MADRID
22ND CONGRESS
JUNE 22 - 25 | 2017
European Hematology Association

Challenges in blood transfusion - Section 3

Red blood cell transfusion: When to transfuse in patients with hematological malignancies?

Miguel Lozano

Department of Hemotherapy and Hemostasis. Institute of Hematology and Oncology. Hospital Clínic. University of Barcelona, Spain

Take-home messages

- High quality evidence is lacking for guiding red cell transfusion in patients with hematological malignancies.
- New randomized controlled clinical trials of enough power are needed to definitively establish the best strategy to indicate RBC transfusion in this population of patients.

Introduction

In the European Union, 18.3 millions of red blood cell (RBC) units were transfused in 2013.[1] In most of the countries of EU, about 40% of them are transfused to patients suffering from neoplasm and blood diseases.[2] Since 1999 high quality evidence has been published to guide RBC transfusion in a wide variety of clinical scenarios such as intensive care units (adult and pediatric),[3,4] sepsis,[5] orthopedic[6] and cardiac surgeries or gastrointestinal bleeding[7]. The evidence suggests that a restrictive hemoglobin threshold for indicating a RBC transfusion is at least as safe and efficacious as hemoglobin concentrations of 90-100 g/L. The restrictive threshold would be hemoglobin concentrations of less than 70 g/L for stable, adult inpatients including those in the intensive care unit and hemoglobin levels of less than 80 g/L for a group of postsurgery patients or those with preexisting cardiac disease.[8,9]

Current state

The patients suffering from hematological malignancies often require RBC transfusion as a consequence of the anemia developed by the disease itself or by the intensive treatment in form of chemotherapy or hematopoietic stem cell transplantation used. Unfortunately, in this group of patients, there are no currently published randomized controlled trials of enough power that help attending physicians to establish the best strategy to indicate RBC transfusions. Thus, to decide the RBC transfusion policy in this type of patients we have to rely on the existing published evidence. However, patients being treated for hematological malignancies represent a unique group of patients with differential characteristics that have to be taken into account when extrapolating the evidence found in other group of patients, such as longer term transfusion dependence.

Probably the most striking difference of patients being treated with intensive chemotherapy /radiotherapy combined or not to hematopoietic progenitor cells transplantation for hematological malignancies with patients included so far in the studies of RBC transfusion threshold is the frequent presence of profound thrombocytopenia (less than $20x10^9$/L) associated with the anemia that hematology patients present in the evolution of its disease. Some *in vitro* research data indicate that platelet interaction with vascular subendothelium is affected by the amount of RBC present is the circulating blood. Escolar *et al.*, using an *in vitro* perfusion system reported that in blood with $200x10^9$/L platelets, the percentage of perfused subendothelium covered by platelets decreased a 44% when the hematocrit was reduced from 41% to 19%.[10] Valeri *et al.* showed in healthy volunteers that the removal of two units of RBC decreased the hematocrit by 15% and the platelet count by 9% and at the same time a 60% increase in the bleeding time. Reinfusion of the two units of RBC previously removed, restored the bleeding time in the donors.[11] It has been suggested that hemorheological factors might explain, at least in part, this observation. The RBC would circulate at the center of the flow, pushing the smaller platelets to the periphery of the flow facilitating its interactions with the subendothelium of the vessels.[12]

The potential effect of low hemoglobin levels in the bleeding of anemic and thrombocytopenic patients with hematological malignancies has been studied in some small randomized controlled trials. Webert *et al.*[13] reported a pilot study where patients with acute leukemia receiving induction chemothera-

py or patients undergoing hematopoietic progenitor cell transplantation were randomized to receive 2 RBC units when hemoglobin level was less than 80 g/L or when the hemoglobin was less than 120 g/L. Sixty patients were enrolled in the study. The proportion of patients presenting clinically significant bleeding and the time to first bleed was not significantly different between the control and experimental group. The experimental group received more RBC transfusions compared to the study group (0.233 *vs* 0.151 patients/days with RBC transfusion, p=0.003). The authors concluded that it was feasible to enroll the needed patients for a large randomized controlled trial to investigate the effect of hemoglobin level on bleeding risk.

Interestingly, Robitaille *et al*. published in 2013 that a randomized controlled trial where two hemoglobin thresholds (70 *vs* 120 g/L) as triggers for RBC transfusion in children undergoing allogeneic bone marrow transplantation were being studied, was closed by the Data Safety Monitoring Board after enrolling 6 patients, because the 3 patients enrolled in the 120 g/L threshold arm developed veno-occlusive disease, while none of the 3 patients in the 70g/L arm did.[14]

Another pilot study was recently published where the feasibility of performing a randomized controlled trial of a low hemoglobin (70 g/L) RBC transfusion trigger versus a high (80 g/L) trigger in patients receiving treatment for acute leukemia. Ninety patients consented and were randomly assigned to each of the study arms. The authors concluded that the primary objective of feasibility was met. Regarding secondary outcomes, there was no statistically significant differences in bleeding events or neutropenic fevers between study arms. The mean number of RBC units transfused to patients in the low arm was 8.2 units per patient and 11.3 units in the high arm (p=0.0003).[15] In addition to those already published, there is one study registered at the Clinical.Trials.gov (NCT01237639) which studied the RBC transfusion triggers in patients undergoing hematopoietic stem cell transplantation (TRIST);[16] the study has recently completed the enrolment of patients but has not yet reported the results.

Table 1. Randomized controlled trials (RCT) on the red blood cell (RBC) transfusion threshold in patients with hematological malignancies.

Author, year, reference	Type of study	Patient population, n	Hemoglobin threshold compared	Primary outcomes	Secondary outcomes	Comment
Webert *et al.* 2008[11]	Multicenter, pilot-randomized controlled	Adult (>16 years) with acute leukemia, induction or consolidation. 60 patients	80 g/L *vs* 120 g/L	Feasibility of conduction a large RCT in this population	Clinically significant bleeding, RBC and platelet transfusions	Promyelocytic leukemia excluded.
Robitaille *et al.* 2013[12]	Multicenter, randomized, controlled	Children (<16 years), allogeneic bone marrow transplantation, 6 patients	70 g/L *vs* 120 g/L	Time to neutrophil recovery	Platelet recovery, number of RBC and platelet transfusions, hospitalization length, overall survival, transplantation related mortality, relapse	Study stopped by Data Safety Monitoring Board after 100% of the 3 patients enrolled in experimental arm developed eno-occlusive disease and none of 3 patients in the control arm
DeZern *et al.* 2016[13]	Pilot, randomized, controlled	Adult (>18 years), acute leukemia, 89 patients	70 g/L *vs* 80 g/L	Feasibility of conducting a large randomized trial	Fatigue, bleeding, response to therapy, vital status, length of hospital stay and number of RBC and platelet transfusions	2:1 (70 *vs* 80 g/L) randomization ratio.
Tay *et al.*[14]	Open-labeled, multicenter, pilot study	Adult, autologous or allogeneic hematopoietic stem cell transplantation, 100 patients	70 g/L *vs* 90 g/L	Feasibility of conducting a large randomized trial	Transfusion requirements, transplant related mortality, acute graft *vs* host disease, veno occlusive disease	Study completed, results not yet reported

Challenges in blood transfusion - Section 3

Future perspectives

New randomized controlled clinical trials of enough power are needed in patients with hematological malignancies to definitively establish the best strategy to indicate RBC transfusion in this population of patients.

References

1. van Hoeven LR, Janssen MP, Rautmann G. The collection, testing and use of blood and blood components in Europe. 2013 report. Strasbourg, France: European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). 2016.
2. Bosch MA, Contreras E, Madoz P, Ortiz P, Pereira A, Pujol MM, et al. The epidemiology of blood component transfusion in Catalonia, Northeastern Spain. Transfusion 2011;51:105-16.
* 3. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.

The first randomized controlled trial of hemoglobin threshold for indicating red blood cell transfusion.

4. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007;356:1609-19.
5. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
6. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
7. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21.
*8. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: Red blood cell transfusion thresholds and storage. JAMA 2016;316:2025-35.

An updated guidelines for red blood cell transfusions.

9. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016;10:CD002042.
*10. Escolar G, Garrido M, Mazzara R, Castillo R, Ordinas A. Experimental basis for the use of red cell transfusion in the management of anemic-thrombocytopenic patients. Transfusion 1988;34: 406-11.

An in vitro study showing the important role of red blood cells in platelet-subendothelium interaction.

11. Valeri CR, Cassidy G, Pivacek LE, Ragno G, Lieberthal W, Crowley JP, et al. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. Transfusion 2001;41:977-83.
12. Uijttewaal WS, Nijhof EJ, Bronkhorst PJ, Den Hartog E, Heethaar RM. Near-wall excess of platelets induced by lateral migration of erythrocytes in flowing blood. Am J Physiol 1993;264:H1239-44.
*13. Webert KE, Cook RJ, Couban S, Carruthers J, Lee KA, Blajchman MA, et al. A multicenter pilot□randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. Transfusion 2008;48:81-91.

One of the few randomized controlled trials of red blood cell transfusion threshold in patients with hematological malignancies receiving intensive chemotherapy.

14. Robitaille N, Lacroix J, Alexandrov L, Clayton L, Cortier M, Schultz KR, et al. Excess of veno-occlusive disease in a randomized clinical trial on a higher trigger for red blood cell transfusion after bone marrow transplantation: a Canadian Blood and Marrow Transplant Group Trial. Biol Blood Marrow Transplant 2013;19:468-73.
*15. DeZern AE, Williams K, Zahurak M, Hand W, Stephens RS, King KE, et al. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. Transfusion 2016;56: 1750-7.

A pilot randomized controlled trial of two transfusions thresholds in patients receiving chemotherapy treatment for leukemia.

16. Tay J, Tinmouth A, Fergusson D, Allan D. Transfusion of red cells in hematopoietic stem cell transplantation (TRIST): study protocol for a randomized controlled trial. Trials 2011;12:207.