Report to Council on ANZSBT research grant funding received 2018

Project title: A feasibility randomised pilot trial of weekly-interval red cell transfusion schedule in myelodysplastic syndromes: REDDS-2 pilot study

Current status:

- The study design and protocol have been finalised with input from our Australian and European colleagues
- The trial has been registered on the Australia and New Zealand Clinical Trials Registry (ACTRN12619001053112p)
- The study has been presented to the Australasian Leukaemia and Lymphoma Group for comment
- Hospital sites and local investigators have been identified in Australia, UK and the Netherlands
- Ethics approval was granted by Monash Health (lead Australian site) HREC on 26th August 2019
- Currently awaiting final governance approval from Monash Health, with an aim to open the study for recruitment in the final quarter of 2019
- Ethics application underway at additional Australian sites
- Contracts being finalized for UK and the Netherlands, with an aim to complete ethics submissions at these sites by early 2020.

We thank ANZSBT for the important funding for this study and look forward to providing further updates.

Background and significance of the problem

Myelodysplastic syndromes (MDS) are a group of haematological cancers, more commonly affecting the elderly, resulting in bone marrow failure and cytopenias. Due to their age and comorbidities, many patients cannot receive the only curative therapy, bone marrow transplant. Transfusions are frequently required, with up to 68% of patients being transfusion dependent. However, there is sparse evidence to guide current transfusion practice, which can vary widely. National and international guidelines highlight the need for further research. The conventional practice is to transfuse patients several units of red blood cells (RBC) every 3-4 weeks, aiming for a 'restrictive' haemoglobin (Hb) target of 80-100g/L, however this approach is largely based upon trials in acute surgical or trauma settings, and the benefit is unclear in elderly outpatient MDS patients.

Further, the goal of transfusion support in MDS is to improve and maintain quality of life (QoL) and physical function, which are of vital importance to elderly outpatients. However, there are a lack of validated tools to measure and physical functional outcomes in this elderly patient population and these have not been investigated in relation to transfusion therapy.

Mathematical modelling suggests that maintaining a more stable Hb between transfusion episodes may improve QoL but this has not be studied in a clinical trial. Current transfusion schedules are also characterised by multiple delays in the intended sequence (e.g. planning transfusion in busy hospital units, requirements of comprehensive pre-transfusion testing). It is thus plausible that weekly transfusions with phenotype or genotype-matched RBCs, without the need to await prospective crossmatching, could be more effective and acceptable to patients and staff.

The REDDS-2 trial

Building on the success of the REDDS-1 trial of haemoglobin thresholds in MDS (presented at ASH in 2018), we are conducting a randomised pilot clinical trial of weekly RBC transfusion using matched RBCs versus current practice, in transfusion-dependent MDS patients. This feasibility study conducted in collaboration with the UK NHSBT will assess i) delivery of a weekly RBC transfusion schedule and ii) QoL and physical function tools. The overarching objective of this pilot

is to inform the design and conduct of a definitive international randomised trial to compare different strategies for RBC transfusion in outpatients with MDS.

Two transfusion treatments (usual transfusion schedule vs weekly matched RBCs) are being studied, with each patient receiving both arms in a randomly allocated sequence. To enable weekly transfusion in a timely manner, extended-matched RBCs will be used in the weekly arm, without the need to await results of prospective cross-matching.

The main outcome is feasibility and deliverability of the weekly RBC transfusion schedule.

Secondary outcomes include:

- Compliance with matching of RBCs
- RBC usage
- Change in Hb measurements
- Change in QoL scores
- Novel physical functional activity thresholds and measurements (assessed by the 6-minute walk test, grip strength, accelerometer measures)
- Adverse events including transfusion reactions and new RBC antibodies
- Novel iron biomarker assays

We aim to enrol 30 patients from sites in Australia, UK and the Netherlands. The study is sponsored by Monash University.

A second part of the study will involve optional qualitative interviews of patients and staff to explore their experiences of the new weekly transfusion schedule, including: potential enablers, barriers, positive and negative experiences, acceptability and comparison to the standard transfusion schedule. This will provide greater in-depth understanding of the weekly transfusion schedule and provide information to develop future clinical transfusion trials. We are working with Dr Elizabeth Pritchard from the Health Sciences Research Unit at Monash University to conduct and analyse patient interviews and staff focus groups at the participating sites in Australia and UK.

The trial forms a major part of my PhD studies.

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