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GUIDELINES FOR THE PREVENTION OF TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE (TA-GVHD)

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Guidelines for prevention of transfusion-associated graft-versus-host disease (TA-GVHD)

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Foreword

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Summary of amendments to the 2011 guidelines

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Abbreviations and definitions

ACSQHC	Australian Commission on safety and Quality of Health Care
ANZSBT	Australian and New Zealand Society of Blood Transfusion
Blood Service	The organisation (or part thereof) that collects, manufactures and distributes fresh blood products. Australian Red Cross Lifeblood and the New Zealand Blood Service fulfil these roles in Australia and New Zealand, respectively.
BSH	British Society for Haematology
EMR	Electronic medical records
HLA	Human Leucocyte antigen
ISBT	International Society of Blood Transfusion
PBM	Patient blood management
RFID	Radio frequency identification
TA-GVHD	Transfusion-associated graft-versus-host disease

Tabulated recommendations

Table 1: Clinical Indications for Irradiation (or equivalent TA-GVHD prevention strategy)

Indication	Recommendation		Section reference
Intrauterine transfusions	R1	Universal irradiation is recommended for intrauterine transfusions	5.1.1
	R2	Due to the increased risk of hyperkalaemia, transfusion of red cells must be within 24 hours of irradiation and the blood as fresh as possible	5.1.1
Neonatal exchange transfusions	R3	Red cells for neonatal exchange transfusion should be irradiated and transfused within 24 hours following irradiation	5.1.2
Infant cardiac bypass surgery	R4	It is recommended that red cells for infant cardiac surgery be irradiated	5.1.3
Neonatal top up transfusions	R5	Irradiation is recommended for neonatal top up transfusions, including neonates who have received prior intrauterine transfusions	5.1.4
	R6	Red cells for top up transfusion must be no more than 14 days following irradiation	5.1.4
	R7	Red cells for large volume neonatal transfusion should be transfused as soon as possible after irradiation and preferably within 24 hours	5.1.4
Acute leukaemia	R8	Irradiation is recommended for patients undergoing cytoreductive therapy for AML and ALL and for a period of 6 months following therapy	5.2.1
	R9	Irradiation is not required when supportive care only is offered	
Allogeneic stem cell transplant recipients	R10	Should receive irradiated cellular blood products from the time of conditioning and for a minimum of 12 months post-transplant, but to continue while there is active GVHD or continuation of immunosuppression for GVHD	5.2.2
Autologous stem cell transplant recipients	R11	Should receive irradiated cellular blood products from the time of initiation of conditioning, with this to be reviewed 6 months post-transplant	5.2.3
Haemopoietic stem cell donors (including autologous and T cell donors)	R12	Cellular blood products should be irradiated during and within seven days prior to the planned collection of stem cells	5.2.4
Chimeric antigen receptor T cells	R13	Irradiation for a period of 12 months following CAR-T cell infusion therapy should be considered	5.2.5

Indication	Recommendation		Section reference
Hodgkin Lymphoma	R14	Irradiation of blood products should continue indefinitely for people with or who have had Hodgkin lymphoma	5.2.6
Non-Hodgkin lymphoma	R15	Irradiation is not recommended, unless indicated due to specific therapies received	5.27
Aplastic anaemia	R15	Cellular products should be irradiated during and following treatment with immunosuppressive therapy including anti-thymocyte globulin or similar T cell depleting therapy (e.g. alemtuzumab) and to continue until all immunosuppression has been ceased (including ciclosporin)	5.2.8
HLA matched and related donors	R16	HLA matched (compatible) or related-donor cellular products must be irradiated	5.3.1
Radiation exposure / accidents	R17	Cellular blood products must be irradiated	5.4.1
Critical bleeding and trauma	R18	Irradiation is not required for critical bleeding or trauma	5.5.1

Table 2: Practice recommendations

Section and subject	Recommendations		Section reference
General transfusion practices	PP1	Minimise unnecessary transfusions	3.1.1
	PP2	Use related and HLA-matched donors only when specifically indicated and then irradiate	3.1.2
Product manufacturing	PP3	Gamma and x-ray are considered equivalent for TA-GVHD prevention	3.3.4
	PP4	Pathogen inactivation technologies are a suitable alternative to irradiation	3.4.1
	PP5	Pre-storage leucocyte depletion reduces the risk of TA-GVHD but is not recommended as an alternative to irradiation in high-risk clinical situations	3.5.2
	PP6	Double leucocyte filtration may further reduce the risk of TA-GVHD however there is insufficient data to recommend its use	3.5.3
	PP7	Red cells in refrigerated storage for 14 days or more have a negligible risk of TA-GVHD and may be used as a suitable alternative wherever irradiated blood is not available	3.6.2
Implementation strategies for institutions	PP8	The optimum approach to prevent TA-GVHD is to irradiate all cellular products issued fresh, irrespective of recipient risk factors. However, it is acknowledged that this approach will not be suitable for most laboratories	4.1.3
	PP9	Most institutions will require irradiated blood to be ordered for recipients at increased risk of TA-GVHD	4.2.1
Identification and communication of at-risk recipients	PP10	Institutions should have processes in place to ensure identification of at-risk patients requiring irradiated blood products, the communication of this requirement to the transfusion laboratory, prescribing and administering professionals and the blood supplier	4.2.2
	PP11	Communication of irradiation requirements should include all clinical services and laboratories involved in the care of patients, including when patients are transferred, or care is shared between centres	4.2.3
	PP12	Communication regarding irradiation should specify the indication, duration or review date, as appropriate	4.2.4
	PP13	Patients should be advised of their irradiation requirement	4.2.5
Products to be irradiated	PP14	Where there are appropriate indications, cellular products including red cells, platelets and granulocytes must be irradiated. Stem cells, donor T cells and chimeric antigen receptor T cells must NOT be irradiated. Cryoprecipitate, fresh frozen plasma and manufactured plasma products do not contain viable T cells and there is consensus that they do not require irradiation	4.3.1
	PP15	Fresh (never frozen) plasma should be irradiated for at-risk recipients	4.3.2

Section and subject	Recommendations		Section reference
Products to be irradiated *continued*	PP16	Deglycerolised thawed red cells should be irradiated if clinically indicated and time permits	4.3.3
	PP17	Red cells should be no more 14 days old at the time of irradiation	4.3.4
	PP18	Platelets and granulocytes may be irradiated at any time during storage	4.3.5
	PP19	Irradiated red cells must be expired no later than 14 days following irradiation	4.3.6
Hyperkalaemia risk	PP20	Where patients are at particular risk of hyperkalaemia, transfusion should occur as soon as possible after irradiation, and ideally within 24 hours	4.3.7
Irradiation dose	PP21	The minimum radiation dose is 25Gy to all parts of the unit, with no part of the unit receiving more than 50Gy	4.3.8
Irradiator management	PP22	Irradiators must be compliant with irradiation safety and security regulations within the relevant jurisdiction.	4.3.9
	PP23	Irradiator installation and safety must be under the supervision of suitably qualified personnel	4.3.10
	PP24	All irradiators must ensure adequate radiation shielding. The security of the irradiator and personnel should also be considered for source irradiators	4.3.11
	PP25	Irradiators must be installed, calibrated and validated to deliver doses outlined above	4.3.12
	PP26	Laboratories must maintain valid calibration curves and the duration of irradiation confirmed regularly in accordance with manufacturer specifications	4.3.12
	PP27	Validation should be performed after maintenance that may affect radiation dose, for example of the turntable	4.3.13
Labelling of irradiated units	PP28	Units to be irradiated should have radiosensitive label appropriate to the type (gamma or x-ray) of radiation used affixed prior to irradiation which confirms to the end user that the label / unit has been irradiated as specified	4.3.14
	PP29	Irradiated units should be immediately labelled to include the date and time of irradiation and any change in expiry date	4.3.15
	PP30	The irradiation status of units must be recorded in the laboratory information system	4.3.16
Irradiation equivalent products	PP31	Where a product is not irradiated, is considered equivalent to irradiation (for example >14 days of age) and is issued in place of an irradiated unit where an irradiated product was otherwise indicated, the unit must be tagged to indicate that it is “Considered irradiation equivalent for the prevention of graft versus host disease,” or similar wording	4.3.17
Inventory Management	PP32	Inventory management should consider the impact of irradiation on wastage, the frequency of transfusion for patients requiring irradiated blood components and the available options for transfusion in emergency situations, such as older blood	4.4.3

Section and subject	Recommendations		Section reference
Inventory Management *continued*	PP33	Wherever possible, inventories should be managed to avoid the need to substitute ABO compatible rather than the ABO identical products solely to prevent wastage of the ABO compatible units	4.4.4
	PP34	Health services should ensure that patients, other treating clinicians and laboratories are aware of the addition and withdrawal of irradiation requirements	4.5.1
Stem cell and T cell products	PP35	Stem cells, donor T cells, chimeric antigen receptor T cells or other cellular products required to engraft, whether allogeneic or autologous must not be irradiated	5.3.2
Emergency transfusion	PP36	Provision of universally leucodepleted red cells and platelets significantly reduces the risk of TA-GVHD. Using the oldest available red cells (or at least>14 days old) would be considered equivalent to irradiation for the prevention of TA-GVHD in at risk patients who are critical bleeding.	5.4.2
	PP37	Laboratories should have a policy on the provision of non-irradiated blood in critical bleeding	5.4.3

Section 1
Introduction

1.1 Scope

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare iatrogenic complication of transfusion. TA-GVHD has a high mortality rate so the focus must be on prevention.

These guidelines cover the pathophysiology of TA-GVHD, equipment dosimetry and maintenance, clinical indications for irradiated blood components, alternatives to irradiation and risk-management approaches to patient identification, component selection and modification and inventory management to prevent TA-GVHD.

1.2 Background

TA-GVHD results from the engraftment of T cells into a susceptible recipient, with the risk associated with an individual transfusion depending on the interplay of several factors, including: 1) the number and viability of contaminating lymphocytes in the transfused cellular component; 2) the susceptibility of the recipient's immune system to the engraftment of donor lymphocytes; and 3) the degree of immunological (human leucocyte antigen, HLA) homology between the donor and the recipient. TA-GVHD can be prevented by reducing or eliminating viable T cells capable of mounting an immune response in cellular blood components prior to transfusion. Traditionally, this has been achieved through the transfusion of gamma irradiation of cellular blood components to recipients perceived to be at risk due to immunodeficiency. While this is an effective strategy, TA-GVHD in immunocompetent individuals is also recognised and, due to the high case-fatality rate, universal gamma irradiation has been applied to some blood components, by some clinical departments or jurisdictions.

Universal irradiation prior to transfusion has been adopted in Australia and New Zealand for platelet concentrates. A large proportion of platelets are transfused to recipients with haematological malignancies who may be at risk and platelet concentrates are always given “fresh” due to room temperature storage. This approach aims to prevent transfusion of at-risk products to at risk patients. The same approach has not been adopted for red cells, where there is an impact on the red cell membrane, causing an increased loss of potassium into the supernatant, affecting the duration of storage.

Since the first edition of these guidelines, there has been increasing evidence that pre-storage leucodepletion reduces, but does not eliminate, TA-GVHD. There is also increasing evidence that cold-stored red cells result in significant loss of T cells and that TA-GVHD is usually due to transfusion of fresh cellular components. Taking into account both the population data and in vitro evidence, irradiation of all fresh products under 14 days of storage as close as possible to the time of administration, would be the ideal preventative strategy, eliminating TA-GVHD from immune competent and immune deficient recipients alike. By ensuring that the component cannot cause TA-GVHD, this eliminates the frequent incidents of transfusion of non-irradiated components to susceptible recipients[1] and does not require the consideration of whether each new immunosuppressive therapy carries an increased risk of TA-GVHD. However, this approach requires on-site irradiators and adequate time to irradiate a large proportion of red cells on issue, which is not practical in most centres.

The increasing evidence for loss of T cell function during component storage and the absence of cases of TA-GVHD beyond 14 days storage[2] indicate that prolonged storage of red cell components is an effective means of TA-GVHD prevention. Irradiating components for a planned transfusion beyond this timeframe does not increase patient safety and may introduce added complications due to red cell membrane changes. Transfusion of red cells beyond 14 days is considered an adequate TA-GVHD prevention strategy and should be considered instead of irradiation.

Local guidelines need to consider the clinical and pre-clinical evidence for TA-GVHD risk and risk reduction techniques. They also consider the availability of local resources, such as blood irradiators, stock management practices and implementation strategies. Finally, clinical practice may vary between jurisdictions and over time, such as the use of related donors, which is actively discouraged within Australia and New Zealand.

Therefore, while these guidelines have considered international guidelines, they may differ to account for local factors.

1.3 Terminology

These guidelines are primarily informative and reflect what the Clinical Practice Improvement Committee believes is the minimum acceptable level of practice. Guidance is provided in the form of recommendations, the strength of which is indicated by the following (modal) terms:

Must Indicates a strongly recommended practice where compliance would be expected.

Should Indicates a recommended practice where compliance would be expected but alternative practices may be acceptable.

May Indicates a practice that is permitted within the context of the guidelines.

Section 2
Essential features of TA-GVHD

2.1 Pathogenesis and clinical features

There are three essential features required for TA-GVHD. Firstly, the graft must contain immunologically competent cells. Secondly, the recipient must possess antigens capable of stimulating a response in the donor. Thirdly, the recipient must not be able to mount an effective immune response to the donor T cells.[3] This latter condition can be met either by recipient immunodeficiency or by similarity of donor and recipient HLA antigens, for example where the donor is homozygous for an antigen present in the recipient.

Survival of lymphocytes following transfusion does not in itself constitute TA-GVHD. Microchimerism following pregnancy or transfusion for trauma is of uncertain clinical significance.[4,5] TA-GVHD requires the T cells to mount an immune response to the host with replication of T cells and inflammation and this does not always arise.

Pathologically, TA-GVHD is characterised by lymphocytic infiltrates in multiple organs.[6] In the skin, mononuclear epidermal infiltrates with bullae formation and vacuolisation of basal cells are typical, but not specific.[6,7] Polymorphs and eosinophils are not seen, the latter pointing to a drug eruption. Bone marrow is typically hypoplastic and may have a lymphocytic infiltrate or haemophagocytosis. The liver shows lymphocytic infiltrates within the portal tracts. Confirmation of the allogeneic nature of the infiltrate should be confirmed, such as by disparate HLA typing, sex mismatch or molecular evidence of chimerism.[7,8]

The clinical features of TA-GVHD include fever (67.5%) followed by multisystem inflammation with rash (80.2%), liver dysfunction (66.4%), pancytopenia (65.2%) and diarrhoea (43.1%).[2] The median time of onset was 11 days following transfusion, although it may occur later in infants. The rash is typically a maculopapular rash and can become erythrodermic. Lymphocytic infiltrates within the liver cause cholestatic hepatitis and the pancytopenia is largely attributed to marrow hypoplasia.

The mortality rate is approximately 90% and no reported treatments are associated with improved outcomes, highlighting the critical importance of prevention strategies.

2.2 Incidence

The rate of TA-GVHD is uncertain. It varies between populations due to the likelihood of HLA similarity amongst different ethnic groups and blood banking practices, including the use of leucodepletion, irradiation and storage stocking practices that influence the age of blood at transfusion. One estimate predicted approximately 1 in 8.3 million transfusions of leucodepleted non-irradiated cells, in countries where irradiation was routine practice for high-risk patients.[9] Incidence rates would be expected to be higher were irradiation not implemented at all. However, approximately half of the reported cases occurred in patients without recognized risk factors.[2]

2.3 Risk factors

2.3.1 Product

In order to promote TA-GVHD, transfused products must contain viable T cells capable of mounting an effective immune response. The absolute number of T cells can be reduced by leucocyte filtration and also declines with product age. Cold storage of red cells also leads to a reduction in T cell viability and a greater reduction in their ability to respond to immunogenic stimuli, possibly due to changes in cell surface receptors.[10]

Specific interventions to reduce T cells functionality, such as irradiation and ultraviolet pathogen inactivation processes, both of which interfere with DNA replication, can sufficiently damage T cells to prevent TA-GVHD.

2.3.2 Patient

Where a patient mounts an effective immune response to the transfused T cells, TA-GVHD may be prevented. Immunodeficient patients therefore appear at greater risk. Patient groups that have been identified to be at risk are discussed in Section 5.

2.3.3 Product and patient: lack of non-self HLA

There are numerous reports of TA-GVHD in immunocompetent hosts. In these cases, the host's ability to recognise allogeneic T cells as foreign may be impaired due to shared HLA antigens. In particular, where a donor is homozygous for an allele present in the recipient, the recipient will not see this antigen as foreign, whereas donor cells will identify one of the host antigens as non-self. This is thought to account for majority of TA-GVHD in non-immunocompromised patients and is likely to contribute to cases in immunodeficient recipients.[2,7]

Section 3
Principles and techniques of TA-GVHD prevention

3.1 General transfusion practices

3.1.1 Minimise unnecessary transfusions

There have been many large trials comparing liberal and restrictive transfusion strategies for red cell showing no improvement in mortality at haemoglobin concentrations that were previously commonly accepted transfusion triggers.[11] Randomised studies with platelets have also favoured more conservative triggers to transfuse.[12] Avoiding transfusion when it is not clinically beneficial is unequivocally good practice, conserves scarce blood supplies and prevents complications of transfusion, including TA-GVHD.

3.1.2 Use related and HLA-matched donors only when specifically indicated and then irradiate

Potentially harmful T cells with HLA similarity are more likely to be found in family members and HLA matched transfusions. While each of these may be required, for example where a patient has an antibody present to a common blood group where family members may also be antigen negative, or for HLA antibody platelet transfusion refractoriness, transfusion from these donors should otherwise not be routine. Where related donors are used, specific TA-GVHD prevention measures must be applied.

Practice points

PP1 Minimise unnecessary transfusions (3.1.1).

PP2 Use related and HLA-matched donors only when specifically indicated and then irradiate (3.1.2).

3.2 Gamma irradiation

3.2.1 Gamma irradiation has been the mainstay of TA-GVHD by inhibiting T cell proliferation. Doses need to be adequate to prevent T cell division while maintaining the integrity of the remaining components within the blood product. Irradiation causes DNA damage, inhibiting the ability of cells to divide. T cells unable to proliferate cannot cause TA-GVHD.

3.2.2 Gamma irradiation is produced from within nuclei by an isotope source; caesium-137 or cobalt-60 are used in source blood irradiators. Irradiation of blood is achieved by exposing units of blood to the irradiation source, typically on a turntable for an appropriate duration to deliver the required dose of radiation. As the source decays, the time taken to irradiate a unit of blood will increase. This requires that the duration of radiation exposure by reviewed regularly and increased to ensure the blood product receives an adequate dose.[13]

3.2.3 Gamma irradiators with a radioactive source are relatively easy to maintain since they require only to ensure exposure to the radioactive source for the correct length of time. The path of a unit of blood through the irradiator needs to be mapped so that the dose of radiation to all parts of the unit fall within specifications.

3.2.4 ~~Although relatively easy to maintain,~~ Having a radioactive source poses potential logistical and security concerns. With the constant production of gamma rays, radioactive sources need to be well shielded to prevent radiation exposure to people working in the vicinity, even when not in use. This is achieved through lead shielding built into the irradiators, making them heavy and requiring consideration of the location and floor load capacity. Caesium-137 and cobalt-60 are not explosive, however if released from the irradiator, are potentially dispersible, posing a security risk. This applies for the life of the irradiator, including transport, installation and disposal. Laboratories must be aware of and comply with local radiation safety and security policies and legislation applicable to them. Disposal of radioactive materials is also logistically difficult and potentially costly. While

irradiators have a long lifespan, decommissioning and disposal costs should be factored into whole of life cost assessments.

3.2.5 Irradiation has been shown to effectively inhibit lymphocyte proliferation. Using limiting dilution assays. Pelszynski et al[14] and Luban et al[15] have shown that 25Gy effectively inhibits T cell proliferation in red cells and platelet concentrates, respectively. Lower doses do have an effect on reducing lymphocyte proliferation, even at doses as low as 5Gy, however there have been cases of TA-GVHD at doses lower than 25Gy.

3.2.6 Irradiation does cause damage to red cells. Increased membrane permeability leads to increased haemolysis accompanied by an increased rate of potassium release following gamma irradiation. This is dose dependent, so irradiation dose should not be excessive. Haemolysis in red cell units remains with acceptable limits for up to 14 days post irradiation, even when irradiated at 14 days post-collection. An increase in phosphatidylserine expressing red cell microparticles has been found in irradiated red cells. While this may have a procoagulant and proinflammatory effect, the clinical significance of this finding is yet to be determined.[16]

3.2.7 Although some studies used lower doses of radiation than currently recommended, platelet morphology, function and survival do not appear to be impaired with radiation.[17-20]

3.3 X-ray irradiation

3.3.1 X-rays are another form of high energy radiation capable of ionising molecules within tissue and causing DNA damage. They have similar or lower frequencies than gamma irradiation and are produced by changes in the energy states of electrons, external to the nucleus, so they do not rely on radioactive decay for their production. X-rays are produced by the excitation and slowing of electrons within an x-ray tube, so they are only produced when required. While there may be more expensive initial outlays and maintenance for x-ray compared with gamma irradiation, x-ray devices do not require additional security measures and decommissioning does not require long term storage of nuclear waste material is not required.

3.3.2 There have been a number of studies showing the efficacy and suitability of x-rays for prevention of TA-GVHD. They have equivalent efficacy in preventing lymphocyte proliferation in mixed lymphocyte culture and mitogen stimulated culture.[21,22] Supernatant haemoglobin and potassium showed irradiation dose dependent increases overtime with minor, clinically insignificant, or no differences between x and gamma irradiated cells, including high concentration red cells for intrauterine transfusion.[21,23,24] Meli and colleagues compared the quality of red cells irradiated with x-ray or gamma rays and found no clinically meaningful differences in 2,3 DPG, lactate, ATP, lactate production, haemolysis or potassium levels in the supernatants of matched units.[25]

3.3.3 There are fewer data on the effect of x-ray irradiation on platelets. However, compared with gamma irradiation, platelet morphology, function and surface markers appear unchanged with x-ray treatment.[26]

3.3.4 Internationally, there is consensus that gamma and x-ray irradiation should be considered clinically equivalent for the prevention of TA-GVHD.[24,27,28] Although there may be subtle increases in haemolysis rates with x-ray compared with gamma irradiation of red cells, these are clinically insignificant when red cells are used within a 14 days expiration period after irradiation.

Practice point

PP3 Gamma and x-ray are considered equivalent for TA-GVHD prevention (3.3.4).

3.4 Pathogen inactivation technologies

3.4.1 Processes to inactivate blood borne pathogens in platelets are licensed and in use internationally. Although there is the potential to apply these to red cells, they are not yet licensed. These technologies interfere with nucleic acid and are able to reduce leucocyte proliferation in the same way they do in pathogens. Multiple studies have shown a reduction in T cell viability and activation following ultraviolet / riboflavin or amotosalen pathogen inactivation systems.[29-35] Implementation of these technologies usually includes cessation of irradiation. At present, pathogen reduction technologies have not been implemented in Australia and New Zealand. In the event that pathogen

reduction technologies are adopted, it will be the responsibility of regulatory agencies and blood component providers to determine efficacy for TA-GVHD and communicate changes to healthcare providers. On the basis of currently available information, pathogen reduction technologies would appear to be suitable alternative to irradiation.[36]

3.4.2 It should be noted that while gamma irradiation does also reduce some pathogens, at the doses used in blood component irradiation it has variable effects on organisms and is inadequate to effectively reduce pathogens.[37]

Practice point

PP4 Pathogen inactivation technologies are a suitable alternative to irradiation (3.4.1)

3.5 Leucocyte depletion

3.5.1 As T cells are responsible for TA-GVHD, removing leucocytes should reduce the potential for TA-GVHD. While there are differences between filters, pre-storage leucocyte depletion typically results in a >4 log reduction in the volume of transfused white cells. There are data suggesting a preferential reduction in T cells with leukodepletion filters[38] although this would need to be validated with each filter. While this is a substantial reduction and in some cases may approach theoretical limits for the number of T cells required, cases of TA-GVHD have been reported following transfusion of leucodepleted blood, even with modern filters[2] and T cell proliferative capacity persists following leucodepletion.[38]

3.5.2 Since the introduction of universal leucodepletion in the United Kingdom only 2 cases of TA-GVHD have been reported to the SHOT program, compared with 12 cases in the 3 years prior to implementation.[27] Therefore, both in vitro and surveillance data strongly suggest a highly protective effect of leucodepletion, although it remains inadequate to recommend it as a sufficient strategy for high risk situations.

3.5.3 Double filtration has shown a further reduction in leucocytes. With a second filtration at 72 hours, this significantly further reduces the number of leucocytes below detectable levels and is likely to reduce them to levels where TA-GVHD is highly unlikely. Double leukodepletion could therefore be a possible approach to risk minimisation when irradiated blood is not available. However, it does also further reduce the volume of red cells within the product. As all red cells and platelets within Australia and New Zealand are leucodepleted prior to storage, leucodepletion at the time of transfusion could feasibly improve the safety of non-irradiated blood. However, most institutions will not stock bedside leucocyte filters, so both filter availability and the reduction in red cells transfused may limit this application. There would also be a need to ensure the individual leucocyte filters used are able to produce results equivalent to those reported in the single study available. For these reasons, double leucocyte filtration is not currently recommended for routine TA-GVHD prophylaxis.

3.5.4 While protective, leucodepletion is not considered equivalent to irradiation and should not be relied upon in circumstances where there are indications for and adequate time to safely source irradiated blood.

Practice points

PP5 Pre-storage leucocyte depletion reduces the risk of TA-GVHD but is not recommended as an alternative to irradiation in high-risk clinical situations (3.5.2).

PP6 Double leucocyte filtration may further reduce the risk of TA-GVHD however there is insufficient data to recommend its use (3.5.3)

3.6 Storage duration of blood

It has been recognised for decades that the majority of cases of TA-GVHD occur following transfusion of blood that is less than 3-4 days old.[39] In their systematic review of all cases of TA-GVHD, Koplovich et al found the 158 cases that reported on the age of the transfused product. Of these, 93.7% were described as fresh or <10 days old with the remainder having storage durations of 11-14 days and no cases outside this time frame.

This is supported by in vitro data showing lymphocyte proliferation declines with storage. By day 14, Mykhailova showed a significant reduction in T cell proliferative capacity compared with that seen at day 7 of storage. By day 21 T cell proliferative capacity was below that thought to be required to induce TA-GVHD.[38] Chang and colleagues showed that there was a marked loss of T cell surface antigens required for activation during cold storage and have suggested this causes impairment in T cell activation and proliferation despite maintaining T cell viability.[10]

Practice point

PP7 Red cells in refrigerated storage for 14 days or more have a negligible risk of TA-GVHD and may be used as a suitable alternative wherever irradiated blood is not available (3.6).

4

Section 4

Practical implementation of TA-GVHD prevention strategies

4.1 Background

4.1.1 The traditional approach to preventing TA-GVHD is to identify patients at risk and to ensure blood products given to them are irradiated. However, approximately half of all reported cases of TA-GVHD occurred in people with no clearly identifiable risk factors. Universal irradiation would therefore be ideal to ensure absolute prevention of TA-GVHD, although this may have a substantial impact on resources, including blood wastage due to reduced shelf-life.

4.1.2 It is also apparent that fresh blood carries a much greater risk of TA-GVHD and older blood, particularly if leucodepleted, carries a negligible risk. Therefore, irradiation of all fresh units immediately prior to transfusion and not irradiating older units where transfusion services have access to on site irradiators, is likely to be a highly effective prevention strategy, also eliminating the need to specifically identify patients at perceived higher risk.

4.1.3 These guidelines suggest that transfusion services either adopt a policy of universal leukocyte reduction for all fresh cellular blood products or maintain irradiation only for patients considered at high risk. While the latter will be required for services that do not have an on-site irradiator, the former can be considered, but is not required, for services with access to irradiation immediately prior to transfusion.

4.1.4 In deciding whether to adopt a universal fresh product irradiation policy, institutions should consider:

- the capacity of the transfusion laboratory to process blood for irradiation in a timely fashion;
- the fate of the blood products, avoiding increased wastage due to irradiated products being issued but not used; and
- the ABO, Rh and Kell composition of red cell inventory, ensuring that irradiation policies do not increase demands for more “universal” blood groups, such as O RhD negative units.

4.2 Universal TA-GVHD safe blood for laboratories with on-site irradiators

4.2.1 Most guidelines have suggested that blood irradiation be recommended only for HLA-matched or -related donors and for immunocompromised. TA-GVHD however also occurs in immunocompetent recipients and it has been argued that a universal approach to irradiation would eliminate this fatal, otherwise unpredictable complication.[40] Indeed, this is the policy currently in Japan where the risk of receiving HLA-similar blood is greater than in many other populations.[41]

4.2.2 There are difficulties in maintaining a completely irradiated red cell inventory due to the shortened shelf-life post irradiation. By contrast, the absence of TA-GVHD cases after 14 days of storage to a reduction in viable reactive T cells, especially when combined with leucocyte depletion, suggests that irradiation beyond this time frame might be unnecessary.

4.2.3 Most TA-GVHD cases are seen when blood is transfused within the first 4 days of storage. Given the significant impact of storage duration on TA-GVHD risk, irradiation of blood issued fresh to patients, and not older blood (>14 days), could effectively achieve a universal TA-GVHD prevention strategy. However, this will only be available in centres with on-site irradiators.

Practice point

PP8 The optimum approach to prevent TA-GVHD is to irradiate all cellular products issued fresh, irrespective of recipient risk factors. However, it is acknowledged that this approach will not be suitable for most laboratories (4.2.3).

4.3 Recipient risk-based approach

4.3.1 Where irradiation of all fresh cellular products is not policy, irradiation of blood components to at risk recipients is advised. It is expected that this will be the approach in most laboratories. The indications for selecting cellular blood products for irradiation are discussed in Section 5.

4.3.2 Failure to identify at risk patients at risk and transfuse with irradiated blood is a commonly reported error, putting patients at risk.[1] Institutions should have processes in place to ensure the identification of patients requiring irradiated blood products, the communication of this requirement to the transfusion laboratory, prescribing and administering professionals and the blood supplier. Transfusion of patients at higher risk of TA-GVHD, as identified by these guidelines, with non-irradiated (or equivalent) cellular products should be reported through institutional haemovigilance processes.

4.3.3 Communication of irradiation requirements should include all clinical services and laboratories involved in the care of patients, including when patients are transferred, or care is shared between centres.

4.3.4 Communication regarding irradiation should specify the indication, duration or review date, as appropriate.

4.3.5 Along with other aspects of their treatment plans, patients should be advised of their irradiation requirements, especially when transfusions may occur in more than one institution.

Practice points

PP9 Most institutions will require irradiated blood to be ordered for recipients at increased risk of TA-GVHD (4.3.1).

PP10 Institutions should have processes in place to ensure identification of at-risk patients requiring irradiated blood products, the communication of this requirement to the transfusion laboratory, prescribing and administering professionals and the blood supplier (4.3.2).

PP11 Communication of irradiation requirements should include all clinical services and laboratories involved in the care of patients, including when patients are transferred, or care is shared between centres (4.3.3).

PP12 Communication regarding irradiation should specify the indication, duration or review date, as appropriate (4.3.4).

PP13 Patients should be advised of their irradiation requirement (4.3.5).

4.4 Irradiation practice

4.4.1 Where there are appropriate indications, cellular products including red cells, platelets and granulocytes must be irradiated. Stem cells, donor T cells and chimeric antigen receptor T cells must NOT be irradiated. Cryoprecipitate, fresh frozen plasma and manufactured plasma products do not contain viable T cells and there is consensus that they do not require irradiation.

4.4.2 Fresh (not frozen) plasma may contain some viable T cells. While not in current common use, irradiation should be considered in appropriate clinical circumstances as a single case of TA-GVHD in an immunodeficient infant has been reported.[42]

4.4.3 Glycerolised frozen red cells are washed prior to transfusion. They show a substantial reduction in lymphocyte responsiveness, however lymphocyte responsiveness remains.[43,44] Irradiation has been shown to minimally impact red cell quality.[45,46] While there has been no reported TA-GVHD following transfusion of deglycerolized red cells, these transfusions are few and data are insufficient to establish firm recommendations. However, as the product may be safely irradiated, this should be considered if otherwise clinically indicated and time permits.

4.4.4 Red cells (or whole blood) units should be no more than 14 days old at the time of irradiation.

4.4.5 Room temperature stored platelet and granulocyte units may be irradiated at any time during their standard storage times.

4.4.6 Irradiated units must be expired no later than 14 days following irradiation.

4.4.7 Where patients are at particular risk of hyperkalaemia, transfusion should occur as soon as possible after irradiation, and ideally within 24 hours.

4.4.8 A minimum dose of 25Gy to all parts of the blood product is required to ensure adequate T cell

inhibition, with no part of a unit receiving more than 50Gy to avoid excessive cellular damage.[47] Irradiation doses are applicable to both gamma and x-ray irradiation.

4.4.9 Irradiators must be compliant with irradiation safety and security regulations within the relevant jurisdiction.

4.4.10 Irradiation installation and safety must be under the supervision of suitably qualified personnel.

4.4.11 All irradiators must ensure adequate radiation shielding. The security of the irradiator and personnel should also be considered for source irradiators.

4.4.12 Irradiators must be installed, calibrated and validated to deliver doses outlined above. Laboratories must maintain valid calibration curves and the duration of irradiation confirmed regularly in accordance with manufacturer specifications.

4.4.13 Validation should be performed after maintenance that may affect radiation dose, for example of the turntable.

4.4.14 Units to be irradiated should have radiosensitive label appropriate to the type (gamma or x-ray) of radiation used affixed prior to irradiation which confirms to the end user that the label / unit has been irradiated as specified.

4.4.15 Irradiated units should be immediately labelled to include the date and time of irradiation and any change in expiry date.

4.4.16 The irradiation status of units must be recorded in the laboratory information system.

4.4.17 Products considered radiation equivalent may be used in place of irradiated products wherever indicated in these guidelines.

4.4.18 Where a product is not irradiated, is considered equivalent to irradiation (for example>14 days of age) and is issued in place of an irradiated unit where an irradiated product was otherwise indicated, the unit must be tagged to indicate that it is “Considered irradiation equivalent for the prevention of graft versus host disease,” or similar wording.

Practice points

PP14 Where there are appropriate indications, cellular products including red cells, platelets and granulocytes must be irradiated. Stem cells, donor T cells and chimeric antigen receptor T cells must NOT be irradiated. Cryoprecipitate, fresh frozen plasma and manufactured plasma products do not contain viable T cells and there is consensus that they do not require irradiation (4.4.1).

PP15 Fresh (never frozen) plasma should be irradiated for at-risk recipients (4.4.2).

PP16 Deglycerolised thawed red cells should be irradiated if clinically indicated and time permits (4.4.3).

PP17 Red cells should be no more 14 days old at the time of irradiation (4.4.4).

PP18 Platelets and granulocytes may be irradiated at any time during storage (4.4.5).

PP19 Irradiated red cells must be expired no later than 14 days following irradiation (4.4.6).

PP20 Where patients are at particular risk of hyperkalaemia, transfusion should occur as soon as possible after irradiation, and ideally within 24 hours (4.4.7).

PP21 The minimum radiation dose is 25Gy to all parts of the unit, with no part of the unit receiving more than 50Gy (4.4.8).

PP22 Irradiators must be compliant with irradiation safety and security regulations within the relevant jurisdiction (4.4.9).

PP23 Irradiator installation and safety must be under the supervision of suitably qualified personnel (4.4.10).

PP24 All irradiators must ensure adequate radiation shielding. The security of the irradiator and personnel should also be considered for source irradiators (4.4.11).

PP25 Irradiators must be installed, calibrated and validated to deliver doses outlined above (4.4.12).

PP26 Laboratories must maintain valid calibration curves and the duration of irradiation confirmed regularly in accordance with manufacturer specifications (4.4.12).

***Recommendations** continued*

PP27 Validation should be performed after maintenance that may affect radiation dose, for example of the turntable (4.4.13).

PP28 Units to be irradiated should have radiosensitive label appropriate to the type (gamma or x-ray) of radiation used affixed prior to irradiation which confirms to the end user that the label / unit has been irradiated as specified (4.4.14).

PP29 Irradiated units should be immediately labelled to include the date and time of irradiation and any change in expiry date (4.4.15).

PP30 The irradiation status of units must be recorded in the laboratory information system (4.4.16).

PP31 Where a product is not irradiated, is considered equivalent to irradiation (for example >14 days of age) and is issued in place of an irradiated unit where an irradiated product was otherwise indicated, the unit must be tagged to indicate that it is "Considered irradiation equivalent for the prevention of graft versus host disease," or similar wording (4.4.17).

4.5 Inventory management

4.5.1 Due to the reduced storage duration associated with red cell irradiation, there is additional complexity when managing an inventory of irradiated units or mixed inventories of irradiated and non-irradiated units.

4.5.2 As platelets have a short expiry, these additional complexities are not seen with irradiated platelets.

4.5.3 Inventory management should consider the impact of irradiation on wastage, the frequency of transfusion for patients requiring irradiation and the available options for transfusion in emergency situations, such as older blood.

4.5.4 Wherever possible, inventories should be managed to avoid the need to substitute ABO compatible rather than ABO identical group solely to prevent wastage of ABO compatible units.

Practice points

PP32 Inventory management should consider the impact of irradiation on wastage, the frequency of transfusion for patients requiring irradiated blood components and the available options for transfusion in emergency situations, such as older blood (4.5.3).

PP33 Wherever possible, inventories should be managed to avoid the need to substitute ABO compatible rather than the ABO identical products solely to prevent wastage of the ABO compatible units. (4.5.4).

4.6 Communication

4.6.1 Health services should ensure that patients, other treating clinicians and laboratories are aware of the addition and withdrawal of irradiation requirements. If patient care is transferred or shared between centres, procedures should be in place to ensure adequate and timely communication of special transfusion requirements.

4.6.2 Efforts should also be made to educate patients about whether they require blood components with any specific modifications.

4.6.3 To successfully implement the recommendations contained within these guidelines, institutional education programmes and protocols should be devised for treating clinicians and emergency department staff, nursing staff, pathology and blood bank staff to ensure adherence both to these guidelines and local policies.

Practice points

PP34 Health services should ensure that patients, other treating clinicians and laboratories are aware of the addition and withdrawal of irradiation requirements (4.6.1).

Section 5
Clinical indications for TA-GVHD safe products

5.1 Intrauterine, neonatal and paediatric practice

5.1.1 Intrauterine transfusions

Intrauterine transfusions (IUT) are typically performed with evidence of severe fetal anaemia. There is a risk associated with the procedure, so the preference is to minimise the number of times canulation is required. For both these reasons, IUT are usually large volumes relative to the size of the fetus and also relatively rapid. In addition to increasing the number of lymphocytes being transfused, this increases the potential risk associated with hyperkalaemia as blood ages. Therefore, fresh blood is recommended. Furthermore, the fetus has an immature immune system,[48] impairing their ability to mount a response to foreign T cells.

Surveillance and case reports have identified a number of IUT associated cases of TA-GVHD. While many are associated with related donors, this is not exclusively the case. For the reasons cited above, guidelines have supported universal irradiation of blood for IUT.[9,27,28,39]

Due to the increased risk of hyperkalaemia, transfusion of red cells must be within 24 hours of irradiation and the blood as fresh as possible.

Recommendations

R1 Red cells and platelets used for IUT should be irradiated.

R2 Red cells for IUT should be as fresh as possible and must be transfused within 24 hours of irradiation.

5.1.2 Neonatal exchange transfusions

Neonatal exchange transfusions have also been associated with TA-GVHD in otherwise normal neonates.[49-51] While some cases have occurred when exchange transfusion is performed subsequent to IUT, this is not always the case. Other guidelines also recommend irradiation for neonatal exchange transfusion.

An exchange transfusion is a relatively large volume of blood, which is often fresh due to concerns over the risks of hyperkalaemia.

These risk factors suggest that red cells for neonatal exchange transfusion should be irradiated and transfused within 24 hours of irradiation.

Recommendation

R3 Red cells for neonatal exchange transfusion should be irradiated and transfused within 24 hours of irradiation.

5.1.3 Neonatal and infant cardiopulmonary bypass surgery

Cardiopulmonary bypass surgery in neonates and infants is required because of congenital heart disease. While congenital heart disease itself is not a risk factor for TA-GVHD, there is an association between congenital heart disease and some congenital immunodeficiencies and these are considered to be at high risk of TA-GVHD.

There have been numerous cases of TA-GVHD following transfusion during cardiopulmonary bypass surgery in adults and children, however it is not clear that the procedure itself is a risk other than for the volume of blood given.[7] The high rates of transfusion, potentially large volumes and the tendency for the use of fresher red cells are predisposing risk factors. There have been cases in TA-GVHD immunocompetent infants. For these reasons it is recommended that red cells for infant cardiac surgery be irradiated.

Recommendation

R4 Red cells for infant cardiac surgery should be irradiated.

5.1.4 Neonatal top up transfusions

There is evidence that the neonatal immune system is less mature, both from epidemiological data (for example the different susceptibility to infections including group B Streptococci) and from analysis of cell types and cytokines. There is also evidence that these changes are dependent on gestational age at birth, although thereafter there appears to be convergence of the preterm and term neonates' immune systems over the first few weeks of life.[48,52] This physiological immunodeficiency has been recognized as a potential cause for TA-GVHD.

It has also been noted that most cases of TA-GVHD occur in neonates with concurrent risk factors, including immunodeficiency. However, Sanders and Graeber noted that most cases of immunodeficiency were diagnosed after the diagnosis of TA-GVHD, including at autopsy.[50] In older children and adults, severe immunodeficiency has had the opportunity to be diagnosed, whereas in the neonate this is not possible unless there are other clinical features of syndromes known to be associated with immunodeficiency. While the British Society for Haematology (BSH) has recommended that top up transfusions do not require irradiation unless there has been prior intrauterine transfusion,[27] they have also extended immunodeficiency to include haemophagocytic lymphohistiocytosis (HLH) on the basis of a single case report and an association with secondary HLH[53] and primary immunodeficiency.[54] They emphasised the importance of recognizing the various ways primary immunodeficiency may present, such as with complex cardiac anomalies, and instituting blood irradiation prior to confirmation of a diagnosis.

Intrauterine transfusion of red cells has been shown to suppress T cell proliferation in neonates.[55] While it is unclear if this leads to an increased TA-GVHD risk, top up transfusion following intrauterine transfusion may pose an additional risk and it is the recommendation to irradiate in this population remains. The same risk is not seen with high dose maternal immunoglobulin therapy.[55]

Despite the lack of an irradiation requirement in the UK, there have been no cases of neonatal TA-GVHD associated with top up transfusions, supporting their recommendation not to irradiate for neonatal top up transfusions.[27] Canadian guidelines also cite insufficient data to support universal irradiation, however do recommend it for very low birthweight infants.[28] A survey of neonatal intensive care units during that guideline development showed 18 of 21 units irradiated all neonatal top up transfusions, however there was strong support from directors to remove this indication.[28] Due to the potential effect of hyperkalaemia in the very low birthweight population, they recommend that level 3 neonatal intensive care units should have on site irradiators to enable transfusion within 24 hours of irradiation.

More recent evidence indicates that hyperkalaemia is seldom seen following transfusion in paediatrics.[56] Although hyperkalaemia increases with the red cell storage lesion, restoration of ATP-driven ion transport following transfusion is likely to return some lost potassium into the cells and provided the rate of transfusion is not excessive, potassium is well tolerated. It is recommended that irradiated red cells for top up transfusion be used within 14 days of irradiation. However, neonates requiring large volume transfusions rapidly may be at increased risk of hyperkalaemia and in these cases, blood should be transfused as soon as possible after irradiation and preferably within 24 hours.

The shortened expiry time of red cells following irradiation could limit the use of paediatric packs from the same donor. A red cell unit split into four units of paediatric use is often supplied to neonates to minimise donor exposure following repeated transfusion. The onus to reduce donor exposure is considered less relevant in Australia and New Zealand, where infection risks, including variant Creutzfeldt-Jacob disease is low. There are very low risks associated either with additional donor exposures or with the transfusion of older (>14 days) non-irradiated leucodepleted paediatric units from the same donor, even in infants with other indications for irradiation. Clinicians should consider and compare these options in discussion with parents. Both are considered acceptable strategies.

Recommendations

R5 Irradiation is recommended for neonatal top up transfusions, including neonates who have received prior IUT.

R6 Red cells for top up transfusion must be no more than 14 days old following irradiation.

R7 For large volume neonatal transfusion red cells should be transfused as soon as possible after irradiation and preferably within 24 hours.

5.2 Haematological disorders

5.2.1 Acute leukaemia

It is highly uncertain whether acute leukaemia itself increases the risk of TA-GVHD. Induction chemotherapy for acute myeloid leukaemia (AML) is associated with a temporary severe leukopenia. Acute lymphoblastic leukaemia (ALL) therapy has more prolonged and repeated lymphocyte suppression. There have been cases of TA-GVHD reported with both ALL and AML, even without other known risk factors for TA-GVHD. The implications of less myelosuppressive therapies, such as hypomethylating agents and bcl2 inhibition are unknown.

Guidelines vary in their recommendations for TA-GVHD prophylaxis in acute leukaemia. Based on the severe immunosuppression and prior cases, these guidelines recommend irradiation for patients undergoing cytoreductive therapy for AML and ALL and for a period of 6 months following completion of therapy. Irradiation is not required when supportive care only is offered.

Recommendation

R8 Irradiation is recommended for patients undergoing cytoreductive therapy for AML and ALL and for a period of 6 months following therapy. Irradiation is not required when supportive care only is offered.

5.2.2 Allogeneic stem cell transplantation

Allogeneic stem cell transplant relies on the engraftment of transplanted T cells. Conditioning and immunosuppressive regimens are required to suppress recipient T cells to facilitate donor T cell engraftment. Thus, allogeneic stem cell transplant is iatrogenic state deliberately designed to induce susceptibility to GVHD.

Chronic GVHD is itself an immunosuppressive condition and where therapy is required, it usually involves specific T cell suppression.

All allogeneic stem cell recipients should receive irradiated cellular blood products from the time of conditioning for a minimum of 12 months post-transplant and then to continue while there is active GVHD or continuation of immunosuppression for GVHD.

Recommendation

R9 Irradiated cellular blood products should be provided from the time of conditioning and for a minimum of 12 months post transplant, but to continue while there is active GVHD or continuation of immunosuppression for GVHD.

5.2.3 Autologous stem cell transplant

Autologous stem cell transplantation carries with it a risk of severe immunosuppression, including T cell depletion. Immune recovery is anticipated, however the evidence for a particular duration of irradiation is minimal. International guidelines generally recommend that irradiation continue for at least 6 months.[9,27] These guidelines recommend a pragmatic approach and to align recommendations for cellular therapies internally.

Autologous stem cell transplant recipients requiring transfusion should receive irradiated products from the time of initiation of conditioning, with this to be reviewed 6 months post-transplant. These timelines may be personalized based on T cell recovery and longer durations may be required based on other therapies received.

Recommendation

R10 Autologous stem cell transplant recipients should receive irradiated cellular blood products from the time of initiation of conditioning, with this to be reviewed 6 months post transplant.

5.2.4 Haemopoietic stem cell donors (including autologous and T cell donors)

The potential to collect transfused viable donor T cells within a stem cell product should be considered when transfusing prior to anticipated stem cell collections. It is recommended that cellular blood products be irradiated during and within seven days prior to the planned collection of stem cells.

Recommendation

R11 Cellular blood products should be irradiated during and within seven days prior to the planned collection of stem cells.

5.2.5 Chimeric antigen receptor T cells

There is no available evidence on the risk or rate of TA-GVHD following CAR-T cell therapy It is acknowledged that this therapy is not myelosuppressive and the risks may depend on the antigen targeted. Therapies prior to CART cells may be more significant at determining the TA-GVHD risk.

While no firm evidence-based practice guideline can therefore be recommended following CAR-T cell therapy, at the time of infusion, consideration of an irradiation for a duration equivalent to autologous stem cell transplants (6 months) is advised. Irradiation of blood products transfused in the 7 days prior to T cell collections, as with stem cells collections, is required.

Recommendation

R12 Following CAR-T cell infusion therapy irradiation for a period of six months should be considered.

R13 Blood products transfused in the 7 days prior to T cell collections should be irradiated, as with stem cells collections.

5.2.6 Hodgkin lymphoma

The occurrence of TA-GVHD has been noted in Hodgkin lymphoma at all stages of disease. It appears unrelated to treatment modality, stage or timing. Immunodeficiency, including impaired heterologous skin graft rejection, has been associated with Hodgkin lymphoma and other lymphoproliferative disorders.[57,58] There is no clear time point beyond which this risk is reversed following treatment. This has led to advice recommending lifelong irradiation of blood components following a diagnosis of Hodgkin lymphoma.

This lifelong requirement creates difficulties in the identification of patients who have been treated for Hodgkin lymphoma in the past and has resulted in transfusion of non-irradiated blood to this group has resulted in a large number of cases where non-irradiated blood has been transfused without incident. Despite SHOT data on 192 patients, these numbers remain substantially less than required to exclude a significant risk of TA-GVHD. British and Canadian guidelines have maintained the indefinite irradiation requirement.[27,28]

By contrast, recent guidelines from the Netherlands have recommended that irradiation for Hodgkin lymphoma is not routinely recommended unless required due to their specific treatment regimen.[9] Acknowledging the need for more data, they also proposed that cases be reported where a patient has received non-irradiated blood despite a recognized indication.

These guidelines recommend that irradiation of blood products continue indefinitely for people with or who have had Hodgkin lymphoma.

Recommendation

R14 People with, or who have had Hodgkin lymphoma should receive irradiated blood products and continue to receive them indefinitely.

5.2.7 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) may be associated with a degree of immunosuppression. B cell immunosuppression is common in B cell chronic lymphocytic leukaemia, in particular manifested as immunoglobulin deficiency.

Although the extent of immunodeficiency may extend beyond B cells, there is no evidence of an increased risk of TA-GVHD associated with mature B or T cell lymphoproliferative disorders. Irradiation is not recommended for TA-GVHD prevention in NHL.

Treatment of non-Hodgkin lymphoma and other mature B and T cell lymphoproliferative disorders may include agents known to be associated with an increased risk of TA-GVHD and in these cases, recommendations pertaining to those specific therapies should be followed.

Recommendation

R15 Irradiation is not recommended, unless indicated due to specific therapies received

5.2.8 Aplastic anaemia

Acquired aplastic anaemia due to autoimmune destruction of haematopoietic precursors results in pancytopenia and a hypocellular bone marrow. T cell immunity is generally not impaired, in fact increased T cell activity is seen in aplastic anaemia with oligoclonal expansion of CD8+/CD28- T cells responsible for haematopoietic stem cell destruction.[59] Therefore, patients with aplastic anaemia are not likely to be inherently at increased risk of TA-GvHD.

Treatment of aplastic anaemia may be with immunosuppressive therapy (IST) or haematopoietic stem cell transplant. IST includes anti-thymocyte globulin (ATG) and ciclosporine, which deplete T cells and inhibit function respectively. These drugs pose a theoretically increased risk of TA-GVHD, especially ATG. While some guidelines have suggested short term requirements for irradiation following ATG, ADDIN EN.CITE ADDIN EN.CITE.DATA [9,27] it is unclear for how long TA-GVHD risk may persist following ATG and cases of TA-GVHD following ATG for aplastic anaemia have occurred many years following treatment. It is recommended that cellular products should be irradiated prior to transfusion only in aplastic anaemia during and following treatment with IST including ATG or similar T cell depleting therapy (e.g. alemtuzumab). While the duration of this requirement is unclear, it is recommended that it be continued while any immunosuppression, including ciclosporin, is continued.

Where aplastic anaemia is treated with haematopoietic stem cell transplantation, the guidelines for irradiation following this procedure should be followed.

Recommendation

R16 Cellular products should be irradiated during and following treatment with immunosuppressive therapy including anti-thymocyte globulin (ATG) or similar T cell depleting therapy (e.g. alemtuzumab) and to should continue until all immunosuppression has been ceased (including ciclosporin).

R17 Where aplastic anaemia is treated with haematopoietic stem cell transplantation, the guidelines for irradiation in that setting should be followed.

5.3 HLA-matched and related donors

5.3.1 As HLA similarity is recognized as the major cause for TA-GVHD, HLA-matched or related donor cellular products must be irradiated prior to transfusion.

5.3.2 Stem cells, donor T cells, chimeric antigen receptor T cells or other cellular products required to engraft, whether allogeneic or autologous must not be irradiated as they will be rendered ineffective.

Recommendation

R18 HLA-matched (compatible) or related donor cellular products must be irradiated.

Practice Point

PP35 Stem cells, donor T cells, chimeric antigen receptor T cells or other cellular products required to engraft, whether allogeneic or autologous must not be irradiated.

5.4 Radiation exposure / accidents

Stem cells are susceptible to the effects of ionising radiation. Pancytopenia is a common and expected complication of radiation exposure due to its effect on bone marrow function. Lymphocytes are commensurately severely reduced,[60] potentially making the recipient at risk of TA-GVHD. Cellular blood products must be irradiated.

Recommendation

R19 Cellular blood products must be irradiated.

5.5 Emergency transfusion

5.5.1 The provision of irradiated blood in emergencies may be limited by stock availability and time. There is no specific requirement to provide irradiated blood for critical bleeding or trauma even when large volumes are expected to be transfused. As the risk of TA-GVHD is low, it is likely that the risks due to delays in the provision of blood will outweigh the risk of TA-GVHD.

5.5.2 The provision of universally leucodepleted red cells and platelets significantly reduces the risk of TA-GVHD. Using the oldest available red cells will also reduce the risk of TA-GVHD in recipients at risk and should be considered in critical bleeding.

5.5.3 Laboratories should have a policy on the provision of non-irradiated blood in critical bleeding.

Recommendation

R20 Irradiation is not required for cellular blood products used for critical bleeding or trauma.

Practice Points

PP36 Provision of universally leucodepleted red cells and platelets significantly reduces the risk of TA-GVHD. Using the oldest available red cells (or at least>14 days old) would be considered equivalent to irradiation for the prevention of TA-GVHD in at risk patients who are critical bleeding.

PP37 Laboratories should have a policy on the provision of non-irradiated blood in critical bleeding

Section 6
Indications removed since previous edition

6.1 Massive transfusion / critical bleeding

6.1.1 The previous edition included emergency large volume transfusion as a possible indication for irradiation. This was based on the finding of persistent B and T lymphoid and myeloid chimerism in the blood of trauma patients transfused with non-leucodepleted red cells [4]. Cases are not prominent in this setting. More recent data have not confirmed frequent engraftment following transfusion in trauma, despite a much larger cohort, possibly due to the effect of leukoreduction.[5] Furthermore, the supply of urgently needed or large numbers of red cells is difficult whether an institution relies on an on-site blood irradiator or irradiated stock from their blood service.

Acknowledgements

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