinatumomab. Two relapsed/refractory ALL patients with high tumor burden and no cyto-reductive pre-phase required treatment interruption or discontinuation due to CRS. CRS could be either prevented or treated by adapting a dexamethasone regimen for patients resulting in no further treatment interruption (due to CRS).
In summary, blinatumomab shows clinical activity in B-precursor ALL. These results have led to a pivotal MRD trial in Europe as well as to a multinational trial in relapsed/refractory B-precursor ALL in US and Europe.

Keywords Acute lymphoblastic leukemia, Immunotherapy, Blinatumomab
Conflict of interest Dr Topp has been reimbursed for consultancy services by Amgen

Sunday 20 October **1600-1730**
HSANZ Symposium 2: Lymphoproliferative Disorders II **Auditorium (Arena B)**

Recent LOH Studies Implicate Specific Gene Inactivation in Non-Hodgkin's Lymphoma

LR Griffiths[1], CA Aya-Bonilla[1], MR Green[1,2], E Camilleri[1], M Benton[1], C Keane[3,4], P Marlton[4], RA Lea[1] M and Gandhi[3,4]
[1]Genomics Research Centre, Griffith Health Institute, Griffith University, Gold Coast, Australia; [2]Department of Oncology, School of Medicine, Stanford University, USA; [3]Clinical Immunohaematology Laboratory, QIMR, Brisbane;[4]Department of Haematology, Princess Alexandra Hospital, Ipswich Road, Woollongabba, Australia

Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL) account for around 50% of all Non-Hodgkin lymphoma (NHL) cases. Despite their high variability in morphology, tumour biology and clinical outcome, common genetic alterations across DLBCLs and FLs have suggested the existence of shared molecular mechanisms. Based on this, we performed a high resolution loss of heterozygosity (LOH) analysis on SNP array data to identify commonly inactivated tumour suppressor genes (TSGs) in FL (n=21) and DLBCL (n=21) cases). Validation of LOH was performed using targeted microsatellites in an independent cohort of controls (115) and NHL cases (24 FLs and 98 DLBCLs) and transcript abundance was measured by qPCR in cases with and without LOH. Gene set enrichment analysis (GSEA) was also performed by comparison of whole genome expression data of cases with LOH vs. cases with retention. Results for the LOH analysis identified 46 common LOH regions across FL and DLBCL containing 262 potential candidate TSGs. Pathway and GSEA showed that these candidate TSGs were involved in important cellular networks that may be deregulated by inactivation of one or more TSGs. Further microsatellite analysis validated LOH of the candidate TSGs; *FASLG, CISH, PTJPR* and *TP53BP1/B2M,* a significant decrease of heterozygosity of microsatellites targeting these TSGs. Of particular interest the PTPRJ gene was identified as a novel NHL TSG, as it was commonly inactivated in 38% (16/42) of all cases; 33% (7/21) of DLBCL cases and 43% (9/21) of FL cases. Also significant down-regulation of PTPRJ was observed in FLs but not in DLBCLs with LOH. Sequence analysis of exons 5 and 13 of PTPRJ showed over-representation of the A1182 allele (rs1566734) the C1054 allele (rs2270992), the C2971 allele (rs4752904) and the haplotype GCAC in LOH cases. Our genetic and expression analyses have implicated inactivation of PTPRJ in FL and DLBCL lymphomagenesis. This TSG negatively regulates key pathways for survival of B-cells (MAPK, PLCy1, PI3K, VEGF and BCR), and may be a novel chemotherapeutic target for NHL treatment.

Keywords Non-Hodgkins Lymphoma, Tumour Suppressor Gene, LOH.
Conflict of interest No

Sunday 20 October **1600-1730**
HSANZ Symposium 2: Lymphoproliferative Disorders II **Auditorium (Arena B)**

Classification of Aggressive B-cell Lymphoma: Are We There Yet?

Debra Norris
QML & Princess Alexandra Hospital, Wooloogabba, QLD, Australia

The aggressive B-cell lymphomas encompasses diffuse large B-cell lymphoma and its large number of subtypes (DLBCL with 18 subentities), but also Burkitt lymphoma (BL), mantle cell lymphoma, and B-lymphoblastic lymphoma. As defined by the REAL classification and then WHO classification of haematopoietic neoplasms, these entities are separated by clinical presentation together with histology, immunophenotype, and cytogenetic abnormalities. However, increasingly we know that molecular abnormalities.and tumor microenvironment also help define the characteristic signatures of these neoplasms, impact prognosis and potentially direct new therapeutic targets.

This presentation will explore the relationship of DLBCL to BL, and the grey zone between them (B-cell lymphoma unclassified with features intermediate between DLBCL and BL (BCL-U).

By gene expression profiling (GEP) at least three subtypes of DLBCL are recognised: germinal centre B-cell –like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL and primary mediastinal B-cell lymphoma (PMBL). The majority of DLBCL cases are distinct from BL, but there is a subset of tumours with GEP profile intermediate between DLBCL and BL, suggesting a spectrum. Recognising this continuum, the 2008 WHO classification included the category of BCL-U.

This presentation will also discuss the impact of MYC rearrangement and potential synergy with BCL2 and BCL6 rearrangements, (so called Double Hit lymphoma) and protein expression, in DLBCL and grey zone lymphoma (BCL-U).

It is clear that genomic studies will play an increasing role in defining and refining disease entities, but cannot be the sole basis for the classification of lymphomas at present. A multiparameter approach to define disease entities as exemplified by REAL/WHO provides a basis for diagnosis and treatment, and will continue to point the way towards further studies.

Keywords Aggressive B-cell lymphoma
Conflict of interest None

Sunday 20 October **1600-1730**
ANZSBT Symposium 1: Obstetric / Neonatal Transfusion **Central Hall A**

Paediatric and Neonatal Transfusion

Simon J Stanworth and Helen V New
NHS Blood and Transplant/ Oxford University Hospitals NHS Trust, *John Radcliffe Hospital, Headley Way, Headington, Oxford, UK*

Survival rates for infants born prematurely have improved significantly, and one factor has included better supportive care including red cell transfusion. The decision to transfuse a neonate can be approached by addressing a series of questions, covering the cause of anaemia, alternatives to transfusion, the need for transfusion and the risks. Recent clinical trials of red cell transfusions have started to inform evidence-based transfusion practice, but have raised uncertainties about neurological outcomes when policies advocating use of fewer red cell transfusions at lower haemoglobin concentration (Hb) thresholds were tested. Red cell transfusions should be considered when the Hb <12g/dl for premature neonates requiring mechanical ventilation support, with lower thresholds applying for oxygen dependent neonates not requiring ventilation or for late anaemia (Hb <7-10g/dl, depending on gestational and post-natal age).
The role of platelet transfusions in neonates is also controversial. Neonatal thrombocytopenia is common in premature infants. The primary causal factors are intrauterine growth restriction/maternal hypertension (presents with thrombocytopenia soon after birth), and sepsis/ necrotising enterocolitis (the common morbidities associated with late thrombocytopenia in neonates >72 hours of age). There is no strong evidence of a relationship between platelet count and occurrence of major haemorrhage, and other factors are considered more relevant in the development of intraventricular and periventricular haemorrhage including cardio-respiratory changes. Platelet transfusions are commonly used as prophylaxis in premature neonates with thrombocytopenia. However, there is widespread variation in the pre-transfusion thresholds for platelet count and evidence of marked disparities in platelet transfusion practice between hospitals and countries. Practice in UK has become more restrictive using lower safe thresholds for platelet transfusion between 20-30x10^9/L. Platelet transfusions are biological agents, which are associated with risks. There have been no recent clinical trials undertaken comparing different thresholds for platelet transfusion in premature neonates, and there is no evidence base to inform safe and effective practice for prophylactic platelet transfusions.

Keywords Neonate, blood transfusion
Conflict of interest None

Sunday 20 October **1600-1730**
ANZSBT Symposium 1: Obstetric / Neonatal Transfusion **Central Hall A**

NAIT Investigation and Management

Bronwyn Williams
Pathology QLD, Haematology Dept, RBWH, Herston, QLD, Australia

Alloimmune thrombocytopenia is a rare condition which may have devastating effects on a fetus / neonate. Prediction of the first affected pregnancy is rarely possible prior to delivery of the infant and more mildly affected infants are not consistently recognised. Appropriate investigation of unexplained bleeding and thrombocytopenia in infants is pivotal for diagnosis of this condition. Subsequent pregnancies, typically result in a more severely affected fetus / neonate in the absence of therapeutic intervention. Risks related to fetal / neonatal thrombocytopenia may be minimised by timely recognition of this condition and institution of appropriate immunomodulatory treatment for the mother. Early recognition of affected neonates is important in screening for adverse events which may be clinically silent in the neonatal period and to allow appropriate supportive care to improve platelet counts and reduce the risk of serious bleeding. Strategies for investigation and management of FMAIT / NAIT will be discussed in this session.

Keywords Alloimmune thrombocytopenia, FMAIT, NAIT
Conflict of interest None

Sunday 20 October **1600-1730**
ANZSBT Symposium 1: Obstetric / Neonatal Transfusion **Central Hall A**

Management of Haemolytic Disease of the Fetus and Newborn

Helen Liley
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The history of the prevention and management of Haemolytic Disease of the Fetus and Newborn (HDFN) includes a number of pivotal discoveries. These breakthroughs included exchange transfusion for neonatal treatment, development of screening programs for maternal blood group antibodies, strategies for managing early delivery to optimize neonatal outcomes, the use of amniocentesis for fetal diagnosis, the first example of intrauterine fetal treatment, the development of one of the earliest and most successful forms of immunoprophylaxis using human antibodies and the non-invasive prediction of fetal blood type using DNA from maternal blood. Subsequently, many of the successes of fetal and neonatal treatment of HDFN have been extrapolated to other problems of pregnancy.

Antenatal and post-natal RhD immunoprophylaxis have markedly reduced but not prevented maternal RhD sensitization, and not unexpectedly, have not reduced other HFDN due to other Rh and non-Rh antigens. Contemporary assessment of affected fetuses utililises ultrasound to estimate fetal anaemia with a high level of accuracy, minimising the need for invasive testing such as amniocentesis or fetal blood sampling. When intrauterine treatment is needed, fetal transfusion via the umbilical vein has replaced intraperitoneal transfusion, and enables prolongation of pregnancy and good outcomes even in hydropic fetuses. Neonatal management comprises intensive phototherapy, selective use of neonatal exchange transfusion and close follow-up for late anaemia, the risk of which is not reduced by intrauterine treatment. Erythropoietic stimulating agents show promise for reducing the need for transfusion for late anaemia in HFDN.

Keywords Haemolysis, Fetus, Newborn
Conflict of interest No

Sunday 20 October **1600-1730**
ANZSBT Symposium 1: Obstetric / Neonatal Transfusion **Central Hall A**

Non-invasive Fetal *RHD* Genotyping

Catherine A Hyland[1], Glenn Gardener[2], Anne Tremmellen[2], K Gibbons[2], Helen O'Brien[1], Glenda Millard[1], Robert Flower[1]
[1]Australian Red Cross Blood Blood Service and [2]Mater Health Services and Mater Medical Research Institute, Brisbane, Qld, Australia

Background
Fetal DNA is released in a cell free form into the maternal plasma during pregnancy. Non-invasive prenatal testing (NIPT) for the fetal *RHD* genotyping has become standard for antenatal care of D negative women who are isoimmunised to the RhD antigen. This is an alternative to amniocentesis as a source of fetal DNA.
Aim
The aim of this paper is to review a replicate testing procedure and interpretative algorithm for an Australian obstetric population.
Study design
In a population study 788 maternal blood samples were collected from 603 participants, gestation age range 7 to 38 weeks. A further 140 samples were provided from 120 participants with clinical risk factors including 110 with an allo-anti-D. Fetal *RHD* genotyping on plasma derived cell free fetal DNA employed real time PCR using a multi-replicate and multi exon test system.
Where samples genotyped as D negative the presence of cell free fetal DNA was verified using the Y-chromosome SRY marker or a placental derived fetal marker.
Outcome measures are fetal cord RhD phenotype on delivery.
Results
For the population study the first sample collected predicted a fetal RHD negative assignment for 209 (34.7%) of cases and required further investigation for 8 (1.3%). Further investigation demonstrated maternal *RHD* genotypic variants in n=6 cases and insufficient target cffDNA for n=2.
For both study groups there is a statistically significant relationship between gestational age and PCR cycle threshold for respective fetal markers ($p<0.001$ for all markers.) The accuracy of the test was 99.5% with no false negatives.
Statistical analysis projected that a reduced exon testing strategy, such as exons 5 and 10, gives the same results as compared to when all three exons are used.
Discussion
NIPT is accurate and safe for fetal *RHD* genotyping for immunized women. Approximately one third of D negative women could have safely avoided anti-D prophylaxis during pregnancy if NIPT had been used to target routine antenatal anti-D prophylaxis.

Keywords Maternal blood test, Fetal RHD genotype, HDFN
Conflict of interest No

Sunday 20 October **1600-1730**
ASTH Symposium 3: vWD **Central Hall C**

Current Issues and Trends in the Management of von Willebrand Disease

Simon A Brown [1,2]
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Inherited defects in von Willebrand factor (VWF) result in the commonest of the inheritable bleeding disorders, von Willebrand disease (VWD). The therapeutic agents available for the management of VWD have changed little over recent decades. Desmopressin (DDAVP) and plasma derived factor VIII/VWF concentrate are the clinician's main armamentarium in managing acute bleeds and for surgical prophylaxis. Despite this stability in therapeutic agents there remains a variable clinical practice in utilizing these therapies and in the management of VWD. In addition there are emerging reports of early studies with recombinant VWF concentrate.

Keywords von Willebrand disease, desmopressin, von Willebrand factor
Conflict of interest No conflict of interest to disclose

Sunday 20 October **1600-1730**
ASTH Symposium 3: vWD **Central Hall C**

Laboratory Testing of von Willebrand's Disease

Robyn Coleman
Sullivan Nicolaides Pathology, Brisbane, QLD, Australia

Sullivan Nicolaides Pathology has recently changed our coagulation testing platform. As part of this change, all the assays for von Willebrand diagnosis currently offered had to be validated on the new platform. Some reagent changes were also evaluated. One example was the consideration of a lupus insensitive APTT reagent for factor assays compared to our current lupus sensitive APTT reagent. It also gave us the opportunity to review why we do things, challenge those things done for historical reasons and consider if we could safely make changes that may be more efficient in terms of workflow and reagent costs. This is an account of our journey of change, our findings along the way and our conclusions.

Keywords von Willebrand, laboratory assays, coagulation
Conflict of interest No

Sunday 20 October **1600-1730**
Nurses Symposium 2: Focus on Apheresis **Meeting Rooms 5/6**

Emerging Role of Nurse Practitioner in Allograft Sibling Donors

Kari Mudie
Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia

Queensland's population is described as having the second fastest growth rate in Australia, and the provision of equitable and accessible healthcare for all is a challenge for Queensland Health that is compounded by geographical disparity, increasing cancer incidence rate and an increasing population. A sustainable and effective health service requires development and employment of strategies, including the expansion and invention of roles.

The Apheresis Nurse Practitioner (NP), a new role to the Royal Brisbane & Women's Hospital (RBWH), is an advanced practice nurse who offers a high level of skill and expertise to efficiently, effectively, safely and appropriately manage patient care within the Apheresis NP scope of practice.
The introduction of the Apheresis NP in the allogeneic sibling donor setting will:

- Improve patient accessibility to Cancer Care Services, RBWH
- Provide delivery of evidence based care, integrating both drug and non-drug based treatment methods, prescribe and review medications for therapeutic effectiveness within the NP scope of practice and according to patient needs
- Provide a service which fills a gap in patient access to Cancer Care Services, RBWH enabling the medical model of care to be more focused on complex and clinically difficult patient management
- Contribute to a sustainable, equitable and effective healthcare service

There is an abundance of literature identifying multiple barriers and facilitators to implementation of the NP role. Successful navigation through these barriers and facilitators will be crucial to successful implementation and long term sustainability of the Apheresis NP role.

Evidence of the efficacy and value of this new role will be provided through:

- Annual audits reviewing the Apheresis NP prescribing practice and consent process
- Meeting of predefined key performance indicators to help define and measure the successful implementation of this role
- Ongoing collaboration between the Apheresis NP and the multidisciplinary team to ensure that the NP role is being utilised effectively and to it fullest potential

Keywords Apheresis, Nurse Practitioner, Allogeneic Donors
Conflict of interest No conflict of interest to disclose

Sunday 20 October **1600-1730**
Nurses Symposium 2: Focus on Apheresis **Meeting Rooms 5/6**

Poor Haemopoietic Stem Cell Mobilizers: A Single Institution Experience

Rosita Van Kuilenburg
Princess Alexandra Hospital, Brisbane, Qld, Australia

High-dose chemotherapy followed by autologous stem cell transplantation is an approved therapeutic intervention in relapsed Hodgkin-lymphoma and Non-Hodgkin lymphoma. In multiple myeloma it remains standard of care in first remission. Unfortunately, a significant proportion of patients fail to mobilize sufficient stem cells due to bone marrow disease, prior treatment, age and genetics as influencing factors.

Haemopoietic stem cell (HSC) autologous transplantation (HSCT-A) requires a minimum number of stem cells, 2-5 10^6 mobilized CD34+cells/kg body weight, to lower transplant costs and mortality. HSC-autologous mobilization is generally accomplished using myelosuppressive chemotherapy in combination with haematopoietic growth factors (G-CSF) or with G-CSF alone.

Patients failing to mobilize and collect an insufficient amount of haematopoietic stem cells, are considered as “poor-mobilizers”. Poor mobilization affects patient outcome and increases resource use.

To maximize HSC harvest in poor mobilizers we need to optimize current mobilization protocols and establish criteria for pre-emptive and immediate salvage in poor haemopoietic stem cell mobilizers.

This paper will discuss the prevalence and management of the “poor mobilization” experience in a single institution.

Keywords Autologous peripheral blood stem cell transplantation, Autologous stem cell mobilization, poor mobilizers

Conflict of interest None

Stem Cell Laboratory – "Behind the Scenes"

CJ Hutchins
Cellular Therapy / BMT Laboratory, Cancer Care Services, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia

The stem cell laboratory is responsible for the collection, processing, testing, cryopreservation, storage and infusion of haemopoietic progenitor cells (HPC) (bone marrow (BM), peripheral blood progenitor cells (PBPC) and cord blood (CB) for allogeneic and autologous transplantation. However many of these procedures require collaboration between scientists in the processing facility and nurses in the collection facility and the bone marrow transplant ward.
In most facilities, nursing staff perform the collection of PBPC (or HPC, Apheresis). Liaison with the stem cell laboratory is required for the generation of CD34+ cell counts in the peripheral blood to determine the scheduling of the apheresis procedure and the prediction of total CD34+ cell counts in the collection. Specific criteria such as correct labelling must be defined by the apheresis unit prior to release of the HPC, Apheresis to the processing facility.
Upon reception in the processing facility, specimens are removed for testing (haematology, viable CD34+ cell counts, colony forming assays (CFU), microbial contamination and other testing procedures). Generally HPC, Apheresis collected for allogeneic transplantation are infused without cryopreservation whereas HPC, Apheresis collected for autologous transplantation are cryopreserved, although the scheduling of donors or the collection of excess CD34+ cells may necessitate cryopreservation of allogeneic HPC. For cryopreservation, cells are concentrated by centrifugation, a cryoprotectant (dimethylsulphoxide – DMSO) and a source of protein (concurrent plasma or Albumex) added, followed by programmed freezing to minimise damage caused by intracellular ice crystal formation and increased extracellular solute concentration. Cryopreserved HPC are stored in the vapour phase of liquid nitrogen for > 5years. Viability post cryopreservation is assessed by the repeat testing of pilot vials or segments for viable CD34+ cell counts (and CFU).
Following receipt of a request for infusion, scientists assess the criteria for release of HPC from the processing facility. For cryopreserved HPC, this includes a check of bag integrity prior to commencement of the recipient's conditioning regimen. On the day of infusion cells are thawed inside sterile plastic bags in a water bath and handed over to nursing staff for infusion. Scientific staff, in collaboration with nursing staff, are responsible for monitoring engraftment and adverse events post infusion.

Keywords Apheresis, Processing, Cryopreservation
Conflict of interest No

Monday 21 October **0830-1000**
HSANZ Young Investigator Session (Baikie) **Auditorium (Arena B)**
O005 **0830**

Durable Survival Benefit for Thalidomide Consolidation Post ASCT for Multiple Myeloma (MM): Extended Analysis of the ALLG MM6 Study

Anna Kalff[1], Nola Kennedy[1], Angela Smiley[1], H Miles Prince[2], Andrew W Roberts[3], Kenneth FBradstock[4], Andrew Spencer[1]
[1] Alfred Hospital, Monash University, Melbourne, VIC, Australia; [2] Peter MacCallum Cancer Institute, Melbourne, VIC, Australia; [3] Royal Melbourne Hospital, Parkville, VIC, Australia; [4] Westmead Hospital, Sydney, NSW, Australia

Aim/Background
To determine whether PFS and OS advantages for thalidomide consolidation post ASCT at 3 years post randomisation in the ALLG MM6 study are durable at later follow-up. To compare overall response rate (ORR) to salvage therapy, incidence of second primary malignancy (SPM) and to assess cost of thalidomide consolidation.
Methods
243 newly diagnosed MM patients post single MEL200 ASCT were randomly assigned to receive indefinite prednisolone maintenance (50mg alternate days) alone (CA = 125 patients) or in combination with 12 months of thalidomide consolidation (100mg/d increasing to 200mg/d after 2/52) (TA = 111 patients). PFS and OS were measured from date of randomisation. Cost of thalidomide per mean life year gained (LYG) was calculated according to exposure and cost of drug.
Results
After a median follow-up of 5.4 years, post randomization estimated 5 yr PFS rates were 27% versus 15% (p=0.005; hazard ratio [HR] 0.16: 95% CI 0.044 to 0.582) and OS rates were 66% versus 47% (p=0.007; HR 0.12: 95% CI 0.028 to 0.558) in TA and CA respectively. Thalidomide remained beneficial irrespective of pre-ASCT B2m level <4mg (p=0.002) and 4+ (p=0.049), however TA patients who achieved VGPR/CR post ASCT no longer had a PFS advantage over VGPR/CR CA patients. Patients required at least 8 months of thalidomide exposure to gain a PFS and OS advantage (p<0.001). Landmark analysis confirmed that PFS/OS benefit was gained within the first 8-12m of therapy. There was no difference in ORR to salvage therapy (62% versus 69%, p=0.5), survival post-progression or incidence of SPM for TA versus CA. Discounted mean LYG for TA patients was 0.92 years (95%CI 0.32 to 1.52), with cost per mean LYG of $15182 (AUD).
Conclusion
PFS and OS advantages ascribed to thalidomide consolidation post ASCT remain highly significant at 5 years. At least 8 months of thalidomide exposure was required to attain the PFS/OS benefit. Further recapitulating previous findings, thalidomide did not impact on ORR to salvage therapy or survival following relapse. Thalidomide consolidation is cost effective in terms of cost per mean LYG.
Keywords Myeloma thalidomide consolidation **Conflict of interest** None

Monday 21 October **0830-1000**
HSANZ Young Investigator Session (Baikie) **Auditorium (Arena B)**
O006 **0845**

ABT-199 Induces Apoptotic Death *In Vivo* and *In Vitro* in Chronic Lymphocytic Leukaemia (CLL) Cells, Potentially Abrogating the Adverse Prognostic Impact of Del (17p)

Mary Ann Anderson[1,2,3], John Seymour[4], David Huang[1], Andrew Roberts[1,2,3]
[1.]Walter & Eliza Hall Institute, [2.]Department of Clinical Haematology & BMT Royal Melbourne Hospital (RMH), [3.]Faculty of Medicine, University of Melbourne, [4.]Department Haematology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Aim/Background
We hypothesised that specific inhibition of Bcl-2 will directly induce apoptosis of CLL cells where it is uniformly highly expressed. ABT-199 is a selective inhibitor of Bcl-2. The specific aims of this work were to determine (i) the activity of ABT-199 *in vitro* and *in vivo* against CLL; (ii) the mechanism-of-action of ABT-199 *in vivo* and (iii) whether efficacy is evident in chemo-refractory patients (pts) with del (17p) CLL.

Methods
Peripheral blood (PB) and bone marrow (BM) (n=43) samples from pts with CLL were tested *in vitro* for cytotoxicity and mechanism-of-action by ABT-199 using flow cytometry (propidium iodide exclusion and JC-1 retention). *In vivo* responses were analysed as part of an ongoing phase I study of ABT-199 in pts with relapsed / refractory CLL (NCT:01328626). PB CLL *in vivo* phosphatidylserine (PS) exposure, in response to the first dose of ABT-199, was measured flow cytometrically. *In vivo* and *in vitro* responses were correlated with p53 status determined by presence of del (17p), immunohistochemistry and sensitivity to Nutlin-3a-induced apoptosis.

Results
CLL is highly sensitive to ABT-199 *in vitro* (median IC_{50} 1.1nM), with death manifest within 4-8 hours. Changes in mitochondrial membrane potential indicate apoptosis as the mechanism of cytotoxicity. *In vivo*, initial dosing is associated with PS exposure on circulating CLL cells 6 hours post ABT-199 and results in a dose-dependent reduction in lymphocytosis within 8 – 24 hours. With ongoing dosing (100 – 600mg/day), 14/15 pts at RMH, 8 with del (17p) CLL, have demonstrated clinical responses (10 partial, 4 complete), consistent with the overall trial population. *In vitro* and *in vivo* responses are equivalent for del (17p) and non-del (17p) CLL.

Conclusion
Selective inhibition of Bcl-2 by ABT-199 shows significant activity against CLL by inducing apoptosis independent of del (17p) or p53 status.

Keywords Chronic lymphocytic leukaemia, ABT-199, p53
Conflict of interest This research was supported by Abbvie and Genentech. Neither company had a role in analysing these data or preparing the abstract.

Monday 21 October **0830-1000**
HSANZ Young Investigator Session (Baikie) **Auditorium (Arena B)**
O007 **0900**

Screening With Spirometry is a Useful Predictor of Later Development of Pulmonary Graft Versus Host Disease in Patients Undergoing Allogeneic Stem Cell Transplantation

Philip Thompson[1], Andrew Lim[1,2], Mark Tacey[3], Ramzi Hijazi[1], Ashley Ng[1,2], Jeff Szer[1,2], David Ritchie[1,2] and Ashish Bajel[1]
[1]Department of Clinical Haematology and Bone Marrow Transplantation, Royal Melbourne Hospital, Parkville [2]University of Melbourne, Parkville [3]Melbourne EpiCentre, The Royal Melbourne Hospital and The University of Melbourne, Parkville

Background
Pulmonary graft versus host disease (pGVHD) complicating allogeneic stem cell transplantation (allo-SCT) presents most commonly as bronchiolitis obliterans syndrome (BOS), characterised by irreversible fixed airflow obstruction, impaired quality of life and high mortality. Treatment has minimal impact. There are no proven screening tests. We sought to identify novel predictors for development of pGVHD.
Methods
Spirometry and DLCO were performed pre-alloSCT, D100 and 1 year post-alloSCT. We retrospectively analysed spirometry, CT and bronchoalveolar lavage results in consecutive patients having allo-SCT from 2004-2010 to identify cases of pGVHD as per NIH consensus guidelines (2005). Spirometry trends and baseline variables were compared between patients with and without pGVHD to identify early predictors and risk factors for pGVHD.
Results
Of 235 assessable patients, 23 (9.8%) developed pGVHD. Median time of onset was day 367 (IQR 144-544 days). FEV1.0 was the best predictor of later pGVHD development. Median FEV1.0 from pre-transplant to D100 in patients later developing pGVHD was -12% (IQR -25% to -1%) vs -1% (IQR -7% to +6%) in those who did not, p=0.0017. From pre-transplant to 1 year, it was -19% (IQR -37% to -6%) vs -3% (-10% to +4%), respectively, p=0.0001. Busulphan-based, but not TBI-based, conditioning increased the risk of pGVHD [HR 9.4 (3.4-23.9), p<0.001]. *In vivo* T-cell depletion with Thymoglobulin was protective, with no cases in 53 patients (p<0.0001). pGVHD was associated with high transplant-related mortality (TRM) [HR 6.6 (2.5-16.4), p<0.001)].
Conclusions
Spirometry is a potentially useful screening test for identification of pre-symptomatic pGVHD. We recommend 3-monthly spirometry surveillance for up to two years post-transplant. Our findings require prospective validation.

Keywords Spirometry predicts pulmonary GVHD. **Conflict of interest**: No

Monday 21 October **0830-1000**
HSANZ Young Investigator Session (Baikie) **Auditorium (Arena B)**
O008 **0915**

Targeting Puma May Present a Viable Therapeutic Option in the Treatment of the Myelodysplastic Syndrome

Andrew Guirguis[1,2], Christopher Slape[1], David Curtis[1,2]
[1.] *Stem Cell Research Group, Division of Blood Cancers, Australian Centre for Blood Diseases, The Alfred Hospital / Monash University, Melbourne, Australia*
[2.] *Department of Clinical Haematology, Alfred Hospital, Melbourne, Australia*

Aim/Background
Early-stage myelodysplastic syndrome (MDS) is characterised by increased apoptosis of haematopoietic progenitors, which contributes to ineffective haematopoiesis. Using a murine model of MDS (NHD13), we have demonstrated that the intrinsic pathway, in part due to activation of p53, mediates the apoptosis. Overexpression of Bcl2 (an anti-apoptotic protein) has been shown to prevent apoptosis; improving blood counts and delaying transformation to acute leukaemia. In this study, we sought to define the contribution of different BH3-only proteins to this process with the aim of determining mechanisms by which apoptosis can be modulated.
Methods
Gene expression analysis was first performed in haematopoietic progenitors within the NHD13 mice. Based on the results, NHD13 mice were subsequently crossed with Noxa, Puma and Bim deficient mice to ultimately generate NHD13 mice deficient in each of these BH3-only proteins. Mice were euthanised at three months of age. Analysis included peripheral blood counts, flow cytometric analysis for apoptosis and progenitor assays – including agars and methylcellulose.
Results
Gene expression analysis within haematopoietic progenitors in the NHD13 mouse revealed a significant increase in Noxa and Puma. Removal of Noxa failed to rescue the peripheral blood cytopenias or apoptosis (measured directly by flow cytometry or indirectly through progenitor assays). However, when Puma (which is also transcriptionally regulated by p53) was removed, apoptosis was rescued indicating that this may be the main driver of apoptosis in this model.
Conclusion
In summary, these findings suggest that Puma may be the main driver of apoptosis within this MDS model. Furthermore, therapeutically targeting Puma may be a viable therapeutic option in the treatment of cytopenias within MDS.

Keywords Myelodysplasia, Apoptosis, BH3-only proteins
Conflict of interest "No conflict of interest to disclose"

HSANZ Young Investigator Session (Baikie) **Auditorium (Arena B)**

O009 **0930**

bine, Oral Cyclophosphamide and Intravenous Rituximab (OFOCIR) as Initial Treatment of Chronic Lymphocytic Leukemia (CLL)

Xavier Badoux[1,2], Giles Best[1], Sara Gabrielli[1], Melanie Sulda[3], Bryone Kuss[3], William Stevenson[1], Stephen P Mulligan[1]
[1]Northern Blood Research Centre, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, NSW, Australia; [2]SEALS, St George Hospital, Kogarah, NSW, Australia [3]Department of Haematology and Genetic Pathology, Flinders Medical Centre, Adelaide, SA, Australia

Background and Aim
Recurrent genomic alterations have been described in patients with CLL. We aim to describe the incidence of commonly described genomic alterations by next-generation sequencing in an elderly population of patients with CLL.
Methods
Pre-treatment peripheral blood (PB) and bone marrow aspirate samples were obtained from 82 patients enrolled on a phase II randomised clinical trial investigating oral fludarabine, oral cyclophosphamide and intravenous rituximab (poFCivR) tolerance in previously untreated fit elderly patients with CLL (ALLG CLL5). Bone marrow aspirates were analysed for CLL-associated genomic changes by FISH. PB lymphocytes were purified by Ficoll gradient separation. DNA was extracted for targeted sequencing of genes including *TP53, ATM, NOTCH1, SF3B1, BIRC3* and *MYD88* using a TruSeq Custom Amplicon Design Panel on a MiSeq Sequencer (Illumina, San Diego). Mutations were compared to reported mutations in the literature and COSMIC database.
Results
47 of 82 patient samples have been analysed at this time. FISH identified 17p deletion in 7 pts (17%), 11q deletion in 1 pt (2%), trisomy 12 in 8 pts (17%), deletion 13q in 18 pts (38%), and no abnormality in 7 pts (15%); not performed (n=5, 11%). By targeted sequencing, mutations were identified in *TP53* (n=6, 13%), *ATM* (n=7, 15%), *NOTCH1* (n=11, 23%), *SF3B1* (n=9, 19%), *MYD88* (n=3.6%) and *BIRC3* (n=1, 2%). Five of 6 mutations in *TP53* occurred in the DNA-binding core domains (exons 5-8) and one mutation in the homo-oligomerization domain. The majority of *NOTCH1* mutations were identified in the PEST domains (5 of 8) and all but one mutation in SF3B1 were identified in the PP2A repeats 5-9.
Conclusion
We demonstrate a high proportion of genomic mutations in fit patients age ‡65 years undergoing first-line therapy for CLL. DNA analysis and correlation with patient characteristics and clinical outcome data is proceeding.
Keywords chronic lymphocytic leukemia, sequencing, elderly
Conflict of interest No conflict of interest to report. Research supported by grants from CLL Global Research Foundation and Cancer Institute of NSW.

HSANZ Young Investigator Session (Baikie) **Auditorium (Arena B)**

O010 **0945**

Conditioning Regimens for Unrelated Donor Haematopoietic Stem Cell Transplantation (UDHSCT) for AML and MDS: Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) study

Abir Bhattacharyya[1], Leonie Wilcox[2], Steven Tran[2], Anthony Dodds[1,3], David Ma[1,3], Jeff Szer[3,4], Peter Bardy[3,5], John Moore[1]

[1]St Vincent's Hospital, Sydney, NSW; [2]ABMTRR; [3]ABMTRR Steering Committee; [4]Royal Melbourne Hospital, Melbourne, VIC; [5]Royal Adelaide Hospital, Adelaide, SA

Background

Unrelated donor transplants continue to increase worldwide due to limitations in the availability of related donors. Survival following HSCT is limited by either Non-Relapse Mortality (NRM) or relapse. There is ongoing debate in the literature about the relative merits of Myeloablative (MAC) and Reduced Intensity (RIC) regimens. A previous ABMTRR study assessing Flu Mel conditioning found excellent disease control in a wide range of malignancies however there has been no direct comparison between MAC and RIC regimens in an unrelated donor setting.

Aim

To determine the effect of the intensity of conditioning regimens on Overall Survival, (OS), NRM and Relapse Rate (RR) following UDHSCT for AML and MDS.

Methods

We conducted a retrospective multi-centre analysis of data from UDHSCT for AML and MDS performed in Australia from 2001 to 2011 for patients 16 years or older. Cord blood transplants were excluded. Conditioning regimens were divided into RIC (Fludarabine/Melphalan and Fludarabine/Busulphan) and MAC.

Results

There were 383 MAC and 177 RIC UDHSCTs performed for AML and MDS. Median age for patients receiving MAC was 41 years(AML) and 46 years(MDS) and for patients receiving RIC was 57 years(AML & MDS). The OS at one year for patients receiving MAC was 59% and for RIC was 58% (p=0.795). The corresponding 100 day NRM, one year NRM and one year RR for MAC and RIC were 16.3% and 20%, 27% and 31% (p=0.203), 14% and 11% (p=0.081), respectively.

Conclusion

Our results demonstrate that outcomes for UDHSCT for AML and MDS are similar with MAC and RIC regimens. A recent European Blood and Marrow Transplantation (EBMT) group registry publication confirmed this finding for related donors. Limitations of our retrospective study include potential selection bias in baseline characteristics of MAC and RIC patients. Prospective comparisons of conditioning regimens with varied intensity are required to define the optimum compromise between NRM and RR in order to maximise overall survival.

Keywords conditioning regimen, allogeneic transplantation, unrelated donor

Conflict of interest None

Monday 21 October **0830-1000**
HSANZ Free Communications 1: Acute Leukaemia 1 **Meeting Room 7**
O011 **0830**

Pre-phase Therapy With Sorafenib Followed by Salvage FLAG-AMSA for Relapsed/refractory FLT3-ITD Positive AML: A Pilot Analysis

Katherine Cummins,[1] Steve Jane,[1] Slavisa Ninkovic,[2] Ali Bazaragan,[2] Gaurav Sutrave,[3] Mark Herztberg,[3] Ashleigh Scott,[4] Steven Lane[4] and Andrew Wei[1]
[1]The Alfred Hospital, Melbourne, Australia; [2]St Vincent's Hospital, East Melbourne, Australia; [3]Westmead Hospital, Westmead, Australia; [4]Royal Brisbane Hospital, Herston, Australia

Aim

To assess the preliminary efficacy of treating patients with relapsed/refractory FLT3-ITD AML using a novel regimen involving the FLT3 inhibitor (FLT3i) sorafenib given for one week prior to FLAG-AMSA salvage. Sorafenib priming may theoretically promote cycling of leukaemic stem cell progenitors, thus sensitising blasts to the effects of chemotherapy (Taylor *et al*, Blood 2012 120: 4049). FLT3i priming also avoids the neutralizing effect of raised FLT3 ligand after chemotherapy (Sato *et al*, Blood 2011 117: 3286). The use of CYP3A4 inhibitors (e.g. azoles) concurrent with sorafenib was avoided to maximise the production of the more active sorafenib N-oxide metabolite.

Methods

Sorafenib 400 mg bd for 7 days followed by FLAG-AMSA (fludarabine 30 mg/m^2/day d1-5, cytarabine 2 g/m^2/day d1-5 starting 4hrs after fludarabine, G-CSF 300 mcg/day sc d0-6 and amsacrine 100 mg/m^2/day d1-3.

Results

Age Sex	CG	FLT3 ratio	Prior therapy	WCC (x10^9 /L) pre and post sorafenib	BM blasts at baseline and post chemo	Response	OS (mo)
17M	N	NA	7+3	0.9 → 0.9	10% →2%	CRi	5
34M	+8	NA	7+3	27.6 → 4.9	43% →70%	Resistant	5
25F	N	NA	7+3	176 → 0.9	30%→33%	Resistant	6
44F	N	0.13	7+3	0.3 → 0.2	55%→ NA	NA	2+
24M	N	0.39	HiDAC-3, AlloSCT	0.6 → 0.5	30% →17%	Resistant	2
62M	N	0.10	7+3	NA → 3.0	20% →<5%	CRi	8+
40F	N	0.73	HiDAC-3, AlloSCT	NA→2.6	60%→<5%	CRi	3+
46M	+8	0.12	HiDAC-3	184.8→2.1	NA→6%	PR	8+

Responses were observed in 4/7 patients. Median observed survival was 6 months. Rapid reductions in peripheral blood blasts after sorafenib were observed in patients with hyperleucocytosis. Analysis is ongoing.

Conclusion

Sorafenib priming prior to FLAG-AMSA has some activity in advanced FLT3-ITD AML. A larger study incorporating correlative studies is warranted.

Keywords AML, sorafenib, FLAG-AMSA, FLT3
Conflict of interest Nil

Monday 21 October **0830-1000**
HSANZ Free Communications 1: Acute Leukaemia 1 **Meeting Room 7**
O012 **0845**

Immunity in Cytogenetically Normal Acute Myeloid Leukaemia (CAML)

Denise Lee[1], Michael Low[1], Victoria Ling[1], Trung Nguyen[2], Zoe McQuilten[3], Stephen Cody[3], Catriona McLean[2,3], Stephen Ting[1,3]
Haematology[1] & Anatomical Pathology[2] Departments, The Alfred Hospital & Monash University[3], Melbourne, Australia

Aim/Background
Improved prognostication is required for patients with cytogenetically normal acute myeloid leukaemia (CAML). We aimed to determine whether quantifying T cell immunity provides additional prognostic information for this patient group.
Methods
A retrospective analysis was performed on diagnostic trephine biopsies of CAML between 2006 and 2011. Primary endpoint was overall survival. Trephine sections were stained for CD3, CD4, CD8 and Granzyme B. Accurate quantification of these cells was performed using a plugin for the Fiji© image analysis software (v1.47s) developed by our biomedical imaging research platform. Survival was estimated using the Kaplan-Meier method and patient categories based on percentage positivity for each immunostain were compared using the log-rank test.
Results
26 patients (11 male (42%)) were analysed. Median follow up was 26 months. 7 patients were in 1st complete remission (CR1); 4 patients were in 2nd CR; 2 patients had stable disease; 9 patients were deceased; 4 patients were lost to follow up. 3/18 patients tested were positive for FLT3 ITD (2 in CR; 1 deceased). 5/14 patients tested were positive for NPM1, of which 1/5 was also FLT3-ITD positive (2 in CR; 3 deceased). Prominent non-specific background stain prevented CD4 analyses. Both CD3 and CD8 >5% vs ≤ 5% groups showed a trend for increased survival (estimated 3-year survival 71% vs. 33%, p=0.054 and 72% vs. 25%, p=0.027, respectively). Granzyme B >1% also had improved survival, although this was not statistically significant (69% vs. 53%, p=0.317).
Conclusion
Increased T-killer cell percentage at diagnosis may be a favourable prognostic indicator in patients with CAML. We propose to further assess the prognostic value of CD3, CD8 and Granzyme B staining, and correlate with molecular markers FLT3 and NPM1, in a larger cohort of CAML.

Keywords T-cell immunity, acute myeloid leukaemia, prognosis
Conflict of interest No

HSANZ Free Communications 1: Acute Leukaemia 1 **Meeting Room 7**

O013 **0900**

Posaconazole Therapeutic Drug Monitoring (TDM) in Haematology Patients: A Retrospective Cohort Study

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Aims / Background
We aimed to review the association between posaconazole (POSA) therapeutic drug monitoring (TDM) and clinical outcome in haematology patients within our institution.
Methods
All haematology and transplant patients treated with POSA between January 2010 and December 2011 were identified from an institutional data base. As part of a unit quality control programme, serum POSA levels were performed weekly via HPLC analysis in in-patients receiving the drug; POSA levels were not routinely performed in out-patient clinics. Dose of POSA was not routinely adjusted based on serum levels obtained. Indications for POSA and clinical outcomes were determined by retrospective review of individual medical records.
Results
Overall 48 patients had been treated with POSA during the time period under review, including 28 patients receiving prophylaxis and 15 POSA as therapy for defined fungal infection. 33/48 patients (69%) had a total of 118 serum POSA levels performed; in 18 of these patients (55%) levels were < 0.5mg/L, and in 22 (67%) levels <0.7mg/L. Maximum POSA level recorded was 2.3mg/L. There was no significant difference between mean POSA levels in patients receiving prophylaxis *vs.* therapeutic treatment (0.63mg/L *vs.* 0.58mg/L respectively; p=0.8). Patients administered POSA post allogeneic stem cell transplantation (SCT) had significantly lower mean POSA levels compared to non-SCT patients (0.49mg/L *vs*. 1.1mg/L respectively; p=0.009). No significant association was demonstrable between POSA serum levels and deranged LFTs. Clinical outcome was identical between patients in whom TDM was *vs*. was not performed; despite the high frequency of patients with serum levels <0.5-0.7mg/ml, no breakthrough / resistant fungal infection occurred in any patient.
Conclusions
With standard dosing in routine clinical practice, low serum POSA levels (<0.5-0.7mg/L) are obtained in a majority of patients. Mean POSA levels are significantly lower post-SCT compared to non-SCT patients receiving the drug. In our experience, no association between POSA levels and liver toxicity or fungal outcome was demonstrable. Our results question the role of routine POSA TDM in haematology patients.
Keywords Posaconazole, therapeutic drug monitoring (TDM)
Conflict of interest No conflicts of interest

HSANZ Free Communications 1: Acute Leukaemia 1 **Meeting Room 7**

O014 **0915**

Panobinostat and Azacitidine Therapy Provides Disease Control in MDS/AML and Increased Peripheral Blood Acetylation Predicts Response

Peter Tan,[1] Andrew Wei,[1] Sridurga Mithraprabhu,[1] Nik Cummings,[1] Michelle Perugini,[2] Kate Reed,[1] Sharon Avery,[1] Sushrut Patil,[1] Patricia Walker,[1] Peter Mollee,[3] Andrew Grigg,[4] Richard D'Andrea,[2] Andrew Spencer[1]

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Aim

We previously reported the safety and tolerability of the oral pan-deacetylase inhibitor panobinostat (LBH589) and azacitidine therapy in MDS/AML (HSANZ 2012). The aim was to assess clinical and correlative laboratory parameters that predict response to therapy.

Methods

Peripheral blood (PB) and bone marrow aspirate was collected at baseline and at the end of cycle 1, 3 and 6 of therapy. PB was also collected weekly during cycle 1. Patient samples were analysed and correlated with clinical response.

Results

40 patients were enrolled with 30 AML and 10 MDS. Median OS in AML responders was 13 months and 7 months in non-responders. There was further evidence of disease control with rapid disease progression in 7 patients who had therapy interrupted for infection or other medical issues. There was similar response in intermediate risk (28%) and adverse risk (25%) karyotype. There was a high response rate in MDS of 50% and the median time to AML transformation was not reached after a median follow-up months. Response was not associated with significant improvements to global quality of life or functional health status scores. Increased PB mononuclear cell acetylation of histones H3 and H4 assessed by flow cytometry and an increase of greater than 50% from baseline predicted clinical response (46% vs 0%). In patients with a high PB blast count, one patient showed reduction in the promoter methylation of GADD45A, an adverse prognostic marker. High expression of HbF at baseline or an increase during therapy was associated with response. Recurrent AML mutations showed responses in patients with activating KRAS (3/6), JAK2 (2/2) and IDH2 (1/3) mutations.

Conclusion

The combination epigenetic therapy with panobinostat and azacitidine provides disease control with associated survival benefit and response is predicted by PB mononuclear cell histone acetylation.

Keywords AML, therapy, epigenetic

Conflict of interest This research was supported by Novartis, Celgene and VCA

Monday 21 October **0830-1000**
HSANZ Free Communications 1: Acute Leukaemia 1 **Meeting Room 7**
O015 **0930**

Outpatient Based Hyper-CVAD is Safe and Not Associated With Increased Toxicity Compared to Inpatient Delivery

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Royal Brisbane and Women's Hospital, Queensland, Australia

Aims
We aimed to examine the safety of outpatient delivery of Hyper-CVAD based chemotherapy in adult acute lymphoblastic leukaemia (ALL) patients treated at our institution.
Methods
All patients >16yrs diagnosed with ALL between 1999 and 2012 and treated with Hyper-CVAD based induction were identified from an institutional database. During this period Hyper-CVAD was the standard induction chemotherapy used to treat ALL at our institution. Hyper-CVAD was routinely commenced as inpatient therapy, then in those patients without significant co-morbidities and available carers it was continued on an outpatient basis whenever possible. As the first cycle was always delivered as inpatient treatment, subsequent analysis is restricted to the 2nd cycle and beyond. Patient outcomes and toxicity events were retrospectively determined by review of individual medical records.
Results
In total 50 patients had been commenced on Hyper-CVAD for ALL during the time period under review. Median age was 37.5 (range 14-73 yrs); 62% were male. Total number of Hyper-CVAD cycles administered was 264, with median number of cycles per patient 6 (range 1-8). Excluding cycle 1 (n=50), 77 cycles were administered on an inpatient basis, and 137 in outpatients. A higher proportion of A cycles were delivered in the outpatient setting compared to B cycles (76% vs 55%; p=0.05). The incidence of grade 3-4 toxicity (infective, neurologic, hepatic, and renal) was not statistically different when inpatient (61%) and outpatient (48%) cycles were compared (p=0.07). The incidence of severe toxicity (predominantly infective and hepatic) was significantly higher in B cycles (75% vs 23%; p=<0.0001), however there was no difference in this rate whether treatment was delivered as inpatient vs outpatient therapy (p=1.0).
Conclusion
Our experience of outpatient delivery of Hyper-CVAD chemotherapy in adult ALL suggests that ambulatory-based chemotherapy is safe without increased toxicity compared to inpatient therapy.
Keywords Acute lymphoblastic leukaemia (ALL); Hyper-CVAD; ambulatory care
Conflict of interest No conflicts of interest

Monday 21 October **0830-1000**
HSANZ Free Communications 1: Acute Leukaemia 1 **Meeting Room 7**
O016 **0945**

Cost Implications of Different Chemotherapy Approaches for Acute Myeloid Leukaemia

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Aim/Background
Chemotherapy outcomes for AML are broadly equivalent. Our aim was to assess the health resource impact of induction and consolidation regimens used in Australia.

Methods
A retrospective analysis of 63 patients †55 years with AML from 2004-2012 receiving induction with standard-dose cytarabine (100mg/m^2 x 7d) or high-dose cytarabine (3g/m^2 bd d1,3,5,7) both with idarubicin 12mg/m^2 d1-3, known as "7+3" [N=27] or "HiDAC-3" [N=36], respectively. Consolidation with "HiDAC" (3g/m^2 bd d1,3,5 x 4 cycles) or "IDAC-2" (cytarabine 1g/m^2 bd d1,3,5 and idarubicin 12mg/m^2 d1-2 x 2 cycles) after 7+3, was compared with "IcE" (idarubicin 12mg/m^2 d1-2, cytarabine 100mg/m^2 x 5d and etoposide 75mg/m^2 x 5d for 2 cycles) after HiDAC-3 induction.

Results
HiDAC-3 and 7+3 were associated with a complete remission (CR) following first induction of 83% and 67% respectively. Neutrophil recovery and median length of stay (LOS) were similar. Using current Australian Refined Diagnosis Related Groups (AR-DRG) and Weighted Inlier Equivalent Separation ($4164/WIES) as an objective measure of cost, 7+3 followed by HiDAC x 4 consolidation resulted in a longer minimum LOS (54 days) and higher cost (15.86 WIES/$66,042) than either 7+3 followed by IDAC-2 x 2 or HiDAC-3 followed by IcE x 2, each with a minimum LOS of 42 days at a cost of 12.09 WIES ($50,355). Additional re-induction cycles due to lower CR rates with 7+3 versus HiDAC-3 will have additional economic implications.

INDUCTION	**7+3 (n=27)**		**HiDAC-3 (n=36)**	**p-value**
CR rate after first cycle	67%		83%	0.12
Days to neutrophils 0.5 x 10^9/L	30		28	0.13
Median LOS (days) / DRG60A WIES	30 / 8.33		30 / 8.33	
CONSOLIDATION (total no of cycles)	**HiDAC (4)**	**IDAC-2 (2)**	**IcE (2)**	
Median length of stay/cycle (total)	6d (24)	6d (12)	6d (12)	
Median DRG60B WIES/cycle (total)	1.88 (7.53)	1.88 (3.76)	1.88 (3.76)	
Total treatment WIES / LOS	**15.86 / 54d**	**12.09 / 42d**	**12.09 / 42d**	
Total cost (without re-induction)	**$66,042**	**$50,355**	**$50,355**	

Conclusion
For younger patients, AML regimens requiring fewer cycles of re-induction and consolidation may represent the most efficient use of health resources.

Keywords: AML, Health economics, chemotherapy. **Conflict of interest:** No

HSANZ Free Communications 2: Myeloma **Meeting Room 8**

O017 **0830**

Efficacy of a New Orally Bioavailable beta-catenin Inhibitor in the Treatment of Multiple Myeloma

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Background
Despite significant improvement in overall outcome of multiple myeloma (MM) patients, the disease remains incurable prompting further exploration for additional therapeutic approaches. Beta-catenin, the central molecule of the Wnt canonical pathway is dysregulated in multiple solid tumours and haematological malignancies, including MM, providing a rationale to evaluate the potential of beta-catenin inhibitors as a therapeutic paradigm for MM.
Results
We have demonstrated that the orally bioavailable beta-catenin inhibitor (BC2059) induced apoptosis in 10 genetically heterogeneous human myeloma cell lines (HMCL). HMCL treatment with BC2059 showed a dose and time dependent inhibition of HMCL viability (IC_{50} ranging 53nM to 247nM). Mimicking the bone marrow microenvironment by co-culturing HMCL with an immortalised human stromal cell line, BC2059 overcame the protective effect of the stromal layer. KMS-18 at IC_{90} (0.22μM) had no stromal pro-survival effect detected. Similarly BC2059 was able to block the proliferative effect of LiCl and r-Wnt3A on HMCL (reduction of $Ki67^{+ve}$ myeloma cells, p=0.038). Moreover BC2059 caused inhibition of TCF transcriptional activity in KMS-11 myeloma cells in a dose-dependent manner. Beta-catenin has been reported to undergo proteasome-mediated destruction and is found to increase post bortezomib treatment. Therefore we evaluated if BC2059 could mitigate this pro-survival stress response. The combination of BC2059 and bortezomib was found to be synergistic in 4/5 HMCL (Combination Index [CI] = 0.4 to 1.1, CI<1.0 indicates synergy). As a single agent BC2059 effectively killed primary MM tumour cells from relapsed and/or refractory MM patients (n=11) in an autologous bone marrow (BM) co-culture assay with a median cell death of 46±7.5% $APO2.7^{+ve}$ cells at 1μM, while the combination of BC2059 and bortezomib was also synergistic (n=3) (Synergistic Quotient [SQ]=1.28-8.22, SQ>1.0 indicates synergy). **Conclusion**
BC2059 effectively kills both HMCL and primary MM tumour cells at clinically-achievable concentrations, can overcome the pro-survival effect of stromal /autologous BM co-culture and is synergistic with bortezomib. BC2059 warrants further evaluation as a potential anti-MM therapeutic.
Key words Multiple myeloma, beta-catenin, synergy.
Conflict of Interest S Horrigan is an employee of BetaCat Pharmaceuticals, USA.

HSANZ Free Communications 2: Myeloma **Meeting Room 8**

O018 **0845**

MEK Inhibition Sensitises Multiple Myeloma to Conventional and Novel Anti-myeloma Therapeutics

Tiffany Khong[1], Sridurga Mithraprabhu[1], Christopher Leow[1], Steve Gerondakis[2] and Andrew Spencer[1,3]

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Aim/Background

While the duration of survival of patients with multiple myeloma (MM) has improved significantly over the past decade, the subsequent development of drug-resistant disease is inevitable. Therefore it is vital to identify novel compounds and strategies that help overcome this drug resistance. The MAPK (RAS-RAF-MEK-ERK) pathway is one of the most commonly dysregulated oncogenic pathways in human cancer. MEK inhibitors (MEKi) have been shown to inhibit tumour growth, induce cell cycle arrest and promote cell death in a variety of solid tumours. Here we report the efficacy of a range of MEKi (GSK1220212, MEK162 and UO126) when tested pre-clinically in combination with novel and conventional anti-MM therapeutics.

Results

11 genetically heterogenous human myeloma cell lines (HMCL) were tested against 3 MEKi (50nM-10mM for 72 hours). A rapid reduction in p-ERK was seen, followed by an elevation in p-MEK, consistent with the loss of p-ERK negative regulation of MEK phosphorylation. Cell proliferation and cell cycle analysis demonstrated a dose-dependent reduction in cell proliferation and an accumulation of cells in G_0/G_1. The levels of BIM, a BH3 pro-apoptotic member of the BCL-2 family was found to increase in all the cells tested in response to escalating doses of MEKi. HMCL and primary MM samples were treated with MEKi in combination with conventional (bortezomib, dexamethasone, melphalan) and novel (iBET151, ABT737, LBH589) anti-MM therapeutics. MEKi was found to promote the synergistic killing of MM in combination with all partner drugs, with high levels of synergy (measured by synergy quotient [SQ] where synergism is defined as SQ>1) seen for highly resistant primary MM tumours (MEKi + melphalan: SQ = 2.82 ± 0.86; MEKi + dexamethasone: SQ = 4.2 ± 0.46) when MEKi was combined with either dexamethasone or melphalan.

Conclusion

This study demonstrates that MEK inhibition represents a potential avenue for the treatment of MM via sensitisation of drug-resistant MM to affordable conventional anti-MM therapeutics and therefore warrants further investigation.

Keywords myeloma, MEK, apoptosis

Conflict of interest None.

HSANZ Free Communications 2: Myeloma **Meeting Room 8**

O019 **0900**

Circumventing Inherent Resistance to Histone Deacetylase Inhibitors by Targeting the Actin Cytoskeleton Pathway in Multiple Myeloma

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Aim
Histone deacetylase inhibitors (HDACi) are novel chemotherapeutics undergoing evaluation in clinical trials for the potential treatment of multiple myeloma (MM) patients. While HDACi have demonstrable synergy when combined with proteasome inhibitors (PI), recent evidence demonstrates that this combination is beneficial only in a subset of patients, clearly indicating that other rational combinations should be explored. In this context we hypothesised that understanding the molecular signature associated with inherent resistance to HDACi would provide a basis for identifying novel therapeutic combinations.
Methods
Baseline gene expression profiling (GEP) of nine human myeloma cell lines (HMCL) categorised as sensitive (5/9), intermediate (2/9) or resistant (2/9) to HDACi was performed followed by ANOVA analysis to calculate fold change in gene expression between sample groups (fold change of >1.5; $p<0.05$). Gene ontology enrichment analysis of differentially expressed probes was performed to identify pathways with significant overexpression (enrichment score of >3 corresponding to significant over expression; $p<0.05$).
Results
Correlation of GEP to HDACi-responsiveness indicated a unique 35-gene signature that was significantly enriched for two pathways - regulation of actin cytoskeleton ($p=0.03$) and protein processing in endoplasmic reticulum ($p=0.02$). Genes that were significantly altered and known to be independently associated with the actin cytoskeleton pathway included FGF9, F2R, OPN3, RGS12 and ELF3. When drugs targeting pathways integral to the actin cytoskeleton (mitogen activated protein kinases – MAPK, phosphatidylinositol 3-kinases – PI3K and focal adhesion kinases – FAK) were utilised in combination with HDACi (LBH589) in resistant HMCLs (U266 and OPM2) and in primary MM (n=6), synergistic cell death was observed in all instances.
Conclusion
This report validates a molecular approach for the identification of novel therapeutic combinations for HDACi for anti-MM treatment in the clinical setting.
Keywords multiple myeloma, histone deacetylase inhibitors, resistance
Conflict of interest The authors declare no conflict of interest

HSANZ Free Communications 2: Myeloma **Meeting Room 8**

O020 **0915**

Arsenic Trioxide, Ascorbic Acid and Dexamethasone Therapy for Relapsed Multiple Myeloma

Duncan Purtill, Bradley Augustson, Julie Crawford, David Joske, Gavin Cull
Haematology Department, Sir Charles Gairdner Hospital, Western Australia

Background/Aim/Methods
Arsenic trioxide (As_2O_3) has proven efficacy in acute promyelocytic leukaemia and theoretical efficacy in multiple myeloma. As_2O_3 has been used in combination with ascorbic acid and dexamethasone at our institution for the treatment of relapsed multiple myeloma. In order to assess the toxicity of this regimen and to explore its efficacy, we retrospectively collected data on all 17 patients who received As_2O_3 for relapsed multiple myeloma.

ResultS
Patients were diagnosed with myeloma at a median age of 61 years (range, 51-70 years) and had a median of 4 lines of therapy before the institution of As_2O_3. The median time from diagnosis to commencement of As_2O_3 was 3 years (range, 9 mo to 12 yr). In all cases, As_2O_3 was commenced as part of the TAD regimen (As_2O_3 0.25mg/kg IV and ascorbic acid 1000mg PO daily for 5 days, then weekly thereafter; dexamethasone 40mg PO for 5 days each month). The median duration of treatment was 4.5 months (range, 10 d to 20 mo). Arsenic therapy was ceased in 3 patients (12%) due to cardiac toxicity (QTc prolongation (n=3), +/- left bundle branch block (n=1)). Responses were assessed according to the European Blood and Marrow Transplant (EBMT) criteria. There were no complete responses. Very good partial response (VGPR), partial response and minimal response were achieved by 1, 4 and 4 patients respectively, resulting in an overall response rate of 53%. A further 5 (29%) patients had stable disease while 3 (18%) patients had progressive disease only. Disease progression eventually occurred in 15 (88%) patients at a median of 4 months after commencing arsenic (95% confidence interval 3-5 months). Two patients remain on therapy with no progression after 3 and 18 months. The 3 patients who ceased therapy due to toxicity exhibited rapid serological progression after arsenic was ceased. There was a trend toward improved overall survival for patients who showed some response to the TAD regimen (n=9) vs those with stable or progressive disease (n=8) (12.8 months vs 3 months respectively, p=0.09).

Conclusion
In our experience, As_2O_3 administered in combination with ascorbic acid and dexamethasone has relatively little toxicity and some disease activity in heavily treated patients with relapsed multiple myeloma. Larger prospective studies are required to further investigate the efficacy of this treatment regimen in multiple myeloma.

Keywords multiple myeloma, arsenic trioxide, salvage therapy. COI None

Monday 21 October **0830-1000**
HSANZ Free Communications 2: Myeloma **Meeting Room 8**
O021 **0930**

MRI Spine as Routine Screening in all Newly Diagnosed Multiple Myeloma: Does it Make a Difference?

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[1]Department of Haematology and Bone Marrow Transplantation, The Townsville Hospital, Townsville, Queensland, Australia

Aims
Screening MRI of the spine in all newly diagnosed multiple myeloma (MM) patients lacks consensus. We aimed to determine the utility of MRI of the whole spine as a routine screening tool in newly diagnosed MM, and whether the clinical predictors of spinal disease correlate with MRI findings.
Methods
A retrospective analysis of data over a 5 year period from January 1 2008 to January 1 2013 at The Townsville Hospital was performed. At this centre, MRI whole spine has been used as a routine screening investigation in all newly diagnosed MM irrespective of symptoms. Patients who did not have an MRI spine at diagnosis (e.g. for a medical contraindication) were excluded. Statistical analysis compared the findings of MRI in patients with and without an indication for MRI. Australian guidelines state indications for MRI are: new or worsening back pain, neurological dysfunction, vertebral crush fracture or extramedullary plasmacytoma.
Results
71 patients with newly diagnosed MM had an MRI of the whole spine over the study period. Of these, 44 (62%) had an indication for MRI. 37 patients (52.1%) had focal myeloma spinal disease. The strongest predictors of spinal disease were back pain ($p<0.001$), new crush fracture ($p=0.003$) and neurological dysfunction ($p=0.048$). Spinal plasmacytomas were found in 13 patients (18.3%) all of whom had an indication for MRI. 3 out of 8 smouldering myeloma patients were upstaged to symptomatic myeloma by the documentation of lytic lesions not identified on plain film. There was no indication for MRI in these patients. Prophylactic surgery or radiation was performed in 17 patients, all of whom had an indication for MRI.
Conclusions
1. Current indications were 100% sensitive for detecting spinal plasmacytomas.
2. MRI of the whole spine upstaged 37.5% of smouldering myeloma patients resulting in the initiation of therapy rather than observation.
3. In symptomatic myeloma patients, indications for MRI correlated with focal lesions and in the absence of indications, MRI did not change therapy.
4. Screening MRI spine remains debatable; a larger prospective trial is needed.

Keywords Myeloma, MRI, plasmacytoma. **Conflict of interest** None to disclose

HSANZ Free Communications 2: Myeloma **Meeting Room 8**

O022 **0945**

LEOPARD: A Phase II Study of Maintenance Lenalidomide and Prednisolone Post-ASCT for Myeloma Incorporating MRD Assessments

Anna Kalff[1], Nola Kennedy[1], Patricia Walker[1], Marion Black[1], Odette Youdell[1] Malgorzata Gorniak[1], Tiffany Khong[1], Lona Estifo[1], Angela Smiley[1], Anthony Schwarer[2], Andrew W. Roberts[3], Philip Campbell[4], Robin Filshie[5], Andrew Spencer[1]
[1]Alfred Hospital, Monash University, Melbourne, Vic, Australia; [2] Box Hill Hospital, Box Hill, Vic, Australia; [3]Royal Melbourne Hospital, Vic, Australia; [4]Geelong Hospital, Vic, Australia; [5]St Vincents Hospital, Melbourne, Vic, Australia

Aim/Background
To document change in disease response in patients with myeloma (MM) post-ASCT who receive RAP. To sequentially quantify MRD in patients who achieve CR by freeLite chain (FLC), hevyLite chain (HLC, in patients with intact IgG or IgA immunoglobulin) and multiparamenter flow cytometry (MFC).
Methods
Newly diagnosed MM patients 6-8 weeks after induction and single MEL200 ASCT commenced RAP until toxicity/relapse (lenalidomide 10mg/continuous daily increasing to 15mg after 8/52 and alternate day prednisolone 50mg). Serum for FLC/HLC was collected every 2/12. Patients in CR had serial BMATs for MFC. This is an interim analysis of first 30 of 60 subjects.
Results
After a median 388 days (107-587), 6 relapsed/progressed, 4 ceased due to AEs, 1 withdrew and 1 died (disease). 16 patients further improved depth of response after commencing RAP, including 4 CR and 9 sCR (7/9 were MRD negative by MFC [MFC-]). Median time to achieving best response was 111 days (28-287). 6 patients relapsed after a median of 221 days (64-308), 1 from CR and 3 from sCR; 4/6 had poor risk cytogenetics, all with +1q in addition to other abnormalities.
18 patients who achieved CR/sCR had MFC studies performed. 11/18 patients were MFC- in most/all samples; 5 had all normal FLC ratios (FLC-), 6 had abnormal FLC ratios (FLC+). 5/18 patients were MFC+ in most/all samples; 4 were FLC- and have not relapsed. 2/18 fluctuated between MFC+ and MFC-. In those who relapsed, 2/4 were MFC+ and 2/4 converted from FLC- to FLC+. 7/18 CR/sCR patients had samples for HLC analysis; 5/7 patients were MFC- in all samples, 3 of which also had normal HLC ratios (HLC-) and were FLC-. 2/7 patients were MFC+/HLC-.
Conclusion
RAP maintenance improved depth of response post-ASCT, with high rates of CR (20%) and sCR (43%), with further improvement to MFC- in some patients. MFC appears more sensitive for MRD than FLC and HLC. Most who relapsed had high-risk cytogenetics, suggesting that RAP maintenance may not benefit this group.
Keywords myeloma lenalidomide maintenance. **Conflict of interest** None

HSANZ Free Communications 3: Thrombosis and Haemostasis **Meeting Room 9**

O023 **0830**

Impact of Self-Administration of Romiplostim by Patients with Chronic Immune Thrombocytopenia Compared With Administration by a Healthcare Provider

Robert Bird,[1] Dominik Selleslag,[2] Ivy Altomare,[3] Ann Janssens,[4] Ingrid Pabinger,[5] Vinod Pullarkat,[6] Helen Wei,[7] Georg Kreuzbauer[8]

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Aim/Background

Romiplostim is a subcutaneously administered thrombopoietin receptor agonist that significantly increases and maintains platelet counts in patients with chronic immune thrombocytopenia (ITP). A post hoc analysis was performed to evaluate the impact of romiplostim self-administration in the home setting (SA group) versus administration by a healthcare provider in a clinical setting (HCP group).

Methods

Outcomes were compared between SA and HCP groups using data from 3 ITP trials in which self-administration was allowed in patients achieving a stable romiplostim dose for ‡3 consecutive weeks. Evaluations were conducted for 12-week treatment intervals. Efficacy endpoints included platelet counts and percentage of weeks with platelets within the target range (50 - 200 10^9/L). Incidence and duration-adjusted rates of adverse events (AEs) were summarized.

Results

Baseline characteristics suggested less severe disease in the SA groups (n=563) than in the HCP groups (n=241). Patients in the SA groups had greater proportions of patients achieving the target platelet range (55%–58% vs 40%–52% for the HCP groups) and greater proportions of weeks with a platelet response (75%–88% vs 47%–76% for the HCP groups). The discontinuation rate of romiplostim was 2- to 5-fold lower in the SA groups than in the HCP groups. Rates of duration-adjusted AEs, serious AEs, and treatment-related AEs were also lower in the SA groups.

Summary/Conclusions

There was no evidence that self-administration of romiplostim reduced efficacy or compromised the safety profile compared with healthcare provider administration, suggesting that self-administration of romiplostim is a feasible option for certain patients with ITP.

Keywords thrombopoietin mimetic, romiplostim, immune thrombocytopenia

Conflict of interest This research was supported by Amgen. The company analysed the data and contributed to the abstract preparation.

HSANZ Free Communications 3: Thrombosis and Haemostasis Meeting Room 9

O024 0845

A Prospective Multi-centre, Single Arm, Phase II Study to Evaluate the Efficacy of a Weekly 100mg dose of Rituximab Over Four Weeks in Patients With Refractory or Relapsing Immune Thrombocytopenia (The R-100 ITP Study)

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Aim
It is well known that standard weekly doses of Rituximab (375mg/m^2) for 4 weeks are effective in immune thrombocytopenia (ITP). This study investigated the efficacy of a weekly 100mg dose over 4 weeks in a well-defined refractory patient group. It also studied the effect of B cell depletion and response duration. Clinical Trials Registration No 320708.
Methods
25 adults with ITP from three New Zealand centres were recruited from February 2009 to April 2013. (10 males and 15 females with a median age of 40 years). Patients were deemed refractory if they had not achieved a platelet count of >30x10^9 /l despite 8 weeks of standard medical ITP therapy. Chronic ITP cases were included if they required immunosuppression to keep platelet counts over 30.
Response definition was as follows: complete response (CR) if platelet count over 100; a partial response (PR) if platelets >50-100; minimal response if platelets between 30-50; no response (NR) if platelets under 30.
Following completion of therapy all patients were evaluated at 4 weeks, 8 weeks and then at weeks 16, 26, 39 and 52.
Results
At 1 month after the end of Rituximab therapy all patients were evaluated for response. There were 8 CR's (32%) and 4 PR's giving an ORR of 48%. The median time to response was 3 weeks from start of therapy and median follow-up of patients was 22 months (5 to 44 months). At 12 month review only one of the patients who had a CR had relapsed, and two patients have had sustained responses at 3 years.
All patients experienced significant B cell depletion.
Conclusion
Low dose Rituximab is an effective and cheaper alternative to standard doses in the refractory situation and can bestow durable responses in around one fifth of patients. This particular study has one of the longest follow-up study periods when compared to previously published studies. There is still no randomised study published which compares the two Rituximab dosing regimens.
Keywords thrombocytopenia, Rituximab, B cell depletion
Conflict of interest None.

Monday 21 October **0830-1000**
HSANZ Free Communications 3: Thrombosis and Haemostasis **Meeting Room 9**
O025 **0900**

When Is Enough…Enough? Developing Consensus of Definition of Failure of Immune Tolerance Induction (ITI) in Patients With Haemophilia and Inhibitors

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Introduction
Immune tolerance induction (ITI) is the preferred management of haemophilia A patients who develop high titre inhibitors against factor VIII. However, the optimal ITI regimen, predictors of ITI outcome, and definitions of successful and unsuccessful ITI remain unclear.
Aim
The aim of this project was to develop a consensus on the definition of ITI treatment failure for Australian clinical practice using a modified Delphi approach.
Methods
Three consecutive surveys were distributed to the directors of 17 haemophilia treatment centres (HTCs) in Australia. Participants were asked to rate their agreement with definitions of ITI treatment failure generated from a literature review.
Results
35 statements regarding ITI achieved consensus (majority agree or strongly agree) during the three rounds. After round 3, four statements achieved majority disagreement, and for two statements no consensus was reached.
Conclusion
Our study demonstrates that clinicians in Australia regard an arbitrary time to assess ITI failure as necessary, but that clinical outcomes of ITI are important in assessing response. Assessment over any six month period without a reduction of 20% in inhibitor titre is suggestive of failure but a reduction in bleeding phenotype may be sufficient to justify continuing ITI. Overall, a period of three or five years of ITI may be necessary to determine response to ITI. Documentation of improvement in clinical measures supported by the laboratory features of factor VIII inhibitor levels and pharmacokinetics is essential in assessing the need success of failure of ITI in these patients.

Keywords Immune Tolerance
Conflict of interest This research was supported by NovoNordisk. The company had no role in analysing the data or preparing the abstract.

Monday 21 October **0830-1000**
HSANZ Free Communications 3: Thrombosis and Haemostasis **Meeting Room 9**
O026 **0915**

Impact of Changing Type of Recombinant Factor VIII Concentrate on Inhibitor Development in Adults with Haemophilia A (HA)

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Aim/Background
This is a two-centre retrospective analysis exploring the relationship between recombinant factor VIII concentrate product switching and inhibitor development in patients with Haemophilia A.
Methods
As part of the national tendering process in 2012, 65 patients who were receiving recombinant FVIII concentrate, Advate or Recombinate treated at The Alfred Hospital in Melbourne and The Royal Adelaide Hospital were switched to Xyntha or Kogenate. Of these, 47 had factor VIII inhibitor testing performed at the time of switch and at least 3 months post. The incidence of post-product switch inhibitor was compared with a control group of 103 patients who remained on Xyntha throughout the same period. A positive inhibitor result was defined as a level of > 0.5 Bethesda Units (BU) confirmed on repeat testing.
Results
Of the product-switched patients, 1 (2.1%) developed a detectable factor VIII inhibitor of 9.6 BU at highest level compared to 2 (1.9% - 1 moderate,1 mild) among the 103 controls with levels of 1.3 BU and 8.4 BU respectively, one of which still requires confirmation. One patient in the control group (mild HA) developed a transient inhibitor at 1.1 BU, which became negative on repeat testing. The single patient in the switch group was aged 37 years with severe HA and was switched from Advate to Kogenate. The inhibitor was detected 7 months post switch. Mean age of those with inhibitors in the control group was 48 years.
Conclusion
The rate of inhibitor development in patients who switched recombinant FVIII product does not appear to be increased in comparison to patients who remained on the same recombinant FVIII concentrate. We plan to combine data from other haemophilia centres throughout Australia to provide a better estimate of the risk of inhibitor development associated with product switch.

Keywords Haemophilia, Factor VIII inhibitor
Conflict of interest No

Monday 21 October **0830-1000**
HSANZ Free Communications 3: Thrombosis and Haemostasis **Meeting Room 9**
O027 **0930**

Assessing the Safety of a Standard Enoxaparin Dosing Regimen (1mg/kg BD) in Obese Patients with Acute Venous Thromboembolism

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Background
In many clinical trials for the treatment of venous thromboembolism with low molecular weight heparins (LMWH), patients with obesity are specifically excluded or under represented.
Aim
To audit the safety of treating obese patients (weighing over 100kg) with enoxaparin at 1mg/kg BD.
Method
A single centre 2 year retrospective audit. Eligible patients were those who had objectively confirmed VTE, weighed greater than 100kg, were treated with therapeutic enoxaparin (1mg/kg BD), and had an anti-Xa level taken 2-6 hours post-dose. Patients with an eGFR< 30 were excluded. The primary outcome was anti-Xa levels as a surrogate to recurrence and bleeding. Secondary outcome measures were major bleeding and recurrence.
Results
72 patients weighing greater than 100kg with confirmed VTE were identified. 34 were excluded (2 for eGFR <30, 3 with no anti-Xa levels, 6 with levels outside of 2-6 hours post dose, and 23 who were treated with doses <1mg/kg BD).
Out of the remaining 38, 23 were male, the median age was 45 (range 26-72, IQR 35-54), with a median weight of 130kg (range 108-220kg, IQR 119-140kg).
The median anti-Xa level was 0.9U/mL with 23/38 (61%) being within the proposed therapeutic range of 0.5-1.0U/mL. 14/38 (37%) had an anti-Xa level above 1.0, with 8/38 (21%) above 1.2U/mL, and 1 patient was subtherapeutic (<0.5U/mL). No (0/38) major bleeding episodes or recurrences were seen at 7 days.
Conclusion
The use of 1mg/kg BD enoxaparin in obese patients with VTE and normal renal function results in unpredictable anti-Xa levels. However with this strategy only 1 patient had a subtherapeutic anti-Xa level while a significant proportion of patients had supratherapeutic anti-Xa levels. No major bleeding or recurrence was observed. These data support the use of an aggressive 1mg/kg BD dosing strategy for obese patients to ensure therapeutic drug levels. It also supports the strategy of measuring anti-Xa levels in this group to allow for dose reduction in those with a supratherapeutic anti-Xa level.
Keywords enoxaparin, obesity, anti-Xa
Conflict of interest None

Monday 21 October **0830-1000**
HSANZ Free Communications 3: Thrombosis and Haemostasis **Meeting Room 9**
O028 **0945**

Peri-Operative Monitoring and Management of Dabigatran in a Tertiary Hospital Population: A Case Series of 15 Patients

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Aim / Background
Dabigatran is a direct thrombin inhibitor used in the treatment of non valvular atrial fibrillation and recently deep venous thromboembolism. There is limited clinical experience with this agent in regards to peri-operative management. There is also no specific reversal agent for this therapy, and hence ensuring adequate haemostasis pre-operatively is important. This study is a prospective observational trial to primarily examine the coagulation parameters of patients taking dabigatran in the peri-operative setting.
Methods
We investigated the use of dabigatran in a series of patients treated at Royal Perth Hospital from August 2011 until currently. As standard coagulation assays are relatively insensitive to the dabigatran effect, specific testing using a dilute thrombin time (Hemoclot) assay was performed in addition to FBP, PT, INR and Fibrinogen. Patients with a low risk of thrombosis (and/or high procedural bleeding risk) had their dabigatran ceased 48hours prior to surgery. Patients with high thrombosis risk (and/or low procedural bleeding risk) had their dabigatran ceased 24 hours prior to surgery. Anticoagulation was recommenced in most patients within 24 hours. Daily blood tests were then obtained to monitor changes in their coagulation parameters. Post operative complications were assessed daily during inpatient stay and at day 30. Result analysis using standard chi-squared test.
Results
Our results show that for most patients with normal baseline creatinine, dabigatran levels less than 50ng/mL (Hemoclot assay) can be reliably predicted by the time of surgery.
Conclusions
A Haemoclot result of <50ng/mL was not associated with operative bleeding in this group of patients. Hence use of the Haemoclot assay has been shown to predict haemostasis in the peri-operative management of patients on dabigatran. We acknowledge the limitations of small sample size. This data may provide useful information to assist further studies, and help inform clinical practice in the peri-operative management of patients on this anticoagulant.
Keywords dabigatran, peri-operative, Hemoclot
Conflict of interest None

Monday 21 October **0830-1000**
ANZSBT Presidential Symposium **Central Hall A**
O029 **0830-0845**

Blood Utilisation in Major Disaster Situations – A 10 Year Review of a Tertiary Adult Trauma Hospital Experience of External Disasters

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Aim
To review blood ordering, blood supply and blood use for victims admitted to Royal Perth Hospital (RPH) from major external disasters 2002 to 2012, and examine emergency plans and Transfusion Medicine (TM) response.
Methods
Emergency operations logs and debrief notes were reviewed for event details, timeline and identification of victims. The State Trauma Registry was reviewed to ensure capture of patient events. Blood product use, blood ordered, and blood and blood products transfused were extracted from TM electronic database.
Results
Eleven major disasters were identified. Victims (102) were transferred to RPH in 10 incidents: 4 planes, 2 boats, 1 bombing, 1 tsunami, 1 cyclone, 1 bus crash. One disaster was in the Perth metropolitan area. For the remaining 9 incidents, the mean travel distance to RPH was 2514 km (range 371-4664 km), mean time from incident to first casualties arriving at RPH 23 hours (median 22 hours, range 4-70). Arrival of victims was often staggered. The number of red cells (includes Whole Blood) cross-matched in first 24hrs: 230 units, transfused 59 (ratio 4:1). O Rh(D) negative uncrossmatched units were not requested. Red cell and Whole Blood crossmatched and transfused for entire admissions was 1077:493 (2.2:1); FFP 205, Platelets 19, and Cryoprecipitate 19 units. Blood use was highest in events with traumatic burns, bombings and boat explosion. Patient identification in major disasters was highlighted as a critical error point with non-english speaking patients.
Conclusion
The remote and overseas locations presented communication and logistic challenges which affected the TM preparedness. Review of inventory management practices suggests maintenance of inventory at agreed upper level and continued monitoring according to type of incident and number of victims admitted, as appropriate management approaches. The number of admitted casualties and blood use in first 24 hours was lower than anticipated, but blood use to support surgical procedures for weeks to months post event, must be considered.

Keywords Transfusion, Major, Disaster
Conflict of interest No conflict of interest

Monday 21 October **0830-1000**
ANZSBT Presidential Symposium **Central Hall A**
O030 **0845**

Monitoring the Red Blood Cell Storage Lesion by Fourier Transform Infrared Micro Spectroscopy

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Aim/Background
Red blood cells (RBC) can be stored for up to 6 weeks before transfusion. During storage RBC undergo biochemical changes summarised in the term 'storage lesion'. Currently it is not clear how this affects the clinical outcome of RBC transfusion. Studies are complicated by donor variation and lack of a single methodology that can monitor a global array of biochemical changes. Infrared spectroscopy can specifically detect changes to the chemical composition and therefore could provide a comprehensive and fast assessment of the status of stored RBC.
Methods
Single cell Fourier Transform Infrared (FT-IR) micro spectroscopy using a synchrotron light source was used to collect the spectra of RBCs that had been subjected to the following conditions: routine refrigerated storage (Day 4 vs Day 35; or Day 14 vs Day 42), experimental exposure to oxidative stress, density separated "young" and "old" RBC, and RBC stored in SAGM or AS-1 additive solutions. Spectra were recorded for 80-100 individual RBC per sample and 2 individual donors were tested. Differences between spectra were analysed using Partial Least Squares regression using The Unscrambler software.
Results
Statistical analysis detected differences in the spectra of RBCs before and after oxidative stress treatment indicating shape change as well as protein denaturation. Spectra from "young" compared to "old" RBC as well as after storage also showed detectable differences, but not for RBC stored in SAGM compared to AS-1 additive solutions.
Conclusion
Our data show some biochemical changes underlying the storage lesion of RBC can be detected with infrared spectroscopy. Application of this novel technique for studying storage associated changes in red cells provides new insights into the changes that define the red cell storage lesion.

Keywords Red blood cell, storage, infrared spectroscopy
Conflict of interest No

ANZSBT Presidential Symposium **Central Hall A**

O031 **0900**

Introduction of Universal Leucodepletion is Significantly Associated With Reduced Morbidity But Not Mortality: Results From a Large Cohort Study

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[1]Monash University, [2]St Vincent's Hospital, [3]Monash Medical Centre, [4]Australian Red Cross Blood Service, [5]Alfred Hospital, [6]Austin Hospital, all in Melbourne, VIC, Australia

Aim/Background
Conflicting results regarding benefits of universal leucodepletion (ULD) in intensive care (ICU) and cardiac surgery (CS) patients have been reported. We investigated the impact of ULD on outcomes in ICU and CS patients in the Australian setting.
Methods
A before/after study on all patients registered between 2005-10 in the ANZ Intensive Care Society Adult Patient Database and ANZ Society of Cardiac & Thoracic Surgeons Cardiac Surgery Database, linked with laboratory and transfusion data, at 3 and 6 hospitals, respectively. Logistic regression assessed the association of ULD with mortality (in all), and infection and new renal impairment (NRI) in CS patients. Linear regression assessed the association of ULD with log-transformed ICU length of stay (LOS) in survivors. Non-transfused controls, selected using a propensity score for RBC transfusion, were analysed to assess for trends over time.
Results
ICU cohort: 5,993 (32%) of 18,480 patients received ‡1 RBC in ICU. After adjusting for age, diagnosis, APACHE III score, Hb, site and transfused products, those post-ULD had a trend to lower mortality (OR 0.84, 95%CI 0.69-1.01, p=0.073) and a significant reduction in LOS of 30hrs (14%, 95%CI 10-19%, p <0.001). In non-transfused, there was no change in LOS post-ULD (p=0.195). *CS cohort:* 6068 (43%) of 14,177 patients received ‡1 RBC within 48hrs. After adjusting for patient, surgical and laboratory parameters (including Hb), site and transfused products there was no association with mortality or infection, however ULD was associated with reduced NRI (OR 0.78, 95%CI 0.63-0.97, p=0.027). In non-transfused there was no difference in mortality, infections or NRI post-ULD. The findings were similar when analysed comparing patients who received only LD vs. any non-LD RBC.
Conclusion
ULD was associated with reduction in ICU LOS in a heterogeneous ICU population and NRI in CS, but not mortality or infection. This is the first study to examine the potential effect of ULD on NRI, and although no conclusions can be made regarding causation, supports previous observational studies on potential benefits of ULD.
Keywords Leucodepletion, cardiac surgery, critical care
Conflict of interest No

Monday 21 October **0830-1000**
ANZSBT Presidential Symposium **Central Hall A**
O032 **0915**

Factors Influencing Red Cell Alloimmunisation: A Study of RhD-Immunised Blood Donors and Beyond

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Aim/Background
Red cell alloimmunisation (development of alloantibodies against foreign red blood cell [RBC] antigens) can complicate care of transfusion-dependent patients due to difficulty in obtaining compatible blood products and delayed haemolytic transfusion reactions. Alloimmunisation can occur following pregnancy or transfusion, and in a select group of Australian anti-D immunoglobulin donors who have been exposed to RhD-positive RBCs to stimulate anti-D production. These anti-D donors exhibit a wide range of responder profiles (High Responder to Non-Responder), although the immunological mechanism for this remains undefined. Our aims were to identify factors that may affect development of anti-D alloantibodies, and to apply our findings to larger cohorts of clinical patients.
Methods
We recruited anti-D donors to our study and genotyped their DNA samples for targeted genetic polymorphisms. We analysed the statistical association between polymorphisms and the anti-D donor responder profile. We also collected data on the phenotypes of RhD-positive RBCs used for immunisation.
Results
We identified that the sex of the donor and at least 15 polymorphisms are associated with a High Responder anti-D donor profile. These polymorphisms are found in genes associated with regulation of immune stimulus, inflammatory responses, and antigen presentation. Additionally, we determined that there was no association between a High Responder anti-D profile and the RBC phenotype used for immunisation, although these High Responder donors more frequently produced incidental anti-C and anti-E than Non-Responder donors.
Conclusion
We have identified several immunologically-relevant genetic polymorphisms that are significantly associated with response to the RhD antigen. These polymorphisms, and their associated genes, may play important functional roles in regulating the immune response to RhD, and to other RBC antigens. Further studies are aimed at investigating maternal DNA samples following pregnancy-related alloimmunisation, and transfusion-dependent patient groups.
Keywords RhD, responder, alloimmunisation **Conflict of interest** None

Monday 21 October **0830-1000**
ANZSBT Presidential Symposium **Central Hall A**
O033 **0930**

Proteasome Inhibition is Feasible and Associated With Rapid Clinical Responses in Refractory Thrombotic Thrombocytopenic Purpura (TTP)

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Aim/Background
Refractory TTP has high morbidity and mortality. Adjunctive rituximab therapy fails to neutralise CD20 negative anti-ADAMTS13 producing cells. Proteasome inhibitors can rapidly reduce pathological antibody production. We report the first 3 patients treated with bortezomib for refractory TTP.
Methods
Case series of bortezomib treatment (1.3mg/m^2 x 4) for refractory TTP defined by acquired ADAMTS13-deficiency, prolonged plasma exchange (PEX) dependence and poor response to standard adjunctive therapies.
Results
Case 1: 53yr F. Refractory to b.d. PEX, n-acetylcysteine, methylprednisolone, cyclophosphamide and rituximab. Pre-bortezomib ADAMTS13 0% (2.2BU inhibitor). Bortezomib from D+27. Time to normal LDH 5d; platelets 25d. Relapse at 9 months successfully re-treated with rituximab, prednisolone and bortezomib.
Case 2: 16yr F. Refractory to daily PEX and rituximab. Pre-bortezomib ADAMTS13 0%. Bortezomib from D+22. Time to normal LDH 6d; platelets 12d. Patient remains in remission at 5 months.
Case 3: 49yr F. Refractory to b.d. PEX, rituximab and prednisolone. Pre-bortezomib ADAMTS13 0% (19.2BU inhibitor). Bortezomib commenced D+17. Time to normal LDH 9d; platelets 19d. Patient remains in remission at 7 months.
Conclusion
Bortezomib is feasible in refractory TTP and associated with rapid responses in combination with PEX and rituximab. The lag between LDH and platelet responses may represent bortezomib-induced thromobocytopenia. Reproducibility across 3 patients (including re-treatment at relapse) provides the first clinical evidence that proteasome inhibition is a promising and potentially life-saving adjunct to current therapy for this disease.

Keywords TTP, bortezomib, ADAMTS13
Conflict of interest None to declare.

Monday 21 October **0830-1000**
ASTH Free Communications 1: Platelet Disorders **Central Hall C**
O034 **0830**

Review of SRA Results for Confirmation of Heparin Induced Thrombotic Thrombocytopenia (HITT)

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Aim/Background
Heparin induced thrombocytopenia (HIT) is an immune mediated disorder associated with heparin therapy with clinically significant HIT defined when patients have both thrombocytopenia and thrombosis. Washed platelet assays such as the serotonin release assay (SRA) are the most useful in the detection of clinically significant HIT antibodies. A review was carried out on all SRA samples tested in the past 3 years. The aim was to assess the effectiveness of SRA in the confirmation of clinically significant HIT.
Methods
The Haematology Department at SEALS, Prince of Wales Hospital has been performing the SRA for HIT confirmation since the 1990's, using the assay described by Sheridan (Blood Vol 67, 1986).
Results
A total of 249 samples were tested for SRA in 2010, of these 42 (16.9%) samples were positive. In 2011, 206 samples were tested for SRA, of these 37 (18%) samples tested positive. In 2012, 220 samples were tested, of these 47 (21.4%) samples tested positive. Overall thrombocytopenia was reported in 100% of SRA positive cases and 90% of SRA negative cases. Thrombosis was reported in 64% of SRA positive cases, all of whom also reported thrombocytopenia. Thrombosis was reported in 20% of SRA negative cases in whom 6 of the 26 cases were not thrombocytopenic. The occurrence of thrombosis (with or without thrombocytopenia) was significantly more frequent in SRA positive cases. Thrombosis without thrombocytopenia was reported infrequently suggesting the clinical trigger for suspecting HIT was thrombocytopenia rather than thrombosis.
4T scores were provided in 46 SRA positive and 104 SRA negative samples. Low probability, intermediate probability and high probability scores were seen in 4.3%, 41.3% and 53.3% SRA positive cases and 33.7%, 44.2% and 22.1% of SRA negative cases. SRA positivity was associated with higher probability for HIT.
Conclusion
Our retrospective review of the serotonin release assay demonstrates SRA positivity is associated with higher pre-test clinical probability of HIT 4T and reported occurrence of thrombosis confirming this functional assay detects clinically significant HIT.
Keywords Serotonin, Heparin, Thrombocytopenia **Conflict of interest** No

Monday 21 October **0830-1000**
ASTH Free Communications 1: Platelet Disorders **Central Hall C**
O035 **0845**

The Relationship Between Antiplatelet Drug Therapy and Platelet Microparticle Formation and Procoagulant Activity in Patients with Cardiovascular Disease

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Aims
Dual antiplatelet therapy with aspirin and clopidogrel is commonly used to prevent recurrent ischaemic events. It is unclear however whether antiplatelet therapy inhibits the platelet microparticle (PMP) formation. The aim of this study was to investigate the relationship between antiplatelet therapy and PMP formation.
Methods
50 patients receiving long-term dual antiplatelet therapy undergoing coronary angiography were recruited. Multiplate impedance aggregometry was used to assess platelet inhibition. Microparticle formation and procoagulant activity in response to adenosine diphosphate (ADP), arachidonic acid (AA) and thrombin receptor activating peptide (TRAP) stimulation was assessed by flow cytometry and Procoag-PL assays respectively. In addition, blood from 10 normal individuals not receiving antiplatelet therapy were incubated *in vitro* with aspirin or a P2Y12 inhibitor (MeSAMP) and subjected to Multiplate and microparticle analysis.
Results
In patients receiving dual antiplatelet therapy, there was a significant decrease in platelet aggregation in response to ADP, ADP-HS, AA and TRAP. Microparticle-associated procoagulant activity was however only inhibited in response to AA only and not to ADP or TRAP. In normals, *in vitro* P2Y12 inhibition resulted in a significant inhibition of platelet aggregation and PMP formation with ADP and AA, whereas aspirin only significantly inhibited AA platelet aggregation and PMP formation.
Conclusion
In vitro P2Y12 inhibition is more effective at preventing PMP release compared to aspirin, however in patients, dual antiplatelet therapy fails to completely inhibit PMP release, particularly in response to ADP and TRAP. This could explain why some patients administered dual antiplatelet therapy experience ischaemic events.

Keywords Dual Antiplatelet Therapy, Platelet Microparticles, Platelet Reactivity
Conflict of interest No

Monday 21 October **0830-1000**
ASTH Free Communications 1: Platelet Disorders **Central Hall C**
O036 **0900**

Storage Pool Disorder Diagnosis: A comparison of Electromicroscopy and Platelet Luminaggrenometry

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Storage Pool disorders, as a cause of bleeding diathesis are difficult to diagnose and have traditionally been a diagnosis of exclusion. There is a paucity of published data comparing Platelet Luminaggrenometry to Electron Microscopy (EM) in the diagnosis of Platelet disorders. Sladky JL et al, Haemophilia, 2012 demonstrated that the PFA-100 does not predict delta-granule platelet storage pool deficiency and Masliah-Planchon J et al, 2008 in a review of delta-storage pool disease, stated that EM is the major tool for diagnosis.
Pathology Queensland introduced Platelet EM to assist in diagnosis Dense Body Deficiency and other platelet ultrastructural defects.

Since 2010 we have performed electron microscopy on 112 samples on 88 patients (61 individual samples and 9 families). A retrospective audit of these cases was undertaken to determine if any other investigations correlated with the presence of Dense Body Deficiency as determined by EM studies. Assessments available included clinical history, coagulation screen, Von Willebrand's screen, PFA-100 and Platelet Luminaggregometry.

In cases where Platelet Lumiaggregometry showed reduced ATP release also showed a reduction in dense bodies on EM. However normal platelet lumiaggregometry and ATP release did not exclude abnormal EM results.

Routine coagulation screens were normal in the majority of patients. When performed, PFA-100 results did not show any consistent pattern in patients with reduced dense bodies. Von Willebrand's Disease was excluded in the majority of patients with abnormal EM.

Based on our experience in patients with unexplained bruising or mild bleeding, EM appears to be the most useful test for diagnosis of Dense Body deficiency. Whilst platelet lumiaggregometry is abnormal in a subset of patients it is not a consistent predictor of Dense Body Deficiency. When there is clinical suspicion of platelet dysfunction, EM should be performed to better identify those patients with Storage Pool Disorder.

Keywords Platelets, Electron Microscopy
Conflict of interest No

ASTH Free Communications 1: Platelet Disorders **Central Hall C**

O037 **0915**

The KIR2DS5 Genotype Confers Protection Against Adult Immune Thrombocytopenia

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Aim/Background

Immune thrombocytopenia (ITP) is an autoimmune disorder of unknown aetiology, characterised by an isolated low platelet count in the absence of other identifiable causes. Killer cell immunoglobulin-like receptors (KIR) control T-cell and Natural Killer cell function via inhibitory and activating signalling pathways. The inhibitory KIR2DL3, KIR3DL2 and KIR3DL1 are up-regulated in the T-cells of patients with ITP in remission relative to those with active disease, and an association of KIR2DS2/KIR2DL2 with ITP has also been reported. No comprehensive KIR analysis in ITP has been performed.

Methods

We performed genotyping of all KIR genes using sequence specific primer polymerase chain reaction (SSP-PCR) on a cohort of 83 adult patients with ITP and 106 age matched healthy volunteers. Multivariable binary logistic regression was used to adjust for age, sex and the effects of other KIR genes

Results

There was an over-representation of KIR2DS3 and under-representation of KIR2DS5 (also protective against other immune mediated disorders) in adult ITP (odds ratio 0.16, C.I. 0.08-0.32, P<0.001). The compound genotype of 2DS2/2DL2 with 2DS5 abrogated the risk of 2DS2/2DL2 and the protective benefit of 2DS5.

Conclusion

We have demonstrated that the KIR2DS5 genotype was independently associated with protection against ITP and have shown the compound genotype of 2DS2/2DL2 with 2DS5 abrogated the risk of 2DS2/2DL2 and the protective benefit of 2DS5. These findings shed new light on the immunobiology of adult persistent/chronic and relapsed ITP.

Keywords genetic association, immune thrombocytopenia, Killer cell immunoglobulin-like receptors

Conflict of interest Roche Products Pty Ltd (Australia) provided a research grant for the coordination of sample assays as a sub-study of clinical trial protocol ML20948. There are no conflicts of interest for LAS, JPN, PC, LW, HT, and MKG.
RB has accepted sponsored travel to overseas conferences from Roche.

Monday 21 October **0830-1000**
ASTH Free Communications 1: Platelet Disorders **Central Hall C**
O038 **0930**

Patients' Preferences for FVIII Reconstitution Devices in Haemophilia A

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Aim/Background
To elicit patients' preferences for FVIII reconstitution devices in relation to ease of use. Intravenous infusion of FVIII for haemophilia A requires FVIII product reconstitution, which can be cumbersome and time-consuming.
Methods
274 haemophilia A patients in Italy, Spain, Austria, Germany and the UK, who had injected their current FVIII treatment ‡20 times, completed an online standardised questionnaire about experiences of treatment and preferences for five unbranded treatment devices. A subsample of 70 men subsequently tested a new prefilled dual-chamber syringe for FVIII reconstitution using unbranded demonstration kits.
Results
Participants, (58% aged under 40 years; mean time since diagnosis 32 years; mean duration on current FVIII treatment 11.5 years; 64% using FVIII prophylactically) took on average 5 minutes to prepare current treatment for injection. Participants preferred the device scenario requiring the least equipment and reconstitution steps, giving this a median rating of 74 out of 100, significantly (23%, $p<0.001$) higher than any of the other scenarios and were significantly more likely to use this prophylactically (<0.001). Among participants who tested the new device, 57% preferred the new device, 19% preferred their current treatment and 24% had no preference. The new device took significantly less time to prepare FVIII for injection (median time 46 seconds compared with 240 seconds to prepare current treatment (based on recall) $p<0.001$) and was rated as significantly easier to use to prepare FVIII for injection than participants' current treatment devices (median ease of use score for the new device 9 out of 10 compared with a median score of 6 out of 10 for current treatment devices $p<0.001$).
Conclusion
The survey results indicate that the prefilled dual-chamber syringe, requiring the least equipment and fewest reconstitution steps, was preferred by patients and most likely to be used prophylactically. The hands-on device testing supports the survey results. This clearly demonstrates both a need for a device that offers ease of use and time efficiency, and a preference for a device that is perceived to offer those advantages over current treatment devices.
Keywords haemophilia, device, patient-preference
Conflict of interest This paper was supported by Pfizer. Medical Team Lead of Pfizer is a co-author of this abstract and assisted with its preparation.

Monday 21 October **0830-1000**
ASTH Free Communications 1: Platelet Disorders **Central Hall C**
O039 **0945**

Evaluation of HIT Functional Testing by Multiplate®

R Gemmell[1], L Cavanaugh[1], S Just[2], B Chong[1]
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Aim
Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of heparin therapy. Prompt diagnosis is necessary and relies on a clinical diagnosis supported by laboratory testing, immunological or functional. The aim of this study was to evaluate the functional whole blood Multiplate® impedance aggregometer for HIT testing and compare with C^{14} Serotonin Release Assay (SRA).
Methods
Whole blood from a single donor, known to be a good responder for HIT functional testing, was collected into Hirudin vacuum tubes. 300µl donor blood was added to 150 µl heparin dilution in the Multiplate® test cell and incubated for 2 minutes, 150 µl patient citrate plasma or serum was added and the impedance across 2 electrodes was measured over 15 minute or 20 minute time intervals. 58 samples previously tested by SRA were used and testing was performed at two concentrations of heparin (0.5IU/ml and 100IU/ml). The inhibition of aggregation by the high concentration was determined for each patient with an inhibition ‡ 60% considered to be positive for HIT.
Results
Results for 4 samples (3 positive and 1 negative by SRA) were inconclusive and excluded from the data.
Of the remaining 54 samples tested, 16 samples were positive and 38 negative when previously tested by SRA.
For the 16 positive SRA: 15 were positive by Multiplate® and 1 negative
For the 38 negative by SRA: 2 were positive by Multiplate® and 36 were negative.
Conclusion
Our evaluation of the Multiplate® technique showed good agreement with SRA for detecting HIT antibodies. This allows use of a non-radioactive method for rapid diagnosis. A prospective study with more donors will be required to validate the method.
Reference
Morel-Kopp M-C et al, Whole blood impedance aggregometry detects heparin-induced thrombocytopenia antibodies. *Thromb Res* 2010; 125(5):e234-9.

Keywords functional HIT, Multiplate®, SRA
Conflict of interest No conflict of interest to disclose.

Monday 21 October **0830-1000**
Nurses Symposium 3: Focus on Transplant/Post Transplant/Treatment Quality of Life
Meeting Rooms 5/6

Quality of Life in Transplantation Patients – What Have We Learned Over the Years?

Monica Fliedner
University Center for Palliative Care, Department of Oncology, University Hospital Bern, Switzerland

When in 1957 Dr. Don Thomas reported the first stem cell transplantation in the scientific literature, quality of life was not the primary focus – survival was more important. Unfortunately the first transplanted patients didn't survive long enough to tell us today about how it was like to undergo treatment, cope with a life-threatening disease, spend a long time in a germ-free environment and return to a normal life after transplantation.
In the first two decades after the important scientific breakthrough the main aim was to reach prolonged disease free survival and to deal with the sometimes life-threatening complications during conditioning, associated with the transplantation itself, during the aplastic phase and in stabilization phase. Returning to a life after transplantation with potential changes of roles within the affected families became more the focus in the 80's and 90's. Defining quality of life and its contributing factors was a major challenge for professions involved in the (after)care of the patients and his family. Social workers, psychologists, nurses, physicians and allied health care professions all aimed at improving the life and preventing major difficulties. Nowadays the focus is on early rehabilitation and prevention of negative impacts on the involved patients and families.
After looking at essential definitions and ways to measure quality of life the presentation will reflect on the challenges of patients, families and the multiprofessional team when facing the journey of transplantation from diagnosis to rehabilitation or into palliation and terminal care. Five major dimensions should be included in any assessment of QOL and planning of support: physical status and functional abilities; psychological status and coping strategies social interactions; the economic status and spiritual aspects. Only if we cover all of these dimensions we can offer the patient a comprehensive support in managing the challenges of transplantation.
Keywords Quality of life, social rehabilitation, livelong journey for patients and families
Conflict of interest No conflict of interest

Monday 21 October **0830-1000**
Nurses Symposium 3: Focus on Transplant/Post Transplant/Treatment Quality of Life
Meeting Rooms 5/6

Exercise After Treatment: Australian Research on Challenges and Solutions

Pam McGrath
Griffith Health Institute, Griffith University, Brisbane, Qld, Australia

There is now substantial evidence that shows exercise provides important benefits to cancer patients in relation to physical fitness, functioning, quality of life, and survival. The focus of the presentation is on recent research that explores haematology patients' engagement with and attitudes towards exercise post-treatment. Findings will be presented on the low levels of exercise reported by haematology patients, the barriers towards engaging in daily exercise, and the interest in an exercise program designed specifically for cancer patients. The presentation concludes with a research-based discussion of initiatives that are designed to support patients in returning to exercise during and post-treatment. The research presented is from a psychosocial perspective with practical implications for supportive care.

Keywords Exercise, psychosocial, qualitative research
Conflict of interest No

Monday 21 October **0830-1000**
Nurses Symposium 3: Focus on Transplant/Post Transplant/Treatment Quality of Life
Meeting Rooms 5/6

Home-Based Nutrition and Exercise Counselling Following High Dose Conditioning and Autologous Stem Cell Transplantation

Yun-Chi Hung[1], Judith Bauer[1, 2], Pamela Horsley[2], Joseph Coll[1], John Bashford[3], Elisabeth Isenring[1, 4]
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Background
Patients experience adverse changes in nutritional status, body composition and quality of life (QoL) after high dose conditioning and stem cell transplantation (SCT).
Aim
To examine the impact of nutrition and exercise counselling on patients' nutritional status, body composition, and QoL at 100 days post-transplant.
Methods
Cancer patients undergoing autologous SCT were consecutively recruited from a private haematology clinic in Brisbane, Australia. At discharge, extended care group (EC) (n=18) received fortnightly telephone counselling from a dietitian and exercise physiologist up to 100 days post-transplant; the usual care group (UC) (n=19) received no intervention after discharge. Nutritional outcomes (patient-generated subjective global assessment and dietary history), QoL (EORTC QLQ C-30 version 3), and body composition (Bod Pod, COSMED USA, Inc.) were assessed at pre-admission, discharge, and 100 days post-transplant. Changes were compared using independent t-tests; results were adjusted using analysis of covariance.
Results
Thirty-seven patients (54% male; mean age 58.7±9.5 years) were recruited. Relative to discharge, EC exhibited clinically important improvements in protein intake (+14.7g; CI95% -6.5, 35.9, p=0.165), cognitive functioning (+7.2; CI95% -7.9, 22.1, p=0.337), and social functioning (+16.5; CI95% -7.3, 40.3, p=0.165) than UC. Relative to pre-admission, UC lost more weight than EC (difference -3.3kg; CI95% -6.7, -0.2, p=0.062); greater weight loss amongst UC was due to greater fat loss (difference -3.3kg; CI95% -6.2, -0.3, p=0.030).
Conclusion
SCT patients provided with nutrition and exercise counselling following hospitalisation may experience better recovery in dietary intake, improvement in QoL components, and less weight loss.

Keywords Nutritional status, exercise, quality of life
Conflict of interest No

HSANZ Free Communications 4: Immunology & Cellular Therapy **Auditorium (Arena B)**
O040 **1000**

Generating T cells with Broad Fungal Reactivity for Adoptive Therapy

0845-0900

Shivashni Deo[1,2], Balaji Virassamy[1], Catriona Halliday[3], Wieland Meyer[3], Sharon Chen[2,3], Tania Sorrell[2,3], David Gottlieb[1,2,4]
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Aim/Background
Filamentous fungal infections (including *aspergillosis, fusariosis, scedosporiosis* and *zygomycosis*) are emerging as the leading cause of invasive fungal infections (IFI) in HSCT patients. Cell therapy using *in vitro* expanded fungus specific T cells may reduce IFI related deaths in these patients. We enumerated fungus reactive cells in the peripheral blood of healthy donors and investigated the possibility of expanding T cells specific for filamentous fungi *in vitro* using our established protocol for expansion of *A fumigatus* T cells (Gaundar et al, Cytotherapy 2012).

Methods
Lysates from germinated spores of *A fumigatus, A flavus, A terreus, F solani, F oxysporum, R oryzae* and *S prolificans* were used as antigen. The numbers of TNF spot forming cells (SFC) in PBMC of healthy donors was quantified by ELISPOT. Individual T cell cultures were performed by stimulating PBMCs with autologous monocyte derived dendritic cells pulsed with 10 g/ml of fungal lysate on Days 0 and 7, followed by expansion with IL-2, IL-7 and IL-15 from Day 7 onwards. Phenotype of cultured cells, cytokine production following re-stimulation with antigen and cross-reactivity with other fungal antigens was assessed by flow cytometry on Day 21.

Results
The median numbers of TNF SFC per $1x10^6$ cells were 648 *(A fumigatus; range 79-2291),* 390 *(A flavus; 3-1863),* 146 *(A terreus; 0-418),* 273 *(F solani; 0-940),* 282 *(F oxysporum; 0-1742),* 158 *(S prolificans; 0-1833)* (n=6) and 19 *(R oryzae; 0-252)* (n=4). T cells specific for *A flavus, A terreus, F oxysporum, F solani* and *S prolificans* were expanded *in vitro,* resulting in >19 fold increase in cell numbers and >90% $CD4^+$ cells in all cases except *F solani* where up to 40% were $CD8^+$ (n=2). Fungus specific responses were $CD4^+$ Th1 mediated in all cases. Overlapping responses between *A fumigatus, A flavus, A terreus* and *F oxysporum* were observed, but not always with *F solani*. *S prolificans* initiated T cell cultures cross-reacted with all *Aspergillus* and with *F oxysporum*.

Conclusion
Cross reactivity of T cells with other fungi indicate presence of common antigens between some filamentous fungi. T cells capable of broad fungal recognition could possibly be generated in a single culture but this requires further investigation.

Keywords stem cell transplant, invasive fungal infections, T cell therapy
Conflict of interest No

Monday 21 October **1000-1100**
HSANZ Free Communications 4: Immunology & Cellular Therapy **Auditorium (Arena B)**
O041 **1015**

Persistence and Efficacy of Second Generation CAR-T Cell Against the LeY Antigen in Acute Myeloid Leukemia

H Miles Prince[1,2,3,4,5], David S Ritchie[1,2,3,4,5], Paul J Neeson[1,2,3], Amit Khot[4], Stefan Peinert[4], Tsin Tai[2], Kellie Tainton [2], Karen Chen[2,] Mandy Shin [2], Dominic M Wall[5, 6,7] Dirk Hönemann[4], Peter Gambell[5,6], David A Westerman[6], Javier Haurat[5], Jennifer A Westwood[1,3,], Andrew M Scott[7], Lucy Kravets[5], Michael Dickinson[2,4], Joseph A Trapani[1,3], Mark J Smyth[1,3], Phillip K Darcy[1,3], Michael H Kershaw[1,3]
[1]Sir Peter MacCallum Department of Oncology, University of Melbourne; [2]Hematology Immunology Translational Research Laboratory, Peter MacCallum Cancer Centre (PMCC); [3]Cancer Immunology Research Program, PMCC; [4]Division of Cancer Medicine, PMCC; [5]Centre for Blood Cell Therapies, PMCC; [6]Diagnostic Hematology, Department of Pathology, PMCC; [7]Ludwig Institute for Cancer Research, Heidelberg, Vic.

Aim/Background
Autologous chimeric antigen receptor (CAR) therapy has demonstrated striking results in relapsed/refractory CLL and ALL. In a phase I study utilizing a novel retroviral vector for CAR anti-LeY T cell therapy of acute myeloid leukemia (AML), we examined the safety and post-infusion persistence of adoptively transferred T cells.
Methods
Following fludarabine-containing pre-conditioning four patients received up to 1.3 x 10^9 total T cells (including T_{CM} cells) of which 14% to 38% expressed the CAR
Results
Grade 3 or 4 toxicity was not observed. One patient achieved a cytogenetic remission, whilst another with active leukemia had a reduction in peripheral blood blasts and a third showed a protracted remission. Using an aliquot of ^{111}In-labeled CAR-T cells we demonstrated trafficking to the bone marrow in those patients with the greatest clinical benefit. Furthermore, in a patient with leukemia cutis, CAR-T cells infiltrated proven sites of disease. Serial PCR of peripheral blood and bone marrow for the LeY transgene demonstrated that infused CAR-T cells persisted for up to 10 months.
Conclusion
Our study supports the feasibility and safety of CAR-T cell therapy in high-risk AML, and demonstrates durable in vivo persistence.
Keywords chimeric antigen receptor T cell therapy, acute myeloid leukaemia
Conflict of interest None

Monday 21 October **1000-1100**
HSANZ Free Communications 4: Immunology & Cellular Therapy **Auditorium (Arena B)**
O042 **1030**

Histone Deacteylase Inhibitors (HDACi) Suppress Toll-like Receptor-induced Dendritic Cell Maturation and Alter Secretion But Not Gene Expression of Polarising Cytokines by Dendritic Cells

Michael Dickinson, Alex Davenport, Pasquale Petrone, H Miles Prince, David Ritchie, Paul Neeson
Peter MacCallum Cancer Center, East Melbourne, VIC, Australia

Aim/Background
HDACi induce cancer cell apoptosis and are in use for T-cell lymphoma. Prior studies have indicated that HDACi are immune-suppressive. In this study, we address this issue by examining the effects of two different HDACi on human monocyte derived dendritic cell (hmDC) biology.
Methods
hmDC were activated by TLR stimuli (LPS or poly:IC). HDACi effect on TLR-induced hmDC activation was assessed by up regulation of co-stimulatory molecules CD80, CD86 and CD83 along with secretion of IL-12p70, IL-10 and IL1 . To address the mechanism for drug-induced altered cytokine secretion mRNA for IL-12p70, IL-10 and IL1 were assessed followed by mir-155 mRNA and SOCS-1 protein. The functional outcome was assessed in an allogeneic MLR.
Results
At doses sub-optimal to induce myeloma cell death, both drugs significantly inhibited TLR-induced hmDC increase in CD80 and CD83, but not CD86. TLR-induced secretion of IL-10 and IL12p70 was reduced while IL-1 secretion was increased. This occurred regardless of drug sequencing. HDACi did not significantly alter expression of IL-12p70, IL-10 or IL-1 mRNA despite changes in protein levels. To reveal the mechanism for the HDACi-induced hmDC IL-12p70 defect, the upstream molecules miR-155 and SOCS-1 were examined. Interestingly, panobinostat but not romidepsin induced mir-155 down-regulation and SOCS-1 protein increase. Subsequently, allogeneic T-cells co-cultured with HDACi/TLR-ligand-treated hmDC secreted lower levels of cytokines (decreased secretion of IFN- , IL-2, TNF, IL-4 and IL-17) compared to those allogeneic T cells co-cultured with control hmDC.
Conclusion
In this study, we show that whilst HDACi impair DC maturation and modulate subsequent T cell responses. Our findings suggest that panobinostat induces the IL-12p70 effect via the mir-155/SOCS-1 pathway, whereas romidepsin induces the effect via a mir-155 independent pathway. This data suggests that HDACi affect the hmDC maturation response to pathogen, and that these drugs may alter the ability of treated patients to raise an effective immune response to pathogens or, indeed, tumour antigens.
Keywords HDACi Immunology dendritic cell
Conflict of interest None

HSANZ Free Communications 4: Immunology & Cellular Therapy **Auditorium (Arena B)**

O043 **1045**

The Safety and Effect of Multiple Doses of Vorinostat on HIV Transcription in HIV-infected Patients Receiving Combination Antiretroviral Therapy

H Miles Prince[5], Julian Elliott[1,2,3], Ajantha Solomon[2,3], Fiona Wightman[2,3], Miranda Smith[2,3], Sarah Palmer[4], Jo Watson[6], Hoy J[1,2], McMahon J[1,2], Lewin SR [1,2,3]
[1]Alfred Hospital, [2]Monash University, [3]Burnet Institute, Melbourne [4]Karolinska Institute, Sweden; [5]Peter MacCallum Cancer Centre, Melbourne; [6]National Association of People Living with HIV, Sydney

Background
One potentially strategy for eliminating latently HIV-infected CD4+ T-cells is to administer histone deacetylase inhibitors to activate HIV transcription. The aims of this study were (i) to determine the safety of vorinostat in HIV-infected patients on cART and (ii) the effect HIV transcription in CD4+ cells in blood and rectal tissue.

Methods
HIV-infected adults on cART (n=20) received vorinostat 400 mg daily for 14 days. Blood was collected at 0, 2, 8 and 24 hrs, and 7, 14, 21, 28 and 84 days. Rectal biopsies at day 0, 14. Cell associated unspliced (CA-US) RNA and HIV DNA were quantified in CD4+ cells from blood (n=17) + rectal tissue (n=10). Changes in CA-US RNA and HIV DNA were determined using paired t-tests (intra-patient change); Wilcoxon signed rank test (all patients); generalized estimating equations (GEE).

Results
Median baseline CD4 count was 721 (range 371–1335) cells/μl and duration of virus suppression was 5.0 (range 2.7 – 13.4) years. There were no high grade AE or drug discontinuations. One participant had a transient increase in plasma HIV RNA while on vorinostat (peak HIV RNA=160 copies/ml). All other participants maintained plasma HIV RNA <20 copies/ml (Roche) throughout follow up. By 8 hours post drug, CA-US RNA, compared to baseline, was significantly increased and remained elevated, including the period after vorinostat dosing ($p<0.001$ at every time point). The kinetics of increase in CA-US RNA varied in each patient. Using a GEE analysis, the mean fold change in CA-US RNA compared to baseline, during vorinostat dosing was 2.53 (95% CI, 1.11-3.01, $p=0.029$) and after vorinostat dosing was 2.78 (95% CI, 1.26-3.91, $p=0.008$). There were no significant changes in HIV DNA in all analyses. In CD4+ T-cells from rectal tissue, there was a trend to an increase in HIV US RNA ($p=0.08$) but no change in HIV DNA ($p=0.59$).

Conclusion
14 days of vorinostat was safe and well tolerated and induced a significant, sustained increase in CA-US RNA in CD4+ T-cells. Treatment was not associated with change in the concentration of HIV DNA suggesting additional strategies will be needed to eliminate latently infected cells.

Keywords: HIV, histone deacetylase inhibitor, vorinostat **COI** None

Monday 21 October **1000-1100**
HSANZ Free Communications 5: CLL **Meeting Room 7**
O044 **1000**

Ibrutinib and the Role of BTK in Haemostasis

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Aim/Background
Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, has demonstrated promising results as a new treatment modality for B-cell malignancies through the inhibition of B-cell receptor signalling. BTK participates in signalling pathways in other cell types, including platelets through the collagen receptor glycoprotein VI. Although BTK inhibition may theoretically impact on normal haemostasis, patients with congenital BTK mutations do not exhibit a bleeding phenotype (Medicine 85:193). Understanding bleeding risk and providing peri-procedural recommendations are of paramount importance. Current empirical peri-procedural recommendations are to withhold drug up to 7 days pre- and post-procedure. To date, there is one unpublished series of 25 CLL/SLL patients receiving ibrutinib, which demonstrated essentially normal Platelet Function Analyser (PFA-100) parameters, and there was no increase in clinically relevant bleeding. We report our local experience.
Methods
Our cohort consisted of 4 patients with 17p deleted CLL that were enrolled into an open label study of ibrutinib at our institution, PMCC. Blood samples for platelet count, coagulation profiles, Light Transmission Aggregometry (LTA) and Thromboelastography (TEG) were assessed prior to and whilst on ibrutinib. These assays were correlated with patient demographics, bleeding risk and/or events.
Results
Collagen-dependent platelet responses, using LTA, were absent in all patients at 2µg/ml concentration, and reduced in all at 10µg/ml concentration. Other agonist-induced responses were preserved. TEG demonstrated normal tracings, values, thrombin generation and haemostatic potential in those patients with preserved platelet counts (n=3); with an expected mild reduction in angle with moderate reductions in platelet counts (n=1). Importantly, despite the reduced collagen response ex vivo, no clinically relevant bleeding episodes occurred in this cohort.
Conclusion
Platelet-function changes following ibrutinib treatment relate to gycloprotein VI/collagen signalling and appear to be identical to those in patients with congenital BTK mutation. TEG tracings, as an overall assessment of haemostatic potential, showed no significant clotting defects apart from those consistent with reduced platelet count. Our studies suggest that there may not be a need for ibrutinib to be withheld beyond the establishment of primary haemostasis. These studies support the safety of the current recommendations.
Keywords Ibrutinib, haemostasis, peri-operative. **Conflict of interest** None

Monday 21 October **1000-1100**
HSANZ Free Communications 5: CLL **Meeting Room 7**
O046 **1030**

CD62L Expression is Associated with Chronic Lymphocytic Leukaemia Cell Survival *in vitro* and Represents a Novel Therapeutic Target in CLL

Melinda Burgess[1,2], Richa Singhania[1], Catherine Cheung[2], Lynne Chambers[2], Brent A Renyolds[3], Louise Smith[2], Peter Mollee[2], Nicholas Saunders[1], Nigel AJ McMillan[4], Devinder Gill[1,2]
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Background
Recent advances in the treatment of chronic lymphocytic leukaemia (CLL) has improved overall patient survival, however the disease remains incurable. There is accumulating evidence that CLL cell resistance to apoptosis is attributable to microenvironmental factors mediated by cell:cell interactions and dysregulation of cytokines signals.
Methods and Results
To dissect the complex microenvironmental interactions present *in vitro,* we profiled the immunophoenotypic changes that occur in long-term CLL peripheral blood mononuclear cell (PBMC) cultures using flow cytometry. The most highly upregulated marker was CD62L (L-selectin). Furthermore, CD62L expression was present in “proliferation and survival niches” in the bone marrow and lymph nodes of CLL patients. The pro-survival role of CD62L was examined using a functional blocking antibody which resulted in the significant loss of CLL cell survival. This cytotoxic mediated response was not abrogated by the presence of stromal cell line HS-5, suggesting that anti-CD62L therapy may be effective *in vivo* where pro-survival signals are intact. Moreover, there was a significant increase in cytotoxic responses when anti-CD62L treatment was combined with fludarabine and mafosfamide.
Conclusion
Immunophenotypic analysis of CLL cultures demonstrated that the expression of several cell surface markers change throughout *in vitro* culture. These markers are suggestive of cell-cell interactions that provide survival signals. Blocking the activation and homing marker, CD62L, regulates CLL cell survival *in vitro and* activates a novel prosurvival signal which induces cell death equivalent to current CLL chemotherapeutics. Overall, CD62L is a novel prosurvival effector that may represent an attractive therapeutic target in CLL.
Keywords CD62L, CLL **Conflict of interest** None

Monday 21 October **1000-1100**
HSANZ Free Communications 5: CLL **Meeting Room 7**
O047 **1000**

Rate of Development of Hypogammaglobulinaemia and Reduced IgG Subclass Levels in Chronic Lymphocytic Leukemia (CLL)

Nikesh Reddy Adunuri [1], O Giles Best[2], Jane A Freeman[3], Cecily J Forsyth[4], Naomi J Mackinlay[2], Ping Han[5], Stephen P Mulligan[1,2,5]
Royal North Shore Hospital[1,2], University of Sydney[1,2], Northern Haematology and Oncology Group[3], North Gosford[4], and Laverty Pathology[5], Sydney, NSW, Australia

Background
Hypogammaglobulinaemia is common in CLL and a significant contributor to infection risk. This can occur in most CLL patients including early stage and stable CLL. We sought to assess the rate at which this develops.
Methods
Longitudinal data on immunoglobulin (IgG, IgA, IgM) and IgG subclass levels were extracted using the first measurement of immunoglobulin levels as day 0.
Results
Of 100 patients, the proportion with IgG, IgA, and IgM deficiency at Day 0 was 16.0%, 22.0% and 45.0% respectively, with a total of 62.0% low in at least 1 class. The median number of days to reduction in IgG, IgA and IgM was 700, 653 and 594 days respectively. There were 16 patients whose immunoglobulin levels did not fall over a median of 1384 days (Range = 304-3011 days). Of 97 patients with IgG subclasses, the proportion with IgG1, IgG2, IgG3 and IgG4 deficiency at day 0 was 21.6%, 15.5%, 37.1%, and 19.6% with a total of 54.6% low in at least 1 IgG subclasses at day 0. The median number of days to subclass deficiency was 381, 1355, 1461 and 1111 days (IgG1-4). Immunoglobulins decrease at different rates.
Conclusion
Hypogammaglobulinaemia is common in CLL with 62.0% deficient in at least one immunoglobulin class and 54.6% in at least one IgG subclass at diagnosis. However immunoglobulin deficiency does not develop in all CLL patients as 16% and 22.6% maintain normal Ig class and IgG subclass respectively.

Keywords CLL, immunoglobulins, hypogammaglobulinaemia, IgG subclass
Conflict of interest The authors have no conflict of interest

Monday 21 October **1000-1100**
HSANZ Free Communications 6: BMT 1 **Meeting Room 8**
O048 **1000**

Allografts for Hodgkin Lymphoma in Australia and New Zealand: Increasing Activity and Improved Outcome

Julian Cooney[1], Ian Nivison-Smith[2], Steven Tran[2], Peter Bardy[3], Anthony Dodds[4], David Ma[4], Jeff Szer[5]
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Aim
Allogeneic haemopoietic cell transplants (HCT) for Hodgkin lymphoma (HL) are few in number but may be increasing. This review describes allograft activity for HL and investigates which factors have significant associations with transplant outcome.
Methods
Patients were included in the study if they had an allogeneic HCT for HL in Australia or New Zealand between 1998 and 2011. Patient characteristics and outcome data were retrieved from the ABMTRR database. Survival proportions were calculated using the method of Kaplan and Meier. Multivariate Cox regressions were used to identify factors which had significant associations with overall survival
Results
A total of 103 allografts were performed in Australia (93) and New Zealand (10) for HL in the 14 years between 1998 and 2011. Activity increased in recent years with 59 (57%) of HCT occurring in the 5 years 2007 to 2011. The median age at transplant was 28 years and 88 (85%) of the allografts were second or third transplants, the majority (77) of these subsequent to previous autografts. Donors were siblings (53, 51%), unrelated volunteers (49, 48%) and 1 parent. Most (92, 89%) recipients received peripheral blood and 49 (48%) were transplanted in remission. Kaplan-Meier overall survival probability at 5 years post-transplant was 43% for all recipients, 26% for those transplanted in 1998 – 2004 and 49% for those transplanted in 2005 – 2011 (P=0.03). Significant independent favourable risk factors for overall survival were HCT performed in years 2005 – 2011 (hazard ratio (HR) 0.45, 95% confidence interval (CI) 0.25 – 0.81, P=0.008) and HCT where the patient was in remission (HR 0.33, 95% CI 0.17 – 0.65, P=0.001).
Conclusion
Numbers of allografts for HL in Australia and New Zealand have increased in recent years while outcome has improved. An allograft with a related or unrelated donor should be considered for patients relapsing after previous autograft, in appropriate disease and patient states. Primary allograft may be considered for patients for whom autologous cells are unavailable.
Keywords Hodgkin lymphoma, allograft, ABMTRR
Conflict of interest None

Monday 21 October **1000-1100**
HSANZ Free Communications 6: BMT 1 **Meeting Room 8**
O049 **1015**

Outcome of Treatment for Relapsed Hodgkin Lymphoma (HL) Following Autologous Stem Cell Transplant (ASCT) Including Recent Use of Brentuximab Vedotin

Wojt Janowski[1], Piers Blombery[2], Andrew Grigg[1,3], David Ritchie[2,3,4], Michael Dickinson[2,3]
[1] Austin Hospital, Heidelberg, VIC, Australia, [2] Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia, [3] University of Melbourne, Parkville, VIC Australia, [4] Royal Melbourne Hospital, Parkville, VIC, Australia

Aim/Background
Approximately half of patients with relapsed HL treated with ASCT relapse again. The optimal treatment in this setting is unclear; allogeneic SCT (alloSCT) for patients with chemoresponsive relapse provides a chance of long term cure. We aimed to describe the treatment patterns and outcomes of patients treated at our institutions with a variety of salvage regimens, including brentuximab.
Methods
All patients with HL relapsed following ASCT at our institutions were identified from transplant databases. Data on treatment regimens, responses, toxicities, time to treatment failure (TTF) and overall survival (OS) were analysed retrospectively.
Results
Thirty nine of 79 patients who underwent ASCT between 1999 and 2012 relapsed. 29 had sufficient data for analysis. Characteristics were: median age 30 yrs (range 15-51); median TTF from first treatment 8 mths, median TTF post-ASCT 10 mths (1-91). Median number of post-ASCT treatments delivered was 2 (1-5). The first salvage therapy was gemcitabine-based in 12 (CR 33%, ORR 83%), brentuximab in 7 (CR 43%, ORR 86%), alloSCT in 2, radiotherapy in 3 (CR 66%) and other chemotherapy in 4 (CR 25%, ORR 75%). Median TTF following first salvage was 7 mths (1-91). Of 13 who went to alloSCT, 46% remain free from treatment failure at a median FU of 21 mths (2-90); all of the 5 in CR prior to alloSCT (MSD=3, MUD=2) remain free from treatment failure at a median of 24 mths (2-90). Median OS from the first relapse post autograft for the whole group was 74 mths (3-103).
Conclusion
Salvage therapies may lead to prolonged OS despite low chance of cure. Single-agent brentuximab appears as effective as conventional regimens and may provide a less toxic bridge to alloSCT. Further studies with brentuximab both as abbreviated salvage and as maintenance therapy post high dose therapy are needed.
Keywords Hodgkin lymphoma, salvage, brentuximab **Conflict of interest** AG/DR/MD: Advisory Board for Takeda. Takeda provided unrestricted funding for collection and analysis of data for patients not treated with brentuximab.

Monday 21 October **1000-1100**
HSANZ Free Communications 6: BMT 1 **Meeting Room 8**
O050 **1030**

Adult Medulloblastoma: The Feasibility and Effectiveness of Utilising High Dose Chemotherapy With Autologous Stem Cell Rescue in Newly Diagnosed Patients

Joel T Collins[1], Manjunath J Narayana[1], Kirk Morris[1], John Casey[1], Po-Ling Inglis[1], Robin Cheuk[1], Thulasi Rajah[1], Thomas Robertson[2], Glen A Kennedy[1]
[1]Royal Brisbane & Women's Hospital, Brisbane, Queensland, Australia
[2]Pathology Queensland, Brisbane, Queensland, Australia

Aims / Background
Medulloblastoma and atypical teratoid rhabdoid tumours uncommonly occur in adults and standardized therapeutic strategies are lacking for adult populations. We present our experience of a paediatric-based protocol comprising craniospinal irradiation followed by sequential cycles of high dose chemotherapy with autologous stem cell rescue as treatment of adult medulloblastoma.
Methods
A standardized treatment strategy for adult medulloblastoma / atypical teratoid rhabdoid tumours based upon the St Jude's paediatric protocol (JCO 2001; 19: 2696) was introduced in our unit in 9/03. Briefly, patients underwent initial G-CSF mobilization pre-36Gy cranio-spinal radiotherapy (with 18.8Gy boost to tumor bed), followed 6wks later by x4 monthly cycles of high dose cisplatin, cyclophosphamide and vincristine chemotherapy with autologous stem cell support. Patients were identified from an institutional database with outcomes retrospectively determined via review of individual medical records.
Results
Seven sequential, newly diagnosed adult patients (medulloblastoma n=6; atypical teratoid tumour n=1) had received treatment between 9/03 and 1/12. Median patient age was 24.5yrs (range 18 to 37.2 years), 71% were male, 6 had standard-risk disease and 1 had high-risk disease as per modified Chang criteria. At a median follow-up post diagnosis of 65mths (range 11-109mths) 6/7 patients (86%) remain alive and disease free with only 1/7 patients experiencing relapse / death; 5yr DFS and OS are identical at 86%. No unexpected toxicity or TRM was observed.
Conclusion
Our experience suggests that cranio-spinal radiotherapy followed by sequential high dose chemotherapy with stem cell support is well tolerated with encouraging outcomes in adult patients with medulloblastoma.

Keywords Medulloblastoma, autologous transplant, adult
Conflict of interest No conflicts of interest

Monday 21 October **1000-1100**
HSANZ Free Communications 6: BMT 1 **Meeting Room 8**
O051 **1045**

Therapy and Outcome of Relapsed Acute Myeloid Leukaemia after Allogeneic Stem Cell Transplantation: Single Centre Experience

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Malignant Haematology & Stem Cell Transplantation Service, Alfred Health, Melbourne

Background
Relapsed acute myeloid leukaemia (AML) after allogeneic stem cell transplantation (SCT) carries a poor prognosis and is a significant cause of mortality in transplant recipients. The optimal salvage strategy for post-SCT relapse remains unclear. We aim to describe treatment, outcomes and prognostic factors for patients who relapse following transplantation at a single institution.
Methods
163 consecutive patients who underwent first allogeneic stem cell transplantation between January 2000 and December 2012 at the Alfred Hospital were analysed. Demographic, disease and transplant data were collected retrospectively. Survival probabilities were estimated using the method of Kaplan and Meier. Cox proportional hazards regression was used for prognostic factors.
Results
Median post-SCT follow-up for the 163 (78 male) patients (median age 47 years, range 17-66) was 12.5 months (range, 0.2-157). 48 of 163 patients (29%) relapsed at a median of 164 days (range, 29-2233) post-SCT. Overall survival post relapse was 24% at 1 year and 14% at 2 years. Salvage therapy included clinical trial therapies (n=3), immune based therapy with donor lymphocyte infusion +/- chemotherapy or cytokines (n=16), or cytoreductive therapy/best supportive care (n=26) with median overall survival of 470 days, 181 days and 41 days, respectively. 3 patients received second allogeneic SCT, one of whom remains alive at 5.1 years. On univariate analysis, factors associated with longer survival following post-SCT relapse were interval to relapse (p=0.05), use of immune-based therapy (excluding chemotherapy alone and withdrawal of immunosuppression alone) (p=0.04), reduced intensity conditioning (p=0.02), and achievement of complete remission with salvage therapy (p<0.0001). There was no association between age, gender, disease status at SCT, donor type, stem cell source, or GVHD on post relapse survival. No difference in outcomes was demonstrated for relapse within 6 compared with 12 months post-SCT (median survival 47 vs 56 days, p=0.54) regardless of salvage strategy.
Conclusion
Relapse of AML following SCT relapse remains a significant therapeutic challenge. Our study emphasises the poor prognosis for patients with relapsed AML after allogeneic transplantation and highlights the need for more effective therapies.
Keywords AML, relapse, allogeneic SCT **Conflict of interest** No

Monday 21 October **1000-1100**
HSANZ Free Communications 7: MDS and MPN **Meeting Room 9**
O052 **1000-1015**

Transfusion Dependency is Associated with Inferior Outcome in Very Low and Low risk IPSS-R Patients: An Analysis by a South Australian MDS Registry

Devendra K Hiwase[1,2,3], Monika M Kutyna[1], Trisha Carr[1], Rakchha Chhetri[1], Peter Harrison[1], Shriram Nath[4], Lakshmi Nath[4], Nick Wickham[4], James Gray[1], Junia V Melo[1], [2,3,] Peter Bardy[1,2,3] Luen Bik To[1,2,3]
[1]Haematology Division, SA Pathology, Adelaide, South Australia; [2]Centre Cancer Biology, Adelaide, South Australia; [3]Department of Medicine, University of Adelaide, SA 5000, [4]Clinpath Laboratories, Adelaide, South Australia

Aim
Although transfusion dependency is associated with inferior survival outcome, it has not been included in risk stratification of recently revised International Prognostic Scoring System (IPSS-R), mainly due to unavailability of transfusion data. This study evaluated impact of RBC transfusion on survival outcome in lower-risk IPSS-R subgroups
Material and Method
To match patient selection criteria used for IPSS-R scoring system, only primary MDS patients who were not treated with disease modifying agents or stem cell transplantation were included for this analysis. Transfusion dependency was defined as at least 1 unit RBC/8 weeks for at least 4 months.
Results
193/300 patients met the inclusion criteria for this analysis. Their median age was 72 years and 64% patients were male. IPSS-R improved further refinement of IPSS risk groups, importantly of IPSS-Intermediate group. Median overall survival (OS) of IPSS-R Very Low, Low, Intermediate, High and Very High risk group was 88.1, 64.6,24.8,11.4 and 9.4 months respectively ($p<0.0001$). The median survival of transfusion dependent Very Low and Low IPSS-R patients were significantly poor than transfusion independent patients (58 vs. 119 months; $p=0.006$). As 94% of IPSS-R higher risk patients were transfusion dependent, we could not assess the impact of transfusion.
Conclusion
Our analysis showed that IPSS-R can provide better risk stratification of MDS patients. We have also demonstrated that transfusion dependency is associated with inferior survival even in Very Low and Low risk IPSS-R group patients. If validated further, refinement of IPSS-R may be required.
Keywords MDS, IPSS-R, transfusion dependency
Conflict of interest This research was supported Novartis Pvt Ltd and Celgene Australia

Monday 21 October **1000-1100**
HSANZ Free Communications 7: MDS and MPN **Meeting Room 9**
O053 **1015**

Cancer Registries May Underestimate the Incidence of Myelodysplastic Syndromes: Results from a Population-based Data Linkage Study

Zoe McQuilten[1], Erica Wood[1], Mark Polizzotto[1], Lynda J. Campbell[2,3], Meaghan Wall,[3] David Curtis[1,4], Helen Farrugia[5], John McNeil[1] and Vijaya Sundararajan[1,2]
[1]Monash University, [2]University of Melbourne, [3]Victorian Cancer Cytogenetic Service, [4]Alfred Hospital and [5]Victorian Cancer Registry, all in Melbourne, VIC

Aim/Background
Myelodysplastic syndromes (MDS) appear to be under-reported to cancer registries, with important implications for cancer and transfusion support service planning and delivery. We linked two population-based databases to estimate MDS true incidence and examine differences between reported and non-reported cases.
Methods
Data from Victorian Cancer Registry (VCR) and Victorian Admitted Episode Dataset (VAED, capturing all hospital admissions) were linked. Incidence rates were calculated based on VCR cases and using additional cases identified in VAED. Differences between reported and non-reported cases were assessed. Multivariate capture-recapture was used to estimate missed cases. This method uses overlapping data sources from a defined population to estimate extent of incomplete case ascertainment, and has not previously been used to estimate MDS incidence.
Results
Between 2003 and 2010, 2692 cases were reported to VCR, and an additional 1562 cases were identified in VAED. Annual incidence rate for those aged ‡ 65y based on VCR was 44 per 100,000 (95% CI 43–45 per 100,000) and 68 per 100,000 (95% CI 67–70 per 100,000) using both data-sets. Cases not reported to VCR were more likely to have a prior malignancy (23% vs. 19%, p=0.003) and to require red cell transfusion (59% vs. 54%, p=0.003). Using the multivariate model, an estimated 1292 cases were missed: the re-estimate was 5546 (95% CI 5438–5655) MDS cases, with an annual incidence in ‡65y of 103 per 100,000 (95% CI 100–106).
Conclusion
We report a higher incidence of MDS using two data sources from a large and well-defined population than reported using cancer registry notifications alone. Until recently, the epidemiology of MDS has been relatively understudied and an improved understanding of the population impact of disease is required. Periodic review of linked datasets, such as those used in this study, provides an opportunity to examine changes in patterns of care, resource use and outcomes in MDS.

Keywords Myelodysplastic syndromes, epidemiology, cancer registry
Conflict of interest No

Monday 21 October **1000-1100**
HSANZ Free Communications 7: MDS and MPN **Meeting Room 9**
O054 **1030**

Iron Overload is Associated With Inferior Survival of MDS Patients: A Report from SA-MDS Registry

Devendra K Hiwase[1,2,3], Monika M Kutyna[1], Trisha Carr[1], Rakchha Chhetri[1], Peter Harrison[1], Shriram Nath[4], Lakshmi Nath[4], Nick Wickham[4], James Gray[1], Junia V Melo [1,2,3], Peter Bardy[1,2,3], Luen Bik To[1,2,3]
[1]Haematology Division, SA Pathology, Adelaide, South Australia; [2]Centre Cancer Biology, Adelaide, South Australia; [3]Department of Medicine, University of Adelaide, SA 5000; [4]Clinpath Laboratories, Adelaide, South Australia

Aim
Regular RBC transfusion leads to increased iron overload. Here we have assessed the impact of iron overload and iron chelation therapy on survival outcome.
Method
We assessed the impact of iron overload, defined as persistent serum ferritin ‡1000 µg/L, on overall survival (OS). We also assessed the impact of iron chelation therapy on survival of MDS patients.
Results
Serial iron studies were performed in 88% of patients (262/296; 88%); 29% (n=87) and 59% (n=175) of patients had mean serum ferritin ‡1000 µg/L and <1000 µg/L respectively. Median OS was significantly lower in patients with persistent serum ferritin level ‡1000 µg/L compared with patients with <1000 µg/L (33 vs. 52 months; p=0.001). Similarly median OS was significantly lower in iron overload Very Low and Low IPSS-R risk group patients (58 vs. 88 months; p=0.01). Sixty-one of the 87 (70%) patients with high mean serum ferritin level were Low/Int-1 IPSS risk group and thus were eligible for iron chelation therapy. However, only 38% (23/61) of eligible patients were treated with iron cheltaion therapy (consensus guidelines). Median survival was significantly higher in IPSS Low/Int-1 patients who had high ferritin levels and were treated with iron chelation therapy (82 vs. 41 months, p=0.02). However there were eight patients (34%) in deferasirox arm received azacitidine therapy compared with four patients (10%) in non-deferasirox group, which could have potentially influenced the survival outcome.
Conclusion
Iron overload is associated with inferior survival even in IPSS-R Very Low and Low IPSS-R. Iron chelation therapy along with/without disease modifying agents can improve survival in MDS patients with iron overload.

Keywords MDS, Iron overload and deferasirox
Conflict of interest This research was supported by Novartis Pvt Ltd and Celgene Australia

Monday 21 October **1000-1100**
HSANZ Free Communications 7: MDS and MPN **Meeting Room 9**
O055 **1045-1100**

JAK2 Inhibitors in Myelofibrosis, Durability of Response to Initial and Sequential Treatment

Tricia Wright, Lisa Magee, Megan Smith, Emily Li, Ashish Bajel, Andrew Roberts
Department of Clinical Haematology & BMT, Royal Melbourne Hospital, Victoria

Aim/Background

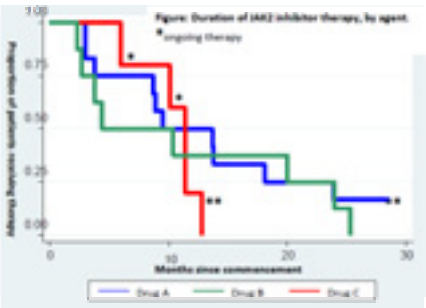
The first FDA approved JAK2 inhibitor ruxolitinib improves symptoms and reduces splenomegaly in some patients with myelofibrosis. Several other JAK2 inhibitors are currently in clinical trials. Emerging data have indicated that JAK2 inhibitors differ in their efficacy and side effect profile. We examined duration of therapy and clinical responses in patients (pts) with myelofibrosis at our centre on treatment with three JAK2 inhibitors, in clinical trials or via compassionate access.

Methods

Data about prior treatment, disease status by international prognostic scoring system (IPSS) or dynamic IPPS (DIPSS), and response according to the international working group (IWG) criteria and 10 point scale symptom assessment questionnaire were collected for 21 poor prognosis pts.

Results

By IWG criteria, 2 of 21 (9.5%) achieved clinical improvement (CI) with first exposure to a JAK2 inhibitor; the remainder had stable disease (SD) as best response. Using a modified response criteria (modCI), including ‡25 % decrease in spleen size and symptom improvement by ‡3 points, an additional 7 of 19 pts responded. Duration of therapy ranged from 2 to >28 months (Figure). Six patients received sequential treatment with different JAK2 inhibitors, of whom 3 achieved modCI and the remaining SD (Table).



Patient	Drug A	Drug B	Drug C
1	3	9.5	6*
2	20	3	2
3	24		13*
4	10	9	
5	25	9	
6		13	11*

Table: Sequential JAK2 therapy: duration of treatment in months. *ongoing therapy

Conclusion

JAK2 inhibitors can provide benefit to pts with debilitating symptoms from myelofibrosis. While the durability and extent of response is variable, patients may benefit by switching to an alternate JAK2 inhibitor despite evidence of progressive disease from prior treatment.

Keywords Myelofibrosis, JAK2 inhibitor
Conflict of interest No

Monday 21 October **1030-1130**
ANZSBT/Nurses Combined Symposium: Anaemia and Transfusion **Central Hall A**

Physiology of Anaemia and Red Cell Transfusion

Jonathan P Wallis
Department of Haematology, Freeman Hospital Newcastle upon Tyne, UK

Oxygen has been instrumental in the geological and biological development of the earth over more than 4 billion years. A source of energy but also highly toxic, our physiology is almost literally playing with fire in utilizing oxygen as a component of life. Red cells carry oxygen from the lungs to the tissues but have a second important role in preventing excessive oxygen toxicity. Microcirculatory vascular control is sensitive to red cell oxygenation levels. Both release of nitric oxide and of red cell ATP have been suggested as mechanisms for this local control of oxygen supply. Most tissues have blood supply and potential oxygen delivery well above their likely oxygen requirements. Microcirculatory control mediated in part by red cells is key to maintaining a safe level of tissue oxygenation. The coronary circulation has the highest demand of any tissue for oxygen removing 60% or more of that bound to the delivered arterial Haemoglobin. Coronary blood supply increases in direct proportion to the cardiac work and output, partly in response to signals from red cell de-oxygenation. Professional cyclists have shown how important Haemoglobin oxygen delivery is to maximize energy output. At rest we tolerate low Haemoglobin well, but anaemia limits cardiac output under stress. We have investigated the effects of anaemia and transfusion on the anaerobic threshold and found a clear relationship with Hb level. (Wright et al., Br J Anaesth. In press) This relationship mimics the effects seen in studies of erythropoietin on exercise capacity. A better understanding of the effect of anaemia and transfusion on exercise physiology will help guide transfusion triggers in different circumstances.
Summary: Oxygen delivery depends on red cell physiology as well as haemoglobin levels and the effect of storage changes in transfused blood may affect these more subtle functions. Triggers for transfusion should take into account likely demands on individual physiology and the effect on quality of life.

Keywords Anaemia, Microvascular, Anaerobic threshold
Conflict of interest No

Monday 21 October **1030-1130**
ANZSBT/Nurses Combined Symposium: Anaemia and Transfusion **Central Hall A**

Preoperative Anaemia Clinics

Joseph Thomas
Strategic Healthcare Group, Indianapolis, USA

The incidence of preoperative anemia in elective surgical patients with a large anticipated blood loss is significant. Anemia and transfusion in the post-surgical patient has been associated with a higher incidence of complications, including infection, a longer hospital stay and increased perioperative mortality. In addition to the type and complexity of surgery, the universal predictors for transfusion requirements are preoperative anemia and a preexisting coagulopathy. Establishing formal protocols for the recognition and management of anemia will ensure that patients are screened prior to surgery and promptly treated if necessary. This program will review logistic challenges that are often encountered by clinicians working to improve preoperative anemia management practices. Best practice preoperative anemia management strategies that have been utilized to reduce the need for perioperative transfusion and optimize patient outcomes will also be reviewed in this program.

Keywords Preoperative, anemia, patient blood management
Conflict of interest Employee of Strategic Healthcare Group

Monday 21 October **1030-1130**
ASTH Symposium 4: Thrombophilia Testing: Is It Worthwhile? **Central Hall C**

Thrombophilia Testing: Is It Worthwhile? Against

Joanne E Joseph
St Vincent's Hospital and University of NSW, Sydney, NSW, Australia

In order for something to be considered "worthwhile" it must be "worth the time, money or effort that is spent on it" and must have some "value or importance". In relation to a particular investigation (such as thrombophilia testing), this would imply that the test result would be informative in establishing a diagnosis, calculating a response to therapy or predicting a recurrence. Thrombophilia testing is performed on a large scale in patients with venous thromboembolism (VTE) and whilst abnormalities are frequently found, the benefits of performing such testing have not been demonstrated and to date, no randomized controlled trials or controlled clinical trials have assessed the benefit(s) of testing for thrombophilia on the risk of recurrent VTE. Until such time that a benefit can be shown, it would appear that in general, thrombophilia testing is NOT worthwhile.

Keywords Thrombophilia Testing
Conflict of interest No

Monday 21 October **1030-1130**
ASTH Symposium 4: Thrombophilia Testing: Is It Worthwhile? **Central Hall C**

Thrombophilia Testing - Is It Worthwhile? - For

Beverley Rowbotham
Sullivan Nicolaides Pathology, Brisbane, QLD Australia

Thrombophilia testing, or genetic screening for susceptibility to venous thromboembolism typically includes testing for AT, PC, PS deficiency, Factor V Leiden and F2 20210A. Despite the wide spread use of this testing over almost 20 years, there is no consensus about who qualifies for testing, its clinical validity and utility. There are, however, patients in whom such testing is clearly of values as it allows them to avoid high risk situations or to utilise targeted prophylaxis if a high risk event can not be avoided.

New research suggests that genome wide association studies will build on the current understanding of the pathogenesis of thrombosis and raise the prospect that risk profiles for development of venous thrombosis can be further refined.

A new perspective is provided by research describing patients' attitudes to medical testing and screening, including genomic screening. These are often positive and patients may perceive a failure to offer testing or screening as an attempt to deny them information about their risk profile for disease and the opportunity to play a role in the management of their health. This perspective may be neglected in the traditional health technology assessment process.

The issue for debate is not whether thrombophilia testing is worthwhile, but for whom is it worthwhile?

Keywords Thrombophilia testing patient
Conflict of interest None

Monday 21 October **1130-1230**
HSANZ: Carl de Gruchy Oration **Auditorium (Arena B)**

My Journey Into and Through Haematology

Trevor Olsen
Wesley Medical Centre, Brisbane, QLD, Australia

Early in the evolution of Clinical Haematology as a specialty, support and care for patients and their families was poor. It was this realisation that lead to the establishment of the Leukaemia Foundation in Brisbane which has now developed into a fully-fledged national organisation. The Leukaemia Foundation of Australia has become an international benchmark for patient support and advocacy and a peak funding body for research.

Private haematology practice has also grown in this time from an environment where few facilities existed into a corporatised national practice where patient care and supervision is equal to Australia's best.

Monday 21 October **1330-1500**
HSANZ ASTH Combined Presidential Symposium **Auditorium (Arena B)**
O056 **1330**

Targeting Acute Myeloid Leukemia by Dual Inhibition of PI3K Signalling and Cdk9-mediated Mcl-1 Transcription

D Thomas[1], J Powell[1], F Vergez[2], D Segal[3], N Nguyen[4], A Baker[4], T Teh[4], E Barry[1], J-E Sarry[2], E Lee[5], T Nero[6], A Jabbour[3], G Pomillio[4], B Green[4], S Manenti[2], S Glaser[3], M Parker[6], A Lopez[1], P Ekert[3], RLock[5], D Huang[3], S Nilsson[4], C Récher[2], A Wei[4,7], M Guthridge[4]
[1] Division of Human Immunology, SA Pathology, Adelaide, SA [2] Cancer Research Center of Toulouse, France [3] Walter and Eliza Hall Institute, Melbourne, Vic [4] ACBD, Monash University, Melbourne Vic [5] Children's Cancer Institute Australia for Medical Research, Sydney, NSW [6] St Vincent's Institute of Medical Research, Melbourne, Vic. [7] Haematology Dept, Alfred Hospital, Melbourne, Vic

Aim
To determine the mechanism of action of PIK-75, which induces potent apoptosis in genetically diverse acute myeloid leukemia (AML).
Results
Resistance to cell death is a hallmark of cancer and renders transformed cells resistant to multiple apoptotic triggers. Mcl-1 is a key driver of cell survival in diverse cancers, including AML. A screen for compounds down-regulating Mcl-1 identified the kinase inhibitor, PIK-75, which demonstrates marked pro-apoptotic activity against cytogenetically diverse primary human AML patient samples. We show that PIK-75 blocks Cdk7/9, leading to transcriptional suppression of MCL-1 protein, alleviating its inhibition of pro-apoptotic Bak. PIK-75 also targets PI3K, which disrupts the association between Bcl-X_L and Bak. The simultaneous loss of both inhibitors of Bak causes rapid apoptosis of AML cells. AML samples lacking Bak were concordantly resistant to PIK-75 killing. Modeling revealed a flexible PIK-75 core linker region allowing it to structurally bind both Cdk9 and PI3K tightly.
Conclusions
PIK-75 significantly reduced leukemia burden and increased the survival of mice engrafted with human AML without inducing overt toxicity. Future efforts to co-target PI3K and Cdk9 with drugs such as PIK-75 in AML are warranted.

Keywords AML, PI3K, Cdk9, apoptosis, Bak
Conflict of interest None

Monday 21 October **1330-1500**
HSANZ ASTH Combined Presidential Symposium **Auditorium (Arena B)**
O057 **1345**

The Depth of *in vivo* Kinase Inhibition Achieved Over the First Month of Nilotinib Therapy Predicts For Subsequent Molecular Response, and Is Closely Related to Nilotinib Plasma Levels

Deborah L White[1,2,3], Verity A Saunders[1], Laura N Eadie[1,2], David Yeung[2,4], Timothy P Hughes[4,3,2,1]
[1] Cancer Theme, SAHMRI, Adelaide, SA, Australia [2] Department of Medicine. University of Adelaide, Adelaide, SA, Australia. [3] Centre for Cancer Biology, Adelaide.[4] SA Pathology, Adelaide, SA, Australia

Aim/Background
The degree of *in vivo* kinase inhibition achieved over the first month of imatinib (IM) therapy is an excellent predictor of subsequent molecular response. Patients achieving >50% *in vivo* kinase inhibition all achieved major molecular response (MMR) by 24 months compared to 56% of patients with <50% *in vivo* kinase inhibition (*p<0.001*). (White JCO 2007). To date, no biomarker which accurately predicts response to nilotinib (NIL) has been reported.
Methods
We have examined the level of *in vivo* kinase inhibition over the first month of nilotinib therapy in a cohort of 70 CP-CML patients in Australia.
Results
A significantly higher proportion of NIL treated patients achieved ‡50% *in vivo* kinase inhibition over the first month of treatment compared to IM treated patients (75% vs 45%. p<0.001). 59 patients are to date examinable at 12 months. A significantly higher proportion of patients (94%) with high *in vivo* kinase inhibition achieved MMR by 12 months when compared to patients with low *in vivo* kinase inhibition (71%)p<0.001. There was a strong correlation between drug levels achieved over the first month of therapy, and *in vivo* kinase inhibition for NIL (p<0.001), but not IM (p>0.05), suggesting early dose intensity may be the key factor for NIL response. IM drug levels >1000ng/ml are associated with a higher rate of MMR. In these NIL treated patients early drug levels (first month) were strongly predictive of MMR by 12 mo (<1000ng/ml – 79% vs >1000ng/ml – 96%. p=0.009).
Conclusion
Preliminary analysis of this cohort of NIL treated patients strongly suggests that the *in vivo* kinase inhibition achieved is higher than observed with IM, and is a significant factor for subsequent molecular response. Importantly the plasma levels achieved over the first month of NIL therapy appear to be a key factor in the achievement of both early *in vivo* kinase inhibition and subsequent response.

Keywords Nilotinib, kinase inhibition CML
Conflict of interest DW and TH receive research support from Novartis and BMS

Monday 21 October **1330-1500**
HSANZ ASTH Combined Presidential Symposium **Auditorium (Arena B)**
O058 **1400**

Evaluation of the N Latex Free Light Chain Assay in the Diagnosis and Monitoring of AL Amyloidosis

Peter Mollee,[1,2] Jill Tate[3], Carel J Pretorius[3]
[1]Department of Haematology, Pathology Queensland, Brisbane, [2]School of Medicine, University of Queensland, Brisbane, [3]Department of Chemical Pathology, Pathology Queensland, Brisbane

Background
We compared a novel assay for free light chain (FLC) quantitation based on monoclonal antibodies (N-Latex, Siemens, Germany) to the established polyclonal antibody-based assay (Freelite™, The Binding Site, UK) in AL amyloidosis.
Methods
Sixty-two diagnostic samples were analysed on a BNII nephelometer, 32 of which also had a post-treatment sample.
Results
In the diagnostic samples: for AL of kappa type, the median involved FLC (iFLC) was significantly lower by the N-Latex assay (289 vs 667mg/L, p=0.0002) whereas for lambda AL the values were similar (148 vs 161mg/L, p=0.84). Measurable disease, defined as a difference between involved and uninvolved FLC (dFLC) >50mg/L was present in 82% by the N-Latex assay compared to 89% by the Freelite™ assay. For diagnostic sensitivity, the FLC ratio was normal in 21% (95% CI, 12-33%) and 15% (95% CI, 7-26%) of patients by the N-Latex and Freelite™ assays, respectively. The combination of serum and urine immunofixation electrophoresis with either FLC assay allowed identification of the amyloidogenic clone in 98% producing comparable sensitivity. For the monitoring samples the median reduction in dFLC was 68% for the N-Latex assay and 77% for the Freelite™ assay (p=0.04). This led to some differences in assigning response categories. Partial response as assigned by both assays predicted overall survival (N-Latex p=0.0015, Freelite™ p=0.022).
Conclusion
There are differences between FLC as measured by the N-Latex and Freelite™ assays, but overall the two assays have similar diagnostic sensitivity. Disease response calculated by both assays predicts survival but more clinical validation is required.

Keywords Amyloidosis, free light chain assay, diagnosis
Conflict of interest Siemens Healthcare supplied N Latex FLC kits free of charge for this study.

HSANZ ASTH Combined Presidential Symposium **Auditorium (Arena B)**

O059 **1415**

Necrotic Platelets Play a Role in Occlusive Thrombi

Minh Hua, Philip J Hogg, Vivien Chen
Lowy Cancer Research Centre, UNSW, Prince of Wales Hospital, Sydney, NSW

Background & Aims
Platelets express heterogeneity within a thrombus with a subset able to support coagulation. The procoagulant platelet had been proposed to be necrotic. Due to overlap in markers of platelet activation and necrosis, the functional relevance of necrotic platelets has not yet been defined. We have recently shown that tagged-GSAO a trivalent arsenical labels a highly activated platelet subpopulation with features of necrosis. We aim to use this compound to explore the functional role of necrotic platelets in *in vitro* and *in vivo studies*.

Methods
In vitro: Flow cytometric analysis of washed human platelets subjected to agonist stimulation, co-labelled with tagged-GSAO & activation markers. In some studies platelets were preincubated with inhibitors of apoptosis or necrosis pathways. *In vivo*: Thrombus was initiated by $FeCl_3$ (collagen & thrombin dependent) or laser injury (thrombin dependent) in murine models in presence of tagged-GSAO, fluorescent platelet and calcium signal markers. Images of real time thrombus formation using confocal intra-vital microscopy were constructed in 3D.

Results
Collagen & thrombin activation generated a subpopulation dual +ve for P-selectin & tagged-GSAO, with features of necrosis: dependence of exogenous calcium, loss of calcein retention and high Annexin-V. GSAO tagged a subpopulation with very high fibrinogen & P-selectin binding suggesting that necrotic platelets are derived from highly activated platelets. Dependence on mitochondrial pathways of necrosis was shown by cyclophilin-D inhibition: %GSAO+ platelets decreased 61% in presence of 2μM cyclosporine A ($p<0.001$). No change in %GSAO+ platelets with pancaspase inhibition (ZVAD-FMK) ($p=0.5677$) indicating intrinsic apoptosis pathways are not involved. In vivo murine studies detected tagged-GSAO in occlusive platelet aggregates initiated by 10% $FeCl_3$, but not in non-occlusive laser injury induced thrombi. The GSAO+ thrombi co-localize with Rhodamine-2 consistent with high sustained calcium of cell death. This suggests platelets undergo necrosis in thrombi induced by certain stimuli and may be associated with occlusive clot.

Conclusion
We propose that platelet necrosis occurs when platelets undergo high level activation, and are seen in occlusive thrombi, potentially converting a haemostatic clot to pathological thrombi. Tagged-GSAO is a tool for exploring the role of necrotic platelets in thrombus formation and a potential biomarker predictive of thrombotic risk in clinical disease states.

Keywords Platelet, Activation, Necrosis **Conflict of interest** None

HSANZ ASTH Combined Presidential Symposium **Auditorium (Arena B)**

O060 **1430**

Tractopods Are Novel Platelet Glycoprotein IIbIIIa Dependent Adhesion StrucTures That Are Dysregulated in Diabetes and Chronic Oxidative Stress

James McFadyen[1], Saheb Al-Daher[1], Warwick Nesbitt[1], Imala Alwis[1], Katrina Ashworth[1], Simone Schoenwaelder[1], Yuping Yuan[1], Mark Cooper[2], Shaun Jackson[1]
[1]Australian Centre for Blood Diseases, Monash University, Melbourne, VIC, Australia [2]Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Background
Diabetes mellitus is one the major healthcare problems of the 21st century with over 80% of diabetes-related deaths due to atherothrombosis. Platelets are central to this process although the mechanisms by which diabetes dysregulates platelet adhesive function remains incompletely understood. Utilising human platelets from individuals with diabetes as well as mouse models of diabetes and chronic oxidative stress, we have investigated the mechanisms responsible for platelet hyperactivity and resistance to standard anti-platelet therapies.
Results
Utilising a high-resolution intravital imaging system we have been able to investigate for the first time platelet adhesion structures at the submicron scale in vivo. Analysis of platelet-endothelial interactions in mouse mesenteric veins has demonstrated that discoid platelets utilise two distinct membrane structures to adhere to the vessel wall. One of these involves classical membrane tethers, whereas a second structure, termed tractopods (Latin: *tractus* – to pull; Greek; *pod* – foot; tractopod = pulling foot), represents a previously unidentified platelet adhesion structure. Studies on transgenic mice lacking GPIb confirmed a key role for this receptor in mediating tether formation, whereas tractopods were primarily mediated by GPIIb-IIIa. Studies utilising TIRF microscopy and electron microscopy demonstrate that tractopods are dynamic actin- and microtubule-containing membrane anchors that are regulated by GPIIb-IIIa signalling processes, independent of TxA2 and ADP. Tractopods are markedly upregulated in diabetes and in mouse models of chronic oxidative stress ($GPx1^{-/-}$ and $ACE2^{-/-}$), leading to increased platelet-vessel interactions in vivo. Significantly, tractopods have limited sensitivity to standard anti platelet agents, however the novel anti-platelet agent (TGX221- a PI3Kβ inhibitor) markedly reduces the level of platelet adhesion in diabetic platelets.
Conclusion
These studies define a novel platelet membrane adhesion structure mediating platelet-endothelial interactions in vivo. Tractopods are redox sensitive, display enhanced adhesiveness in diabetes and have limited sensitivity to standard antiplatelet agents. Inhibition of PI3Kβ signalling may represent an attractive approach to reduce tractopod adhesion and diabetic platelet hyperactivity.
Keywords Platelets; Diabetes; oxidative stress
Conflict of interest None

Monday 21 October **1330-1500**
HSANZ ASTH Combined Presidential Symposium **Auditorium (Arena B)**
O061 **1445**

"Fast-track" Rapid Warfarin Reversal to Facilitate Elective Surgery: Extending the Safety and Efficacy Profile to High-risk Patients With Cancer

Kate Burbury[1], Tim Byrne[2], Hilmy Ismail[2], Alexander Heriot[2], Ray Dauer[1], David Westerman[1], John F Seymour[1,3], Kay Kenchington[2], Bernhard Riedel[2]
[1]Division of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. [2]Division of Cancer Surgery, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia. [3]University of Melbourne, Parkville, VIC, Australia

Background
Peri-procedural management of patients on long-term warfarin remains a common and important management dilemma, with a lack of high-quality data guiding this complex process. A more convenient and reliable method, utilizing low-dose intravenous vitaminK ($VitK_{IV}$), shown to be safe and efficacious in a general elective surgical population, has been expanded to surgical procedures in cancer populations who are at high-risk of both thromboembolism and bleeding to demonstrate safety, efficacy and utility of fast-track warfarin reversal and validation of the process.
Methods
A prospective, single-arm study, at a dedicated cancer centre, patients on warfarin with planned surgery, were administered 3mg $VitK_{IV}$ 18-24 hours prior to procedures. Primary outcomes were safety, efficacy and correlation of vitK-dependent factor levels.
Results
71 patients underwent 82 episodes of active warfarin reversal, expanding the cohort experience to 260. No patient suffered an adverse reaction to $VitK_{IV}$, 99% achieved INR≤1.5 on the day of planned surgery. All proceeded to surgery without deferment. One patient (with recurrent thromboembolism and suboptimal INR prior to reversal) suffered a DVT, day 9 post-procedure, while on bridging heparin. The 7 procedural-related bleeding episodes, were attributable either to the surgical procedure or "over-anticoagulation" with post-operative bridging heparin and warfarin recommencement. $VitK_{IV}$ restored INR and VitK-dependent factor activity for surgery — with a predictable pattern of depletion/repletion with warfarin therapy and subsequent reversal, respectively.
Conclusion
The efficacy, safety, reliability and convenience of this process have rendered it standard care for peri-procedural warfarin management at a number of Australian health institutions and endorsement by Australian/New Zealand consensus guidelines.
Keywords Warfarin; peri-procedural anticoagulation **Conflict of interest** None

Monday 21 October **1330-1500**
ANZSBT Symposium 2: Patient Blood Management **Central Hall A**

Patient Blood Management (PBM): Current Status and Future Directions

Mark A Popovsky
Haemonetics Corporation & Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, USA

PBM involves the avoidance of blood transfusion to a patient who does not need one and providing the right product at the right time, in the right dose, to the right patient who does. Observed variation in transfusion practice in procedures including CABG and orthopedic surgery is often inexplicable from an evidence-base perspective. Despite improved safety measures, the risks of blood transfusion are not insignificant, of which transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and immunomodulation are the most significant. Allogeneic blood transfusion is associated with poorer outcomes, including infection, increased length of stay and increased ventilation time. Prospective randomized, controlled studies (TRICC, FOCUS) do not demonstrate a benefit for blood transfusion at Hgb >7-8g/dl. PBM should be a multidisciplinary & multimodality approach. The key elements include: 1) correction of preoperative anemia and management of iatrogenic anemia; 2) lowering the transfusion "trigger" in stable, asymptomatic patients; 3) use of single RBC transfusions followed by assessment; 4) reducing inappropriate FFP transfusions; 5) use of transfusion alternatives (i.e. cell salvage); 6) use of technology to assess hemostasis (i.e.Thromboelastography); 7) hemostatic agents in surgery. New data extraction tools are now available which make accurate data accessible on transfusion practice on a timely basis. These tools provide the linkage between transfusion decisions by clinicians & clinical outcomes. These tools lead to improved patient care and reduced costs. By comparing best practices involving comparable patients and procedures, the quality of transfusion care improves. Future work must focus on mitigating the storage lesion and using "high value" blood components.

Keywords Patient blood management
Conflict of interest Employee of Haemonetics Corporation

Monday 21 October **1330-1500**
ANZSBT Symposium 2: Patient Blood Management **Central Hall A**

Transfusion Safety Officer's Role in Patient Blood Management

Joseph Thomas
Strategic Healthcare Group, Indianapolis, USA

Physicians and nurses order and administer most of the millions of blood products that are transfused each year throughout the world. While health care resources and the public have focused on the safety of the blood product itself, the actual process of transfusion, from physician ordering practices to nursing administration, has received very little attention. International audits have identified significant gaps in clinical knowledge and proficiency related to the transfusion process, raising significant patient safety concerns. An emerging role, the Transfusion Safety Officer (TSO), has been established in hospitals to close these identified gaps and optimize transfusion safety. The roles and responsibilities of the Transfusion Safety Officer will be explored in the presentation, including a day in the life of a TSO. The compelling need for TSOs as part of a comprehensive blood management program will also be explored during this presentation.

Keywords Transfusion safety officer, transfusion safety, patient blood management
Conflict of interest Employee of Strategic Healthcare Group

Monday 21 October **1330-1500**
ANZSBT Symposium 2: Patient Blood Management **Central Hall A**

Blood Utilisation Studies

Jonathan P Wallis
Department of Haematology, Freeman Hospital Newcastle upon Tyne, UK

Variation in blood use per head of population between different countries is striking. In western style health systems the use of red cells varies 2 fold from 30 to 60 units per 1000 population per year. Platelet and plasma use vary even more. Adjusting transfusion rates for the demographic structure of the population can eliminate some of this variation and allow more accurate comparison of transfusion rates between countries. However population demographics and local factors can only explain some of these differences.

In the North East of England we have monitored red cell use by indication over 10 years and have observed very substantial reduction in surgical transfusion rates mainly due to acceptance of lower post operative transfusion triggers (Tinegate et al., Transfusion 2013; 53:483-9). Evidence from clinical studies suggests that this is safe. Transfusion for medical indications has changed little over the same periods and other than for Gastro-intestinal bleeding, there is a dearth of clinical trials to guide red cell transfusion practice in medical patients , especially those with bone marrow failure.

Over the 10 years in which the overall use of red cells has declined, in the UK we have seen an increase in platelet use that is currently about 4.5 units per 1000 population per year. A regional survey shows that the majority of units are given as prophyllaxis for patients with bone marrow failure. In some countries surgical use is much higher especially in cardiac departments.

At present we cannot say for certain what is the ‘correct’ transfusion rate for red cells or platelets. Comparative transfusion epidemiology can however help inform blood services of areas of possible overuse and underuse. Accurate data and observation by others can be powerful effectors of change in themselves.

Keywords Transfusion rates, demographics, international
Conflict of interest None

Monday 21 October **1330-1500**
Nurses Symposium 4: Panel Discussion **Meeting Rooms 5/6**

Myeloma in the Matrix – Quest for the Oracle

Tracy King[1,2], Toni Lindsay[3], Kari Mudie[4], Kate White[1], Carmel Woodrow[5]
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[2] *Institute of Haematology, Royal Prince Alfred Hospital, Sydney, NSW, Australia*
[3] *Psycho-oncology Service, Royal Prince Alfred Hospital, Sydney, NSW, Australia*
[4] *Apheresis Unit, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia*
[5] *Cancer Services, Princess Alexandra Hospital, Brisbane, QLD, Australia*

Multiple Myeloma (MM) remains a cancer characterized by significant heterogeneity, increasingly complex and advancing treatment schedules, significant morbidities and toxicities associated with therapy and no curative intent. The heterogeneity in outcomes alongside an ever changing treatment pathway allow for significant uncertainty experienced by the patient and their family and friends. Nurse's role in the delivery of best supportive care often focuses on helping those affected by myeloma to manage significant uncertainty, disease related morbidities (bone, renal and immune) and ongoing and often concurrent toxicities that occur, and are experienced at an individual level.

This comprehensive case presentation will explore the complex nature of one patients' unique journey with myeloma. The clinical case will be presented in detail alongside the personal experiences of the patient as he learns to live with myeloma through a range of intensive treatment modalities. The session will utilize a panel of nursing and allied health specialists to help deconstruct and explore the symptoms, toxicities and psychological effects whilst proposing examples of best supportive care offered. There will be a focus on peripheral neuropathy, role of plasma exchange, stem cell collection in high risk groups, psychological effects of steroids, coping with uncertainly and the patient's central role in self management and learning to live well with myeloma.

Objectives
It is anticipated that this session will allow for participants to better appreciate and identify the complex supportive care needs of those affected by MM and to develop skills and strategies to help manage these needs through the various stages of a diagnosis of MM.

Keywords Myeloma, supportive care, case presentation
Conflict of interest: None

Monday 21 October **1530-1630**
Combined HSANZ/ASTH Symposium: New Antithrombotic Therapies
Auditorium (Arena B)

An Update on Antiplatelet Therapy

Marco Cattaneo
Medicina 3, Ospedale San Paolo. Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

The interaction of ADP with its platelet receptor P2Y12 plays a crucial role in platelet activation and thrombogenesis. This article reviews the pharmacology and clinical trials of specific antagonists of P2Y12.

Clopidogrel is a thienopyridine with proven antithrombotic efficacy, but it has some important drawbacks: i) it is a pro-drug that needs to be metabolized to its active metabolite; ii) it has a delayed onset and offset of action; iii) there is high inter-individual variability in pharmacological response.

Prasugrel is also a thienopyridine, with faster onset of action and more uniform inhibition of platelet function compared to clopidogrel, accounting for lower incidence of ischemic events in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) and higher incidence of both non-CABG related bleeding complications.

Two direct and reversible P2Y12 antagonists, Cangrelor and Ticagrelor, are characteriSed by rapid onset and reversal of platelet inhibition. Cangrelor may be particularly useful for bridging patients on antiplatelet treatment who need to undrgo CABG surgery. Ticagrelor proved to be superior to clopidogrel in preventing major adverse cardiac events (MACE) in ACS patients, but, like prasugrel, was associated with higher frequency of non-CABG-related bleeding complications. Importantly, the incidence of cariovascular and total mortality in ticagrelor-treated patients was significantly lower than in clopidogrel-treated patients. In addition to inhibiting P2Y12, ticagrelor inhibits the intracellular clearance of adenosine. The resulting increase in extracellular adenosine may have additional therapeutic effects, because it enhances coronary blood flow and further inhibits platelet function.

Because P2Y12 regulates the pro-inflammatory effect of platelets, P2Y12 inhibitors may have clinically relevant anti-inflammatory effects.

Keywords Thienopyridines, ticagrelor, P2Y12
Conflict of interest Lecture and advisory board honoraria, research support by Eli Lilly, Daiichy Sankyo, AstraZeneca, The Medicnes Company, Sanofi Aventis.

Monday 21 October **1530-1630**
Combined HSANZ/ASTH Symposium: New Antithrombotic Therapies
Auditorium (Arena B)

New Oral Anticoagulants

David Keeling
Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, United Kingdom

Heparin (unfractionated and low molecular weight) and vitamin K antagonists have been the mainstay of anticoagulant therapy for decades. We are now entering a new era of anticoagulation. The new oral anticoagulants are direct inhibitors of either thrombin (dabigatran) or factor Xa (e.g. rivaroxaban, apixaban). These oral direct inhibitors (ODIs) are given in fixed dose with no monitoring and have been compared with warfarin for treatment and secondary prevention of DVT and PE and for stroke prevention in atrial fibrillation. They are not recommended for patients with mechanical heart valves.
The trials in VTE and PE will be examined.
The use of these new drugs raises several issues including:

- adherence
- their effect on routine coagulation tests
- how to measure the degree of anticoagulation (when necessary)
- their use peri-operatively
- the issue of their non-reversibility and treatment of major bleeds
- which anticoagulant to use for each indication as choice increases

These issues will be explored in this session.

Keywords new anticoagulants
Conflict of interest I have received honoraria for attending Advisory Boards from Pfizer, Bayer, Boehringer Ingelheim, Daiichi-Sankyo

Monday 21 October **1530-1630**
ANZSBT Symposium 3: Age of Red Cells **Central Hall A**

The RBC Storage Lesion and Strategies for Its Mitigation

Mark A Popovsky
Haemonetics Corporation & Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, USA

While a large number of number of retrospective studies associate allogeneic RBC with worse clinical outcomes (i.e. increased morbidity and mortality, infection rate), this is a highly controversial area. Per unit of RBC transfused, the risk of perioperative infection in cardiac surgery may increase 29% ($p < 0.001$). Randomized, prospective studies are ongoing in an attempt to answer the "old blood/new blood" question. It is likely that older RBC have negative effects on select clinical populations (e.g., critical care, older patients). Complex biochemical, morphological and cellular changes that take place during liquid RBC storage. As RBC age viscoelastic changes occur which impair transit through the microvascular bed. Compared with fresh RBC, 28 day old RBC demonstrate a 68% reduction in oxygen delivery. While there is significant variation from donor to donor, the general pattern includes the following: 1) changes which affect vascular tone by scavenging or preventing the synthesis or preventing the synthesis of nitric oxide (e.g., free hemoglobin, microparticles, release of ATP, asymmetric arginine); 2) clearance of stored intact RBC that induces cytokine storm in the transfusion recipient; 3) generation of pro-coagulant activity; 4) generation of eicosanoids (prostaglandins, leukotrienes). Hemolysis and ferric compounds have been implicated as possible important suppressors of macrophage function. These changes are relevant because blood is frequently overused (by 25-40%) and older RBC are frequently transfused. Studies from the USA suggest that 25% of RBC are older than 28 days. In addition to being immunosuppressive, allogeneic blood is also pro-tumoral. This may explain why cancer recurrence in transfused colon cancer patients is significantly increased. If subsequent studies confirm the deleterious impact of older-stored RBC on at least select transfusion recipients, transfusionists have several options to improve patient care: 1) modify the supply chain so that fresher RBC are transfused; 2) reduce the storage lesion. Modifying the supply chain will require better informatics between blood center and hospital, so that the blood center can "visualize" the blood inventory and a "just in time" delivery system is adopted. Remote electronic refrigeration tied to the hospital information systems are available to enable this approach. A new red cell storage solution (SOLX®) has been developed which decreases microparticle formation, increases ATP levels and improves by 30% red cell recovery and survival. Solutions like SOLX may represent the direction for transfusion medicine to improve red cell quality.
Keywords Storage lesion, Red cell storage solution, SOLX
Conflict of interest Employee of Haemonetics Corporation

Monday 21 October **1530-1630**
ANZSBT Symposium 3: Age of Red Cells **Central Hall A**

Red Cell Storage Lesion – Product Implications

Rosemary L Sparrow
Research & Development, Australian Red Cross Blood Service, Melbourne, Victoria, Australia

Concerns about the “age of blood” have invigorated interest to better understand the biological effects of storage on the quality of red cell components. Recent laboratory-based research is providing new insights not only into the physico-biochemical changes that occur to red cells during storage, but also the potential implications of these changes following transfusion, particularly for critically ill patients. It is recognised that red cells are not simply vehicles that transport oxygen, but have a critical role in blood rheology and can influence immunological, thrombotic and vascular responses directly or indirectly. Refrigerated storage of red cells subjects the cells to non-physiological conditions. Variability in how well a particular red cell component maintains “freshness” is an added dimension to the complexity of understanding the effects of storage on the quality of red cell components.

This brief presentation will focus on aspects of our red cell storage lesion research and point to potential future strategies that could be considered to further enhance the quality of red cell components.

Keywords red cells, storage lesion, transfusion
Conflict of interest None

Monday 21 October **1530-1630**
ANZSBT Symposium 3: Age of Red Cells **Central Hall A**

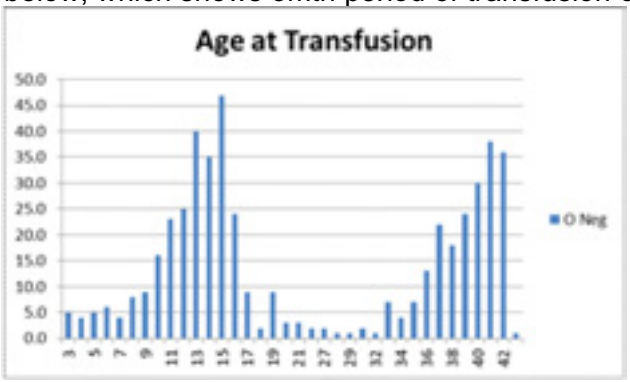
The Impact of Reduced Shelf-Life on the Red Cell Supply Chain in Australia

Stuart Chesneau
Australian Red Cross Blood Service, Melbourne, VIC, Australia

The Australian Red Cross Blood Service (the Blood Service) issued 763,550 red cells to Health Providers in 2012/13 at an average age at issue of 9 days, allowing a further 33 days of usable life for a standard red cell. In the event of a reduced shelf-life of, say, 28 days there would be implications in cost and risk management at both the Blood Service and the Health Providers. Some examples are:

Blood Service – Though the average age at issue was 9 days, there was a wide distribution of ages across issued stock with 36% being issued at greater than 10 days old. To reduce that spread and to increase usable life, there would need to be a reduction in inventory held. This would increase risk of shortages, which would only be mitigated by increasing the reliability form day-to-day of stock entering inventory. This would be achieved by smoothing collection volumes across the week, meaning greater weekend collection targets at increased cost. The reduction in inventory would increase stock turn, already considerable at just over 60.

Health Provider – The reduction would be felt most at the Health Provider end and would test their current waste management strategies. In a hub and spoke network, it is common for the spoke hospital to receive conservative levels of inventory and to recycle any unused stock to the hub hospital to maximise the opportunity of transfusion. This results in the double hump of transfusion evident in the chart below, which shows 3mth period of transfusion of O Neg at a hub hospital.



The first wave is from stock received from the Blood Service, the second is recycled from spokes. The multiple depot approach to inventory management would be challenged in a reduced shelf-life scenario and would need rigid controls. The likely outcomes would be greater wastage at the spoke hospitals and higher costs due to more frequent transfers of smaller volumes between sites.

In general, a reduced shelf-life would bring a number of challenges to the blood sector supply chain in regards to inventory and risk management and would result in a higher per unit cost.

Keywords Inventory, Stock turn, Waste
Conflict of interest None

Monday 21 October **1530-1630**
Nurses Workshops (Session A) **Meeting Room 5**

1 How To Make a Practice Change Using a Time Out Checklist Tool

Diana Moore
Mater Health Services, Brisbane, QLD, Australia

Aim/Background
It has been acknowledged that patients do suffer unintended harm as a result of diagnostic, treatment, and communication failures. Adverse events more commonly are caused by failures in systems and processes that lead individuals to make errors or fail to correct them before they reach the patient. In Australia today approximately 1 in 10 patients suffer an adverse event during a hospital admission. The ability to successfully treat patients with cancer has resulted in multiple courses of chemotherapy being given over a prolonged period in a variety of treatment settings changing the disease trajectory. Cancer chemotherapeutic agents are one of several categories of medications that have a high risk of causing significant patient harm due to many agents having a limited margin for error in dosing and are toxic even at therapeutic doses. Therefore the risk of error exists every time chemotherapy doses are calculated, prescribed, transcribed, prepared and administered. A chemotherapy incident that caused significant harm was reviewed using the root cause analysis (RCA) process and identified that a final barrier was required at the bedside leading to a timeout checklist being developed. The timeout checklist tool has provided our unit with the ability to ensure all nurses administering chemotherapy have permission to stop and ask the question have all tasks been completed before they proceed with chemotherapy.
Results
The timeout checklist tool was implemented in 2010 and clinical audits have been conducted at three time points revealing that the checklist was being used 100% of the time. Compliance rate for completing the checklist was: T1 88%; T2 100%; T3 100%. However there are inconsistencies in documentation of the allergy/history check.
Conclusion
Creating cultures of safety requires a fundamental shift in the behaviours of healthcare leaders, clinical teams and healthcare professionals challenging them to accept that even the most highly skilled, highly trained health care professional will make mistakes. The benefits of a time out checklist are threefold: i) a discipline in how we check chemotherapy has been enforced; ii) a culture for medication safety has been created; and iii) an educational tool for novice nurses.

Keywords chemotherapy errors, checklist tool, patient safety
Conflict of interest No conflict of interest to disclose

Monday 21 October **1530-1630**
Nurses Workshops (Session A) **Meeting Room 6**

2 Writing Conference Abstracts and Giving Conference Presentations: Strategies for Success

Alexandra McCarthy
School of Nursing and Institute of Health and Biomedical Innovation, Queensland University of Technology & Division of Cancer Services, Princess Alexandra Hospital, Brisbane, QLD, Australia

The aim of this seminar is to discuss the:

- Characteristics of an effective presentation
- Characteristics of a winning abstract
- Strategies for oral preparation and presentation
- Using visual aids
- Managing questions

Keywords Abstract writing, conference presentation
Conflict of interest None

Monday 21 October **1530-1630**
Nurses Workshops (Session A) **Meeting Room 7**

3 How To Make The World Your Oyster – Maximising Your Opportunities In Haematology Nursing

Kate White
Cancer Nursing Research Unit, Royal Prince Alfred Hospital, Camberdown, NSW, Australia

Abstract not available at time of going to print

Monday 21 October **1530-1630**
Nurses Workshops (Session A) **Meeting Room 8**

4 Receptivity: Strategies for Engaging Individuals in Supportive Care

Pam McGrath
Griffith Health Institute, Griffith University, Brisbane, QLD, Australia

Considerable progress has been made in documenting the psychosocial needs of cancer patients and their families. However, recent research indicates the importance for supportive care service delivery planning of moving from a needs-based perspective to one that also embraces the notion of receptivity. Receptivity is defined as the range of factors (individual, social, and geographical) that impact on an individual's desire or ability to receive or engage with supportive care services designed to meet his or her needs. The presentation will provide examples of how notions of receptivity impact on service delivery and program development decision-making. Recent research findings will be presented on factors that facilitate or obstruct receptivity to supportive care. The ideas will be applied to a case example of planning for a support group for haematology patients. The presentation concludes with a range of supportive care initiatives that are designed to meet the challenge of finding innovative strategies that address receptivity factors to ensure supportive care services reach those in need.

Keywords Receptivity, supportive care, qualitative research
Conflict of interest No

Monday 21 October **1530-1630**
Nurses Workshops (Session A) **Meeting Room 9**

5 How To Overcome Obstacles in Infection Control in a Combined Oncology / Transplant Unit

Jodie Marsh, J Kanakis, M Davidson
The Townsville Cancer Centre, Townsville Hospital, Townsville, QLD, Australia

The intent of this presentation is to look at overcoming obstacles in infection control in a combined Oncology / HPSC Transplant unit. This session will explore outbreak procedures, antibiotic stewardship, protective isolation, environmental cleaning and implementing the use of disposables. The concepts will be based on our experience with a VRE outbreak and the subsequent issues that this created such as increased findings of colonised MRGN and ESBL in patients.

Keywords Infection control
Conflict of Interest None

Monday 21 October **1730-1830**
HSANZ Masterclass 1 **Meeting Room 7**

Myelofibrosis

Srdan Verstovsek
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Myelofibrosis (MF) is a hematologic malignancy characterized by extramedullary hematopoiesis, progressive anemia, bone marrow fibrosis, and osteosclerosis. Symptoms include spleno- and hepato-megaly, progressive anemia and other peripheral blood cytopenias, pruritis, constitutional symptoms, including fatigue, night sweats, and loss of appetite, and bone pain, all of which lead to very poor quality of life. Prognosis depends on several risk factors; International Prognostic Scoring systems have been developed for prognosis assessment. Median survival ranges from 2 to 15 years, depending on the number of negative prognostic factors present. Hydroxyurea has traditionally been the primary choice for cytoreduction and management of splenomegaly. In cases of painful splenomegaly refractory to treatment, splenectomy can be used; however, the procedure is risky. Peripheral blood cytopenias can be treated with androgens, corticosteroids, immunomodulatory agents, and erythropoietin. To date, the only potentially curative treatment is allogeneic stem cell transplantation. However, fewer than 10% of patients are eligible due to comorbidities and advanced age. Patients in transformation to acute leukemia have very poor prognosis but may derive benefit from hypomethylating agent therapy. The discovery of the JAK2 V617F mutation in 50-60% of patients with MF, led to the clinical development of JAK inhibitors. The JAK inhibitor ruxolitinib is the first drug therapy to be shown to consistently improve the signs and symptoms of MF and is so far the only drug therapy approved in the US and Europe to treat MF. Importantly, ruxolitinib is effective regardless of the presence of the JAK2 V617F mutation. Ruxolitinib has been shown to significantly reduce splenomegaly and disease symptoms and improve quality of life, with modest toxicities. Anemia is the main side effect of ruxolitinib; however, with dose reductions and appropriate management, nearly all patients, including those with transfusion-dependent anemia, can be maintained on treatment. In addition to significant improvements in symptom burden, early results suggest that ruxolitinib also prolongs survival, and long-term treatment may slow the progression of bone marrow fibrosis. Newer JAK inhibitors in late-stage clinical development may provide additional options to treat patients with this debilitating disease.

Keywords myelofibrosis, JAK2 V617F, JAK inhibitor
Conflict of interest Research support from Incyte Corporation, Astrazeneca, Lilly Oncology, Roche, Geron, NS Pharma, Bristol Myers Squibb, Celgene, Infinity Pharmaceuticals, YM Biosciences, Gilead, Promedior, SBio.

Monday 21 October **1730-1830**
HSANZ Masterclass 2 **Meeting Room 8**

Aggressive Extranodal Lymphomas

Andrés JM Ferreri
Unit of Lymphoid Malignancies, Department of Onco-Hematology, San Raffaele Scientific Institute, Milano, Italy

Aggressive extranodal lymphomas constitute an heterogeneous group of rare forms of lymphomas that exhibits particular clinical, biological and diagnostic features. Analyzed together, the incidence of these lymphomas is rapidly increasing with respect to nodal counterparts with rates ranging from 3% to 7%/year vs. 1.7 - 2.5%/year. These figures are conditioned by the varied definitions of primary extranodal lymphomas used by different authors. Usually, a primary extranodal lymphoma is defined by the presence of a clinically dominant lesion in the organ defining the extranodal nature of the lymphoma, associated or not to minor additional disease, which should consists of <25% of the total tumour burden. Some authors consider an extranodal lymphoma as “primary” also in the case of involvement of regional lymph nodes. More “relaxed” definitions exist (p.e., with concomitant involvement of other extranodal organs), which result in confusing conclusions from related literature. These varied definitions have also conditioned information about the overall prognosis of extranodal lymphomas. Large retrospective studies seem to suggest a significant worse prognosis of patients with extranodal lymphomas in comparison to patients with nodal lymphoma counterparts when only cases with limited disease were considered, whereas prognosis seems to be better among extranodal lymphomas when cases of advanced disease were considered. Discordant results have been also reported. From a diagnostic and therapeutic points of view, most forms of primary extranodal lymphomas need for specific diagnostic and staging procedures, and some structural, biological and immunological characteristic of the organs where lymphoma arose strongly condition therapeutic choice and outcome. In practice, during this presentation, diagnosis, staging, prognosis, treatment, and outcome of five cases of different primary extranodal lymphomas (CNS, testis, mediastinum, stomach, and vessels) will be discussed.
Investigation of extranodal lymphomas at different sites may provide opportunities to learn more about the host factors and mechanisms involved in the lymphoma development. This may lead to improvements in the clinical management and cure rates.

Keywords Extranodal Lymphoma Treatment

Monday 21 October **1730-1830**
ANZSBT Masterclass 3 **Central Hall A**

Getting Started in Transfusion Research

Simon J Stanworth[1], Zoe McQuilten[2]
[1] *NHS Blood and Transplant/ Oxford University Hospitals NHS Trust*, *Oxford. UK*
[2] *Monash University, Melbourne, VIC, Australia*

In this small interactive session, we will cover the key stages involved in taking forward patient orientated clinical research in transfusion. We will use examples of current research projects, and share ideas on how to progress research questions. The steps required may include:

- Formulating and agreeing the research question,
- Understanding of actual practice,
- Clinician surveys of opinion and interest,
- Patient involvement
- Systematic reviews of previous related research,
- Searches for on-going (registered) studies,
- Trials of feasibility
- Research Team
- Definitive randomized trials.

We will also consider when clinical trials may not be the best form of design. This will introduce the role of registries and data linkage activities.

Keywords clinical research, evidence, blood transfusion
Conflict of interest None

Monday 21 October **1730-1830**
ANZSBT Masterclass 4 **Meeting Room 9**

Effective Use of POC Analysis to Guide Transfusion Support

Sibylle Kozek-Langenecker
Department of Anaesthesia and Intensive Care, Evangelical Hospital, Vienna, Austria

It is not a test itself but rather the therapeutic and/or logistic consequence in patient management following indicative tests results what improves quality of care. The strength of point-of-care coagulation tests (POCT) in bleeding management is the prompt detection of the leading pathomechanism(s) of bleeding which permits fast and targeted correction. Thereby, an early goal-directed bleeding management may prevent further blood loss and transfusion requirements and secondary - by avoiding their respective risks - improve outcome, survival, and cost-effectiveness. The primary outcome benefit of reduced bleeding has been confirmed by a Cochrane review for viscoelastic POCT including rotational thromboelastometry (ROTEM) and thrombelastography (TEG). More recent randomized clinical trials extended this observation for secondary outcome benefits. Accordingly, the evidence-based guideline of the European Society of Anesthesiology ESA on the management of severe perioperative bleeding recommends the application of transfusion algorithms incorporating predefined transfusion triggers to guide haemostatic intervention during intraoperative bleeding (GRADE 1B) and the application of transfusion algorithms incorporating predefined transfusion triggers based on POC coagulation monitoring assays to guide haemostatic intervention during cardiovascular surgery (GRADE 1C).

Point-of-care tests should have only one pipetting step per methodological definition; ROTEM and TEG currently require more steps. These tests, however, deliver indicative test results in a timely manner: clotting time (CT), clot formation time (CFT), amplitude 10 (A10), comparison of these values in corresponding assays (EXTEM – APTEM, EXTEM – FIBTEM, INTEM – HEPTEM) permit differential diagnosis of coagulopathy. Not only the time until initial fibrin strand formation are recorded (similar to the routine plasma-based tests aPTT, PT, TT) but also the dynamics of clot formation and the quality of the clot are analyzed in whole blood. These functional parameters correlate with the risk of bleeding.

Platelet function tests performed at the point-of-care in severe bleeding may facilitate differential indication for desmopressin, platelet transfusion, recombinant factor VIIa versus other procoagulant strategies.

Keywords rotational thromboelastometry, thrombelastography, guidelines
Conflict of interest honoraria for lectures and travel reimbursement from TEM Innovations

Monday 21 October **1730-1830**
ASTH Masterclass 5 **Central Hall C**

Vascular Malformations/Post-Thrombotic Syndrome

Leonardo Brandao
The Hospital for Sick Children, Toronto, Canada

Abstract not available at time of going to print

Monday 21 October **1730-1830**
ASTH Masterclass 6 **Meeting Room 6**

Anti-platelet Drugs

Marco Cattaneo
Ospedale San Paolo. Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

The interaction of ADP with its platelet receptor P2Y12 plays a crucial role in platelet activation and thrombogenesis. This article reviews the pharmacology and clinical trials of specific antagonists of P2Y12.

Clopidogrel is a thienopyridine with proven antithrombotic efficacy, but it has some important drawbacks: i) it is a pro-drug that needs to be metabolized to its active metabolite; ii) it has a delayed onset and offset of action; iii) there is high inter-individual variability in pharmacological response.

Prasugrel is also a thienopyridine, with faster onset of action and more uniform inhibition of platelet function compared to clopidogrel, accounting for lower incidence of ischemic events in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) and higher incidence of both non-CABG related bleeding complications.

Two direct and reversible P2Y12 antagonists, Cangrelor and Ticagrelor, are characteriSed by rapid onset and reversal of platelet inhibition. Cangrelor may be particularly useful for bridging patients on antiplatelet treatment who need to undrgo CABG surgery. Ticagrelor proved to be superior to clopidogrel in preventing major adverse cardiac events (MACE) in ACS patients, but, like prasugrel, was associated with higher frequency of non-CABG-related bleeding complications. Importantly, the incidence of cariovascular and total mortality in ticagrelor-treated patients was significantly lower than in clopidogrel-treated patients. In addition to inhibiting P2Y12, ticagrelor inhibits the intracellular clearance of adenosine. The resulting increase in extracellular adenosine may have additional therapeutic effects, because it enhances coronary blood flow and further inhibits platelet function.

Because P2Y12 regulates the pro-inflammatory effect of platelets, P2Y12 inhibitors may have clinically relevant anti-inflammatory effects.

Keywords Thienopyridines, ticagrelor, P2Y12
Conflict of interest Lecture and advisory board honoraria, research support by Eli Lilly, Daiichy Sankyo, AstraZeneca, The Medicnes Company, Sanofi Aventis.

Monday 21 October **1630-1730**
Nurses Masterclass 7 **Meeting Room 5**

Adherence/ Compliance to Oral Chemotherapy - The Role of Nurses Within the Multiprofessional Team

Monica Fliedner
University Center for Palliative Care, Department of Oncology, University Hospital Bern, Switzerland

The treatment with oral antitumor drugs is nowadays established for a variety of diseases. Initially in oncology it was assumed that patients facing a life-threatening disease would fully comply with the treatment as agreed to. But we now know that also these patients need to learn self-care management strategies to arrange their lives facing an often life-long therapy. The definition of adherence (Haynes et al 1979) is the basis for understanding and managing the potential challenge.

Consequences of non-adherence could be the risk of recurrence of the disease, not reaching the state of remission (stable disease), suffering from side effects and eventually higher health care costs because of additional contacts with health care providers. In the light of multiple risk factors as described by WHO (2003) patients need the motivation and continuous support in the daily intake of the drugs and dealing with the potential aggravating side effects at home.

Using a case study from clinical practice the master class will look at the influences of the oral therapy on the patients and his family. Continuously providing patient education is one of the key strategies to promoting adherence. More specifically the following questions will be discussed:

- Which potential risk factors for non-adherence do we have to look for, which difficulties do patients report on?
- Which direct or indirect methods can be used in clinical practice to assess adherence?
- What does the patient need to learn to be able to manage the therapy independently?
- Which interventions are successful in supporting the patient?

The role of the nurse as part of the interprofessional team will be reflected on and (potential) responsibilities will be discussed. Necessary competencies of nurses that are helpful in supporting the patient in adhering to the therapy will be reviewed.

Keywords adherence, oral therapy, patient management, patient education, nursing roles
Conflict of interest No conflict of interest

Notes:

Tuesday 22 October **0830-1000**
HSANZ Symposium 3: Myeloid Disorders **Auditorium (Arena B)**

New Insights into the Pathogenesis and Prognosis of Myelodysplastic Syndromes (MDS)

Alan List
Moffitt Cancer Centre, Tampa, USA

The International Prognostic Scoring System (IPSS) has served as a universal tool for outcome discrimination of MDS patients since 1997. Although prognostically useful, the IPSS captures only a third of cytogenetic abnormalities encountered in MDS and does not consider the impact of the severity of cytopenias or transfusion dependence. The IPS S was revised in 2012 (IPSS-R) based upon analysis of a large data involving over 7800 patients. The revised tool segregates cytogenetic abnormalities into 5 different prognostic categories with the incorporation of eight additional, less common chromosome abnormalities. He IPSS-R shows reproducible discrimination in progression free and overall survival, but its major benefit lies in its ability to refine outcome discrimination for patients with IPSS Intermediate risk disease. Although originally developed for previously untreated patients, retrospective analyses show that the IPSS-R is valid for patients receiving active treatment. The emergence of whole exome sequencing (WES) has revealed gene mutations that have both biological and clinical relevance. Three gene mutations, including *RUNX1*, *NRAS*, and *TP53,* are strongly linked to the hematologic phenotype of severe thrombocytopenia and increased bone marrow myeloblasts. Moreover, in multivariate analysis controlling for clinical features, 5 specific mutations offer prognostic discrimination independent of IPSS; these include *TP53, E ZH2, ETV6, RUNX1*, and *ASXL1*. Gene mutations involving core components of the spliceosome complex have emerged as the first gene class linked to the phenotypic hallmark of MDS, i.e., cytological dysplasia. Mutations of one slicing machinery component, *SF3B1*, are specifically associated with ring sideroblasts, demonstrable in more than 75% of RARS patients. Both the complexity of mutation load and the specific genes mutated have emerged as strong biological prognostic variables that are only now be incorporated into prognostic models. Moreover, specific gene mutations have also shown promising utility as biomarkers for response to therapy. These include mutations involving *TP53* and response to lenalidomide, and mutations involving chromatin modifying genes with response to azanucleosides.

Keywords MDS, pathogenesis

Tuesday 22 October **0830-1000**
HSANZ Symposium 3: Myeloid Disorders **Auditorium (Arena B)**

Towards the Eradication of Leukaemia Stem Cells in Myeloid Malignancies

Steven Lane
Queensland Institute of Medical Research & Royal Brisbane and Women's Hospitals, Brisbane, Australia

Myeloid blood cancers such as acute myeloid leukaemia (AML), myelodysplasia (MDS) and myeloproliferative neoplasms (MPN) are aggressive malignancies with high mortality rates. Research from our lab and others has demonstrated the presence of disease-initiating stem cells in myeloid malignancies and confirmed that these stem cells mediate disease recurrence after chemotherapy. We have identified discrete genetic pathways that regulate the long-term survival of AML stem cells in vivo. Moreover, using genetic and pharmacologic approaches we have been able to eliminate AML stem cells in syngeneic and humanized models of AML. In this presentation, I will discuss genetic and pharmacologic strategies to target disease-initiating stem cells in AML and related myeloid malignancies.

Keywords AML, leukaemia stem cells, cancer
Conflict of interest None

Tuesday 22 October **0830-1000**
HSANZ Symposium 3: Myeloid Disorders **Auditorium (Arena B)**

Prognostication and Therapy of Polycythemia Vera

Srdan Verstovsek
Department of Leukemia, The University of MD Anderson Cancer Center, Houston, Texas, USA

Polycythemia vera (PV) is a BCR-ABL–negative myeloproliferative neoplasm characterized primarily by erythrocytosis, but also by leukocytosis, thrombocytosis, poor quality of life and splenomegaly in some patients. The main complications of the disease are thrombosis and related vascular complications. Major criteria for diagnosis of PV are elevated hemoglobin (> 18.5 g/dL for men or > 16.5 g/dL for women) and presence of the JAK2V617F mutation. Minor criteria include trilineage myeloproliferation in bone marrow, low erythropoietin levels, and endogenous erythroid colony growth. Patients with PV can have near normal life expectancy or, in a minority, significantly reduced survival depending on the presence of certain risk factors. In everyday practice, risk stratification is important to identify patients most at risk for thrombotic complications and guide treatment decisions on implementing therapies that reduce those risks. Patients at high risk of thrombotic complications are those older than 65, or with a history of thrombosis. New prognostic factors, e.g. leukocytosis or high JAK2V617F allelic burden have not yet been proven to be significant in prospective studies. Therapy for low-risk patients generally includes phlebotomy when indicated and low-dose aspirin. High-risk patients should be initially treated with hydroxyurea or interferon-alpha (IFN). For younger patients, IFN is a good first-line therapy (particularly pegylated forms) given its lack of teratogenicity and potential for inducing cytogenetic and molecular remission. For patients with resistance to or intolerance of HU and IFN, a non-specific alkylating agent such as busulfan can be used; however, because of its leukemogenicity it should be reserved for use in patients with short life expectancy. For patients who are intolerant of or resistant to HU, clinical trials testing JAK inhibitors represent a promising option. Initial results from a phase II study of the JAK2 inhibitor ruxolitinib in patients with PV who are resistant to or intolerant of HU show that the drug can eliminate the need for phlebotomy, improve symptom burden, and reduce splenomegaly in almost all patients. Two phase III studies are underway for possible approval of ruxolitinib as second line therapy for PV. Other JAK inhibitors and novel agents (e.g. histone deacetylase inhibitors) are also being studied in PV.

Keywords polycythemia vera, JAK2 V617F mutation, risk stratification
Conflict of interest Research support from Incyte Corporation, Astrazeneca, Lilly Oncology, Roche, Geron, NS Pharma, Bristol Myers Squibb, Celgene, Infinity Pharmaceuticals, YM Biosciences, Gilead, Promedior, SBio.

Tuesday 22 October **0830-1000**
ANZSBT Symposium 4: Haemovigilance and Transfusion Governance **Central Hall A**

Hemovigilance - SHOT

Dafydd Thomas
Morriston Hospital ABMU Health Board, Swansea, Wales, UK

The development of hemovigilance over the last two decades has shown the value of close observation of transfusion practices and has led to a number of developments that have improved patient safety. SHOT has recently presented it's 16th Annual report at the Royal Society of Medicine in London.
SHOT continues to be a confidential reporting system relating to the clinical and laboratory issues relating to transfusion, but SHOT also receives data on near miss events that can very often highlight important trends in practice. Over recent years the compulsory reporting of events and reactions to MHRA, UK has been required under European Law set out in the European Blood Directive.
Despite the scrutiny given to hemovigilance and the regulation of this area it is perhaps surprising that the errors reported continue to increase. Whilst certain types of reports have plateaued or even decreased others have emerged as problems. In addition despite the efforts made by transfusion practitioners in individual hospitals and trusts, in trying to assess the competencies relating to transfusion, amongst students junior doctors and nurses it is apparent that even competent practitioners who have been assessed satisfactorily still make errors – usually due to distraction or systems that are prone to fail.
The general public would be amazed that the data fields needed for a safe cross-match can be incorrectly completed, indeed on many occasions each day in busy hospitals, samples arrive for analysis completely unlabeled. Interestingly technology may help with the speed of many tasks but, whilst initially designed to improve process and safety, problems still occur either through equipment failure, non-availability from time to time or when being used by untrained or stressed individuals.
The most recent SHOT report both highlights all the reports received during 2012 but also compares the trends over the last 16 years of reporting. The ongoing value of such a national reporting system is the ability to pick similar reports from the total that may indicate a specific problem. The individual hospital may take many years to see two such incidences and therefore not recognize the development of emerging problems. This phenomenon was described by a previous Chief Medical Officers report advocating the NHS in the UK needed to be an organization with a memory. Over the last three years attempts have been made to start benchmarking events and errors for hospitals of similar size and transfusion activity. It is a hypothesis that this ongoing benchmarking may be even more useful in helping SHOT understand why these errors in transfusion practice continue.

Keywords Haemovigilance, Benchmarking, Patient ID, MHRA,
Conflict of interest No

Tuesday 22 October **0830-1000**
ANZSBT Symposium 4: Haemovigilance and Transfusion Governance **Central Hall A**

Blood Management in Queensland: Future Directions

Jeannette Young
Queensland Health, Brisbane, QLD, Australia

The provision of an adequate, safe, secure and affordable supply of blood and blood products is vital to the delivery of quality and safe health care in Queensland. As such Queensland Health continues to seek ways to maintain and improve its management and use of blood and blood products.

Following the structural changes to Queensland Health in 2012, in line with the implementation of the National Health Reform Agreement, the role of the Queensland Department of Health underwent a transformation. While the overall management of the public healthcare system remains the responsibility of the Department of Health, its role is primarily that of policy development, planning, funding and performance monitoring. Under the new structure Hospital and Health Services are now independent statutory bodies responsible for the delivery of quality and safe health services in their local area.

This presentation outlines the current arrangements and future plans for the effective, efficient, safe and secure management of blood supply and usage in Queensland, in the context of the Department of Health's new role, and the devolvement of responsibility for the provision of health care to local Hospital and Health Services. These include blood and blood product supply planning; the devolvement of the budget for blood and blood products to Hospital and Health Services; the development of a Queensland implementation plan for the National Blood and Blood Product Wastage Reduction Strategy; arrangements for haemovigilance data collection, validation and analysis; and the development of Queensland's Blood Supply Emergency and Contingency Plan.

Keywords Queensland Blood Management
Conflict of interest No

Tuesday 22 October **0830-1000**
ANZSBT Symposium 4: Haemovigilance and Transfusion Governance **Central Hall A**

Governments' Agenda for Blood Transfusion in Australia

Leigh McJames
National Blood Authority Australia, Canberra, ACT, Australia

Governments are committed to promoting safe, high quality management and use of blood products, blood related products and blood related services in Australia. In support of this objective they have approved a wide ranging agenda to support improvements in the sector, encompassing research and development, haemovigilance, development and implementation of patient blood management at a hospital level, education and training and collection of data. This presentation outlines the agenda and progress so far.

Keywords Government Program Transfusion
Conflict of interest No

Tuesday 22 October **0830-1000**
ASTH Free Communications 2: Thrombosis and Haemostasis **Central Hall C**
O062 **0830**

The Interpretation of Laboratory Assays to Classify Patients With Mild Haemophilia A and the Discrepant Phenotype

EM Duncan, SE Rodgers, SJ McRae
Haematology Division, SA Pathology, South Australia

Aims/Background
A sub-group of mild Haemophilia A (HA) families have a method related discrepancy in FVIII:C results, whereby the 1-stage clotting assay (FVIII:C-1) is significantly higher than the 2-stage clotting assay (FVIII:C-2) or the chromogenic assay (FVIII:C-chr). These families are important to identify because individuals may be mis-managed or risk a missed diagnosis. It is recommended that laboratories should include the FVIII:C-chr when investigating HA, but there are no guidelines as to the criteria to classify results as equivalent or discrepant. Our aim is to describe technical information that can influence the classification of such patients.
Method/Results
We compared the results of a standard FVIIIC-1 assay (Siemens) with a chromogenic assay (Hyphen Biomed) in patients with HA and a normal population. The FVIII:C-chr was optimised to use a longer incubation time (8 – 10 minutes) for factor Xa generation, so as to more readily detect the low FVIII:C of the discrepant group. Using this approach we found a cut-off of 1.60 as the optimal ratio of FVIII:C-1 to FVIII:C-chr to distinguish between the discrepant and equivalent groups in 78 mild patients. However, in patients with FVIII:C-chr less than 10 IU/dl, the separation of the groups was not always clear. Normal donors (n 90) also showed variable assay discrepancy, with ratios ranging from 0.60 to 1.40 (mean 0.99). The upper limit was well below the ratio of 1.60 found to separate the two HA groups. We also propose that FVIII antigen (FVIII:CAg, Stago) can assist classification. In 38 equivalent patients the mean (SD) FVIII:C-1, FVIII:C-2 and FVIII:CAg were 12.7 U/dl (9.4), 10.0 (8.2) and 10 (14.0) respectively. In 23 discrepant patients the parallel results were 36.0 (8.6), 14.0 (3.2) and 59.0 (33), with the FVIII:CAg levels usually higher than factor VIII:C-1 and FVIII:C-2 and consistent with a qualitative defect. Family members with HA generally all have the same classification as either equivalent or discrepant. F8 gene analysis is helpful, especially when a mutation has been previously associated with assay discrepancies.
Conclusion
Information provided by FVIII:C-chr, FVIII:CAg and F8 gene mutation analysis is helpful to confirm a diagnosis of mild haemophilia A made using FVIII:C-1, and assist with decisions about the patient's phenotype.

Keywords Haemophilia A, Factor VIII, Laboratory assays
Conflict of interest None

Tuesday 22 October **0830-1000**
ASTH Free Communications 2: Thrombosis and Haemostasis **Central Hall C**
O063 **0845**

A Multicentre Prospective Randomised Controlled Trial (PREVENT) for Assessment of Postoperative Bleeding and Thrombosis Outcome After Prophylaxis With Enoxaparin or Rivaroxaban for Hip and Knee Arthroplasty

A Khalafallah[1,2], AM Aqeel[3], M Latif[1], Rebecca Li[1], M Sexton[1], A Albarzan,[1] SK Singh[1] JC Batten[1,2], D Penn[1,2], R Butorac[1,2], D Edis[1,2], P Van Winden[1,2], B Einoder[1,2], L McLeod-Mills[3], R Hau[3], L Hayes[3]
[1]Launceston General Hospital; [2]Calvary Private Hospital, [3]School of Human Life Sciences, UTAS, Launceston, Tas, [3]Northern Health, Melbourne, VIC, Australia

Background and Aims
Patients undergoing major orthopaedic surgery are at a higher risk of developing venous thromboembolism (VTE). The purpose of this study is to thoroughly assess post-operative bleeding and VTE-outcomes in patients with knee or hip arthroplasty after standard prophylaxis with enoxaparin versus the new oral anti-Xa; rivaroxaban.
Study Design
A prospective randomised controlled safety study with parallel assignment of enoxaparin 40 mg daily SC versus rivaroxaban 10 mg PO daily. The primary outcome is to assess postoperative bleeding during use of the study medications for 14 days in total knee replacement (TKR) and 35 days in hip replacement (THR).
Results
We report on 712 patients who underwent elective THR (323) and TKR (389) from Jan 2010 till Dec 2012. The median age was 67 years (range 26-90) with a male to female ratio of 348:364. The median pre-admission Hb level was 138 g/L with a median day 2 post-operative Hb of 103g/L and day 4 of 102g/L. The average amount of blood loss postoperatively was 250 ml, with no difference between patients who received rivaroxaban versus enoxaparin. Overall median stay in hospital was 6 days, with a range between 1-44 days. The median hospital stay in the rivaroxaban group was 5 days (1-22) versus 6 days (2-44) in the enoxaparin group. Calf ultrasound were performed routinely to exclude asymptomatic DVT and also when patients were symptomatic. There were 8 non-occlusive DVTs (5 rivaroxaban; 3 enoxaparin) versus 4 occlusive DVTs (1 rivaroxaban; 3 enoxaparin) reported. One patient developed PE in the enoxaparin group. Patients reported convenience with oral rivaroxaban (86%), versus 29% for subcutaneous enoxaparin.
Conclusions
Our preliminary analysis shows that rivaroxaban has a similar safety profile to enoxaparin in term of bleeding, with non-inferior efficacy in prevention of VTE after arthroplasty. Oral rivaroxaban administration was more convenient for the patients.
Keywords Arthroplasty, rivaroxaban, enoxaparin, bleeding, efficacy, safety, VTE.
Conflict of interest None

Tuesday 22 October **0830-1000**
ASTH Free Communications 2: Thrombosis and Haemostasis **Central Hall C**
O064 **0900**

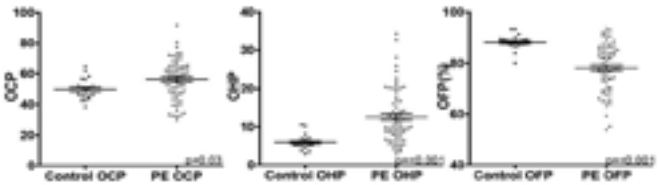
Enhanced Coagulation and Reduced Fibrinolytic Potential in Long-term Survivors of Pulmonary Embolism

Vincent Chow[1,2], Caroline Reddel[1,2], Gabrielle Pennings[1,2], Austin Ng[2], Jennifer Curnow[1,2], Leonard Kritharides[1,2]
[1] ANZAC Research Institute, Sydney, NSW, Australia [2] Concord Hospital & University of Sydney, Sydney, NSW, Australia

Aim/Background
Hypercoagulable and/or hypofibrinolytic states are risk factors for venous thromboembolism including acute pulmonary embolism (PE). Currently, screening for thrombophilia is targeted towards identifying a specific defect. We performed the Overall Hemostatic Potential (OHP) Assay, a global coagulation assay, to assess whether hypercoagulable and/or hypofibrinolytic states are present in long-term survivors of acute PE.

Methods
Long-term survivors of an acute PE (Jan 2000-June 2005) were prospectively invited to undergo functional and clinical assessment. Citrated plasma was collected for OHP assays and compared with healthy age and sex matched controls. Fibrin time curves were generated by spectrophotometry measuring absorption each minute for 100 minutes after the combination of tissue factor and tissue plasminogen activator with plasma and buffer resulting in formation and degradation of fibrin clot.

Results
OHP Assays were performed in 67 long-term survivors of single PE (7.9±1.4 years after PE) and 20 age (61.7±11.2 vs 56.6±6.4 years, p=0.06) and sex (males: 60% vs 48%, p=0.45) matched healthy controls. Survivors of PE were more hypercoagulable as reflected by significantly higher Overall Coagulation Potential (OCP-56.4±13.0 vs 49.9±6.9, p=0.03) and had impaired fibrinolysis with higher Overall Hemostatic Potential (OHP-12.6±7.0 vs 5.9±2.0, p<0.001) and lower Overall Fibrinolytic Potential (OFP-78.1±9.4 vs 88.2±2.9, p<0.001) compared with controls.



Conclusion
Enhanced coagulation and reduced fibrinolytic potential persists in long-term survivors of PE. The OHP Assay may be a novel screening tool to screen for thrombophilic states and guide duration of anticoagulation therapy following PE.

Keywords Pulmonary embolism, overall hemostatic potential, hypercoagulable
Conflict of interest Nil

Tuesday 22 October **0830-1000**
ASTH Free Communications 2: Thrombosis and Haemostasis **Central Hall C**
O065 **0915**

Management and Outcomes of Single Subsegmental PE (SSPE) at Waitemata DHB (WDHB): A Retrospective Audit

Divya Mehta, David Simpson, Tracey Woulfe, Vicki Rolfe-Vyson, Valerie Rowland, Mark Barnett, Eileen Merriman
North Shore Hospital, Auckland, New Zealand

Aim/Background
It is not known whether filling defects in subsegmental arteries on multidetector CTPA correlate with true SSPE on pulmonary angiography. Despite this, the current ACCP guidelines do not differentiate between PE in segmental and subsegmental vessels, and many patients receive at least 3 months full dose anticoagulation. The strategy employed at WDHB in haemodynamically stable patients with SSPE is to perform bilateral lower leg compression ultrasound (CUS) and withhold anticoagulation if this is negative; the bilateral CUS is then repeated in 7-10 days. Over 60 patients with SSPE diagnosed by CTPA have been managed in this way and reported in the literature; without recurrent symptomatic venous thromboembolism (VTE) during 3 month follow-up. The aim of our study was to document management strategies of SSPE at WDHB, along with 3 month rates of VTE recurrence (DVT and PE).
Methods
Study patients were identified by retrospective audit of data from the Haematology VTE database. All patients presenting with SSPE between June 2005 and May 2012 were included. Data collected included provoking factors, treatment dose and duration, rates of VTE recurrence (DVT and PE) within 3 months of SSPE diagnosis, bleeding, and all-cause mortality.
Results
49 patients were included in this study. 16 patients were managed with serial lower limb USS alone; none of these patients had a VTE recurrence within 3 months of SSPE diagnosis. The remaining 33 patients received anticoagulation, often at prophylactic dose initially. Two of these patients had major bleeding episodes, and anticoagulation was terminated. 25 of the remaining patients were continued on longer term anticoagulation ranging from 6-12 weeks; again there were no symptomatic VTE recurrences, however 2 had asymptomatic incidental VTE within 3 months.
Conclusion
Withholding anticoagulation in patients with SSPE and negative serial bilateral CUS is a safe and effective management strategy with a low risk of VTE recurrence.
Keywords SSPE, treatment, VTE recurrence
Conflict of interest No conflict of interest to disclose

Tuesday 22 October **0830-1000**
ASTH Free Communications 2: Thrombosis and Haemostasis **Central Hall C**
O066 **0930**

TRACKER FACTORy: Telemonitoring Tool for Haemophilia Care in New Zealand

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Aim/Background
The information age has brought digital healthcare solutions to patients and clinicians to assist with the complexities associated with healthcare. In New Zealand, 4 in 5 homes are connected to the internet, suggesting that an opportunity exists for clinicians to connect with patients through telemonitoring. The WFH *Guidelines for the Management of Haemophilia* (2012) Principles of Care recommend timely assessment and intervention for bleeds. Launched in 2012, the TRACKER FACTORy web program and smartphone application allow real time reporting of bleeds and factor usage by haemophilia A and B patients and facilitates analysis and reporting of the information by treatment centres (HTCs).
Methods
Following 18 months of experience with TRACKER FACTORy, the opportunities and challenges of this haemophilia telemonitoring tool are reported from the cross-functional healthcare team, patient and developer's perspectives.
Results
TRACKER FACTORy facilitates timely intervention by the cross-functional healthcare team through real time recording and reporting of bleeds. The tool is available to all haemophilia patients and HTCs in NZ and offers a consistent approach to data capturing and reporting nationally. Electronic reports may contain less detailed contextual information than treatment diaries, but improve HTCs' analytical capability. The quality of information depends on timely and accurate reporting by patients and their acceptance of, and access to, technology. Regular software updates by smartphone manufacturers necessitate ongoing maintenance.
Conclusion
Telemonitoring can support haemophilia patient care by facilitating real time reporting of bleeds and timely involvement of the cross-functional medical team. Although telemonitoring may not be suitable for all patients, early experience with TRACKER FACTORy confirms its broad potential application in haemophilia care.

Keywords haemophilia, technology, monitoring
Conflict of interest This paper was supported by Pfizer New Zealand, developer of TRACKER FACTORy. Associate Medical Director of Pfizer New Zealand is a co-author of this abstract and assisted with its preparation.

Tuesday 22 October **0830-1000**
ASTH Free Communications 2: Thrombosis and Haemostasis **Central Hall C**

O067 **0945**

Safety and Efficacy of Acute Arthrocentesis for the Management of Haemarthrosis in Paediatric Patients With Severe Haemophilia A

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Aim/Background
Quality of life for patients with severe haemophilia is determined by their orthopaedic status. The pathology of haemarthropathy is related to the number of joint bleeds as blood and haemosiderin inflames the synovium and induces cartilage damage. Replacement factor prophylaxis beginning in childhood has reduced but not eliminated spontaneous joint bleeding. Since 2000, our centre has managed acute haemarthrosis by normalising factor levels followed by arthrocentesis performed by the rheumatologist to remove blood, washout the joint and instill corticosteroids.

Methods
A retrospective review of all patients attending the haemophilia clinic at Princess Margaret Hospital for Children was undertaken. Clinical and radiologic outcome was assessed from the medical and radiology records.

Results
38 boys with severe haemophilia A (FVIII<1%) attended the clinic between 2000 and 2013 of whom 16 required 36 arthrocenteses for clinically diagnosed acute haemarthrosis. In 1 patient septic arthritis was diagnosed by joint aspiration and managed appropriately. In all others the joint was washed out and semi-soluble corticosteroids were instilled in standard doses.
Safety: No child developed septic arthritis or haemarthrosis related to the procedure.
Efficacy: Many children have clinically normal joints and have plain xray with near normal findings. MRI reveals early joint changes. No patient has had an orthopedic procedure and none are planned for synovectomy or joint replacement.

Conclusion
Acute arthrocentesis is safe to perform for the management of haemarthrosis in severe haemophilia A. Longterm efficacy is supported by the excellent joint status of children treated in this cohort. The multidisciplinary clinic needs to encourage early attendance for arthrocentesis in all children with severe haemophilia. This study supports the essential role of the rheumatologist in the treating team.

Keywords Haemophilia A, Arthrocentesis, Paediatrics.
Conflict of interest No

Tuesday 22 October **0830-1000**
Nurses Free Communications 2: Focus on Quality of Life & Survivorship
Meeting Rooms 5/6

O068 0830

An Exploratory Study of the Care Experiences of Patients Diagnosed with Myeloma

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[2] *Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia*

Aim/Background
Myeloma is an incurable blood cancer that predominately affects the elderly. Developments in the treatment of myeloma have resulted in better disease outcomes for some groups but survival has not improved for older patients. This pilot study explores the unmet physical and supportive care needs of older patients diagnosed with myeloma. The primary objectives are;

1. To examine patients' experience of care from diagnosis to 6 months post;
2. To identify gaps in service provision from the perspective of treating clinicians and GPs.

Methods
20-30 newly diagnosed myeloma patients, aged over 65 years, will be recruited. Disease and demographic data with be collected from patients' medical records. Patients will complete validated measures at T1 (3 to 6 weeks post commencement of treatment) and T2 (8-12 weeks post T1). Measures include the EORTC QLQ 30 and the-MY20; the Distress thermometer and problem checklist; the HADS; Morisky Medication Adherence scale-8 and the Supportive Care Unmet Needs Scale. Six months after diagnosis patients will participate in an audio tapped interview to describe their experience of living with myeloma and their experience of care. Patients' treating clinicians and GPs will be invited to take part in a taped, telephone interview to explore their perceptions of service gaps in care provision for patients diagnosed with myeloma.
Conclusion
Findings from this study will be used to develop a novel model of nurse-led, case management that will target gaps in the provision of care and services for older people diagnosed with myeloma.
Keywords Myeloma, Nurse led-care
Conflict of interest This research is supported by an unrestricted grant by Celgene. The company has had no role in preparing the abstract.

Tuesday 22 October **0830-1000**
Nurses Free Communications 2: Focus on Quality of Life & Survivorship
Meeting Rooms 5/6

O069 **0845-0900**

What Factors Influence Whether a Person with Multiple Myeloma Would Participate in a Physical Activity Program?

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[4] Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, Australia,
[5] Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia

Aim/Background
Current evidence suggests that physical activity is safe and feasible for people with Multiple Myeloma (MM) and has a positive effect in alleviating disease and treatment – related symptoms and improving quality of life. The aim of this qualitative study was to gain an insight into what people with MM would prefer in the delivery of a physical activity program in regards to structure, timing in the treatment trajectory, location and the integration of any perceived useful resources.
Methods
Semi – structured interviews were conducted with people treated for MM within the preceding 2 – 12 months. Interviews were analysed using the constant comparison coding method. This method reduced the data down to the main themes which were then explored.
Results
Twenty – four interviews were conducted. Most participants reported an exercise program was feasible. The strongest preference for a program was 2 – 8 months following treatment. Participants were interested in targeted programs guided by a health care clinician with knowledge of MM. Preferences for location and mode of delivery varied. Light to moderate exercise was preferred and information about physical activity was highlighted as a requirement but to reduce information overload, it was suggested information be provided following treatment.
Conclusion
The delivery of a physical activity program for people with MM needs to take into account the varied preferences in relation to the location, structure and type of activity that is feasible for the individual. The findings suggest that an individualised program involving clinicians and organisations that have experience and expertise with MM would be successful. There also needs to be an option for home based physical activity as treatment for MM is ongoing and hospital appointments may make it difficult to commit to a program. A home based program may also meet the needs of people with myeloma living in remote regions.
Keywords Multiple Myeloma, Physical Activity, Preferences **COI** None

Tuesday 22 October **0830-1000**
Nurses Free Communications 2: Focus on Quality of Life & Survivorship
Meeting Rooms 5/6

O070 **0900**

Identifying and Addressing the Supportive Care Needs of the 'Complex' Patient with Multiple Myeloma within a Nurse Practitioner Led Clinic

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Multiple Myeloma is a predominantly incurable plasma cell disorder that accounts for approx 10% of all haematological malignancies. A definitive characteristic of myeloma is its propensity to affect primarily older individuals. The recent evolution of a range of effective novel treatments have increased the ability to repeatedly achieve control of the condition and/or gain control for extended periods, allowing many people to live with myeloma as a chronic condition.

The Haematology service identified a cohort of patients whom the Fitch Model classifies as having 'complex care needs' requiring more than the usual level of supportive care assessment and intervention (Victorian Supportive Care Policy 2009). The 'complexities of care' affecting these patient include an incurable malignancy diagnosis, highly complicated and toxic drug therapy regimens all in the context of advanced age, multiple comorbidities, pre-existing polypharmacy, culturally and linguistically diverse backgrounds and geographic and/or social isolation.
This presentation outlines the experience of establishing a dedicated nurse-led service to support patients with these complex care needs, particularly in the early phases of illness management. The specific objectives of the service are to ensure/improve adherence to the treatment regimen; increase patient satisfaction with the experience of care; improve consistency and coordination of care; facilitate early identification and intervention of treatment and disease related adverse effects; and facilitate early identification and management of supportive care needs within an ambulatory care context.
The service used validated supportive care screening and symptom assessment tools within an NP-led model of joint Haematologist-Nurse Practitioner consultations, identifying needs, facilitating referrals and developing individualised information resources, following patients via telephone consultants and ad hoc clinical review.

The presentation explores the framework for the service, developing care pathways, addressing unmet supportive care needs of this group, addressing oral chemotherapy risks and requirements of the advanced practice nursing roles.
Keywords Myeloma, Nurse-Led services; supportive care
Conflict of Interest No conflicts of interest to declare

Tuesday 22 October **0830-1000**
Nurses Free Communications 2: Focus on Quality of Life & Survivorship
Meeting Rooms 5/6

O071 **0915**

Mental Adjustment to Cancer and its Relation to Anxiety, Depression and Quality of Life in Patients Preparing to Undergo Allogeneic Stem Cell Transplantation

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Aim
Mental adjustment and coping have been identified as important factors for quality of life (QoL) and mental health in cancer patients. This study examines the impact of different responses to the diagnosis of cancer on psychological distress and QoL in patients preparing to undergo allogeneic stem cell transplantation (SCT).
Methods
The Mental Adjustment to Cancer Scale is a 40-item questionnaire addressing reactions of patients to having cancer. Data were collected on 147 pre-SCT patients (55% male; median 45 years) between 2005 and 2012. QoL and psychological distress were measured using the World Health Organization QoL - Bref and Brief Symptom Inventory-18 scales, respectively.
Results
Anxious pre-occupation, Helpless-hopeless and Fatalism adjustment responses were all strongly positively correlated with anxiety (all $p<0.01$), depression (all $p<0.001$) and global distress (all $p<0.001$). Fighting spirit was negatively correlated with depression ($p<0.01$) and global distress ($p=0.05$). In QoL analyses shown below, Helpless-hopeless coping had a negative correlation with all domains (physical, psychological, social, environmental) of QoL. In contrast, Fighting Spirit was positively associated with these same QoL parameters.

n=147	Physical QoL	Psychological QoL	Social QoL	Environmental QoL	Health Satisfaction
Helpless-Hopeless	r= -0.26 (p=0.004)	r= -0.47 (p<0.001)	r= -0.22 (p=0.013)	r= -0.4 (p<0.001)	r=- 0.37 (p<0.001)
Fighting spirit	r= 0.37 (p<0.001)	r= 0.40 (p<0.001)	r= 0.36 (p<0.001)	r= 0.3 (p=0.001)	r= 0.28 (p<0.001)

Conclusion
These results highlight the striking impact of coping responses to cancer on psychological distress and QoL prior to allogeneic SCT and should be considered when planning supportive interventions to maximise QoL.
Keywords Transplantation, quality of life, coping style **COI** None

Tuesday 22 October **0830-1000**
Nurses Free Communications 2: Focus on Quality of Life & Survivorship
Meeting Rooms 5/6

O072 0930

Development of a Nurse-led Survivorship Intervention for Long-term Survivors of Hodgkin Lymphoma

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Background
The increasing numbers of Hodgkin Lymphoma (HL) survivors has raised awareness of the need to optimise long-term health outcomes and quality of life for this group of people.
Objective
To develop and pilot-test the feasibility and potential of a nurse-led survivorship intervention to enhance survivors of HL awareness of health risks and adoption of healthy lifestyle behaviours.
Methods
A pre-test, post-test design. Thirty survivor participants and 30 healthy controls were recruited. Data were collected using the General Health Index and the Health Promoting Lifestyle Profile II at four time points. The intervention included: i) exploration of knowledge of health risks and lifestyle behaviours; ii) delivery of a tailored education package; iii) screening for unmet supportive care needs and iv) development and delivery of a tailored survivorship care plan.
Results
A considerable profile of unmet need was identified. More than half of the survivor participants (57%) reported some level of fatigue for most of the time in the last two weeks; 47% reported feeling a lot of worry; 37% reported sleep problems; and 23% reported feeling depressed. Statistically significant improvements were seen for several domains. These included: physical activity (p=0.014); nutrition (p=0.0005); stress management (p=0.002) and health promoting lifestyle (p=0.005) from baseline to 6 months. No additional resources were required to provide the intervention as all aspects were delivered within existing resources of the haematology late effects clinic.
Conclusion
The nurse-led intervention was shown to be feasible and demonstrated significant potential to improve awareness of health status and healthy lifestyle behaviours. A randomised controlled trial is now needed to further test the efficacy of the intervention; determine optimal dose and the best time to deliver the intervention to prevent the levels of unmet needs reported by this study group, being reported by survivors of HL in the future.
Keywords: Survivorship, nurse-led, Hodgkin Lymphoma
Conflict of interest: None

Tuesday 22 October **0830-1000**
Nurses Free Communications 2: Focus on Quality of Life & Survivorship
Meeting Rooms 5/6

O073 **0945**

Integrating Nurse Practitioner Roles into an Expanding Metropolitan Bone Marrow Transplant Service to Meet Changing Needs

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[2] *Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia*

Background
Nurse Practitioners (NP) increasingly contribute to improved service delivery and patient outcomes. NPs are well positioned to meet the complex care needs of bone marrow transplant (BMT) recipients, and can be well placed to monitor and manage patient care throughout the lengthy BMT process. The Royal Melbourne Hospital (RMH) provides one of the busiest comprehensive BMT services in Australia undertaking 149 transplants from January 2012 to June 2013. This service will grow as RMH amalgamates with Peter MacCallum Cancer Centre (PMCC) to form the Victorian Comprehensive Cancer Centre (VCCC), and indication for BMT increases. In 2009 the Victorian Department of Health (DOH) made funding available to develop Oncology NP roles. A review of current services highlighted that NP roles could address the gaps in the existing services and support the future amalgamation and expansion.
Aim
To integrate three NP positions within a BMT service and evaluate the initial impact of this NP model of care.
Method
A systematic review of BMT services at RMH and PMCC focusing on current models of care and predicted future impacts on service was undertaken. Two NP positions (BMT donor / apheresis; pre and acute post BMT) were proposed and accepted by the funding body and hospital executive. A third position was already in place at the PMCC servicing BMT long-term follow-up and care. Candidate positions were filled.
Results
Two NP candidate positions are in place, and whilst they continue to develop advanced practice roles, both contribute to patient reviews and care management in ambulatory and clinic settings under clinical mentorship/supervision. Emerging advance roles include autonomous donor and patient assessment, ordering and interpretation of diagnostic investigations; medication management of apheresis procedures and BMT related adverse effects. An increase in patient numbers are being reviewed collaboratively; and a more streamlined service and patient flow is apparent with a stronger focus on patient centred and holistic approach to care. Roles will continue to develop after endorsement and provide autonomous nurse led clinics alongside strong clinical nursing leadership within the unit. This paper will describe this initiative; highlight successes, challenges and progress to date.
Keywords Nurse Practitioner, BMT, Remodelling Services **COI** None

Tuesday 22 October **0830-1000**
HSANZ Lab Haematology Symposium 1: Iron Deficiency and Automated Analyser Parameters **Meeting Room 7**

The Investigation of Iron Deficiency

Robert Bird
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Abstract not available at time of going to print

Tuesday 22 October **0830-1000**
HSANZ Lab Haematology Symposium 1: Iron Deficiency and Automated Analyser Parameters **Meeting Room 7**

The Use of RDW-SD to Discriminate Thalassaemia Trait From Iron Deficiency

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Differentiation between these common causes of red cell microcytosis is important clinically, as failure to identify a thalassaemia trait may lead to an unpredicted thalassaemia major which can affect quality of life or, in the case of alpha thalassaemia, lead to death in utero.

Dating back to the early 1970's, studies have evaluated the usefulness of automated parameters in assisting in the differentiation of thalassaemia trait from iron deficiency. Parameters commonly studied include red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and red cell distribution width CV (RDW-CV). In addition to these automated parameters, a number of formulas incorporating at least two red cell parameters have been proposed to assist in differentiation (Mentzer, 1973; England and Fraser, 1973; Srivastava and Bevington, 1973; Shine and Lal, 1977; Ricerca *et al*, 1987; Green and King, 1989; Jayabose *et al*, 1999).

The use of the automated parameter red cell distribution width SD (RDW-SD) to assist in the discrimination of both alpha and beta thalassaemia trait from iron deficiency was evaluated in a large community laboratory in Brisbane, Australia. The evaluation incorporated comparison to previously studied parameters and formulas. While all managed to discriminate a varying proportion of cases of both alpha and beta thalassaemia trait from iron deficiency, because of the high sensitivity (97% alpha thalassaemia and 96% beta thalassaemia) and specificity (95% for both alpha and beta thalassaemia), RDW-SD showed most promise as a simple, automated parameter that could be used as a sensitive and specific predictor of both alpha and beta thalassaemia trait.

Keywords RDW-SD, thalassaemia, iron deficiency
Conflict of interest No

Tuesday 22 October **0830-1000**
HSANZ Lab Haematology Symposium 1: Iron Deficiency and Automated Analyser Parameters **Meeting Room 7**

The Immature Platelet Fraction - An Automated Parameter for the Quantitation of Thrombopoiesis

Leanne Sinclair
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The Immature Platelet Fraction (IPF%) is a quantitative marker of the rate of thrombopoiesis, analogous to the reticulocyte count for erythropoiesis. Sysmex offer this as a standard test on the XE-5000 and the new XN series, but it requires loading of specific IPF Master Software on the XE-2100.

This test offers the ability to assess whether thrombocytopenia is caused by increased platelet consumption or destruction or failure of production. An elevated IPF% has been reported as an aid to the diagnosis of immune thrombocytopenia or as an early indicator of bone marrow recovery after stem cell transplantation or chemotherapy. Prophylactic platelet transfusions may be able to be reduced by using the rise in IPF% as an early predictor of platelet regeneration. The IPF% has been proposed as an indicator of thrombotic risk in reactive thrombocytosis or in association with myeloproliferative neoplasms, renal transplantation and cardiovascular disease. New areas of study include disseminated intravascular coagulation, anti-platelet therapy, sepsis, liver cirrhosis, and myelodysplastic syndromes. It may have future applications in monitoring the effectiveness of treatment of thrombocytopenia.

The reference interval was established on 114 normal patients as 0.7-5.5% with a mean of 2.0%, median of 1.6%, and standard deviation of 1.2%. Stability studies showed that specimens should be analysed within 8 hours of collection and stored at room temperature, with no significant difference between storage at room temperature or 4 ^{0}C within the 8 hour time frame. Some patient studies are discussed.

Disadvantages of the IPF% include its limited availability, stability requirements, limited QC range and lack of an external quality assurance program. Its appeal as an automated parameter is that it can easily be incorporated into routine testing, either as a pre-ordered or a reflex test for the investigation of thrombocytopenia.

Keywords Immature platelet fraction, Sysmex, thrombocytopenia
Conflict of interest No

Tuesday 22 October **1030-1130**
HSANZ Symposium 4: Plasma Cell Disorders **Auditorium (Arena B)**

Post-Autograft Consolidation and Maintenance Therapy for Myeloma

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Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

High-dose therapy with autologous stem cell transplantation (ASCT) for multiple myeloma (MM) is considered the standard frontline treatment for eligible patients to-date. Novel anti-myeloma agents, such as thalidomide (T), bortezomib (V) and lenalidomide (R) are being incorporated post-ASCT as consolidation and maintenance treatments in an effort to prolong survival of myeloma patients.
Consolidation therapy post-ASCT in myeloma: Ladetto et al recruited 39 patients who had achieved at least a vgPR after ASCT and were treated with 4 courses of VTD. CR increased from 15% after ASCT to 49% after VTD. Molecular remissions were observed in 3% of patients after ASCT and in 18% after VTD; these patients had superior outcome compared with the others (PFS at 42 months: 100% vs. 57%). In another randomized Italian trial, two cycles of consolidation therapy (TD or VTD) were started 3 months after the second ASCT. In the TD arm, consolidation improved the CR rate from 40% to 47%. In the VTD arm, the CR rate was increased from 49% to 61%. Patients who received VTD had a greater reduction in residual tumour burden compared with TD (5 vs. 1 log reduction, by PCR, respectively). RVD has been also examined as consolidation treatment following ASCT: 2 cycles increased the CR plus sCR rate from 35% after ASCT to 52% after consolidation. Lenalidomide and bortezomib have been investigated also as single-agent consolidation treatments with encouraging results.
Maintenance therapy post-ASCT in myeloma: Thalidomide maintenance prolonged PFS in 3 randomized studies, while bortezomib maintenance has also increased PFS in several small studies. Lenalidomide maintenance prolonged PFS in two large randomized trials. In the French study (IFM 2005-02), after a median follow-up of 34 months, the median PFS was 42 vs. 24 months for lenalidomide and placebo arm, respectively ($p<10^{-8}$), but this has not been translated in an OS benefit yet (5-year OS probability: 81% for both arms). The incidence of secondary primary malignancies (SPMs) was 3.1/100 patient-years with lenalidomide and 1.2/100 patient-years with placebo. The US-based trial (CALGB-100104) showed a median TTP of 46 months for the lenalidomide arm vs. 27 months for the placebo arm, at a median follow-up of 34 months. Interestingly, despite a crossover of patients with disease progression from the placebo to the lenalidomide arm, an improvement in OS was observed favouring lenalidomide (3-year OS rate: 88% versus 80%; p=0.03). Of the 231 patients treated with lenalidomide, 18 developed SPMs (7.8%), whereas 6 of the 229 patients (2.6%) treated with placebo developed SPMs.

Key words multiple myeloma, consolidation, maintenance
Conflict of interest Honoraria from Janssen-Cilag and Celgene.

Tuesday 22 October **1030-1130**
HSANZ Symposium 4: Plasma Cell Disorders **Auditorium (Arena B)**

New Guidelines for the Diagnosis and Management of Amyloidosis

Peter Mollee
Pathology Queensland, Princess Alexandra Hospital and University of Queensland, Brisbane, QLD, Australia

Amyloidosis is a rare but devastating condition caused by deposition of misfolded proteins as aggregates in the extracellular tissues of the body, leading to impairment of organ function. High clinical suspicion is required to facilitate early diagnosis. Correct identification of the causal amyloid protein is absolutely crucial for clinical management in order to avoid misdiagnosis and inappropriate, potentially harmful treatment, to assess prognosis and to offer genetic counselling if relevant. This review summarises the current evidence on which the diagnosis and subtyping of amyloidosis is based, outlines the limitations of various diagnostic techniques particularly in an Australian and New Zealand context, and discusses optimal strategies for the diagnostic approach to these patients. Recommendations are provided for when to particularly suspect amyloidosis, what investigations are required, as well as an approach to accurate subtyping of amyloidosis.

In AL amyloidosis, the commonest amyloidosis subtype, there is limited consensus on what constitutes 'standard' treatment. This talk will outline recent guidelines from the Medical Scientific Advisory Group of the Myeloma Foundation of Australia to provide clinicians with a current, practical and evidence-based approach to the management of AL amyloidosis.

Keywords Amyloidosis, diagnosis, treatment
Conflict of interest Dr Mollee is a member of Celgene Australia's Myeloma Advisory Board

Tuesday 22 October **1030-1130**
ANZSBT Symposium 5: Transfusion of plasma **Central Hall A**

Transfusion in Critical Care

Sibylle Kozek-Langenecker
Department of Anaesthesia and Intensive Care, Evangelical Hospital Vienna, Austria

Transfusion of fresh frozen plasma (FFP) has historic origin. With the introduction of synthetic colloids, indication for FFP switched from fluid therapy to prophylaxis for bleeding, therapy for coagulation disorders. But with the current restrictions for hydroxyethyl starches from European pharmacovigilance authorities transfusion of FFP for volume therapy may again increase especially in critically ill patients due to the lack of evidence for alternatives (gelatine, dextrans) and cost considerations (albumin). Disadvantages, however, remain, such as citrate overload (leading to reduced myocardial function, arrhythmias, increased neuromuscular excitability), transfusion-related infections, immunomodulation (TRIMM), volume overload (TACO) and acute lung injury (TRALI). The latter complication can be reduced by the use of SD plasma. FFP is contraindicated in patients with plasma intolerance and confirmed IgA deficiency.

With the introduction of coagulation factor concentrates, indication for FFP is further restricted to rare specific clinical situations: plasma exchange in thrombotic thrombocytopenic purpura and adult haemolytic uremic syndrome, substitution of coagulation factor V, XI or vWF:CP in patients with hereditary or acquired deficiencies (massive transfusion). Other congenital coagulopathies are primarily treated with coagulation factor concentrates e.g. haemophilia A is treated with factor VIII concentrates – also in critical illness. The effect of oral anticoagulants or of a severe vitamin K deficiency is recommended to be reversed rapidly by administration of prothrombin complex concentrates (PCC). If in such emergencies no concentrates are available, FFP > 20 ml/kg could be considered as an alternative - with lower efficacy compared to factor concentrates.

Use of an early goal-directed approach with point-of-care coagulation monitoring and physiology–driven use of coagulation factor concentrates and avoiding FFP reduced costs, improved patient outcome and survival in trauma, major cardiovascular and liver surgery. One myth encouraging the use of FFP is the perception that overt coagulopathy with microvascular bleeding can be corrected by FFP dilution. Systematic reviews repeatedly showed that there is no proof for the efficacy of FFP in reversing clinically relevant clotting disorders and reducing blood loss. The therapeutic choice of 1:1 mostly used in the US may be – at least in part – be explained by the fact that factor concentrates have not been available until recently. Although there is a considerable survival bias in these retrospective studies, the observation indeed supports the concept that high doses of plasma given early are required to substitute for acquired coagulation factor deficiencies.

Keywords fibrinogen concentrate, severe bleeding, guidelines
Conflict of interest honoraria for lectures and travel reimbursement from Baxter, Biotest, CSL Behring, Octapharma

Tuesday 22 October **1030-1130**
ANZSBT Symposium 5: Transfusion of plasma **Central Hall A**

Platelet Transfusions in Haematology

Simon J Stanworth[1] and Erica M Wood[2]
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[2] *Monash University, Melbourne, VIC, Australia*

Thrombocytopenia in patients with haematological malignancies can be due to several factors, including the disease itself, the effects of chemotherapy and other medications, and infections. The ready availability of platelet concentrates has undoubtedly made a major contribution to the management of thrombocytopenic bleeding. Despite efforts to improve the safety of platelets for transfusion, such as bacterial screening, there continues to be uncertainty about the optimal use of *prophylactic* platelet transfusions for the prevention of haemorrhage in patients with bone marrow failure.

Two randomised controlled trials of prophylactic platelet transfusions have recently been completed in adults with thrombocytopenia due to haematological malignancies or their treatment. Both found a no-prophylaxis approach led to higher rates of World Health Organization (WHO) grade 2-4 bleeding overall. Wandt et al. powered the clinical trial around numbers of platelet transfusions, and reported that rates of bleeding were significantly increased in the no-prophylaxis group for both autologous haemopoietic stem cell transplantation (autoHSCT) and acute myeloid leukaemia (AML) subgroups, although increased by differing degrees. TOPPS was a randomized, parallel-group, open-label, non-inferiority trial conducted at 14 UK and Australian centres. The primary end-point was WHO grade 2-4 bleeding up to 30 days from randomization. Platelet usage was markedly reduced in the no-prophylaxis arm in both studies. WHO grade 2-4 bleeding grade occurred in 151/300 patients (50%) in the no-prophylaxis group compared to 128/298 (43%) in the prophylaxis group (adjusted difference in proportions 8.4%, 90%CI 1.7-15.2%: p-value for non-inferiority 0.06). A pre-specified subgroup analysis identified very similar proportions of bleeding between treatment arms in autologous haemopoietic stem cell transplantation patients. Prophylactic platelet transfusions are more effective in chemotherapy/allogeneic HSCT patients than autologous HSCT, and prophylactic platelet transfusions should remain the standard of care for chemotherapy/allogeneic HSCT patients. A high 'burden' of bleeding remains in many patients despite prophylaxis, and factors other than those addressed by prophylactic platelet transfusions are important in determining bleeding risk.

Keywords Haematology Malignancy, platelet transfusion
Conflict of interest None

Tuesday 22 October **1030-1130**
ASTH Symposium 5: Congenital Platelet Disorders **Central Hall C**

Congenital Platelet Disorders

Marco Cattaneo
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Congenital abnormalities of platelet function (PFD) are associated with heightened risk for bleeding. Typically, patients with PFDs have mucocutaneous bleeding of variable severity and excessive hemorrhage after surgery or trauma.

The diagnostic laboratory assessment appropriate for the evaluation of suspected inherited PFD should be based on a two-step diagnostic strategy: the first step, based on screening tests, helps raising a diagnostic hypothesis, which should then be tested in the second step, which is based on the use of specific tests. The first step should include: complete blood cell count, examination of the peripheral blood smear and assessment of platelet aggregation. Although light transmission aggregometry (LTA) is the most widely used platelet function test, it is relatively insensitive to defects of platelet secretion; for this reason, laboratory tests that measure platelet aggregation and secretion simultaneously, such as lumiaggregometry, should be preferred to traditional LTA. The second step includes specific tests (e.g., flow cytometry, Western blotting, DNA analysis, etc.).

PFD may be classified in 6 categories: 1) Defects of receptors for adhesive proteins; 2) Defects of receptors for soluble agonists; 3) Defects of signal transduction; 4) Defects of platelet granules; 5) Defects of membrane phospholipids; 6) Miscellaneous platelet function disorders.

Platelet transfusions should be used only to treat severe bleeding episodes. Recombinant Factor VIIa can be used in patients with severe bleeding episodes who do not respond to platelet transfusion because of alloimmunization. Fibrinolytic inhibitors or the vasopressin analogue desmopressin (DDAVP) should be used in all other circumstances.

Keywords Platelet function disorders, platelet aggregation, platelet secretion
Conflict of interest Lecture and advisory board honoraria, research support by Eli Lilly, Daiichy Sankyo, AstraZeneca, The Medicnes Company, Sanofi Aventis.

Tuesday 22 October **1030-1130**
ASTH Symposium 5: Congenital Platelet Disorders **Central Hall C**

Post-thrombotic Syndrome

Leonardo Brandao
The Hospital for Sick Children, Toronto, Canada

Abstract not available at time of going to print

Tuesday 22 October **1030-1130**
HSANZ Lab Haematology Symposium 2: Genome Sequencing **Meeting Room 7**

Genome Sequencing Methodologies for the Haematology Laboratory

Russell Saal
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Somatic mutation status in haematological malignancy is being used with increasing frequency to make treatment decisions. Current methods for the analysis of these mutations are time consuming, costly and difficult to validate in the current regulatory environment. The list of potentially clinically significant mutations is growing rapidly and will undoubtedly change over time as the results of large scale clinical trials become available. Therefore cost effective methods that have the ability to adapt to rapidly changing clinical requirements need to be adopted.

Several applications of next generation sequencing technology hold the promise to solve some of the issues confronting pathology laboratories. Targeted re-sequencing (TRS), whole exome sequencing (WES) and whole genome sequencing (WGS) each have their own limitations. Platforms are currently expensive but with increasing competition and greater uptake, costs are expected to decline. TRS has high sensitivity but is relatively inflexible, requiring development of new assays as new markers are discovered. WES has lower sensitivity and may miss some important mutations/translocations due to limitations in the exome sequence capture technologies. WGS is currently expensive and has similar sensitivity issues but is unlikely to miss mutations/translocations. Sensitivity issues may be overcome as improved analysis algorithms are developed. New external quality assurance programs will have to be developed to ensure regulatory requirements are fulfilled.

While there are significant challenges in the adoption of this new technology in diagnostic settings, WES and WGS utilising a targeted analysis are the preferred approaches as they negate the need for extensive assay redesign and validation resulting from advances in cancer genomics.

Keywords Leukaemia Genomics
Conflict of interest Nil

Tuesday 22 October **1030-1130**
HSANZ Lab Haematology Symposium 2: Genome Sequencing **Meeting Room 7**

Efficacy of Exome Sequencing Acute Myeloid Leukemia in a Clinical Setting

Paul J Leo[1], Gregory Boxall[2], Mahmoud Basal[4], Anna Brown[4], Matthew Brown[1], Richard J D'Andrea[4], Brooke Gardiner[1], Devinder Gill[3], James Gray[5], Paula Marlton[2,3], Mhairi Marshall[1], Russsel Saal[2] and Thomas J Gonda[6]
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Recurrent genetic alterations found in the leukaemia cells of acute myeloid leukaemia (AML) provide prognostic information and are increasingly being used to direct therapy. We describe a pilot project using whole exome sequencing to detect clinically relevant mutations in historical AML samples.

Methods

Whole Exome Sequencing was performed on DNA from 97 participants with detailed pathology. SNPs and small indels were called using Genome Analysis Toolkit (GATK) and annotated with ANNOVAR. CREST, exomeCopy and ExomeDepth were used for large deletion/insertion detection. Additionally a cohort of 957 control exomes (germline DNA) was processed in an identical manner in order to quantify the false positive rate of detected mutations.

Results

We demonstrated that exome sequencing with modest sequencing depth can detect SNPs and structural variations such as the FLT3-IDT over a broad range of blast counts and Allelic Ratios and present those preliminary results.

Future Research

This project had now been extended using Nextera Rapid Exome Capture to establish that data can be reproduced in clinically meaningful time fame. Additionally a significant proportion of this cohort will be sequenced using whole genome sequencing to quantify those mutations that are not accessible with exome capture methods.

Keywords AML , Next Generation Sequencing, Clinical Pathology
Conflict of interest None

Tuesday 22 October **1130-1230**
ANZSBT: Ruth Sanger Oration **Auditorium (Arena B)**

A Work in Progress

Amanda Thomson
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Developments in the processing and storage of blood had led to widespread acceptance and uptake of transfusion as part of the management of a broad range of medical and surgical conditions. However, in the mid 1980's emergence of AIDS and recognition of the potential for the spread of infectious agents via blood changed the reputation of transfusion. Reports of successful management of medical and surgical procedures without transfusion support also raised questions about the indications for blood. These were the early seeds of practice change.

The 1990s saw the birth of the quality and safety focus in healthcare. Change was needed to deliver the level of care patients should expect. The role of specialist nurses began to emerge. Transfusion improvement programmes later followed. A framework of guidelines, standards and governance has progressively developed to support and improve care. Best practice now focuses on a patient-centred approach.

Essential to the quality of care is education: to provide foundation knowledge, awareness of new evidence and 'unlearning' of old beliefs. Our modern world provides both opportunities and challenges.

This presentation aims to sketch some personal perspectives of this 'work-in-progress'.

Tuesday 22 October **1330-1500**
HSANZ Symposium 5: Immunity and Disease **Meeting Room 7**

An Update on the Use of Donor Lymphocyte Infusions

Stephen Mackinnon
University College London, UK

There is a strong graft-versus-leukaemia/lymphoma (GVL) effect following allogeneic stem cell transplantation (SCT) mediated by T cells of donor origin. This antitumor effect is seen in some diseases such as chronic myeloid leukemia (CML) following standard myeloablative conditioning and is enhanced by chronic graft-versus-host disease (GVHD). This GVL activity is more important following nonmyeloablative or reduced intensity conditioning SCT where the chemoradiotherapy is less likely to eliminate residual disease. The most directly compelling evidence for the presence of GVL has been provided by the efficacy of donor lymphocyte infusions (DLI) in generating anti-tumour responses, particularly for relapsed chronic-phase CML. Response rates and durability appear lower with myeloma and AML/MDS, and minimal with ALL. More recently, data suggest that indolent lymphoid malignancies may have durable responses to DLI following reduced intensity SCT, though longer follow up will be required to determine whether this results in long-term cure. Issues that remain to be resolved include the precise nature of the effector cells and their target antigens, the best strategies for separating GVL from GVHD and their effect on the durability of responses, and the role of adjuvant chemotherapy/cytokines.

Keywords donor lymphocyte infusion, graft-versus-tumour, adoptive immunotherapy
Conflict of interest No

Tuesday 22 October **1330-1500**
HSANZ Symposium 5: Immunity and Disease **Meeting Room 7**

Inducible Caspase 9 Safety Switch for Adoptive T cell Therapy

Siok Tey
Bone Marrow Transplant Laboratory, Queensland Institute of Medical Research; Department of Haematology and Bone Marrow Transplantation, Royal Brisbane and Women's Hospital

Unlike conventional pharmaceutical agents, cellular therapeutics are not metabolised or excreted; indeed, the cells can persist and proliferate. Whilst this attribute contributes to the clinical efficacy of cellular therapy, any unwanted effect will also persist and may worsen with time. "Suicide gene" technology is a form of cellular safety switch that enables the conditional elimination of adoptively transferred cells in the event of adverse reactions. In allogeneic stem cell transplantation, suicide genes can improve the safety of donor T cells, which, whilst useful in mediating graft-versus-leukaemia effect, can also cause life-threatening graft-versus-host disease. Suicide gene technology has been studied mainly in the context of haploidentical transplantation, where donor T cells have a narrow therapeutic index. This talk will present the use of a novel suicide gene, inducible caspase 9 (*iCasp9*), to improve the safety of donor T cells in haploidentical transplantation, from its pre-clinical development through to the implementation and results of a first-in-human study. *(N Eng J Med, 2011. Nov 3;365(18):1673-83).*

Keywords Haploidentical transplantation, gene therapy, cell therapy, T cells
Conflict of interest None

Tuesday 22 October **1330-1500**
HSANZ Symposium 5: Immunity and Disease **Meeting Room 7**

The Immunopathogenesis of Hodgkin Lymphoma

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UQ School of Medicine, Experimental Haematology, Translational Research Institute & Department of Haematology, Princess Alexandra Hospital, Brisbane, QLD, Australia

In Epstein-Barr virus (EBV) classical Hodgkin lymphoma (EBV^+ cHL), Hodgkin-Reed Sternberg cell antigen presentation is intact, with viral expression restricted to sub-dominant latent-antigens including LMP1/2A. Large epidemiological studies have reported differential HLA-class I (HLA-I) susceptibility to EBV^+ cHL. The functional basis for these observations is unknown. HLA-I molecules present viral peptides for recognition by $CD8^+$ T-cells, and it may be that the relative risk of developing EBV^+ cHL is due to HLA-I alleles influencing the magnitude of $CD8^+$ T-cell immunity against relevant EBV-specific antigens. However this remains speculative, with immunological evidence lacking. Several non-HLA-I linked genetic susceptibility loci have been identified, and HLA-I associations may simply represent markers for genes of diverse functions that are in linkage disequilibrium to the HLA-I region. An Australasian Leukaemia and Lymphoma Group observational study to address this fundamental question was undertaken, utilizing 4 distinct but complimentary experimental approaches. The data to be presented will illustrate that differential HLA-I-associated susceptibility to EBV^+ cHL reflects altered EBV latent antigen-specific $CD8^+$ T-cell immune hierarchies. For lymphomas expressing a restricted set of poorly immunogenic proteins, even modest $CD8^+$ T-cell responses against relevant tumor-associated proteins confer protection, with broad implications for vaccine design.

Keywords HLA, Hodgkin Lymphoma, EBV
Conflict of interest No conflicts of interest to declare.

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 1: Clinical Transfusion **Central Hall A**
O074 **1330**

Consent for Transfusion – How are we Measuring up to the Guidelines and Standards?

Linley Bielby[1], Lisa Stevenson[1], Jo Perillo[1], Bridget Glazebrook[1], Peter Beard[1], Clare Hennessy[1,2], Marija Borosak[1,2,3]
[1] Blood Matters Consent Working Party, Blood Matters Program, Department of Health Victoria, Australia. [2]Eastern Health, Arnold Street, Box Hill, Victoria, Australia [3] Melbourne Pathology, Victoria Parade, Collingwood, Victoria, Australia

Background
Blood Matters aims to improve clinical transfusion (Tx) practice. The introduction of Australian Commission on Safety and Quality in Healthcare Standards has increased the emphasis for a formalised informed consent process.
Aim
To audit hospitals in Vic, Tas, ACT and NT to determine if:
- Blood & blood product Tx consent policies are available, and consistent with current Australian guidelines/standards
- Blood product administration was undertaken with consent
- Patients understood the consent process.

Method
140 hospitals that transfuse were invited to participate. The 3 part audit included:
- Part A – Desktop audit of hospital-wide blood Tx policy
- Part B – Audit blood Tx consent practice
- Part C – Audit patients understanding of consent.

Audits were entered electronically by each participating hospital.
Result
110 hospitals (79%) submitted data. Tx consent policy was reported in 105 (95%) hospitals, with 48% having a designated Tx consent form. Informed consent was documented in 75% (n=1345) of Tx episodes with red cells comprising 92% of the episodes. Patients recall: being asked to give consent (n=1086 episodes, 80%), being involved in the decision-making process (n=945, 69%), receiving verbal information (n=1167, 86%), receiving written information (n=439, 32%), risks explained (n=931, 68%), and the risks of not receiving a Tx explained (n=672, 49%).
Conclusion
Compliance with current consent guidelines to policy was high. Consent practice, showed documentation in 75% of episodes. Only 69% of patients report being involved with the decision-making process and alternatives to Tx were offered in only 7% of episodes. Results highlight that improvement is required in the areas of documentation of consent and provision of information to patients including risks of, and alternatives to Tx.

Key words Consent, policy, guidelines **Conflict of interest** None

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 1: Clinical Transfusion **Central Hall A**
O075 **1345**

Electronic Blood Tracking: Lessons Learnt From the UK Experience

Helen Atkinson, Gina Aitken, Michelle Britton
Royal Hobart Hospital (RHH), Hobart, Tas, Australia

Aim/Background
Purchase of an electronic access and tracking system for blood fridges was approved after an incident involving administration of incompatible packed red cells collected from a remote blood fridge. This is one component of a complete electronic blood tracking (EBT) system for checking and monitoring all stages of the transfusion process. These systems are widely used in the UK but there is little experience in Australian Hospitals. We became aware of a number of challenges in the implementation of this electronic technology.
The study aim was to learn from the UK experience to determine the most effective strategies for the successful implementation of an EBT system in RHH.
Methods
Visits were made to four UK hospitals with varying demographics, size, EBT systems and duration of use of EBT. Discussions were held with a variety of stakeholders in each institution: laboratory staff, transfusion nurses, ward staff, medical staff, data managers and patients. Differing methods of change management implementation including advertising, education and training, rollout and troubleshooting were explored. Our "assumptions" surrounding the change process were explored.
Results
Many lessons were learnt including

- "Do's and don'ts" of a successful change from the "time honoured" processes of patient identification and blood product administration.
- The many unforeseen scenarios which should be validated by the systems' provider before "going live" in order to avoid the many pitfalls along the way.
- "Change management" issues were not the major cause of a failure to meet the expected outcomes of improved patient safety.

Conclusion
The benefits of an EBT will only be fulfilled by a combination of a well implemented change management plan, a robust IT system, ongoing funding commitment and a well established relationship with both service providers and users. EBT is a tool, not a magic bullet and will not remove individual responsibility for haemovigilance.
The principal author gratefully acknowledges the support of an ANZSBT travel grant which made this work possible.
Keywords Electronic access, Blood tracking, Blood refrigerator **COI** None

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 1: Clinical Transfusion **Central Hall A**
O076 **1400**

High Therapy-related Complications and Mortality in TTP and TMA: Data from the Australian Registry

Sunelle Engelbrecht[1,2], James Sloane[1], Renee Best[1], Zoe McQuilten[1,2,3], Paul Cannell[4], Danny Hsu[5], Nikky Isbel[6], Joshua Kausman[7], Stephen Opat[1,3], Louise Phillips[1], Mark Polizzotto[1], David Roxby[8],Chris Ward[9], Erica Wood[1,3], Solomon Cohney[1,10]
[1]Monash University, [2]Australian Red Cross Blood Service, [3]Monash Medical Centre [4]Royal Perth Hospital Perth WA, [5]Liverpool Hospital, [6]Princess Alexandra Hospital Brisbane QLD, [7]Royal Children's Hospital, *[8]Flinders Medical Centre SA, [9]Royal North Shore Hospital Sydney, [10]Western Hospital [1,3,7,8,10]Melbourne, VIC [5,9]NSW*

Aim/Background
Thrombotic thrombocytopenic purpura (TTP) and thrombotic microangiopathies are rare, making clinical trials difficult. Australian TTP Registry (ATTPR) data are valuable in assessing current therapy (Rx), complications of Rx, and outcomes.
Methods
Analysis of Rx, complications and outcomes in all verified ATTPR cases.
Results
92 cases were analysed in 84 patients. Median age was 45yrs (15–83), 57% female, 14% relapses and 50% with ≥1 precipitant (infection 25%, malignancy 11%, autoimmune 17%, medication 14%, pregnancy/postpartum 4%, HSCT 3%, solid organ 3%). ADAMTS13 was available in 65 cases (<10% in 31/65). Rx data were available for 82 cases: 78/82 (95%) received PEx (FFP in 29%; CDP in 31%; both FFP/CDP in 38%; albumin/FFP in 1%). PEx was by centrifugation in 74%, membrane filtration in 12% and unknown in 14%. Plasma infusions were used in 11/82 cases (without PEx in 4). Additional Rx included: corticosteroids 70%, rituximab 30%, cyclophosphamide 4%, vincristine 2%, and azathioprine 1%. Rituximab was used more in idiopathic than secondary (35% vs 26%), relapsed than de novo (46% vs 28%), and ADAMTS13<10% than >10% (39% vs 18%). 8 cases received platelet (plt) transfusions. Complications of Rx included fluid overload (4%), allergic reactions (14%, including anaphylaxis in 2%), citrate toxicity (4%), infection (11%), and other (5%). Outcomes included: ongoing therapy 21%, complete remission (CR) without impairment 49%, CR with impairment 10%, death in 15%.
Conclusion
Our data show that complications of TTP Rx and mortality remain high. Careful monitoring for Rx-related side-effects is required. Ongoing research is needed to optimise current Rx and find additional targeted therapy.
Keywords thrombotic thrombocytopenic purpura; ADAMTS13; registry
Conflict of interest The ATTPR received an unrestricted educational grant from Alexion Pharmaceuticals Australasia. The company had no role in data collection, analysis or preparing the abstract.

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 1: Clinical Transfusion **Central Hall A**
O077 **1415**

From "Clinical Transfusion Practice" to "Patient Blood Management", The Evolving Message of BloodSafe eLearning Australia

Louise English[1], Trudi Verrall[1], Michele Wood[1], Amanda Thomson[2]
[1]*BloodSafe eLearning Australia, Women's and Children's Health Network, Adelaide*
[2] *Consulting Medical Editor, BloodSafe eLearning Australia, Sydney*

The NHMRC/ASBT Clinical Guidelines on the Use of Blood Components (2002) have been replaced with guidelines aligned with clinical disciplines and promoting patient blood management practices. BloodSafe eLearning Australia has been mandated by the National Blood Authority (NBA) to develop courses based on these guidelines to support healthcare education and organisational implementation.

The Critical Bleeding/Massive Transfusion course, based on the first NBA, Patient Blood Management (PBM) Guideline was released in 2012. This course has been popular with over 2,500 professionals completing it within six months of its release.

A new course is currently being developed to support the second module of the PBM guidelines: Perioperative. A national learning needs analysis of transfusion nurses was conducted in February 2013, which included questions on organisational attitudes and education related to PBM.

When asked what the attitude was towards PBM at their organisation:
- 25% responded that the attitude was "What is patient blood management?"
- 25% replied that staff feel "It's easier just to give some blood if needed"

Identified education methods included:
- 50% used the printed guidelines as a method of delivering PBM education
- 44% stated that their transfusion committee was utilised for PBM education
- 40% currently had no particular PBM education provided

The new focus of the PBM guidelines, coupled with these survey responses, highlighted to BloodSafe eLearning Australia that some general PBM education was urgently needed to improve current understanding and attitudes. A core part of the perioperative course currently under development will be an overview of PBM principles. The drivers for change to a PBM focus will be explained along with the principle of the three pillars of PBM. It is hoped the course will enhance healthcare professional's knowledge, and influence positive attitudes and behaviours.

Keywords eLearning, Patient Blood Management Blood Transfusion
Conflict of interest No

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 1: Clinical Transfusion **Central Hall A**
O078 **1430**

Transfusion Burden After Allogeneic Haematopoietic Stem Cell Transplant

Annette Le Viellez, Duncan Purtill, Richard Herrmann, Julian Cooney, Matthew Wright, Paul Cannell
Department of Haematology, Royal Perth Hospital, Perth, WA, Australia

Aim
To assess overall transfusion burden and to identify factors associated with increased transfusion after adult allogeneic haematopoietic stem cell transplantation
Method
All patients who received their first allogeneic HSCT at our institution from January 2004 until December 2011 were included. Patient, donor and treatment information, including cumulative number of red cell and platelet transfusions at days 30, 90 and 365 post-transplant were collected retrospectively.
Results
174 patients underwent HSCT for acute leukaemia (47%), other haematological malignancy (44%) or other diagnosis (3%) at a median age of 42 yr. 153 (87%) received peripheral blood stem cells, 14 (8%) bone marrow, 7 (4%) cord blood. Recipient-donor pairs were ABO identical pre-transplant in 98 cases (56%), minor incompatible in 33 cases (19%) and major incompatible in 43 cases (25%). The median number of red cell and platelet units transfused by day 30 was 4 (range: 0-20) and 4 (0-32) respectively. Factors influencing the number of units transfused are summarised in the table. After day 30, 70 patients (40%) received further red cell transfusion(s) and 66 patients (38%) received platelet transfusion(s). The median time to last red cell transfusion was 12 days after transplant, and 16 days for platelets.

Factors influencing number of units transfused to d30	Red cells (median)	P value	Platelets (median)	P value
ABO identical vs non-identical	4 vs 6	**<0.001**	4 vs 5	0.15
Donor: matched related vs unrelated	4 vs 4.5	**0.05**	3 vs 5	**0.003**
Stem cell source: peripheral blood vs marrow vs cord blood	4 vs 4 vs 11	**0.003**	4 vs 7 vs 16	**<0.001**
Conditioning: MA vs RI	4 vs 3	0.1	4 vs 4	0.99
Disease stage: early vs intermediate vs advanced	2 vs 5.5 vs 4	0.08	3 vs 4 vs 5	**0.02**
Patient sex male vs female	4 vs 4	0.07	4.5 vs 3	0.14

Conclusion
The overall transfusion burden after allogeneic HSCT is lower than initially expected. The transfusion burden is higher for patients with ABO incompatible donors, unrelated donors or cord blood grafts and in those with more advanced disease at transplantation.
Keywords Transfusion-burden, allogeneic-HSCT **COI** None

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 1: Clinical Transfusion **Central Hall A**
O079 **1445**

Why the 'Checks and Compliance' in Transfusion Practice Are Important and How Haemovigilance Reporting Supports Compliance With Blood and Blood Product Standard 7

Lisa Stevenson, Helen Atkinson, Gerald Bates, Peter Beard, Linley Bielby, Philip Crispin, Merrole Cole-Sinclair, Amanda Davis, Clare Hennessy, Chris Hogan, Bridget Glazebrook, Geoff Magrin, Ellen Maxwell, Scott McArdle, Tina Noutsos, Jo Perillo, Richard Rogers, Carole Smith, Theresa Williamson, Erica Wood
STIR Expert Group, Blood Matters Program, Department of Health, Victoria, and Australian Red Cross Blood Service

Background
Health services are to comply with the new National Safety and Quality Health Service Standards. Laboratories undergo accreditation with the National Association Testing Authority, which completes the regulation loop for blood. Blood and Blood Product Standard 7 (B&BP Standard 7) include the requirement to ensure reporting and management of transfusion-related adverse events (AEs). Blood Matters collects haemovigilance (HV) data and provides recommendations for improved practice through the Serious Transfusion Incident Reporting (STIR) system.
Methods
STIR has standard definitions and case report forms for adverse reactions and process-related incidents. All cases are reviewed by a multidisciplinary expert group.
Results
From 2006 to 2011, STIR has received 851 notifications of transfusion episodes resulting in 860 AEs and incidents: 55 institutions have reported 1 event. 56% were associated with red cell transfusion and acute reactions were the most frequently reported event type (51% total events). Consequences ranged from no clinical impact to serious AEs. Failure of checks and compliance with local policy and guidelines accounted for 43% all events, with "wrong blood in tube" the most common at 24% and "incorrect blood component transfused" at 7%, including 8 ABO incompatible transfusions. Failure of correct patient identification (ID) was the most common compliance failure for all process-related events, with 244 cases related to incorrect patient ID. Reports providing summary findings, demographics, deidentified case studies and recommendations disseminate information to health services (for review and action) and the community.
Conclusion
Safety and quality are important in transfusion medicine and it is the responsibility of all participants in the transfusion chain to protect patients from harm. Participation in HV activities and compliance with B&BP Standard 7 can assist health services to provide safer transfusion for their patients.
Keywords Haemovigilance, compliance, standards
Conflict of interest No

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 2: Tranfusion Science and Laboratory/Inventory Management **Meeting Room 8**
O080 **1330**

A Dynamic Mathematical Model of Red Cell Clinical Demand to Assess the Impact of Blood Shortages and Transfusion Restriction Policies

Zoe McQuilten[1,2], Geoff Mercer[3], Louise Phillips[1], Thiansiri Luangwilai[3], Richard Brown[2], Ieva Ozolins[1], Allen Cheng[1] and Erica Wood.[1]
[1]Monash University, Melbourne, Victoria; [2]Australian Red Cross Blood Service; [3]Australian National University, Canberra, Australian Capital Territory

Aim/Background
Estimating change in clinical demand for red blood cells (RBC) in a disaster, as well as triaging introduced in response, is essential to plan effectively for a major blood shortage. We developed a dynamic RBC demand model to assess the impact of restriction policies on RBC use and patient outcomes.
Methods
A compartmental dynamic model was developed in which patients require RBC acutely (within an hour), urgently (24-hours), semi-urgently (1-7 days) or non-urgently, Outcomes included death, remaining or transitioning to more/less urgent categories. A mathematical model was developed with transitions governed by differential equations and calibrated to a baseline scenario of adequate blood supply (using population-based hospital admission datasets, clinical registries and RBC issues). Distribution into urgency categories was based on the prospective BloodHound study of utilisation of >5000 RBCs. Scenarios were investigated comparing various blood supply limitations to this baseline. Transition rates between urgency categories under these scenarios were established by clinician survey.
Results
In the baseline 21-day scenario, patients requiring the most RBCs were: other surgery (n=2162), medical anaemia (n=1916), malignant haematology (n=1092) and gastrointestinal haemorrhage (n=1115). A policy of withholding RBC for all non-urgent indications results in an estimated reduction of only 1007 (11.2%) RBCs, and, if extended to semi-urgent, a reduction of 2567 (28.5%) RBCs. This estimate takes into account that some deferred patients may still require RBCs during the 21-day period (e.g. patients with chronic transfusion requirements).
Conclusion
Preliminary findings from the model indicate that restrictions that withhold transfusion from non-urgent patients have minimal impact on RBC demand, and may not be sufficient to address changed demand and/or decreased supply during a disaster. Using this model, the effects of different restriction policies, including of different durations with various 'lead-in' times to implement, and across different patient groups, can be evaluated.
Keywords Red cells, contingency planning
Conflict of interest No

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 2: Tranfusion Science and Laboratory/Inventory Management **Meeting Room 8**
O081 **1345**

National Inventory Management Framework (NIMF) Project

Prem Parmar[1], Jo Cameron[2], Terry Jones[1], Rebecca Heland[2], Joanna Nicoloulias[1]
[1] Australian Red Cross Blood Service; [2] National Blood Authority, Australia

Aim

The NIMF project aims to define appropriate red cell inventory levels at health providers and the Blood Service and provide better practice guidelines for effective red cell inventory management. The outcome will be to optimise red cell inventory across the sector to ensure stock is held where it is best placed to provide for patient needs, maintain security of supply and minimise product wastage.

Methods

Red cell inventory bands, developed using safety stock calculations were applied to calculate inventory for a Proof of Concept (POC) hospital. The inventory bands for the hospital were calculated based on the average and variability of the number of red cells that were issued to the hospital against the average and variability of the number of red cells that were transfused. The calculation was at ABO and Rh level, and trigger levels for orders and delivery were revised.

Results

The POC was successful and the hospital was able to operate effectively under revised inventory levels with two routine red cell deliveries per day. The number of urgent deliveries did not increase and sufficient blood was available to meet clinical need. Efficiencies in inventory management were gained, such as having less blood to count and handle and fewer deliveries to manage. The hospital has chosen to maintain the levels as their routine practice, and has further reduced their routine deliveries to one per day.

	Total red cell inventory (units)	Deliveries per day	Orders placed per delivery
Pre – POC	332	2.8	3.9
POC	241	2.1	1.1
% Reduction	*27.4%*	*25.0%*	*71.8%*

Conclusion

Following the successful POC the project has progressed to pilot stage, where this endorsed methodology is being tested at an additional seven sites.

Keywords Inventory, efficiency, red cell
Conflict of interest No

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 2: Tranfusion Science and Laboratory/Inventory Management **Meeting Room 8**
O082 **1400**

Platelet Inventory Management

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New Zealand Blood Service, Auckland, New Zealand

Background
NZBS operates five manufacturing sites nationwide and runs six blood banks in New Zealand hospitals. A further 34 blood banks are operated in New Zealand hospitals by District Health Boards (DHBs). In NZBS operated blood banks products are sold to DHBs at the time of issue to patients. At DHB operated blood banks products are sold to DHBs at the time of transfer from NZBS to the blood bank. Platelets are collected in New Zealand from Monday to Friday and have a five day shelf life.
Aim
To use inventory modelling techniques to improve platelet stock utilisation.
Methods
Historic daily averages of the following production and inventory parameters for the 2012 calendar year were obtained from the NZBS reporting system: units collected, daily opening stock, units issued to patients via NZBS blood banks, sales to DHB blood banks, units expired. A spreadsheet was created with calculations to predict inventory levels, given expected collections, sales to DHBs and issues to patients, and to remove platelets from inventory after five days if not transfused. Predicted inventory levels were compared with actual inventory levels and mean error values determined. Daily collection levels were then modelled to establish patterns of collection which gave the highest and most consistent daily stock levels.
Results
Calculated inventory levels for levels for the Northern, Waikato and Central regions were accurate to an average absolute error of 7%, 3% and 4% respectively. Platelet inventory utilisation in the NZBS Northern Region from 2009 has shown a recent improvement with this model; 2009 73%, 2010 79%, 2011 80%, 2012 82%, 2013 to 30th June 88%.
Conclusion
The optimised collection patterns are now being implemented throughout NZBS to reduce expiry levels without compromising safety. Improved understanding of platelet inventory behaviour can lead to more efficient production planning and better inventory utilization with minimal impact on product availability.

Keywords platelet, inventory, management
Conflict of interest No

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 2: Tranfusion Science and Laboratory/Inventory Management **Meeting Room 8**
O083 **1415**

Preliminary Results for Non-invasive Foetal RHD Genotyping Pilot and Attitudes Towards Prophylactic Anti-D IgG in New Zealand

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Aim/Background
In New Zealand, postnatal prophylactic anti-D immunoglobulin is administered post delivery or after a sensitizing event. New Zealand has an opportunity to introduce antenatal Rh(D) prophylaxis. Non-invasive foetal *RHD* genotyping has been used to guide antenatal anti-D usage, limiting the exposure of this human blood product to women who would benefit: those carrying a Rh(D) positive foetus. This has the potential to reduce the usage of postnatal anti-D by around one third. A validation of non-invasive *RHD* genotyping is currently underway at NZBS – preliminary results are reported. The perceptions of women towards receiving anti-D immunoglobulin were recently investigated in a NZBS audit of 191 who received anti-D. A high number expressed negative comments.
Methods
As part of an ongoing pilot validation, 34 maternal plasma samples from Rh(D) negative women were genotyped using FAM- and Red610-labelled probes in duplex to detect *RHD* exons 5, 7 and 10 from circulating free foetal DNA. *SRY* and *CCR5* were used as foetal and total DNA controls, respectively.
Results
100% specificity and sensitivity were observed. 24 showed the presence of *RHD. RHD* was not detected in 9 samples. 1 sample showed a signal characteristic of a D-variant and is being investigated further.
Conclusion
Despite the current small sample size, these preliminary results are promising, showing a high sensitivity and specificity. In light of women in New Zealand expressing a high rate of negative comments around receiving anti-D immunoglobulin, a robust non-invasive *RHD* assay such as this, and its capacity to reduce the number that need to receive anti-D, is beneficial. This reduces concern in pregnant women and puts less pressure on the anti-D immunoglobulin supply. This assay could also help in the management of alloimmunized pregnancies.

Keywords RHD, ffDNA, anti-D immunoglobulin
Conflict of interest None

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 2: Tranfusion Science and Laboratory/Inventory Management **Meeting Room 8**
O084 **1430**

Non-invasive Prenatal Testing (NIPT) for Fetal *RHD*: Moving Towards Automation

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[1] Research & Development Australian Red Cross Blood Service Brisbane, Queensland, Australia. [2] Mater Health Services, Brisbane, Queensland, Australia

Background
NIPT for fetal *RHD* has been performed by the Blood Service since 2007 & offered since 2009 for pregnancies in which an RhD negative mother is allo-immunised for anti-D. The current manual protocol is suitable for low volume testing but is expensive, laborious & time consuming, thus unsuitable for high throughput population screening.
Aim
To compare performance of the current validated protocol with an automated protocol which includes a simplified interpretative algorithm.
Methods
Plasma was separated from maternal whole blood samples, using a two-step centrifugation process. For the validated protocol cell free DNA (cfDNA) was isolated using a QIAamp Minelute Virus Spin Kit method and *RHD* exons 4, 5 and 10 (quadruplicate), *SRY* and *CCR5* (duplicate) were then amplified by qPCR. For the High throughput procedure cfDNA extraction & PCR set-up were integrated using the QIAsymphony SP/AS, & the DSP virus/Pathogen midi kit v1. *RHD* exons 5 & 10 (triplicate) as well as a single *CCR5* reaction were then amplified by qPCR. Test outcome: "*RHD* detected", "*RHD* not detected" or "*RHD* inconclusive "according to number of *RHD* exon replicates amplified within each protocol.
Results
44 1st trimester, 150 2nd trimester and 22 3rd trimester samples were tested (n=216) and *RHD* fetal predictions were concordant for all but two 1st trimester samples. These 2 cases (6 & 9 weeks gestation respectively) were inconclusive by the validated protocol, and "*RHD* not detected" (6 wk) &" *RHD* detected" (9wk) using the High Throughput protocol. A subsequent sample from the 6 wk case was collected at 12 wks and high throughput testing indicated *RHD* detected.
Conclusion
For samples obtained at a range of gestational ages greater than 9 weeks, fetal *RHD* genotyping using a reduced exon and replicate strategy within an automated high throughput procedure was comparable to the current validated method. The exon 5 and 10 high throughput strategy, that is expected to delineate rare *RHD* variants, provides a basis for moving toward a fully automated procedure.
Keywords *RHD*, cell free fetal DNA, maternal **Conflict of interest** No

Tuesday 22 October **1330-1500**
ANZSBT Free Communications 2: Tranfusion Science and Laboratory/Inventory Management **Meeting Room 8**
O113 **1445**

Platelet Microparticles Contribute to the Procoagulant Activity of Cryopreserved Platelets

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Aim/Background
Freezing platelets with dimethylsulfoxide (DMSO) at -80 °C extends the shelf-life from 5 days to 2 years. Cryopreserved platelets are activated, as evidenced by increased CD62P and phosphatidylserine (PS) expression. Further, cryopreserved platelets have been shown to stem bleeding more effectively than liquid-stored platelets. The aim of this study was to elucidate the mechanisms responsible for the procoagulant activity of cryopreserved platelets.
Methods
Buffy coat-derived platelet concentrates were frozen at -80 °C using DMSO (5% final concentration) as a cryoprotectant. Cryopreserved platelets (n=8) were thawed at 37 °C and reconstituted in a unit of thawed frozen plasma. The procoagulant activity of platelets and platelet microparticles, using supernatant, was assessed prior to freezing (PF) and post-thawing (PT), with the following assays: microparticle enumeration by flow cytometry, clotting potential by thromboelastography (TEG), FXa-induced clotting time (Procoag-PPL assay) using a coagulation analyser, and thrombin generation potential using a calibrated automated thrombogram (CAT).
Results
Freeze/thawing significantly decreased the R-time (PF: 8.9 ± 0.7 min; PT: 4.1 ± 0.3 min) and MA (PF: 67.8 ± 4.3 mm; PT: 59.6 ± 3.7 mm), as measured by TEG. There was also a significant increase in the number of platelet microparticles (PF: 373 ± 113 x 10^6/unit) following cryopreservation (PT: 43,479 ± 10,430 x 10^6/unit). Further, platelet supernatant, enriched for microparticles, induced in a significant reduction of the FXa-based clotting time (PF: 86 ± 19 secs; PT: 11.09 ± 0.6 secs). Similarly, platelet supernatants from cryopreserved units had significantly more thrombin generation potential, as measured by CAT (peak; PF: 36.09 ± 4.52 nM; PT: 341.92 ± 56.74 nM) and a reduced lag time (PF: 7.97 ± 0.41 min; PT: 3.00 ± 0.41 min), compared to liquid stored units.
Conclusion
Platelet cryopreservation results in the generation of PS-expressing platelet microparticles which have a procoagulant phenotype. Understanding the haemostatic profile of these components will help to ensure the best clinical use of these specialised components.
Keywords Platelet, cryopreservation, microparticles
Conflict of interest The authors have no conflict of interest to declare

Tuesday 22 October **1330-1500**
ASTH Free Communications 3: Laboratory Assessment of Thrombosis **Central Hall C**
O085 **1330**

Thrombin Generation Maybe a Better Surrogate Measure of in-vivo Anticoagulation in the Era of New Oral Anticoagulants (NOAC)

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Background
The in-vivo therapeutic range between effective anticoagulation and excess bleeding is narrow, and often requires monitoring. Traditionally, the international normalized ratio (INR) of 2.0-3.0 has been a crude surrogate, but only measures the time to the *start* of clot formation without evaluating total clot formation, and cannot be used for evaluating anticoagulants other than warfarin. The arrival of NOACs has highlighted the need for better anticoagulation tests, particularly since reversal agents are unavailable. Thrombin generation (TG) using Calibrated Automated Thrombogram (CAT©) which measures total thrombin formation and may provide a more wholistic measure of in-vivo anticoagulation.
Aim
Determine the therapeutic range of TG parameters based on the current "gold-standard" therapeutic INR range of 2.0-3.0 for warfarin, as well as describe TG parameters with enoxaparin and rivaroxaban.
Methods
De-identified INR and spiked plasma samples of rivaroxaban and enoxaparin were evaluated for thrombin generation parameters using the CAT. All samples were processed using CAT guidelines.
Results
37 INR samples (range: 1.0-4.2) were evaluated. The therapeutic INR range (2.0-3.0) correlated with median endogenous thrombin potential (ETP) of 364 (range: 203–595) nM.min and thrombin peak of 177 (range: 87-200) nM, with a clear distinction from normal INR of 1.0-1.2. Rivaroxaban-spiked plasma were evaluated and produced a more concave curve with a marked decrease in thrombin peak comparable to warfarin but without significant difference in ETP. Enoxaparin-spiked plasma produced curves similar to warfarin. Evaluation of other NOACS are ongoing.
Conclusion
TG maybe a better surrogate measure of in-vivo anticoagulation. Further evaluation of TG parameters with NOACs, using a therapeutic warfarin INR of 2.0-3.0 as a surrogate gold standard, may help determine the therapeutic range for these new oral anticoagulants.
Keywords thrombin generation, NOACS, ETP
Conflict of interest No

Tuesday 22 October **1330-1500**
ASTH Free Communications 3: Laboratory Assessment of Thrombosis **Central Hall C**
O086 **1345**

Increased Global Hypercoagulable State Amongst Patients With Schizophrenia on Long-term Antipsychotic Therapy

Vincent Chow[1,2], Caroline Reddel[1,2], Gabrielle Pennings[1,2], Elizabeth Scott[3], Tundra Pasqualon[4], Austin Ng[2], Thomas Yeoh[2], Jennifer Curnow[1,2], Leonard Kritharides[1,2]
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[2] *Concord Hospital & University of Sydney, NSW, Australia*
[3] *Brain & Mind Research Institute & University of Sydney, Sydney, NSW, Australia*
[4] *Department of Psychiatry, Croydon Health Centre, Sydney, NSW, Australia*

Aim/Background
Recent meta-analyses suggest patients with schizophrenia on long-term antipsychotics are at increased risk of venous thromboembolism (VTE). We performed the Overall Hemostatic Potential (OHP) Assay, a global coagulation assay, and sought to investigate whether there is a global hypercoagulable state in patients with schizophrenia taking long-term antipsychotics.
Methods
Citrated plasma was collected for OHP assays from patients with schizophrenia on long-term antipsychotic therapy and compared with healthy age and sex matched controls not taking antipsychotics. Fibrin time curves were generated by spectrophotometry measuring absorption of 405nm each minute for 100 minutes after the combination of tissue factor and tissue plasminogen activator with plasma and buffer resulting in formation and degradation of fibrin clot.
Results
89 patients with schizophrenia (antipsychotic treatment-15.9±9.7yrs) and 30 age and sex-matched healthy controls were recruited. Patients with schizophrenia had higher BMI, higher rates of smoking and higher levels of inflammatory markers CRP and neutrophil to lymphocyte ratio than controls. Whereas D-dimer, fibrinogen and platelet count did not differ between controls and patients with schizophrenia, the overall coagulation potential (OCP-54.0±12.6 vs 45.9±9.1, $p=0.002$) and overall haemostatic potential (OHP-12.6±5.8 vs 7.2±3.7, $p<0.001$) were higher and overall fibrinolytic potential were lower (OFP-76.6±9.8%vs 84.9±6.4%, $p<0.001$) in patients with schizophrenia relative to controls.
Conclusion
Hypercoagulable and hypofibrinolytic states are present in patients with schizophrenia on long-term antipsychotic medications. The OHP assay may be a useful screening tool to detect and screen for VTE in this at-risk patient group.
Keywords Schizophrenia, Overall Hemostatic Potential, Hypercoaguability
Conflict of interest None

Tuesday 22 October **1330-1500**
ASTH Free Communications 3: Laboratory Assessment of Thrombosis **Central Hall C**
O087 **1400**

The Importance of Bethesda Assays in the Diagnosis and Monitoring of Thrombotic Thrombocytopenic Purpura (TTP) Patients

Yusra Harahsheh[1,2], Grace Gilmore[1,2], Jim Thom[1,2], Quintin Hughes[1,2], Jasmine Tay[1,2], Lisa Holmes[1,2], Ross Baker[1]
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[2] *Department of Coagulation Research, Royal Perth Hospital, Perth, WA, Australia*

Aim/Background
Thrombotic Thrombocytopenic Purpura (TTP), is an often fatal disease if left untreated. It occurs as a result of microthrombi dissemination, formed as a result of excess platelet deposition to the uncleaved von Willebrand factor (VWF), due to a deficiency of the protease ADAMTS13. Several TTP patients had consecutive samples taken during the TTP episode, and post plasma exchange treatment. Their ADAMTS13 activity levels were tested alongside an in-house anti-ADAMTS13 ELISA to measure their antibody titre and a Bethesda Assay to measure the presence of an inhibitor, and the trends noted.
Methods
ADAMTS13 activity was measured using TECHNOZYM® ADAMTS-13 Activity Kit (Technoclone, Vienna, Austria). An in house ELISA was used to detect anti-ADAMTS13 autoantibodies, using full length rADAMTS13 protein. Test samples were standardized against a series of normal controls to determine positivity (>1.2 ratio). 1 Bethesda unit represents the amount of inhibitor present in the patient's plasma to inactivate 50% of the ADAMTS13 present in the standard human plasma. Patient plasma samples were incubated 50:50 with standard human plasma for 2 hours at 37ºC. A level > 1 was determined to be positive for ADAMST13 Inhibitors.
Results
The patients screened so far all demonstrated high autoantibody titres during the TTP episode, alongside high Bethesda scores (>3) and low activity levels (<5%). Immediately post treatment, activity levels returned to high normal levels (>90-100%), whilst the antibody is <1.2, yet inhibitor levels are borderline (0.5-1.1). In the samples post treatment, activity levels are shown to reduce to below the normal range, yet the antibody titre remains <1.2, whilst the inhibitor levels remain borderline. In a month/s post treatment the ADAMTS13 activity levels return to normal and the antibody titre remain negative. No inhibitor is present.
Conclusion
TTP is an often difficult disease to treat at times, yet performing a Bethesda assay alongside an antibody titre and ADAMTS13 activity assay may be an important aid for the clinician in TTP patient monitoring. Also, by routinely checking the patient's level of inhibitor may be a method of early detecting/preventing a TTP relapse.
Keywords TTP Bethesda Inhibitor Monitoring
Conflict of interest None

Tuesday 22 October **1330-1500**
ASTH Free Communications 3: Laboratory Assessment of Thrombosis **Central Hall C**
O088 **1415**

Patients with Unprovoked Thrombosis and No Identified Thrombophilia have Impaired Fibrinolysis Detected by the Global Overall Haemostatic Potential Assay

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Background
The majority of patients with clinically unprovoked thrombosis do not have a demonstrable hypercoagulable state identified by routine tests. The Overall Haemostatic Potential (OHP) assay is an inexpensive global coagulation assay measuring fibrin generation and fibrinolysis, and has previously been shown to identify hypercoagulable states in patient groups with antiphospholipid syndrome and during pregnancy.
Aims Our aim was to compare OHP assay results from a retrospectively identified group of patients with clinically unprovoked arterial or venous thrombosis and no identified thrombophilia, with a gender-matched control group from the normal population and a group with thrombosis and a known inherited thrombophilia.
Method
Patients referred for investigation of thrombosis had OHP assays performed and recorded in a database from which a study group of 20 patients were identified with no known clinical provocation and no inherited or acquired thrombophilia. The results were compared with 64 normal controls, and 14 patients with inherited thrombophilia. An independent samples T-test was used to test for significant differences.
Results
The study group showed significantly impaired fibrinolysis compared to normals ($p \leq 0.01$), but no difference in overall fibrin generation. No difference in fibrinolysis was seen between the normal controls and the group with inherited thrombophilias.
Conclusion
Impaired fibrinolysis appears to contribute to hypercoagulable states in patients with no known cause for unprovoked thrombosis, but not in patients with an inherited thrombophilic defect. The OHP assay is a simple global test that can identify hypercoagulability, and may ultimately be used to inform recurrence risk assessment and anticoagulation duration in these patients.

Keywords Thrombosis, global coagulation assay, fibrinolysis
Conflict of interest None

Tuesday 22 October **1330-1500**
ASTH Free Communications 3: Laboratory Assessment of Thrombosis **Central Hall C**
O089 **1430**

The Laboratory Challenge of Lupus Anticoagulant Testing

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[2] *Department of Haematology, SEALS North, NSW Health Pathology, Australia*

Aim/Background
The aim of this study was to evaluate a lupus sensitive APTT (low phospholipids and silica as activator) and a resistant APTT (high phospholipids) reagent and to ensure we were following the current Lupus guidelines[1]. This testing was carried out as a quality assurance exercise. It was also to help further test development in our laboratories and to reduce LA testing to two tests: dRVVT and APTT LS/LR.

Methods
376 test and normal plasmas were run undiluted with Vital ® APTT LS and APTT LR reagents using Stago Compact® analyser. The normal reference range for APTT LS and LR was determined from 47 normal donors; and the 99th percentile for the % correction using the equation [(screen-confirm)/screen] x100 was determined in order to establish a local cut-off value.

Results
The normal reference range for APTT LS was 30-42 seconds and for APTT LR was 26-39 seconds (n=47). 313 of the 376 samples were ≤42 seconds for APTT LS. The % correction for each sample was calculated and the 99th percentile for the 313 samples was shown to be 25.4% which compares well with 25.5% of the 47 normal donors. The 376 samples were then re-evaluated for LA. The original result was based on Activated Partial Thromboplastin Time (APTT) using TriniCLOT aPTT S ®; VitaClot ® silicon clotting time (VCT); and dilute Russell's Viper Venom Test (dRVVT) using STA ® screen and confirm, while the new is using the dRVVT unchanged and the new % correction cut-off with APTT LS/LR. By using the new method of dRVVT and APTT LS/LR, 342 of the 376 results (91%) would be unchanged. Incorporating a 1:1 mixing test for all APTT LS >42 seconds excludes samples which showed prolonged APTT due to other reasons.

Conclusion
By combining the dRVVT screen and the confirm testing with APTT LS/LR testing, we are confident that we are continuing to detect the presence of LA while meeting the current lupus guidelines[1].

Reference
1. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, de Groot PG. Update of the guidelines for lupus anticoagulant detection. *J Thromb Haemost* 2009; 7; 1737-40.

Keywords Lupus anticoagulant, APTT, dRVVT.
Conflict of interest No conflict of interest to disclose

Tuesday 22 October **1330-1500**
ASTH Free Communications 3: Laboratory Assessment of Thrombosis **Central Hall C**
O090 **1445**

The Effect of Adenosine/lidocaine/magnesium on Thrombin Generation

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Institute of Health and Biomedical Innovation, QUT, Brisbane, QLD, Australia

Aim/Background
Adenocaine® (adenosine and lidocaine) plus magnesium (Mg^{2+}) infusion has the ability to fully correct coagulopathy in a rat model of hemorrhagic shock. To elucidate if thrombin generation is a potential mechanism for the correction of coagulopathy was seen in our rat haemorrhage model, we examined the effect of adenosine, lidocaine and magnesium on thrombin generation in normal pooled plasma (NPP).
Methods
Calibrated automated thrombography (CAT) was used to measure thrombin generation parameters in NPP preincubated with adenosine, lidocaine and magnesium (ALM) and combinations thereof up to 5 mM each. Clotting was triggered with both PRP and PPP reagent and thrombin parameters were measured using Thrombinoscope™ software (Thrombinoscope BV, The Netherlands).
Results
When PRP reagent triggered clotting in NPP, an increase in lidocaine concentration (0-5mM) significantly increased the thrombin peak (p=0.014) and a non-significant increase in ETP was observed. Adenosine and magnesium did not show any significant correlations with dose. The combination of AL at concentrations representative of the Adenocaine® bolus and *in vivo* rat circulation post-infusion, significantly increased thrombin peak (p=0.03) and ETP (p=0.04). When AL was combined with Mg^{2+}, a non-significant increase in ETP and thrombin peak were observed. Interestingly, when PPP reagent triggered clotting there was a dose dependent increase and correlation in ETP with lidocaine concentration (p=0.016) yet thrombin peak was lower than NPP. In addition, there was an increase in lagtime and time to peak for all concentrations of lidocaine when compared to NPP alone ([L]=5mM; lagtime p=0.001, ttpeak p=0.0001). ALM in combination showed significant increases in lagtime, time to peak and decreases in thrombin generation and ETP when compared to NPP.
Conclusion
Lidocaine increases thrombin generation *in vitro* in normal pooled plasma. The differences observed between PRP and PPP activating reagents possibly suggest differences in ALMs ability to generate or activate endogenous procoagulant phospholipids.

Keywords thrombin generation, adenocaine, coagulopathy
Conflict of interest None

Tuesday 22 October **1330-1500**
Nurses Free Communications 3: Focus on Quality Improvement **Meeting Rooms 5/6**
O091 **1330**

Remote Control: Regional Families' With Inherited Bleeding Disorders and Healthcare Professionals' Attitudes Towards Telehealth Services

Joanna McCosker, Desdemona Chong, Simon Brown, Wendy Poulsen, Moana Harlen
Haemophilia Centre, Royal Children's Hospital, Brisbane, Australia

Aim/Background
The Queensland Children's Haemophilia Centre (QCHC) is a state-wide service which provides treatment, care, and support in Queensland or Northern NSW. To enhance access to treatment for regional families regular outreach clinics have been developed to provide face-to-face contact for families in their local hospital settings. The aims of this study were to assess the attitudes of healthcare professionals and families to telehealth clinics and ascertain the effectiveness of this strategy to improve the care for families in regional Queensland.
Methods
Telehealth clinics were provided over a period of one and a half years. Regional families and healthcare professionals who attended were emailed a questionnaire using a 5-point Likert-type scale to assess their satisfaction and experience of using the telehealth clinics. Descriptive statistics were used to assess questionnaire responses.
Results
Fourteen individuals from 9 families and 10 health care professionals responded to the surveys. The average number of telehealth clinics attended by families was three. Mean scores on satisfaction variables showed families were highly satisfied with the telehealth experience. Reasons rated as "highly important" for participating in telehealth clinics included: ease of attending, reduced time and cost, involvement of both local hospital and health care professionals. Mean scores also showed that health care professionals were highly satisfied with the use of telehealth clinics, but to a slightly lesser extent than families.
Conclusion
Overall both families and staff expressed positive attitudes towards telehealth clinics however there were some components of care considered better addressed in face to face clinic reviews. Nonetheless telehealth clinics have allowed the QCHC team to ensure appropriate clinical follow up (for example 6 monthly reviews for families with severe haemophilia) where previously at most annual reviews were possible. The QCHC team plan to continue telehealth clinics and to build on this improvement in patient management for regional and remote families with inherited bleeding disorders

Keywords telehealth haemophilia satisfaction
Conflict of interest None

Tuesday 22 October **1330-1500**
Nurses Free Communications 3: Focus on Quality Improvement **Meeting Rooms 5/6**
O092 **1345**

Pioneering Survivorship – Providing Care to Patients of Regional and Rural South-West Victoria

Donna Lever[1], Kate Schofield[1], Jane Sharp[2]
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[2] *Western District Health Service, Hamilton, Vic, Australia*

Aim:
The Barwon South West Regional Integrated Cancer Service (BSWRICS) supports (a) regional population residing within Geelong, the Surf Coast, and rural and remote communities extending to the South Australian border. BSWRICS was awarded Victorian Department of Health funding to address cancer survivorship issues for those living in this diverse and geographically extensive region. This project implemented two nurse led clinics to provide patient centred care with a focus on empowerment of the individual, managed primary care and improved use of health resources during the survivorship period. This decision was supported by growing evidence of nurse led clinics and their success to provide holistic care and focus on goals for long term health and well-being.
Method:
Commencing in July 2012, the 18 month project has designed, implemented and commenced evaluation of a nurse led survivorship service within multiple curative treatment trajectories. A focus on the sustainability of the intervention was a focus of the team. Initiated at the regional cancer centre, the survivorship model of care and nurse led clinic was then tailored and implemented into the rural cancer facility.
The study participants were recruited at completion of chemotherapy and/or radiotherapy treatment with curative intent.
Results:
The project utilised the Health Literacy Questionnaire, Assessment Quality of Life (AQoL), Health evaluation in Quality (HeiQ) to evaluate the patient's measure of quality of life, health literacy and acceptance of the process by the participant and care providers. The participants were surveyed before, one week after and finally 3 months post the nurse led intervention. Interim project results and the challenges experienced by this innovative project will be discussed.

Keywords nurse led, survivorship, regional and rural
Conflict of interest None

Tuesday 22 October **1330-1500**
Nurses Free Communications 3: Focus on Quality Improvement **Meeting Rooms 5/6**
O093 **1400**

Quality Improvement in the CML Clinic: A Nurse Co-ordinator Based Intervention

Kylie Porch, Stephen Opat, Jake Shortt
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Aim/Background
Tyrosine kinase inhibitors (TKIs) have vastly improved the prognosis of CML patients. However, most data exists in the setting of closely monitored clinical trials. We aimed to benchmark CML outcomes in a general haematology clinic to identify patients at risk of treatment failure and quality improvement opportunities.
Methods
CML patients treated at Monash Health were identified through public clinic lists and *BCR-ABL* laboratory records. Patients were interviewed by a CML nurse co-ordinator to obtain a holistic overview of current disease and psychosocial status.
Results
33 patients (median age 50, range 21-83; M/F 19/14) with a median duration since diagnosis of 27m (range 2 – 81m) were identified. 11/33 (33%) were English 2nd language patients. 9/33 (27%) had been treated as part of a clinical trial. 32/33 were in chronic phase (CP) of which 23 (72%) remained on 1st line TKI (16 imatinib [IM], 7 nilotinib [NIL]), 8 (25%) on 2nd line TKI (2 IM, 4 NIL, 2 dasatinib) and 1 on 3rd line NIL. Rates of switching from first line TKI for failure or intolerance were similar for IM (5/22) and NIL (2/9). No patient was identified with current TKI intolerance > grade 1. No CP patient had a current suboptimal response by ELN guidelines. The only progression from CP occurred in a non-adherent patient with alcohol dependence. 3 (10%) patients had at least 2 years of CMR with potential eligibility for IM cessation. 10 (30%) patients with adequate responses despite psychosocial risk factors for non-adherence were identified.
Conclusions
A nurse coordinator-based audit confirmed that current outcomes for CML-CP patients in a public clinic are excellent. 'At risk' patients were effectively identified for targeted intervention. A significant number of patients (10%) were also flagged for potential IM cessation. Improved access to nurse coordinators is likely to benefit patients with chronic haematological disorders in the public hospital setting.

Keywords CML, nurse co-ordinator, quality improvement
Conflict of interest Novartis provides salary support for KP.

Tuesday 22 October **1330-1500**
Nurses Free Communications 3: Focus on Quality Improvement **Meeting Rooms 5/6**
O094 **1415**

Minimising Clots in the HPC,A Collection Products

Sushil Narayan, Marianne Fenton
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Aim/Background
Over last 2 years, incidents of varying degrees of clots in pre-processed HPC,A collections had been noticed. Since 2010, incidents appear to have increased, with 9 (9.4%) occasions in 2011. In-depth investigation to isolate and minimise the causes of clots in the HPC,A Collection Products was undertaken.
Methods
A comprehensive investigation was undertaken to isolate the root causes for clots in the HPC,A collections and to implement effective corrective actions including literature searches, flow-chart, suppliers and peers feedback, process review and auditing.
Results
The review showed that the prevalence of clots in fresh HPC,A collection and HPC,A collection stored overnight were similar. Used less peripheral access (4.3% in 2011) when compared to CVAD vascular access (95.7%). CVAD insertion and management techniques were examined, as were complication rates and the catheter patency management of dysfunctional CVAD. No major deficiencies in the CVAD insertion were identified. ACDA and IV calcium interaction and line swaps were not an issue. Selected critical materiel specification review showed no changes in manufacturing or handling. ACDA priming, consumption and use on cell separator was not an issue. Non-positional COM.TEC pressure alarms were associated with access and clot problems. Standard HPC,A collection procedure used locally was consistent with other facilities nationally. Retrospective CVAD Audit of current MedComp provided no further clues. During the prospective audit of the current MedComp CVAD, the relation between inadequate CVAD patency, presence of clots on the CVAD when removed and the appearance of clots in the HPC,A collection became more obvious. The trial of new silicone MedComp CVAD and prospective audit showed that the new silicone MedComp CVAD was better with CVAD patency and minimal clots in the HPC,A collections were observed.
Conclusion
The CVAD trial outcome showed that the use of new silicone MedComp CVAD resulted in the reduction of clots seen in HPC,A Collections from 35.7% to 10%. With a further 50 procedures using the new silicone MedComp CVAD, the clot rate of 2% was achieved, similar to our historical rates, and sustained in 2013. As CVAD access is critical for many patients with cancer for delivery of treatment and supportive care and HPC,A Collection procedures, a new limited data set is now being collected prospectively to monitor and regularly report on this issue.
Keywords Clots in HPC,A Collections, Clots, CVAD. **Conflict of interest** None

Tuesday 22 October **1330-1500**
Nurses Free Communications 3: Focus on Quality Improvement **Meeting Rooms 5/6**
O095 **1430**

Subcutaneous Bortezomib

Jo Brownlee[1], Kim Clark[1], Sharron Ellis[1], Mark Smith[2], Letita Moorhouse[3]
[1]Haematology Day Ward, Christchurch Hospital, Christchurch, New Zealand
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Background
Bortezomib is used as the first line treatment for patients diagnosed with multiple myeloma. In the Haematology Day Ward at Christchurch Hospital we treat between 20-25 patients with multiple myeloma, who are being treated with weekly cyclophosphamide, bortezomib and dexamethasone. Skin reactions to subcutaneous bortezomib are known side effects. These have been described as a patch of redness with or without itch or discomfort. In the Haematology Day Ward we have noticed through feedback from the patients and through our nursing assessment that many patients are experiencing discomfort, erythema, tracking, skin pigmentation changes, dry skin, itchiness, with a small number developing cellulitis. The size of the skin reaction varied. We have decided to assess whether using a different administration technique reduces the development of skin reactions.
Aim
To assess whether a change in the way we administer subcutaneous bortezomib minimised the type of skin reactions experienced by the patients.
Method
For the purpose of this audit we have formulated a nursing initiated skin assessment form and a patient assessment tool. This will review the efficacy of the air sandwich technique in comparison with the standard technique (as per Canterbury District Health Board Policy) and the angle of administration (45 or 90 degrees). The nursing initiated skin assessment form will enable us to document from no reaction to severe reactions. This would cover reactions such as erythema, pain at injection site, blisters, skin discolouration, dryness, tracking, cellulitis and the diameter of the possible skin reaction. The patient assessment tool will be completed by the patient whilst at home. We will ask our patients to score their experience following subcutaneous bortezomib.
Conclusion
We are currently conducting this audit in the Haematology Day Ward. We will present our findings and conclusions at the conference.

Keywords Reducing skin reactions
Conflict of interest None

Tuesday 22 October **1330-1500**
Nurses Free Communications 3: Focus on Quality Improvement **Meeting Rooms 5/6**
O096 **1445**

Bortezomib Use in Myeloma: A Single Centre's Identification for Safer Methods of Individualised Delivery

Tracy King[1,2], Rebecca Meti[1], Doug Joshua[1], Theresa Nielsen[3]
[1] *Institute of Haematology, Royal Prince Alfred Hospital, Sydney, NSW, Australia*
[2] *Sydney Nursing School, Cancer Nursing Research Unit, Sydney, NSW, Australia.*
[3] *Sydney Cancer Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia*

Background
Recent TGA approval of subcutaneous (SC) bortezomib, its reimbursement in the upfront setting and increased access to bortezomib based clinical trials has allowed significant individual variation in its use in patients with multiple myeloma (MM). Traditionally anti cancer drug delivery is dominated by protocols not suited to variance. MM is a complex haematological disease and a number of factors can potentially impact on the optimal delivery of bortezomib. Increasingly patients are reporting extended waiting times in the administration of their dose. With increasing number of patients treated in ambulatory care settings, optimal charting of protocols is an essential component for timely delivery.
Aim
a) To audit bortezomib use over a 10 month period in relation to route, indication, scheduling, charting and frequency of blood monitoring, b) To identify and develop a way to individualise bortezomib therapy in a safe way.
Methods
An audit of dispensed bortezomib from pharmacy logs over a 6 month period was undertaken, with a further 4 months to be completed. Powerchart was also reviewed to identify the frequency of relevant blood tests and indications for therapy. All treatment charts were reviewed to determine variations in ordering, scheduling and protocol use.
Results
Over the six month period 430 doses of bortezomib were given and a 100% increase in monthly doses was observed between the 1st and 6th month. Of the doses administered 74% were given SC and 26% Intravenous (IV). 24% of doses were given in the context of a clinical trial. 36% received bortezomib for frontline and 64% for progressive disease. Two thirds of patients received bortezomib bi-weekly and 4 different bortezomib based regimens were identified. The frequency of blood monitoring within a cycle varied due to patient and / or treatment factors. Inconsistencies in charting were common upon chart review.
Conclusions
There is a high level of variability with bortezomib use in those with myeloma. The development of a standard prescribing chart for bortezomib to allow for clear documentation of variances required is being developed to safely enable individualisation of therapy and reduce waiting times.
Keywords Bortezomib, myeloma, audit **Conflict of interest** None

Tuesday 22 October **1330-1500**
HSANZ: Auditorium (Arena B)

QAP Morphology/Morphology Interactive Case Presentations

Surender Juneja & Katherine Marsden

The slides for this session can be viewed in Meeting Room 3 on Level 1

Tuesday 22 October **1530-1630**
HSANZ Symposium 6: Lymphoproliferative Disorders III **Auditorium (Arena B)**

Current Treatment Strategies for Acute Lymphoblastic Leukaemia

Max S Topp
Department of Internal Medicine at the University of Würzburg, Germany

Acute lymphoblastic leukaemia is a rare condition in adults with an incidence of 1:100.000 patients per year. Risk-adapted protocol have been utilized to offer allogeneic haematopoietic stem cell transplantation to high risk patients identified to have either hyperleukocytosis at diagnosis, genetic alteration such as being Philadelphia positive or harbouring the 4/11 translocation or immunological subgroups.

Recent advances in implementing paediatric based protocols for adult patients have led to a substantial increase in achieving a haematological remission and ultimately a high cure rate as well. Furthermore, integrating elements of targeted therapy elements such as Rituxan for CD20 positive B-precursor ALL or utilizing tyrosine kinase inhibitors for Ph positive ALL during induction therapy and after an allogeneic HSCT have further improved the outlook for ALL patients.

In addition to these advances, standardized minimal residual disease (MRD) monitoring with either flow based methods or through PCR based technologies have established MRD persistence/relapse after induction chemotherapy as the most important adverse risk factor for ALL patients. Hence MRD based treatment algorithms are now being implemented in different study groups resulting in early detection of patients with unfavourable clinical cause and who are then deemed as a high risk group.

Subsequently, an allogeneic HSCT is also offered to these patients who in turn can revert the high probability of relapsing. Nevertheless, despite performing an allogeneic HSCT, the majority of these patients will relapse. Hence new treatment options are urgently needed for such patients. This may be accomplished by introducing Nelarabine into frontline therapy for T-precursor ALL. For B-precursor ALL, two promising agents, blinatumomab and inotuzumab are currently being investigated in clinical trials for their single agent activity in either MRD relapsed/refractory patients or in patients with full blown haematological relapse.

Keywords Acute lymphoblastic leukemia, Pediatric based protocols, minimal residual disease
Conflict of interest Dr Topp has been reimbursed for consultancy services by Amgen

Tuesday 22 October **1530-1630**
HSANZ Symposium 6: Lymphoproliferative Disorders III **Auditorium (Arena B)**

Lessons from the Investigation of Familial Lymphoproliferative Disorders

Jennifer R Brown
CLL Center, Dana-Farber Cancer Institute & Harvard Medical School, Boston, USA

Chronic lymphocytic leukemia is one of the most familial of all cancers, with up to 15% of patients having a 1st or 2nd degree relative who also has a related lymphoproliferative disorder. Families with apparent Mendelian inheritance of CLL are not uncommon in the literature. Much effort has been devoted to trying to elucidate the genetic basis of this predisposition. The relatively limited evidence to date suggests that familial CLL does not differ significantly biologically from sporadic CLL. Linkage and candidate gene association studies have not yielded genes that are altered in a significant fraction of familial CLL. Genomewide association studies have identified common loci in the population which are associated with small increased risks of CLL, but taken together these alleles account for only about 15% of the inherited risk of CLL. Studies of individual families with apparently Mendelian inheritance of CLL have identified presumably higher risk single nucleotide polymorphisms or copy number variants, often in genes implicated in CLL more generally, but these events have generally been unique to those families. These results to date suggest that familial predisposition to CLL may arise from low frequency or rare variants of intermediate penetrance. Ongoing efforts applying next generation sequencing to the germline of affected families will hopefully add additional insights in the coming years.

Keywords familial CLL, germline, next generation sequencing
Conflict of interest Dr. Brown has no relevant conflicts of interest

Tuesday 22 October **1530-1630**
ANZSBT Symposium 6: Under the Radar **Central Hall A**

The Role of Platelet Rich Plasma and Mesenchymal Stem Cells in Musculoskeletal Medicine

Mark Young
Mater Medical Research Institute; QLD University of Technology; QsportsMedicine, Brisane, QLD, Australia

Over the last five years, emerging biotherapies have offered a potential sea change in the treatment of degenerative musculoskeletal conditions. However, most of the touted benefits of interventions such as platelet rich plasma (PRP) and mesenchymal stem cells (MSCs) have yet to be proven in clinical trials.

It is known that the alpha granules of platelets contain mesenchymal tissue growth factors, including: PDGF, TGF, FGF, VEGF, IGF-1, and EGF. In vitro, these growth factors produce differentiation of tissue MSCs and proliferation of progenitor cells. Autologous platelets are easily obtained, and now can be precisely administered within degenerate mesenchymal tissues, with the expectation of creating new tissue. However, even though the techniques appear safe, the evidence of efficacy is still weak. In Australia there are a number of different methods to produce growth factor rich, or leucocyte rich PRP, and many patients with no other options are being offered these interventions. This talk will provide a brief overview of techniques, indications and legislation for PRP applications.

There is also an increasing trend in the use of multi-potent MSCs as a cellular therapy for regeneration of musculoskeletal tissues. Currently, clinical trials are underway for autologous and allogeneic MSCs in the regeneration of bone (phase 3), cartilage (phase 2) and tendon (phase 1) degenerative conditions.
Traditionally, MSCs have required manipulation and expansion but in Australia, biotechnology companies are now promoting non-expanded MSCs, derived from abdominal adipose tissue and bone marrow, as a therapeutic treatment. These cells are harvested and administered within the same appointment, meaning the TGA biological frameworks do not apply. The result is that biotechnology companies offer financial incentives to practitioners to administer these treatments, before safety and efficacy of the techniques has been established.

Keywords Multipotent; Growth-Factors; Regeneration
Conflict of interest None

Tuesday 22 October **1530-1630**
ANZSBT Symposium 6: Under the Radar **Central Hall A**

Reinfusion Drains

Tyson Doneley
Orthopaedics, QEII Hospital, Brisbane, QLD, Australia

Abstract not available at time of going to print

Tuesday 22 October **1530-1630**
ANZSBT Symposium 6: Under the Radar **Central Hall A**

Speaker withdrawn

Tuesday 22 October **1530-1630**
ASTH Symposium 6: Paediatric Haematology **Central Hall C**

MY9 Disorders in Haematology

Jeremy Robertson
Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia

Abstract not available at time of going to print

Tuesday 22 October **1530-1630**
ASTH Symposium 6: Paediatric Haematology **Central Hall C**

Familial Haemophagocytic Lymphohistiocytosis: History and Perspectives

Ilia Voskoboinik, Joseph A Trapani
Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, VIC, Australia

Cytotoxic T lymphocytes and natural killer cells, collectively called cytotoxic lymphocytes, eliminate virus-infected or malignant cognate target cells. They achieve this by secreting a pore-forming protein, perforin, and pro-apoptotic serine proteases, granzymes, into the immune synapse between the killer and a target cell.

Failure to deliver functional perforin results in a fatal immunoregulatory disorder Familial Haemophagocytic Lymphohistiocytosis (FHL). FHL is an autosomal recessive disease associated with mutations in one of four genes, which either encode perforin (*PRF1*) or proteins that are essential for its delivery to the synapse, *UNC13D* (Munc13-4), *STX11* (Syntaxin11) and *STXBP2* (Munc18-2). The loss of cytotoxic lymphocyte function leads to uncontrolled activation and proliferation of cytotoxic T lymphocytes, cytokine storm, macrophage activation and eventual organ failure leading to death. The only curative option is bone marrow transplantation.

Historically, FHL has been considered a disease of infancy, with most children being diagnosed before the age of 6 months. However, more recently, it has become apparent that the onset and clinical features of FHL can vary considerably, and that some cases of “atypical” FHL may not present until late childhood, adolescence or even adulthood.

“Atypical” FHL can be manifested as increased susceptibility to certain viral infections, eg. EBV, or as idiopathic systemic inflammation. Recently, we discovered that 50% of individuals, who carried bi-allelic mutations in perforin, but remained disease-free until the age of 10, developed a range of haematological cancers as their primary pathology. Furthermore, we found that a cohort of adult cancer patients, who presented with dual primary tumours, melanoma and B cell lymphoma, had significantly higher frequency of monoallelic perforin mutations.

Overall, the clinical and experimental data strongly suggests that FHL is a far broader clinical syndrome than previously suspected, and should be considered in the differential diagnosis of many immune-based disorders.

Keywords haemophagocytosis, cytotoxic lymphocytes, cancer
Conflict of interest None

Tuesday 22 October **1530-1630**
Nurses Workshops (Session B)

For abstracts of the concurrent workshops, refer pages 121 to 125

Tuesday 22 October **1630-1730**
HSANZ Masterclass 8 **Meeting Room 3**

Waldenstroms Macroglobulinaemia

Meletios A Dimopoulos, Evangelos Terpos, Efstathios Kastritis
Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Waldenström's macroglobulinaemia (WM) is a rare disorder defined by the infiltration of the bone marrow by lymphoplasmacytic cells which produce a monoclonal IgM. The extent of marrow infiltration (or other lymphoid organs), the quantity and the chemical properties of the monoclonal IgM determine the spectrum of the clinical and laboratory disorders of WM. Specific criteria for initiating therapy have been proposed and an international prognostic index (ISSWM) for symptomatic patients has been developed in order to improve prognostication.
Survival and homing of WM cells largely depends on PI3K/Akt and NF-κB signalling, while deregulated miRNAs, upregulated IL-6 expression, altered chemokine production (i.e. CCL-3) and mast cells within the WM microenvironment further support the WM cell survival. Recently, the identification of a somatic mutation in the MYD88 gene was found in ~90% of WM patients. Importantly, the disruption of MYD88 pathway signalling induces apoptosis of WM cells.
Alkylating agents and nucleoside analogues were the backbone of therapy for several decades. Rituximab has minimal toxicity, but, as a monotherapy is associated with modest response rates and a transient increase of serum IgM ("IgM flare") in 30%-80% of patients, which may exacerbate IgM-related complications. Combination of rituximab with chemotherapy (such as DRC) improved response rates but CRs are infrequent. Combinations with more intensive chemotherapy (R-CHOP) or nucleoside analogues (FR or FCR) induce higher response rates but with significant toxicity. Bendamustine with rituximab is a promising combination with less toxicity. However, almost all patients with WM will relapse after initial therapy.
Proteasome inhibitors have been also used in WM. Single agent bortezomib induces major responses in 25%-60% of WM patients but in combination with rituximab major responses may be as high as 50%-80%. Bortezomib reduces IgM levels rapidly and is not myelotoxic. However, peripheral neuropathy remains a major toxicity of bortezomib; alternative schedules and dosing or route of administration (sc) may reduce neurotoxicity. Carfilzomib is also promising but further investigation is needed. Monoclonal antibodies (alemtuzumab and ofatumumab), everolimus (mTORC inhibitor) and perifosine (Akt inhibitor) have shown encouraging results. Ibrutinib, a BTK inhibitor, induced significant response rates in pretreated patients with WM and has been granted a breakthrough therapy designation by the FDA.

Key words Waldenström's macroglobulinaemia, biology, therapy
Conflict of interest Honoraria from Janssen-Cilag, Onyx and GSK.

Tuesday 22 October **1630-1730**
HSANZ Masterclass 9 **Meeting Room 6**

Biology and management of del 5q in MDS

Alan List
Moffitt Cancer Centre, Tampa, USA

Abstract not available at time of going to print

Tuesday 22 October **1630-1730**
HSANZ Masterclass 13 **Meeting Room 7**

Hodgkin Lymphoma – ABVD, BEACOPP, Brentuximab and Beyond

Max S Topp
Medizinische Klinik und Poliklinik II, Universität Würzburg, Germany

Hodgkin Lymphoma (HL) is highly curative disease by combining chemotherapy with involved field radiotherapy. For early/favourable HL standard therapy is based on the ABVD combination and is applied to patients both in US, Europe and Australia. For advanced/unfavourable HL most countries outside Europe would consider 8 courses of ABVD as the standard chemotherapy + radiotherapy. In contrast the majority of European study groups would favour 6 cycles escalated BEACOPP as the standard therapy and applying radiotherapy only to PET positive lymph nodes. A recent Cochrane analysis of 11 different regimens in 9993 patients demonstrated that 6x BEACOPP esk is associated with 10% survival benefit over 8x ABVD. Secondary malignancies rate is not statically significant between both groups. Currently strategies identifying early response through interim PET are performed in many national trials and may result in sparing some patients from being over treated. In addition, anti-CD30 directed chemotherapy with Brentuximab, which has the highest single agent activity reported in HL yet, is integrated in frontline therapy for further reduction of toxicity and is currently tested in both early disease HL and advanced HL. In addition a bispecific antibody construct targeting CD30 on the HL cells and activating NK-cell through CD16 has shown clinical activity in heavily treated HL patients and may further strength immunological approaches of treating HL without the toxicity of chemotherapy.

Keywords: Hodgkin Lymphoma, Intensive Chemotherapy, Immunotherapy
Conflict of Interest: Consultancy for Affimed.

Tuesday 22 October **1630-1730**
ANZSBT Masterclass 10 **Meeting Room 8**

Red Cell Phenotyping and Genotyping for Transfusion

Jonathan P Wallis
Department of Haematology, Freeman Hospital Newcastle upon Tyne, UK

The session will explore and discuss, through analysis of cases and the literature, the value or otherwise of extended antigen phenotyping, genotyping and pre-emptive extended antigen matching in different populations requiring blood transfusion.

Keywords Antigen phenotyping,genotyping, tranfusion
Conflict of interest None

Tuesday 22 October **1630-1730**
ANZSBT Masterclass 11 **Meeting Room 7**

Changing Transfusion Culture - What Works

Joseph Thomas
Strategic Healthcare Group LLC, Indianapolis, USA

Abstract not available at time of going to print

Tuesday 22 October **1630-1730**
ASTH Masterclass 12 **Meeting Room 5**

Management of Venous Thromboembolism (VTE) – Controversial Areas

David Keeling
Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, United Kingdom

Despite the availability of comprehensive evidence-based guidelines there are difficult and controversial areas in the management of venous thromboembolism. Institutions and even countries disagree on the importance of calf vein thrombosis with some rigorously detecting and treating it and others deliberately not looking for it.
The need to treat proximal deep vein thrombosis and pulmonary embolism is accepted but which patients with an unprovoked first event should have long-term anticoagulation has become a difficult clinical decision.
We are uncertain how to reduce the incidence of post-thrombotic syndrome seen in a substantial number of patients.
How hard to look for an undiagnosed underlying cancer has become a contentious issue particularly in the United Kingdom following the recent publication of a guideline from the National Institute for Health and Clinical Excellence.
Whilst we are wrestling with these dilemmas we are entering a new era of oral anticoagulation and have to solve the logistical problems of introducing them into our clinical practice despite cost pressures.
These issues will be explored in this session.

Keywords anticoagulation, venous thrombosis
Conflict of interest I have received honoraria for attending Advisory Boards from Pfizer, Bayer, Boehringer Ingelheim, Daiichi-Sankyo

Wednesday 23 October **0900-1000**
HSANZ Free Communications 8: Lymphoma **Auditorium (Arena B)**
O097 **0900**

Adding High-dose Intravenous (IV) Methotrexate (MTX) to Standard Therapy is Associated With Lower Central Nervous System (CNS) Relapse in Patients With High-risk Diffuse Large B-cell Lymphoma (DLBCL)

Chan Y Cheah[1,2], Kirsten E Herbert[1,2], Kacey O'Rourke[3], Glen A Kennedy[3], Anupkumar George[1], Pasquale Fedele[4], Shuh Ying Tan[4], Stephen S Opat[4,5], Kate Burbury[1], Max Wolf[1,2], Elchanan H Januszewicz[1], Michael Dickinson[1], David Westerman[1,2], H Miles Prince[1,2,5], Dennis A Carney[1,2], Simon J Harrison[1,2] and John F Seymour[1,2]
[1]Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [2]University of Melbourne, Parkville, Melbourne, Victoria, Australia, [3]Department of Haematology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia, [4]Department of Haematology, Monash Medical Centre, Clayton, Victoria, Australia [5]Monash University, Clayton, Victoria, Australia

Aim/Background
CNS relapse of DLBCL is a devastating and typically fatal complication and the optimum strategy for prevention of remains unclear, although it is recognised intra-thecal (IT) chemotherapy alone is inadequate.
Methods
We performed a multi-centre, retrospective analysis of patients with DLBCL considered to have a high risk for CNS relapse as defined by two or more of: 1) multiple extranodal sites 2) raised serum LDH 3) B-symptoms, OR involvement of specific high risk anatomical sites. Patients treated from 1996 – 2011 were included. We compared 3 strategies of CNS directed therapy: IT MTX in conjunction with (R)-CHOP chemotherapy "group 1"; (R)-CHOP chemotherapy with two cycles of high-dose IV MTX (1-3g/m^2) in addition to IT MTX "group 2"; dose-intensive antimetabolite-containing chemotherapy (R)-Hyper-CVAD or CODOX-M/IVAC) including both IT and IV MTX "group 3".
Results
Overall, 208 patients were identified, with 32, 134 and 42 in groups 1, 2 and 3, respectively. Baseline risk factors for CNS relapse were comparable between groups. With a median follow up of 3.7 (range 0.4–18.6) years, 19 CNS relapses occurred (7, 11 and 1 in groups 1, 2 and 3 respectively). The 3-year actuarial incidence of CNS relapse was 17.6% (95% CI 1.5–48.8), 7.3% (0.6–25.9) and 2.4% (0.0–59.2) in groups 1, 2 and 3, respectively (P=0.026). In univariate analysis, rituximab and use of IT MTX were not associated with a reduction in CNS relapse.
Conclusion
The use of IV MTX and dose-intense chemotherapy were associated with lower incidence of CNS relapse compared with IT chemotherapy alone.
Keywords diffuse large B-cell lymphoma, CNS relapse, CNS prophylaxis
Conflict of interest None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 8: Lymphoma **Auditorium (Arena B)**
O098 **0915**

Immunohistochemical 'Cell of Origin' Classification is Highly Predictive of Clinical Outcome in an Unselected DLBCL Cohort

Zheng Wang, Beena Kumar, Sanjeev Chunilal, Stephen Opat, Jake Shortt
Monash Health, Melbourne, VIC, Australia

Aim/Background
Distinguishing activated B-cell (ABC) from germinal centre B-cell (GCB) DLBCL by expression profiling provides independent prognostic information. Histological algorithms seeking to separate ABC from GCB have had mixed published results. We tested the prognostic value of IHC cell of origin determination on an unselected cohort of DLBCL specimens.

Methods
All DLBCL biopsies at Monash Health from 2005-2010 were tracked from the pathology reporting system to generate a tissue microarray of 53 cases. Lymphomas were classified using both Choi and Hans algorithms by a pathologist blinded to patient outcomes. Survival and clinical data were determined retrospectively from case notes.

Results
Survival data was available for 49/53 cases (median follow-up 40m; range 0-90m). Samples were from initial diagnosis (*n*=47), relapse (*n*=5) or autopsy (*n*=1) and included DLBCL NOS (50/53), anaplastic DLBCL (2/53) and PMBCL (1/53); 8 had transformed disease. Subclassification by Choi disclosed 27 as ABC, 21 as GCB; 5 were indeterminate. Choi and Hans' diagnoses were generally concordant (43/48 cases). The majority of cases received RCHOP-based initial therapy. ABC and GCB cohorts were matched for age (median 64 *vs.* 59yrs, p=0.41) and gender (both 32% female), however ABC patients were more likely to have a high risk IPI (24 *vs* 58%, p=0.01). Median overall survival was not reached for ABC or GCB cases (48% *vs.* 10% mortality at median follow-up 12m *vs.* 55m respectively; p=0.01 for survival difference [log rank]).

Conclusion
IHC-based cell of origin classification provided significant prognostication in an otherwise unselected cohort of predominantly DLBCL-NOS. The worse outcome of ABC subtype is partially explained by an association with higher IPI. Our analysis further validates IHC as a means to distinguish ABC from GCB DLBCL without the complexity of gene expression profiling.

Keywords DLBCL cell of origin, Immunohistochemistry
Conflict of interest None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 8: Lymphoma **Auditorium (Arena B)**
O099 **0930**

Positive End of Treatment, But not Interim, PET-CT Scans Predict Inferior Outcome in Patients with Primary Mediastinal B-cell Lymphoma

Chan Y Cheah[1,2], Michael S Hofman[2,3], John F Seymour[1,2], David S Ritchie[1,2], Andrew Wirth[1,2], H Miles Prince[1,2,4], Max Wolf[1,2] Elchanan Januszcewicz[1], Dennis A Carney[1,2], Kirsten Herbert[1,2], Simon J Harrison[1,2], Kate Burbury[1,2], Constantine S Tam[1,2]
[1]Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [2]University of Melbourne, Parkville, Melbourne, Victoria, Australia, [3]Centre for Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [4]Monash University, Clayton, Victoria, Australia

Aim/Background
Published data concerning the value of PET-CT scanning in primary mediastinal B-cell lymphoma (PMBCL) are lacking.
Methods
We performed a retrospective analysis of 28 patients with PMBCL to determine the rates of positivity and predictive value for disease relapse for interim (after cycles 2-4) and end of treatment PET-CT scans. PET-CT scans were interpreted using 1) visual analysis, 2) 5-point scale and 3) change( ) in SUVmax (>70% v ≤70%). Patients were treated with CHOP+/-R (*n*=21), DA-EPOCH-R (*n*=4) or HyperCVAD+/-R (*n*=3). Radiotherapy was delivered to 17 (61%) of patients, primarily as a planned component of therapy.
Results
After a median follow up of 2.6 (range 0.4 - 11) years, four patients have relapsed, of whom two have died from disease. The actuarial 2-year PFS and OS rates are 86% and 94%, respectively. Of 24 patients with interim scans, by the stated analytic methods 29-37% were positive; positive predictive values (PPV) of interim PET for relapse were 14-22%. A positive interim scan was not associated with inferior PFS regardless of method of interpretation. End of treatment PET was positive in 24-32%; PPV for relapse was 12-50%. Positive scans scored by visual analysis and 5-point scale were associated with inferior PFS. Several patients with persistent metabolically active residual mass underwent biopsies which showed necrosis but no lymphoma.
Conclusion
There is no role for routine interim PET given its poor PPV for relapse and the generally favourable prognosis of PMBCL. Positive end of treatment PET scan by visual analysis or 5-point scale predicts inferior PFS but an inflammatory response resulting in metabolic abnormality is not infrequently observed and is difficult to differentiate from residual disease. Metabolically active residual masses should be biopsied prior to further treatment decisions.
Keywords primary mediastinal B-cell lymphoma, PET-CT; interim PET-CT;
Conflict of interest None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 8: Lymphoma **Auditorium (Arena B)**
O100 **0945**

Evaluation of the Nanostring® nCounter GX Human immunology Panel (HIP) to Characterise B-cell and T-cell Lymphoproliferative Disorders in Formalin-fixed Paraffin-embedded (FFPE) Samples

Piers Blombery, Jonathan Weiss, Hongdo Do, Alexander Dobrovic, David Westerman, Jason Ellul, Richard Tothill, David Ritchie, Michael Dickinson
Peter MacCallum Cancer Centre, Victoria, Australia

Aim/Background
FFPE processing of tissue fragments RNA, hampering PCR amplification required for conventional gene expression profiling (GEP) platforms. The Nanostring® nCounter analysis system GEP platform does not require an amplification step. The aim of this proof-of-principle project was to evaluate the performance, in our hands, of the Nanostring® off-the-shelf 511-gene HIP panel as a way of distinguishing subtypes of B and T-cell lymphoproliferative disorders (LPDs) and to demonstrate that this platform is an appropriate method for GEP using standard archival FFPE diagnostic specimens for future planned projects at our centre.
Methods
24 archival diagnostic samples representing various B and T-cell LPDs were chosen (22xFFPE, 1xbone marrow aspirate and 1xbone marrow trephine). Histological subtype was confirmed using current WHO criteria (2008) and recognised immunohistochemical classifiers (GCB vs. ABC). A 39 gene novel classifier for GCB vs ABC was created by testing the CodeSet against annotated publicly available GEP data (GSE4475, GSE10172, GSE22470). RNA extracted from samples was analysed using the nCounter analysis system with the HIP.
Results
21/22 FFPE samples yielded RNA of acceptable quality. The novel classifier correctly predicted GCB vs. ABC subtype in 10/10 cases. In T-cell LPDs, hierarchical clustering using a subset of genes in the CodeSet separated ALCL into ALKpos and ALKneg and identified one case which was characterised by prominent expression of KIR markers.
Conclusion
The Nanostring® HIP can distinguish GCB from ABC subtypes of DLBCL as well as different groups of T-LPDs, and provides useful and interpretable information from RNA extracted from standard diagnostic FFPE tissue. The nCounter analysis system has been adopted at our centre for future planned studies of FFPE tissue.

Keywords Gene expression profiling, lymphoma, Nanostring
Conflict of interest No

Wednesday 23 October **0900-1000**
HSANZ Free Communications 9: Acute Leukaemia **Meeting Room 6**
O101 **0900**

Phospho-Flow Analysis to Identify Lesions in B-ALL

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Aim/Background
While significant progress has been made to identify various subtypes of B cell acute lymphoblastic leukaemia (B-ALL), in approximately 25% of cases the underlying lesion remains unclear. Mullighan et al. have recently demonstrated in the paediatric setting that many of these high risk cases have gene expression profiles akin to those observed in Ph^+ ALL, and importantly are associated with genetic lesions which result in activated kinase signalling.
Methods
Here we report the use of phospho-flow to identify the underlying chromosomal and mutational aberration in a 36 year old ALL patient, diagnosed with standard risk B cell ALL who relapsed early after allogeneic stem cell transplant.
Results
Samples of blood from diagnosis and bone marrow collected at the time of relapse were thawed and both revealed a small but significant population of $CD10^+19^+$ cells which co-expressed high levels of CRLF2. These cells also showed elevated STAT5 phosphorylation, which was decreased *in vitro* upon JAK, but not ABL, inhibition. Based on these finding re-examination of the diagnostic cytogenetics analysis using FISH revealed a cryptic t(X;14), which results in the upregulation of CRLF2 and is often associated with JAK mutations distinct from JAK2 V617F occurring in myelodysplastic/myeloproliferative disorders. Indeed, direct sequencing of both JAK1 and JAK2 revealed a JAK2 R687S mutation (approximately 30%).
Conclusion
This case clearly demonstrates that the screening of patients by phospho-flow allows for the identification of candidate genes/pathways which can then be interrogated specifically using standard techniques (Sanger sequencing) or next generation genomic approaches, to identify treatment approaches in this group of high risk patients. Currently, we are examining a large patient cohort applying phospho-flow as a screening tool.
Keywords ALL, kinase inhibition, JAK
Conflict of interest DW and TH receive research support from Novartis and BMS

Wednesday 23 October **0900-1000**
HSANZ Free Communications 9: Acute Leukaemia **Meeting Room 6**
O102 **0915**

Comparison of Two Paediatric Protocols: BFM-95 is Less Deliverable than FRALLE-93 without Improving Long Term Outcomes in Young Adults with Acute Lymphoblastic Leukemia (ALL)

Pohan Lukito [1], Jay Hocking [1, 2], Jia Wei Woo [2], Anthony P Schwarer [2], David J Curtis[1]
[1]Alfred Health Haematology, Melbourne, VIC, Australia. [2]Eastern Health Haematology, Box Hill, VIC, Australia

Aim/Background
Retrospective analyses show that young adults (15-40 yrs) with ALL benefit from paediatric-adapted regimens although it is unclear which paediatric regimen is best tolerated in this population. This study aims to compare the deliverability and long-term outcome of two paediatric protocols used for young adults with ALL.
Methods
We performed a retrospective analysis of all adult patients with ALL treated with either a BFM-95 high risk protocol or the FRALLE-93 protocol at the Alfred and Box Hill Hospitals between 2005 and 2012. As the primary outcome, we analysed the proportion of patients who reached the maintenance phase of the protocols having received all blocks of therapy. Another measure of tolerability was the proportion of patients proceeding to allogeneic stem cell transplantation due to therapy related toxicity. Secondary outcomes included complete remission (CR) rate after induction, overall survival and disease free survival.
Results
A total of 9 and 21 patients were analysed for the BFM-95 and the FRALLE-93 protocols respectively. There were no statistically significant differences in patients' demographics. Only 3 patients (33%) in the BFM group had reached the maintenance phase of protocol compared to 18 (86%) patients in the FRALLE-93 group (p= 0.004). Furthermore, 3 patients (33%) proceeded to transplant due to toxicities of BFM, whilst no patients in the FRALLE-93 group were removed off protocol due to toxicity. Importantly, the CR rate (89% vs 100%) and disease free survival at 3 years (81% vs 78%) were not significantly different between the BFM-95 and FRALLE-93 treated patients.
Conclusion
BFM-95 high risk protocol is less deliverable than FRALLE-93 in young adults with ALL. This study indicates that paediatric protocols are not all the same in terms of tolerability when applied to the adult population.

Keywords ALL, young adults, BFM protocol
Conflict of interest None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 9: Acute Leukaemia **Meeting Room 6**
O103 **0930**

Do Younger Patients with Monosomal Karyotype Acute Myeloid Leukaemia Benefit from Conventional Induction Chemotherapy?

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Aim/Background
Monosomal karyotype (MK) is classified as a poor prognostic factor in adult patients with acute myeloid leukaemia (AML). The survival outcome is dismal even when treated with intensive chemotherapy, and reported 4-year overall survival is between 0 to 10% in clinical trials. The aim of this study was to compare outcomes of patients with MK AML at our centre and that of published data.
Methods
Cytogenetic records of all patients diagnosed with AML in our centre between 1 January 2000 and 31 December 2012 were reviewed retrospectively. Patients with MK AML aged 16 and above at the time of diagnosis were included in the analysis.
Results
Thirty patients were identified to have MK as defined by Breems et al 2008. The mean age of the cohort was 64 years (range: 39.9-81.9) with 19 (63.3%) age greater than 60. Concurrent complex karyotype, abn(17p), and -5/5q- occurred in 28 (93.3%), 16 (53.3%) and 27 (90.0%) patients respectively. Ten (33.3%) of the patients were suitable for conventional AML induction chemotherapy, of which 9 were younger than 60. Seven achieved complete remission with 3 proceeding to allogeneic stem cell transplant afterwards. One patient was transplanted in second remission. The estimated 4-year overall survival for the whole group was 13% (95% CI: 1 - 25%) with a median survival of 3.1 months (95% CI: 1.67-5.53). Those who received conventional AML induction chemotherapy had a significantly better 4-year overall survival of 38% with a median survival of 11.5 months (95% CI: 3.9-19.2, p-value <0.05).
Conclusion
Although the outcome for patients with MK AML is poor, this small series suggests that younger patients should be considered for AML induction therapy followed by allogeneic stem cell transplant.

Keywords Acute myeloid leukaemia, monosomal karyotype
Conflict of interest No conflict of interest to disclose

Wednesday 23 October **0900-1000**
HSANZ Free Communications 9: Acute Leukaemia **Meeting Room 6**

O104 **0945**

Outcomes of Patients with Relapsed Acute Myeloid Leukaemia (AML) Who Did Not Receive Allogeneic Stem Cell Transplantation (SCT) in First Remission (CR1)

Shaun Fleming, Andrew Lim, Naomi Sprigg, Ashish Bajel, Andrew Roberts, Jeff Szer, David Ritchie
Royal Melbourne Hospital, Melbourne, Vic, Australia

Aim
To determine the outcome of remission induction therapy for AML in first relapse.
Methods
A retrospective review of patients identified through our institutional leukaemia and pathology databases between January 2000 and December 2011 was undertaken. Inclusion criteria were age < 70 years, AML by marrow criteria, confirmed prior CR1, relapse, no prior transplant, treated with either reinduction chemotherapy or immediate transplantation at relapse. Patient data were analysed for MRC and ELN risk category, duration of CR1, post-relapse salvage type, attainment of second remission, relapse free survival (RFS) and overall survival (OS) from relapse.
Results
Of 341 patients with AML, 194 received remission induction chemotherapy of whom 154 achieved CR1. Fifty were excluded due to receiving SCT in CR1. Of the remainder (n=104), 73 patients relapsed, of which 39 received either salvage induction chemotherapy (+/-subsequent transplantation) (n=29) or immediate allogeneic transplantation without further induction (n=10). For the entire cohort of 73 patients with relapsed AML the 5-year OS was 18%. In the group of 39 patients receiving further therapy, the overall rate of second remission (CR2) rate was 69%, and the median RFS was 343 days, with 5-year RFS and OS of 30.5% and 36% respectively. Risk factors for worse 5yr-OS were age>50 years (0% vs. 51%, p=0.0002), CR1 duration<8 months (chosen on basis of earlier unit transplant data) (13% vs. 46%, p=0.0002) and other than good risk by MRC classification (80% vs. 27%, p=0.06). Long-term survival was only seen in patients attaining CR2 and received an allogeneic SCT at first relapse or CR2, longer-term survivors in patients older than 50 have been seen since an institutional policy change allowing for SCT. Most relapses post CR2 were at <7 months, with 75% at <1 year. A scoring system based on age>50, CR1<8 months and cytogenetics other than good predicted for a 5-year OS of 46%, 39% and 10% for 1, 2 or 3 risk factors respectively.
Conclusion
Relapsed AML portends a poor overall prognosis. Patients with early relapse, age >50 years and other than good risk AML have a very poor prognosis at relapse. Patients in these groups require novel strategies to maintain remission.
Keywords Acute Myeloid Leukaemia, Relapse, Second Remission
Conflict of interest No conflict of interest to disclose

Wednesday 23 October **0900-1000**
HSANZ Free Communications 10: BMT 2 **Meeting Room 7**
O105 **0900**

Unrelated Umbilical Cord Blood Transplantation (UCBT) for Adults: Low Relapse Rates Without Excessive Transplant Related Mortality

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Aim/Background
For stem cell transplant recipients lacking an optimally matched adult donor, UCB has emerged as an important graft source with potential advantages. We evaluated the outcomes of patients who underwent unrelated UCBT as per institutional guidelines (patients † 45 years, minimal co-morbidity and chemo-sensitive disease).
Methods
We reviewed consecutive UCBT patients with a minimum 1 year follow up. Data analysed included HLA matching, cell dose, disease characteristics, conditioning, engraftment, chimerism, overall survival (OS), relapse and non-relapse mortality (NRM).
Results
21 UCB transplants were performed between March 2006 and June 2012 (AML=10, ALL=5, CML=2, Hodgkin lymphoma=2, others=2). The median age of the recipients was 29 years (y) (range 19-48y). Patients predominantly received fludarabine; cyclophosphamide and TBI based conditioning (n=20). Conditioning was myeloablative in 47% of the patients. Recipients received either single (n=5) or double (n=16) partially matched cord units (matched at least 4 of 6 HLA antigens). The median cell dose was 4.12 x 10^7 TNC / kg (range =1.92 -6.52 x10^7 TNC / kg). Neutrophil recovery (‡0.5 X 10^9/L) occurred in 95 % cases at a median of 25 days (d) (range 9-54d). The cumulative incidence of platelet recovery (‡20 X 10^9/L) was 90 % and occurred at a median of 52d (range 0-181d). The incidence of Grade II-IV acute graft versus host disease (GVHD) at day 100 was 48% (95% CI 25-70%). Chronic GVHD incidence at 1 year was 52% (95% CI 29-75%). Median follow for the survivors was 25 months (range 12-68 months). OS, NRM and incidence of relapse at median follow up of 25 months were 71% (95% CI 53-94%), 14% (95% CI 0-30%) and 15% (95% CI 0-31%) respectively.
Conclusion
UCBT is an effective alternative for patients without optimally matched adult donors. Careful patient selection and refinement of transplant techniques can result in low relapse rates without excessive transplant related mortality.

Keywords Cord blood, transplantation, relapse **Conflict of interest** No

Wednesday 23 October **0900-1000**
HSANZ Free Communications 10: BMT 2 **Meeting Room 7**
O106 **0915**

Impact of a Community-Based Lifestyle Modification Program on Health Behaviours, Fatigue and Quality Of Life in Long-Term Survivors of SCT

Helen McLauchlan[1], Daniela Klarica[1], Trish Walker[1,2] Sharon Avery[1]
[1]*Late Effects Clinic, Malignant Haematology and Stem Cell Transplantation Service, Alfred Health.* [2]*Department of Clinical Haematology, Monash University, Melbourne*

Background/Aim
A critical need for SCT survivors to address lifestyle to minimise risk for future chronic illness has been identified. This study aims to assess changes in nutrition, physical activity (PA), fatigue levels and quality of life (QoL) in long-term survivors of SCT engaging in a 12 month lifestyle intervention project.
Methods
53 SCT survivors (‡2 years in ongoing remission) received an individually tailored community based PA program, group activities, motivational strategies & dietary advice. Patient reported outcome measures including FACIT fatigue, Godin Leisure Time Activity and Rapid Eating Assessment for Patients (REAP) questionnaires were administered at baseline and following 6 & 12 months of participation. 5 QoL domains (physical, social, emotional, functional, transplantation specific) were assessed using the FACT-BMT. Interim 6 month evaluation results are presented.
Results
6 month evaluations are available for 26 participants (54% male, median 53 years). Median time since either autologous (35%) or allogeneic (65%) SCT was 7 years (range, 2-15.4). Median baseline fatigue score was 44.5 (range, 20-52) with a possible range between 0 the worst to 52 the best possible. Clinically meaningful improvement in fatigue levels were reported by 31% at 6 months. Referencing only moderate and strenuous PA, significant improvements were achieved at 6 months with 69% reporting sufficient PA to achieve substantial health benefits compared with 23% at baseline (p=0.002). 6 month PA levels were significantly correlated with enhanced physical (p=0.04) and emotional (p=0.02) QoL and reduced fatigue (p=0.03). A trend to enhanced overall QoL was observed with higher PA levels at 6 months. 69% of participants report a reduction in 27 unhealthy eating behaviours captured by the REAP with the median number of undesirable nutrition behaviours reducing from 5 (range 0-9) to 3 (range 0-11), p = 0.05.
Conclusion
Health promotion is an essential component of optimal survivorship care. Our data demonstrates the potential of an individualised community-based physical activity program coupled with nutritional advice to improve healthy lifestyle behaviours, enhance quality of life and reduce fatigue levels in long-term survivors of SCT.
Keywords Quality of Life, Fatigue, Transplantation **COI** None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 10: BMT 2 **Meeting Room 7**
O107 **0930**

Enteral *Versus* Parenteral Nutritional Support Post Allogeneic Haematopoietic Cell Transplantation – Results of a Randomised Controlled Trial

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Background/Aims
Nutritional support post allogeneic HPCT has proven efficacy in preventing malnutrition post-HPCT. However, there is no consensus as to the most efficacious approach to supplemental feeding post-HPCT, leading to wide variation in clinical practice with respect to use of enteral (EN) *vs.* parenteral (PN) feeding. We aimed to determine the tolerability and efficacy of EN *vs.* PN in adult patients undertaking HPCT.

Methods
Prospective randomized study in patients undertaking HPCT with either myeloablative or reduced intensity conditioning (RIC). Patients were randomized to receive either EN or PN after commencing HPCT conditioning if they could not maintain adequate oral nutritional intake, defined as maintaining >60% of daily caloric requirements. Patients with severe gastro-intestinal toxicity, including severe mucositis, were excluded from randomisation. The primary endpoint was tolerance of route of supplemental nutritional support, defined as <30% of patients needing to change to the alternative route of support for any reason.

Results
In total 38 patients were enrolled onto the study, including 9 patients undertaking myeloablative and 29 patients RIC HPCT. Only 19 patients (50%) required nutritional support post-HPCT. Of these 19 patients, only 9 (47%) were able to be randomized between EN (n=5) and PN (n=4), with 10 patients excluded from randomization due to presence of gastrointestinal toxicity in 8 and withdrawal of consent in 2. The 5 patients randomized to EN met on average 74% of their goal nutrition and 100% required changing to PN due to (gastro-intestinal) intolerance. The 4 patients receiving PN met on average 91% of requirements, with none requiring change to EN.

Conclusions
For adult patients undertaking HPCT, supplemental feeding with EN commencing at failure to maintain adequate oral nutritional intake is not feasible, due to the presence of significant gastrointestinal toxicity in these patients at this time. Further study is required to determine whether prophylactic nasogastric tube placement would improve the feasibility and tolerance of EN in this patient population.

Keywords enteral nutrition (EN); parenteral nutrition (PN); allogeneic haematopoietic cell transplantation (HPCT). **Conflict of interest** None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 10: BMT 2 **Meeting Room 7**

O108 **0945**

Retrospective Analysis of Allogeneic Transplantation for Acute Lymphoblastic Leukaemia in a Single Centre

Jason Butler, Cameron Curley, Elango Pillai, Siok-Keen Tey, Geoffrey Hill, James Morton, Simon Durrant, Glen A Kennedy
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Aim/Background
Outcomes for adult patients with relapsed acute lymphoblastic leukaemia (ALL) remain poor. Early allogeneic stem cell transplantation may be an effective strategy to prevent relapse.
Methods
All patients (n=123) transplanted at our unit between January 2000 and March 2012 were obtained from an institutional database, and included in this retrospective analysis. All patients received T-replete grafts, with standardised GVHD prophylaxis of cyclosporine and methotrexate (D+1,3,6, and 11). Survival analysis was performed using the Kaplan-Meier product limit technique.
Results
Median age at transplant was 30.18 (range 15.2 to 66.2). 87 (70.7%) were transplanted in CR1, 21 (17.3%) in CR2, 4 in CR3 or beyond, 8 in early relapse post CR1, and 3 with primary refractory disease. 50 (40.6%) had sibling donors; 73 (59.4%) underwent VUD transplants. 113 (91.9%) received PBSC, the remainder unstimulated bone marrow. 111 (90.2%) had CyTBI conditioning, with a further 10 receiving Flu-Mel120. Median overall survival (OS) was 8.6 years. 3 year relapse-free survival (RFS) was 72% (median RFS not reached). 14 (11.8%) died from non-relapse related causes. For patients treated with Flu-Mel120, 3 year overall survival was 88.9%. Transplantation in CR1 was associated with superior outcome (HR= 4.5; 95% CI 2.2 – 9.2, P<0.001) compared with CR2.
Conclusion
Allogeneic stem cell transplantation in CR1 is associated with prolonged survival, and low relapse risk. Reduced intensity conditioning with FluMel-120 is effective and well-tolerated, and may broaden the eligibility for allogeneic transplantation.

Keywords Acute lymphoblastic leukaemia, allogeneic transplantation
Conflict of interest None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 11: Iron and Obstetrics **Meeting Room 8**
O109 **0900**

Appropriateness of ADAMTS13 Level Requests to a Reference Laboratory: Is Routine Pre-testing Haematology Advice Needed?

Kylee Maclachlan, Jennifer Butler, Erica Malan, Sunelle Engelbrecht, Erica Wood
Monash Medical Centre, Melbourne, VIC, Australia

Background/Aims
Significant clinical overlap exists between thrombotic thrombocytopenic purpura (TTP) and other thrombotic microangiopathies. ADAMTS-13 levels <10% may aid differentiation between disorders; however, normal ADAMTS-13 levels do not exclude idiopathic TTP, and occasional secondary TTP may have levels <10%. We analysed the correlation of ADAMTS-13 levels with clinical details provided to our laboratory, the tertiary referral centre for ADAMTS-13 testing in VIC/TAS.

Methods
2 year retrospective audit of all ADAMTS-13 requests from within our institution and referred from elsewhere. Review included availability of clinical details, age, sex, origin of the referral, and ADAMTS-13 result.

Results
311 requests were received for ADAMTS-13 levels (92 in 2011, 138 in 2012, 81 in 2013 to date) on a total of 164 patients (pts). 74% of requests were outside referrals. 34 pts had repeat samples, with the most being 18 on 1 pt (over multiple relapses).
35 pts had levels below the reference range (LLN 40%) with 21 being <10%. Of the 21 pts with <10%, the range was <1- 5.2%, (with 15 pts<3%), 15 were female and 6 male, median age 50y (17-79y).
No clinical details were provided for 26/164 pts, and of these 23 had levels >40%. Secondary TTP was suspected in 16 pts, (aetiologies including SLE, pancreatic cancer, renal transplant, HELLP) of which only 1 was low (30%). Alternative Dx to TTP/HUS were provided on 14 pts (including DIC, pancytopenia, liver failure, sepsis and FHx TTP). 6 requests were cancelled, at least 3 after discussion between the treating team and haematology.

Conclusion
Only small numbers of suspected idiopathic TTP had severe deficiency, and significant numbers had clear alternate diagnoses. Discussion with haematology may improve uncertainty amongst requesting physicians regarding role/utility of ADAMTS13 testing.

Keywords TTP, ADAMTS-13, audit
Conflict of interest No

Wednesday 23 October **0900-1000**
HSANZ Free Communications 11: Iron and Obstetrics **Meeting Room 8**
O110 **0915**

Antenatal Haemoglobinopathy Screening Patterns Within a Large Obstetric Service. Working Towards a Standard of Care

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Prince of Wales Hospital/SEALS Laboratory, Sydney, NSW, Australia

Aim/Background
Clinically significant haemoglobinopathies are chronic, serious medical conditions for which antenatal screening can predict their occurrence and severity. In Australia, antenatal screening is not standardized and practices are evolving as the population becomes more ethnically diverse. Often, testing is done on an ad hoc basis without risk factors clearly documented reflecting a lack of universal agreement and understanding of screening processes. This study is the first to describe antenatal screening practices in Australia and uses data to propose a set of detailed guidelines for antenatal patients to ensure appropriate and timely testing.
Methods
Request forms for haemoglobin electrophoresis in antenatal patients were prospectively collected over 16 months. Data was extracted and coupled with ancillary testing and results were collated from laboratory records. Obstetric data was obtained from a database of antenatal patients from our area health service.
Results
462 patients were included. The average gestation was 25.8 weeks with “Pregnancy” the most common stated indication. No indication or clinical information was stated in 8% of cases. Gestational age was documented in 54% of cases. In 15% no contact details of the referrer were documented and in only 25 cases was partner screening traceable. 82% had no abnormalities detected. Of positive results, thalassemia trait was most common. All patients had a recent full blood count available and 52% of patients had recent iron studies. The mean haemoglobin was 111.6g/L and mean MCV was 80.5fL at the time of testing. Ethnicity was documented on the request form in 3%. After Australasia, the most common ethnicity of patients was South East Asia and the Middle East. The mean turnaround time from collection to assay completion was 3.6 days.
Conclusion
Referral patterns in our health service are diverse and reflect our changing population and care practices. Detailed guidelines are required and we propose a comprehensive algorithm for general use.

Keywords Haemoglobinopathy, pregnancy, screening
Conflict of interest None

Wednesday 23 October **0900-1000**
HSANZ Free Communications 11: Iron and Obstetrics **Meeting Room 8**
O111 **0930**

Prevalence of Iron Depletion in Australian Blood Donors

Hannah Salvin[1], Sant-Rayn Pasricha[2], Denese Marks[1], Joanna Speedy[2]
Australian Red Cross Blood Service, Sydney NSW[1] or Adelaide SA[2], Australia

Aim/Background
Blood donors are at increased risk of iron depletion (ID) due to iron losses during donation. ID may pose a significant health risk, and donors with ID are more likely to develop anaemia. We determined the epidemiology of ID in Australian blood donors to inform future interventions.

Methods
A nationally representative cross-sectional study sampling whole blood (WB) and apheresis (APH) donors from 21 randomly selected donor centres was conducted. All donors eligible to donate or deferred for a low or falling haemoglobin (Hb) were eligible. Hb and ferritin were measured, and donor demographics and donation history recorded. Prevalence of ID (ferritin <15 ng/mL) was calculated and compared across donation frequencies and age groups. Prevalence of anaemia (Hb<120 female; Hb<130 male) and total equivalent WB loss was also calculated.

Results
A total of 3049 donors (530 new donors and 2519 repeat donors) were recruited. Of these, 1873 and 242 donors had exclusively made either WB or APH donations in the last 2 years respectively. The prevalence of ID in female new donors was 12%, and was higher in WB exclusive donors who had made 2 (20.1%), 3 (32.5%), 4 (34.0%), 5 (30.3%), or 6+ donations (29.7%) in the last 2 years ($p<0.001$-0.018 for difference from new donors, Fisher's exact test). Age also significantly affected prevalence of ID (16-24yrs 28.1%; 25-50yrs 23.0%; 51+ yrs 18.8%, $p=0.0012$ Fisher's exact test). In males, the prevalence of ID was 1.3% in new donors and was higher in WB exclusive donors who had made 4 (8.0%) or 6+ donations (11.6%) in the last 2 years ($p<0.001$, $p=0.006$ respectively for difference from new donors). In APH exclusive donors, donation frequency did not affect ID in males ($p=0.860$) or females ($p=0.529$). Total equivalent WB loss (mL) in the last 2 years correlated with ferritin levels ($p<0.001$; $r=-0.305$), but only accounted for 10.1% of the variation. The overall prevalence of anaemia was 6.2% in females and 2.3% in males.

Conclusion
ID is an important issue in Australian blood donors, especially in young females and frequent WB donors. Future interventions to address donor iron deficiency should target these high-risk groups to optimise donor health and ensure the blood supply.

Keywords Prevalence; Iron depletion; Blood donation
Conflict of interest No conflict of interest to disclose

Wednesday 23 October **0900-1000**
HSANZ Free Communications 11: Iron and Obstetrics **Meeting Room 8**

O112 **0945**

Iron Carboxymaltose (IC) Delivers Marked Benefits in Efficacy, Economics and Safety as Compared with Iron Sucrose (IS) and Polymaltose (IP)

Azhar Munas, Senthil Lingaratnam, Kate Burbury
Division of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, Vic, Australia

Background
The delivery of IV iron is only PBS reimbursed when utilising IP, which is both inefficient in busy ambulatory care (AC) areas and is not infrequently complicated by side-effects and infusion toxicities. The key issue is delivery in AC, which (for IP) can occupy a patient chair and nursing time for up to 8hours. IS is associated with less toxicities and infusion time than IP, however for similar efficacy, generally needs to be administered on repeated occasions a week apart. IC allows adequate dose delivery with dramatically reduced infusion times (15 min) and low rates of toxicity. This markedly improves productivity in busy AC areas.

Methods
Retrospective data collected on all patients given intravenous IV iron infusions at PeterMac from January 2011 to December 2012. All infusions were given in the AC unit according to protocol. Patient demographics, infusion reactions, time in AC area and parameters pre- and post iron infusion – including Hb, MCV, serum ferritin – were collected from patient medical records, AC and pharmacy data.

Results
63 patients received 102 infusions: IC 48, IS 32, IP 22. Median follow-up was 60 days with a range of 21 to 211 days. Median dose of iron with each infusion: IC 1000 mg (500-1000), IS 400 mg (200-400), IP 1000 mg (500-2000). Adverse drug reactions were most frequent in the IP group (9.1%). These were hyper or hypotension with one episode of bradycardia. The IS group had 6.3% adverse reactions and the IC group only 2.1%. All preparations resulted in improvement in key parameters – with change recorded as median (range). Hb: IC +10g/L (-26-+59), IS +11.5 g/L (-18-+66) and IP +15g/L (-20-+24). ; MCV: IC +6fl (-5-+21), IS +4 (+1-+18) and IP +3 (-1-+13)); serum ferritin: IC +57 mM (-37-+1965), IS +6 (-745-+28) and IP +110 (-15-+988). The median time (range) in AC unit was IC 63 min (46-87), IS 87 min (67-146) and IP 487 min (424-538). The cost of 100mg of IC is $47.95, for IS $27.90 and for IP is $10.06

Conclusion
Although cost IC preparation is more than IS and IP, this is far outweighed by the cost attributable to delivery of infusion and the occupation of time-critical AC service delivery. Importantly IC is both safe and efficacious.

Keywords Iron Carboxymaltose **Conflict of Interest** None

Wednesday 23 October **0900-1000**
ANZSBT Symposium 7: The Future of Transfusion **Central Hall A**

Blood Cell Manufacture – Biological and Engineering Challenges

Mike Doran
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Introduction

Blood cell transfusions have become a mainstay of modern medicine. The challenge associated with the maintenance of an adequate supply of clean and rare donor cell populations has motivated the development of technologies that aim to enable blood cell manufacture. However, blood cell manufacture is a non-trivial process that requires careful consideration of the biological challenge of replicating haematopoiesis *in vitro* and the engineering hurdles associated with the production of extraordinarily high cell numbers. This talk will discuss (1) The feasibility of using various stem cell populations as input into blood cell manufacturing processes, (2) the required meaningful cell numbers/output, and (3) the various bioreactor systems that have been developed with the goal of enabling the manufacture of meaningful cell numbers.

Cell input

The most commonly reported stem cell input into blood cell manufacturing processes has been umbilical cord blood-derived haematopoietic stem cells (HSC) into red blood cells, neutrophil precursors or platelets. However, recent developments in embryonic stem cell, induced pluripotent stem cells, and directed differentiation may enable greater yields than cord blood-based protocols and further reduce the risk of product contamination.

Meaningful cell numbers and the economics

Single units of red blood cells, platelets and neutrophils contain $2x10^{12}$, $5.5x10^{10}$, and $2x10^{10}$ cells per unit respectively. Both red blood cells and platelets are routinely collected and banked at an estimated cost of $AU300 and $AU400, respectively. By contrast the estimated cost for the production of a unit of red blood cells is >$USA8000, and the bioreactor volume required to meet 2010 Australian red blood cell demands (at a max density of $5x10^7$ cells/ml) is ~2,800,000 litres.

Bioreactors and blood cell manufacture

We will discuss high-density bioreactors developed by our team and others. Such systems reduce bioreactor working volumes as well as the protein and growth factors required by the culture. These incremental increases in bioreactor efficiency will contribute to making blood cell manufacturing a reality.

Keywords Blood cell manufacture
Conflict of interest None

Wednesday 23 October **0900-1000**
ANZSBT Symposium 7: The Future of Transfusion **Central Hall A**

Molecular Blood Group Genotyping – An Update

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The number of recognised blood group systems (currently 33) has significantly increased in recent years as the genetic polymorphisms producing red cell antigens continue to be discovered. While the most frequent genetic changes determining blood group genotypes are single nucleotide polymorphisms (SNPs), inactivating mutations such as deletions and splice-site mutations also result in complex structures including multiple new epitopes or null phenotypes. . Molecular genetic amplification systems provide a systematic basis for typing of these polymorphisms. Several systems, using platforms such as array analysis and single nucleotide primer extension, currently have CoE marking, although none have achieved IVD accreditation in Australia. Reliable high throughput DNA extraction, depth of coverage (number of replicate tests) and minimisation of post-amplification manipulation are important issues when comparing the reliability of systems for routine high throughput genotyping. Optimisation of interpretative algorithms, also required for high throughput analyses, should include consideration of polymorphisms that prevent antigen expression other than the specific coding region (for example the GATA box mutation in the Duffy system). Standardisation of molecular genetic terminology also remains a significant issue, as complex naming, varying between manufacturers, may make reports difficult to interpret. In countries where these systems have been applied, systematic identification of donors has provided a database of rare types or low frequency combinations for finding compatible donors. In addition, typing the foetus via free foetal DNA provides information for complex antenatal management. Where it has been applied, genotyping is an inexpensive addition to the tools for problem solving in complex serological investigations and developing an inventory of donors typed for many polymorphisms in a single procedure.

Keywords blood groups, molecular typing
Conflict of interest None

Wednesday 23 October **0900-1000**
ASTH Symposium 7: NOACs: What's Changed? **Central Hall C**

New Oral Anticoagulants in the Real World: RELYable or Not?

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Following the pivotal phase 3 trials comparing the new oral anticoagulants (dabigatran, rivaroxaban and apixaban) to vitamin K antagonists for the prevention of ischaemic stroke in atrial fibrillation, all 3 of these agents have received regulatory approval. Most post marketing data relates to dabigatran as this direct thrombin inhibitor was the "first cab of the rank". In New Zealand and elsewhere, concerns were raised regarding the rate of haemorrhagic complications particularly in the elderly and those with renal impairment, and also the need for either a new antidote or the demonstration of efficacy of established pro-haemostatic agents. However post-marketing analysis from the FDA (USA) and international small cohort studies have largely allayed these concerns, and overall patients who have been prescribed dabigatran have similar outcomes and discontinuation rates to the RE-LY study. In the FDA comparison, 10,000 dabigatran patients had lower rates of gastrointestinal and intracranial haemorrhage when compared to warfarin, and in a large study of approximately 14000 patients in Denmark, mortality and intracranial haemorrhage were less with dabigatran. Areas potentially requiring further research include those requiring coronary stents, catheter ablation procedures for AF, thrombolysis for ischaemic stroke, and optimal perioperative and reversal strategies including novel antidotes.

Keywords Atrial fibrillation, anticoagulation, new oral anticoagulants
Conflict of interest No

Wednesday 23 October **0900-1000**
ASTH Symposium 7: NOACs: What's Changed? **Central Hall C**

Laboratory Monitoring of NOACs: Is it Necessary?

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Novel oral anticoagulants which directly inhibit either thrombin or factor Xa are now available in Australia for specific indications: stroke prevention in patients with atrial fibrillation and the prevention or treatment of venous thromboembolism. These agents are small molecules with predictable pharmacokinetics and pharmacodynamics in patients with normal renal function and consequently they have been administered in fixed doses to large numbers of patients in Phase III studies, without the need for monitoring. The transition from controlled clinical trial dosing to use in general patient populations has highlighted a number of clinical circumstances in which laboratory testing is desirable including: bleeding, prior to surgery or invasive procedures, particularly if required urgently, overdosage, patients with declining renal function or at the extremes of body weight, assessment of compliance, dose evaluation in patients with recurrent thrombotic events on anticoagulants and as NOAC reversal agents enter clinical trials, laboratory testing will be desirable to evaluate their efficacy. Routine coagulation assays may provide qualitative information about the relative presence or absence of anticoagulant effect attributable to these agents, but as NOACs become more widely used, in higher risk patient populations and in more complex clinical scenarios than studied in clinical trials, then specific drug levels will be necessary to guide patient management. Although such assays are now more widely available, relevant clinical correlative studies are still lacking. Phase IV studies such as the Anticoagulant and Reversal Events Study (ARES), an ASTH collaborative study, and International registries have been established to gather this data, which will be required before evidence based recommendations can be made.

Keywords NOACs
Conflict of interest None

Wednesday 23 October **1100-1230**
HSANZ Symposium 7: Disease Updates **Auditorium (Arena B)**

Treatment of Relapsed Multiple Myeloma

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Treatment of relapsed multiple myeloma (MM) continues to present a therapeutic challenge. The immunomodulatory drugs (IMiDs) thalidomide, lenalidomide and pomalidomide, and the proteasome inhibitors (PIs) bortezomib and carfilzomib have dramatically improved clinical outcomes for patients with relapsed/refractory MM.
The combination of lenalidomide and dexamethasone (Len/Dex) is approved for the treatment of patients with relapsed and/or refractory MM. Results from pivotal phase III trials in this setting have demonstrated that Len/Dex extends overall survival compared with high-dose dexamethasone alone. Optimal clinical benefits are seen when Len/Dex is initiated at first relapse and continued, beyond best response, until disease progression. Importantly, lenalidomide has a predictable and manageable tolerability profile, with minimal neurotoxicity, allowing long-term administration. Pomalidomide is a novel IMiD which has shown remarkable activity in patients who were refractory to both bortezomib and lenalidomide in phase II and III studies. Both lenalidomide and pomalidomide have been combined with PIs, conventional chemotherapeutic agents and monoclonal antibodies with very promising results.
PIs are also important for the management of relapsed/refractory MM. Bortezomib, either alone or in combination with other chemotherapeutic agents or IMiDs, induces high overall response rates in patients with relapsed disease. However, resistance to bortezomib and neurotoxicity associated with the treatment remain challenging issues. Carfilzomib is a novel, well tolerated, irreversible proteasome inhibitor with minimal neurotoxicity. Carfilzomib demonstrates promising activity in myeloma patients who are refractory to bortezomib and IMiDs.
Despite advances in anti-myeloma treatment, nearly all patients will eventually relapse or become refractory to these drugs. Numerous agents are currently in development for the treatment of relapsed/refractory MM. The more promising include new PIs (eg, oprozomib and marizomib), monoclonal antibodies (eg, daratumumab and other anti-CD38 antibodies, elotuzumab, siltuximab, tabalumab), and signal transduction modulators (eg, perifosine). These emerging agents with diverse mechanisms of action have demonstrated promising anti-tumor activity in patients with relapsed/refractory MM, and rationally designed combinations with established agents are being investigated in the clinic. These new agents are creating opportunities to target multiple pathways, overcome resistance, and improve clinical outcomes, particularly for those patients who are refractory to approved novel agents.
Key words multiple myeloma, consolidation, maintenance
Conflict of interest Honoraria from Janssen-Cilag, Celgene, Millenium and Onyx.

Wednesday 23 October **1100-1230**
HSANZ Symposium 7: Disease Updates **Auditorium (Arena B)**

Secondary CNS Lymphoma

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Central nervous system (CNS) dissemination is a rare (4-5%) but usually fatal complication of aggressive lymphomas. Prophylaxis modalities to prevent CNS dissemination in aggressive lymphomas cannot be widely applied to every lymphoma patient since it is associated with increased risk of neurotoxicity. Therefore, identification of high-risk patients as the best candidates to receive CNS prophylaxis constitutes a major endpoint in the management of these malignancies. Various risk factors and models for CNS recurrence have been described. Parameters reflecting the extent and proliferation of the disease, like elevated serum lactate dehydrogenase levels, involvement of multiple extranodal sites, advanced stage, and high age-adjusted International Prognostic Index score, as well as the involvement of specific anatomic sites, like testes, orbit, paranasal sinuses, have been identified and confirmed as important to predict CNS dissemination. Management of this complication in aggressive lymphomas with conventional-dose chemotherapy is associated with disappointing results, while some preliminary but encouraging experiences suggest a potential role of high-dose chemotherapy and stem cell transplantation. The analysis of recent clinical studies could led to advancement in the prognosis of aggressive lymphomas, but several questions regarding the optimum chemotherapy combination, the best conditioning regimen and the role of radiation therapy and intrathecal chemotherapy remain still unanswered. Discussion will be focused on the critical analysis of current data on the risk of CNS dissemination in aggressive lymphomas, the clinical presentation of secondary CNS lymphomas, the efficacy of CNS prophylaxis and the efficacy of available therapeutic options.

Keywords CNS Aggressive Lymphoma

Wednesday 23 October **1100-1230**
HSANZ Symposium 7: Disease Updates **Auditorium (Arena B)**

Emerging Therapies for Myelodysplastic Syndromes

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Our expanding understanding into relevant biologic systems that contribute to ineffective hematopoiesis and survival of the MDS clone has provided critical insight for development of therapeutics that extend interfere with an array of critical processes across the disease pathogenetic spectrum. We know that biologic pressures within the bone marrow microenvironment are alone sufficient to support emergence of myelodysplastic clones by creating a conducive microenvironment that with time, fosters emergence of genetic events leading to environment autonomy. With this perspective, two distinct categories of agents are emerging that target either conducive environmental pressures, or the MDS clone per se. Among the former, the best example is immunosuppressive therapy and the success of antithymocyte globulin in a subset of younger MDS patients. Recognition of the role of innate immune activation in MDS has led to the development of new agents targeting toll-like receptor (TLR) signaling as well as soluble activators such as S100A9. Others target downstream events such as interruption of TGF-beta signaling with the TGF beta-R1 kinase inhibitor LY2157299, or the Activin-A receptor IIA/B ligand traps, sotatercept and ACE-536; and finally p38 MAPK (Arry614) and JAK1 inhibitors (INCB39110) that can suppress cellular apoptotic response and inflammatory cytokine generation, respectively. Perhaps the best example of disease selective therapies is lenalidomide. Our knowledge of the enzymatic targets of lenalidomide in deletion 5q MDS and the role of p53 in the hematologic features of the disease has led to new trials with agents that are either p53 specific such as cenersen, or target the dual specific phosphatase PP2A, which is up regulated upon lenalidomide resistance. Others include agents that target the malignant stem cell through inhibition of Hedgehog signaling (PF-04449913), mechanisms of azanucleoside resistance (birinisat), HDACs and survival signals (ON1910). The paradigm for future MDS treatments can be expected to evolve with our knowledge of the disease biology, targeting not only the MDS clone, but also the surrounding microenvironment.

Keywords MDS

Wednesday 23 October **1100-1230**
ANZSBT Symposium 8: Transfusion Transmitted Infection **Central Hall A**

Epidemiology and Biology of HBV

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Hepatitis B virus (HBV) is the most common chronic viral infection in humans with whom it has been associated for 35,000 years. HBV diversified into nine genotypes (A-I) largely associated with population groups and specific areas. Natural infection in immunocompetent humans is mostly asymptomatic with 95% recovery. In immunodeficient individuals such as newborn and young children, chronic infection establishes for life with clinical outcome in part related to genotype. Long-term high viral load (VL) in genotype B/C explains high frequency of vertical transmission. Other genotypes seroconvert to anti-HBe decreasing viral load before age 15 limiting vertical transmission. Transmission then becomes related to sexual activity or blood contact except for genotype E where very high viral load in young children drives horizontal transmission. Recombination between genotypes occurs in co-infected individuals, vaccination, passive immunisation and antiviral therapy participate in viral diversity.
Since 1970 diagnosis of chronic HBV infection and blood screening relied on the detection of surface protein antigen (HBsAg). Anti-core indicates contact with HBV and anti-HBs recovery from the infection. Nucleic acid testing (NAT) improved the sensitivity and specificity of HBV detection. Covalently closed circular DNA in the nucleus of infected cells serves as template for transcription into either pre-genomic RNA from which viral DNA is produced and encapsidated or shorter RNAs translated into 7 viral proteins. Splicing of pre-genomic RNA produces additional proteins as well as incomplete non-infectious particles released in circulation. Smaller RNA templates are also transcribed and translated into surface proteins that aggregate in large excess of HBsAg.
HBsAg and HBV DNA are not always co-detected. HBsAg+/ DNA- and DNA+ /HBsAg- are found in 2-9% of infected individuals. Both indicate HBV infection and potential infectivity. The latter is called ‘occult HBV infection’ or OBI. OBI is characterised by low viral load median 20IU/ml), anti-HBc+ and/or anti-HBs. It reflects the accumulation of mutations over decades affecting all functions of HBV biology: HBsAg escape mutants undetected by host immune system and assays, impaired viral replication, production and excretion of viral proteins. OBI prevalence in donated blood ranges between 1:100 and 1:20,000. Being10-30% infectious by transfusion, OBI detection justifies costly screening with sensitive HBV NAT.

Key words Hepatitis B virus, genotype, recombination, occult HBV, splicing
Conflict of interest None

Wednesday 23 October **1100-1230**
ANZSBT Symposium 8: Transfusion Transmitted Infection **Central Hall A**

Modelling for the Residual Risk of Viral Transmission

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The risk of the major transfusion-transmissible viral infections (termed 'residual risk') is now so low in most developed countries that it cannot be measured by direct estimation from the infection rate in recipients. This necessitates an alternative approach and led to the development of mathematical models to estimate residual risk. Modelled estimates underpin optimal patient consent. In Australia the residual risks for the predominant transfusion-transmissible viral infections (TTIs); HIV, HCV, HBV and HTLV are estimated and published annually using a 'multiple' model approach. The 2012 estimates are significantly less than 1 in 1 million per transfused unit for all but HBV, which is estimated at approximately 1 in 538,000.

Residual risk modelling was pioneered in the mid 1990's by two separate groups of US investigators. The probabilistic model they developed, the Incidence Rate/Window Period model (I/WP model) remains today the most widely applied method. As the name suggests it is based on assessing the incidence rate (i.e. rate of new infection) and estimating the probability that such a donor would donate in the testing 'window period' (i.e. the period prior to the test target being detectable in the bloodstream). The incidence rate is estimated by the rate of 'seroconversion' (i.e. positive donors with prior negative result for the virus) among repeat donors. Testing window periods (WP) are unique for each test and the shorter their duration the lower the residual risk. The I/WP model has been refined over time and also applied to other TTIs including; human cytomegalovirus, West Nile virus (WNV) and hepatitis A virus. One key assumption of the I/WP model is that the majority of the residual risk is associated with WP donors. This appears true for HIV, HCV, and HTLV but is less so for HBV where HBsAg-negative, chronic occult infection (OBI) constitutes a distinct risk. Since anti-HBc is almost always detectable in OBI the risk is accounted for where universal anti-HBc testing is performed. However, in countries like Australia where anti-HBc is not mandated the OBI risk needs separate estimation. Using a novel method, the OBI risk component in Australia for 2012 was estimated at approximately 1 in 982,000 per transfused unit which constituted 55% of the overall HBV residual risk of approximately 1 in 538,000 per transfused unit.

New models have evolved in response to outbreaks of transfusion-transmissible arboviral infection (e.g. West Nile virus and dengue virus). As these are 'seasonal' and the risk 'focal' in nature they have required a new approach based primarily on the incidence of infection and the probability of asymptomatic viraemia among donors.

Keywords Infectious disease, viral infection, modelling
Conflict of interest No

Wednesday 23 October **1100-1230**
ANZSBT Symposium 8: Transfusion Transmitted Infection **Central Hall A**

Emerging Threats to the Australian Blood Supply

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Australia has one of the safest blood supplies in the world, particularly in terms of the low reported incidence of transfusion-transmitted infections. Emerging transfusion-transmissible pathogens are a constant threat to this safety record, with arboviruses such as West Nile virus (WNV), chikungunya virus (CHIKV) and dengue virus (DENV) recently threatening the safety of the blood supply globally. Climate change is predicted to increase the transmission of many vector-borne pathogens, including arboviruses, representing a significant threat to the maintenance of a safe future blood supply.

Dengue outbreaks have increased in size and frequency in Australia. In 2008/2009 north-eastern Australia experienced a large epidemic, with three separate outbreaks. During this epidemic, anti-dengue IgM sero-prevalence was measured in blood donors to estimate the rate of subclinical infection and the associated transfusion-transmission risk. Moreover, increased rainfall may lead to favourable conditions for mosquito reproduction, resulting in increased arbovirus transmission. Above average rainfall was recorded in many areas of Australia in late 2010 and into 2011. The seroprevalence of antibodies against the two arboviruses most likely associated with clinical disease in Australia, Ross River virus (RRV) and Barmah Forest virus (BFV), was investigated in blood donors after increased rainfall, and these data were used to assess risk to the Australian blood supply. Collectively, these studies provided novel data to underpin optimal evidence-based risk assessment and policy development relating to arbovirues and blood supply safety in Australia.

Australia is constantly threatened by the emergence and establishment of viruses, including arboviruses such as DENV (this already occurs regularly in North Queensland), but also WNV and CHIKV. The likelihood of establishment depends on a range of factors including current importation rates, climate change, rates of protective immunity in the population and vector abundance. Alternative blood safety approaches may be required in the future, with pathogen reduction technology (a process designed to inactivate pathogens in blood products) offering a similar level of safety and cost-effectiveness.

Keywords Risk, safety, climate
Conflict of interest No

Wednesday 23 October **1100-1230**
ASTH Symposium 8: Consultative Haematology **Central Hall C**

Atypical Haemolytic Uraemic Syndrome

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Abstract not available at time of going to print

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