Impact of Blood Transfusion on Hematopoietic Stem Cell Transplantation Outcome

Thesis

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By

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✍ **Mariet George Waheeb**

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Introduction

The improvements in clinical outcomes for hematopoietic stem cell (HSCT) or progenitor cell (HPC), both peripheral blood and bone marrow) transplantations have resulted in an increase in the number of procedures performed. HSCT transplantations are used to treat hematologic malignancies, solid tumors, aplastic anemia/marrow-failure states, and a continuously expanding list of autoimmune and inherited metabolic and immunodeficiency diseases. The increase in the number of HSCT transplantations performed has impacted transfusion services, not only in hospitals where transplantations are performed, but also in hospitals that do not perform transplantations but may become involved in managing patients before or after the procedure ***(Resnick et al., 2008).***

Haematopoietic stem cell transplant (HSCT) patients often require intensive blood component support. Transfusion may be complicated by transfusion transmitted infection (TTI) – both viral and bacterial, transfusion-associated (TA)-GvHD, febrile non-hemolytic transfusion reactions (FNHTR), transfusion-related acute lung injury and platelet transfusion refractoriness ***(Radia and Pamphilon, 2011).***

Patients undergoing Hematopoietic Stem Cell Transplant are traditionally high volume users [3.8] units/patient (autologous HSCT) [6.4] units/patient (allogeneic HSCT).

Historically, the HB thresholds of 10g/dL were used but Early guidelines in the 1990s suggest levels between 6 and 10g/dL depending on situation and co-morbidities of the patient ***(Kekre et al., 2011).***

The established guidelines for platelet transfusion are:

- A threshold of 10 x 10^9/L for prophylactic platelet transfusion.
- A higher threshold of 20 x 10^9/L in patients with fever, sepsis, splenomegaly and other well established causes of increased platelet consumption.

(European Directorate for Quality of Medicines and Healthcare, Strasbourg. EU Guide to Preparation, 2010).

Aim of the Work

To investigate the relationship between blood transfusion and the following sequels that has been recognised to hematopoietic stem cell transplantation such as the incidence of infection, veno occlusive diseases, acute and chronic GVHD and overall survival.

General Principles of Blood Transfusion

Transfusion of blood and blood components (ie, RBCs, platelets, plasma, and cryoprecipitate) is one of the most common medical procedures performed in the developed world. However, the decision to transfuse or not to transfuse is one of the more complex decisions made by medical practitioners. Clearly no medical intervention is without risks, but in principle, these risks should be offset or justified by immediate or long-term benefits. A better understanding of the risks of transfusion has transformed transfusion medicine through the accelerated development of more sophisticated donor testing (eg, ever-improving infectious disease tests), pretranfusion testing, recipient identification, and multiple improvements in blood component characteristics and quality (eg, leukoreduction, irradiation, pathogen inactivation). These developments have resulted in improved safety profiles for transfused components and a perception of minimal risk ***(Szczepiorkowski and Dunbar, 2013).***

Indications of blood transfusion:

- **Red blood cells**

RBC transfusions are used to treat hemorrhage and to improve oxygen delivery to tissues. Transfusion of RBCs should be based on the patient's clinical condition. Indications for RBC transfusion include acute sickle cell crisis (for stroke prevention), or acute blood loss of greater than 1,500 mL or 30 percent of blood volume. Patients with symptomatic

anemia should be transfused if they cannot function without treating the anemia ***(Klein et al., 2007).***

Symptoms of anemia may include fatigue, weakness, dizziness, reduced exercise tolerance, shortness of breath, changes in mental status, muscle cramps, and angina or severe congestive heart failure. The 10/30 rule— transfusion when a patient has a hemoglobin level less than or equal to 10 g per dL (100 g per L) and a hematocrit level less than or equal to 30 percent—was used until the 1980s as the trigger to transfuse, regardless of the patient's clinical presentation ***(Ferraris et al., 2007).***

In 1999, a randomized, multicenter, controlled clinical trial evaluated a restrictive transfusion trigger (hemoglobin level of 7 to 9 g per dL [70 to 90 g per L]) versus a liberal transfusion trigger (hemoglobin level of 10 to 12 g per dL [100 to 120 g per L]) in patients who were critically ill. Restrictive transfusion practices resulted in a 54 percent relative decrease in the number of units transfused and a reduction in the 30-day mortality rate. The authors recommended transfusion when hemoglobin is less than 7 g per dL, and maintenance of a hemoglobin level between 7 to 9 g per dL. Recently updates support the use of restrictive transfusion triggers in patients who do not have cardiac disease ***(Sharma et al., 2011).***

- **Plasma transfusion**

Plasma transfusion is recommended in patients with active bleeding and an International Normalized Ratio (INR) greater than 1.6, or before an invasive procedure or surgery if a patient has been anticoagulated. Plasma is

often inappropriately transfused for correction of a high INR when there is no bleeding. Supportive care can decrease high-normal to slightly elevated INRs (1.3 to 1.6) without transfusion of plasma ***(Holland and Brooks, 2006).***

- **Plateletes transfusion**

Platelet transfusion may be indicated to prevent hemorrhage in patients with thrombocytopenia or platelet function defects. Contraindications to platelet transfusion include thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia. Transfusion of platelets in these conditions can result in further thrombosis. One unit of apheresis platelets should increase the platelet count in adults by 30 to 60 × 10 per μL (30 to 60 × 10 per L) ***(King et al., 2008).***

General principles of transfusion support

The appropriate use of blood components according to pre-defined policies helps to minimize complications.

Red cell transfusion policy:

Red cells should be matched for ABO and Rhesus D type. Extended patient phenotyping eg for Kell, Duffy, Kidd, MNSs antigens is advisable in patients having long-term transfusion support eg patients with sickle cell disease, thalassemia, severe aplastic anaemia and myelodysplastic syndromes. This allows selection of red cell units matched for some significant antigens e.g. Rhesus and Kell and aids antibody identification if it occurs.

Red cells should be cross-matched against the patients serum by standard techniques prior to transfusion. Thresholds

should be defined for hemoglobin and hematocrit below which red cell transfusions are always given although the evidence on which to base these is sparse. Suggested arbitrary cut off points are Hb <8.0 g/dL and haematocrit <25% unless there is significant cardiac impairment or symptoms of anaemia.

In adults 1 unit of red cells raises the Hb by 1.0 g/dL whereas in children the volume of blood to be transfused is derived from the formula:

Volume = Increase in Hb (g/dL) required x 4 x weight (kg)

Platelet transfusion policy:

PCs should be ABO and Rh compatible wherever possible since ABO incompatibility may reduce the expected count increment (CI) by 10–30%.

Group O PCs should be tested for high titre anti-A, B and if positive should only be transfused to group O recipients to avoid haemolysis caused by passive administration of antibody.

If Rh D positive platelets are given to an Rh D negative woman of child-bearing potential it is recommended that 250 IU polyclonal anti-Rh (D) immunoglobulin should be given. This dose would cover up to 5 adult therapeutic doses of platelets given over 6 weeks and should be given subcutaneously in thrombocytopenic patients. Since the chance of Rh immunization is probably <5% anti-D may be omitted and the patient's serum screened at intervals or prior to a red cell transfusion.

The established guidelines for platelet transfusion are:

1- A threshold of 10 x 10^9/L for prophylactic platelet transfusion.

2- A higher threshold of 20 x 10^9/L in patients with fever, sepsis, splenomegaly and other well established causes of increased platelet consumption.

3- A threshold of >50 x 10^9/L if an invasive procedure is planned, e.g. central line insertion.

- PCs are contraindicated in patients with thrombotic thrombocytopenic purpura (TTP).

(European Directorate for the Quality of Medicines & Health Care (EDQM), 2016).

Dose of Transfusion:

- In adults the usual dose of platelets is 3 x 10^{11} (adult therapeutic dose - ATD) in a volume of 2 00–300 mL
- In children 15–30 kg transfuse 0.5 ATD (volume 100–150 mL); in children <15 kg a proportionately smaller volume is given.

Rate of transfusion:

- Adults 1 ATD is given usually in <60 minutes
- Children e.g. 2–5 mL/kg/hr

The outcome of platlet transfusions can be monitored by:

- Looking for cessation of bleeding:
- Measuring the platelet count the following day.

A persistent value <20 x 10^9/L suggests refractoriness

(Radia and Pamphilon, 2011)

Table (1): Component type selection for hematopoietic stem cell transplantation crossing the ABO barrier

Type of Mismatch	Transplantation		Transfusion	
	Donor Type	Recipient Type	Red Blood Cell	Platelets[a] /Plasma
Major	A	O	O	A AB
	B	O	O	B AB
	AB	O	O	AB
	AB	A	A O	AB
	AB	B	B O	AB
Minor	O	A	O	A AB
	O	B	O	B AB
	O	AB	O	AB
	A	AB	A O	AB
	B	AB	B O	AB
	A	B	O	AB
Bidirectional	B	A	O	AB

[a]Platelets stored in additive solution reduce the volume of incompatible plasma transfused.

Clinicians responsible for the prescription of blood, blood components and fractionated blood products should have a proper understanding of the potential harmful effects of the therapy so that the risk — benefit ratio of the proposed treatment may be properly assessed ***(Basu and Kulkarni, 2014).***

Fortunately, the majority of side effect of blood transfusion are mild and do not seriously endanger the patient's well-being. There are lethal complications which maybe either immediate or remote.some reactions which may be mild in a relatively fit patients, become serious in a recipient already suffering from other complex medical or surgical conditions. Unwanted effects of transfusion may go unrecognized, either because sign and symptoms are missed or attributed to other problems or because there are so remote in time from the transfusion ***(Maxwell and Wislon, 2006).***