When to transfuse and how much in hematologic malignancies

The two main blood components commonly transfused to patients with hematologic malignancies are red cells and platelets. A number of randomized-controlled trials (RCTs) have been conducted to inform safe and effective use of platelets. The ready availability of platelet concentrates has undoubtedly made a major contribution to the supportive management of thrombocytopenic bleeding. But the optimal use of prophylactic platelet transfusions for the prevention of hemorrhage remains controversial. Two RCTs of prophylactic platelet transfusions have recently been completed in adults with thrombocytopenia due to hematologic malignancies or their treatment. Both found a no-prophylaxis approach led to higher rates of World Health Organization (WHO) grade 2–4 bleeding overall. There is ongoing discussion about whether the effectiveness of prophylactic platelet transfusions may differ between sub-groups of patients with hematologic malignancies, and whether a no-prophylaxis approach is non-inferior to prophylactic platelet transfusions in autologous hematopoietic stem cell transplantation. In contrast to use of platelets, there is very little evidence available to direct optimal use of red cells in patients with hematologic malignancies. Many patients with myelodysplasia will become red blood cell transfusion-dependent during the course of the disease, but few data exist to inform the optimal transfusion threshold and target hemoglobin concentration that translate into a significantly improved quality of life for these patients.

Learning goals

At the conclusion of this activity, participants should be aware that:
- recent trials have started to address fundamental issues of effectiveness for use of a blood component (platelets) by comparison to a no-transfusion policy for inpatients receiving therapy for hematologic malignancies;
- the results of 2 recent randomized trials have indicated that prophylactic platelet transfusions overall reduced bleeding rates in patients;
- there is evidence that the effectiveness of prophylactic platelet transfusions may differ between sub-groups of patients with hematologic malignancies. Further research is necessary to establish whether a no-prophylaxis approach is non-inferior to prophylactic platelet transfusions in patients receiving autologous hematopoietic stem cell transplants, and whether prophylactic platelet transfusions are a (cost)-effective use of resources in these patients, and how these findings might relate to outpatients with chronic thrombocytopenia;
- there is minimal evidence for the optimal use of red cells for inpatients with hematologic malignancies;
- information is required on a range of key clinical outcomes, including health related quality of life (HrQoL). It is unclear whether higher hemoglobin concentration thresholds for red cell transfusion in patients with myelodysplasia might improve HrQoL.

Introduction

This article will provide an evidence-based review on the use of blood components in patients with hematologic malignancies, with a specific focus on platelet transfusions in this session. One primary source of information is systematic reviews (see References list). This article will not address the question as to whether there are clinically significant differences in product type, e.g. ABO identical versus non-identical platelet transfusions, for which the reader is referred to other reviews.1-3

In addition, space precludes a detailed review of the risks of transfusion. Red cells and platelets for transfusion are biological interventions, which are also scarce and costly. Non-infectious risks are well recognized as more common adverse effects compared to the generally very low risks of transfusion-transmitted infection, whether viral or bacterial. One important theme from this paper is the need to better understand how use of blood components for transfusion can be tailored to patient factors, for example, in the case of platelet transfusions, an assessment of the risk of bleeding.

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Use of platelet transfusions

Patients with hematologic malignancies often develop severe thrombocytopenia either as a consequence of the disease or its treatment, including chemotherapy and stem cell transplantation. Platelet transfusions are commonly administered to raise the low platelet count and reduce the risk of clinical bleeding (prophylaxis) or stop active bleeding (therapy). The ready availability of platelet concentrates has undoubtedly made a contribution to the supportive management of thrombocytopenic bleeding in patients with hematologic malignancies, and the use of platelet transfusions to treat bleeding in association with severe thrombocytopenia is standard care in this patient group. But many audits have indicated that the most common indication for administration of platelet transfusions to thrombocytopenic patients with hematologic malignancies is prophylaxis (up to 69% of platelet transfusions in hematology patients). Several areas of clinical controversy concerning the prophylactic use of platelet transfusions are the focus of research. 1) What platelet count threshold should be used to trigger the transfusion of prophylactic platelets? 2) What is the optimal platelet dose to prevent thrombocytopenic bleeding? 3) Are prophylactic platelet transfusions superior to a strategy of therapeutic only platelet transfusions for the prevention of severe thrombocytopenic bleeding? 4) Should different policies be applied for support of transient severe thrombocytopenias (inpatients), or for chronic thrombocytopenia due to bone marrow failure (typically outpatient management).

The effectiveness of prophylactic platelet transfusions in clinical trials has historically been assessed by the measurement of a surrogate marker: the platelet count increment (at 1 h and/or 24 h post transfusion). However, a small difference in the platelet count increment may be of no clinical significance because there is no difference between the treatment arms in patients’ propensity to bleed. Therefore, an assessment of bleeding is now viewed as a more clinically relevant measure of the efficacy of platelet transfusions. The majority of trials have used the WHO system, or a modification of this system to grade bleeding. A limitation of these scoring systems is that the categories are relatively broad and subjective. Another limitation is that the modified WHO grades are partially defined by whether a bleeding patient requires a blood transfusion. The threshold for transfusion may vary between clinicians and institutions, and so the same level of bleeding could be graded differently.

Four randomized-controlled trials (RCTs) have investigated different platelet count triggers in patients with hematologic and oncological malignancies. A meta-analysis of these studies showed no increase in the number of patients who had a significant hemorrhage, and a significant reduction in the number of platelet products required using a threshold of $10^9$ platelets/L. Based largely on the Italian trial, guidelines for platelet transfusion in many countries have recommended that the platelet count trigger for prophylactic transfusions is $10^9$ platelets/L, with a common acceptance that selected hematology patients with additional risk factors, such as sepsis or invasive infections, might benefit from higher thresholds.

More recent research interest has focused on the optimal dose of platelets. The dose of platelets transfused was originally based upon the perceived need to raise the patient’s platelet count above a certain ‘safe’ threshold. It has been suggested that patients require only $7 	imes 10^9$/L per day to maintain hemostasis, based on a study of 51Cr-labeled platelets in patients with stable thrombocytopenia secondary to bone marrow failure. Platelets have been shown to provide an endothelial supportive function in intact blood vessels. Animal studies have shown that thrombocytopenia is associated with the gradual thinning of the vessel wall endothelium over time, and that, if thrombocytopenia persists, gaps gradually occur between adjacent endothelial cells. This thinning and fenestration of the endothelium is accompanied by the increased use of circulating platelets to prevent loss of red blood cells (RBCs) through these ‘gaps’ (petechiae occur due to RBC loss via these endothelial fenestrations).

Nine RCTs have addressed the question of optimal platelet dose in patients with hematologic or oncological malignancies. Five of these studies have compared low dose versus standard dose, and 4 studies have compared standard dose with high-dose platelet transfusions. A meta-analysis of 6 of these studies showed no evidence of a difference between low-dose and standard-dose platelets or between standard-dose and high-dose platelets in the number of patients who experienced at least one episode of clinically significant bleeding. This meta-analysis was dominated by the findings of the largest trial, which enrolled 1351 patients. This RCT showed there was no significant difference in the number of patients who bled between the low-dose ($1.1 	imes 10^{10}$ platelets/m$^2$), medium-dose ($2.2 	imes 10^{10}$ platelets/m$^2$) and high-dose ($4.4 	imes 10^{10}$ platelets/m$^2$) arms. Overall, a low-dose transfusion policy reduced patients’ total platelet requirements, but at the expense of a higher number of platelet transfusions. Overall, a general finding across all prophylactic platelet transfusion trials, including the 2 largest studies comparing different thresholds or doses, mentioned above, has been the lack of any difference in results for hemostatic outcomes between trial arms (i.e. no increased bleeding in the restrictive policy arms for transfusion by lower threshold or dose). This has, therefore, raised questions about the exact size of benefit of using platelet transfusions as prophylaxis to prevent bleeding.

With this in mind, 2 RCTs of prophylactic platelet transfusions have now been completed in adults with thrombocytopenia due to hematologic malignancies or their treatment. Both found a no-prophylaxis approach led to higher rates of World Health Organization (WHO) grade 2-4 bleeding overall. Platelet usage was markedly reduced in the no-prophylaxis arm in both studies.

Wandt et al. powered a clinical trial in Germany around numbers of platelet transfusions, and reported that rates of bleeding were significantly increased in the no-prophylaxis group for both autologous hematopoietic stem cell transplantation (autoH SCT) and acute myeloid leukemia (AML) subgroups, although increased by differing degrees. TOPPS was a randomized, parallel-group, open-label, non-inferiority trial conducted at 14 UK and Australian centers, which recruited 600 patients. The primary end point was WHO grade 2-4 bleeding up to 30 days from randomization. WHO grade 2-4 bleeding grade occurred in 151 of 300 patients (50%) in the no-prophylaxis group compared to 128 of 298 (43%) in the prophylaxis group (adjusted difference in proportions 8.4%, 90% CI: 1.7-15.2%; P-value for non-inferiority 0.06). The
proportion of patients developing WHO grade 2-4 bleeding, therefore, was reduced by 7% overall when receiving prophylactic platelet transfusions; to achieve this, patients in the prophylactic arms received 61% more platelet transfusions. Further sub-group analyses have been completed in TOPPS, which compared treatment effects between (autoHSCT) (n=421) and chemotherapy/allogeneic HSCT (chemo/alloHSCT; n=179) patients. A pre-specified sub-group analysis in TOPPS identified very similar proportions of bleeding between treatment arms in autoHSCT patients. By contrast, the reduction in proportion of patients experiencing WHO grade 2-4 bleeds seen in the prophylaxis arm was of greater magnitude in chemo/alloHSCT than autoHSCT patients.35 The full implications of the results in both recent trials need to be considered after secondary manuscript publications and when systematic reviews have been up-dated. Uncertainty also surrounds any potential cost saving with a policy of no-prophylaxis in patients. In autoHSCT patients, some savings generated through lower platelet use in the no-prophylaxis arm appeared to be offset by cost increases elsewhere, e.g. additional red cell transfusions which were documented in the TOPPS trial.35

Although patients who received prophylactic platelet transfusions had fewer bleeds in TOPPS, a high base-line bleeding rate remained (43% of patients had WHO grade 2-4 bleeding). It seems clear that a high ‘burden’ of bleeding remains in many patients despite platelet transfusion prophylaxis, and, therefore, factors other than those addressed by prophylactic platelet transfusions are important in determining bleeding risk. Of interest, recent animal model data seem to confirm these findings. In a mouse model, different grades of thrombocytopenia were induced and the animals subjected to different modes of occlusive thrombus formation, ischemic stroke or hemorrhage.34 A wide range of severity of thrombocytopenia was induced in animals including virtually complete platelet depletion. The researchers did not observe any signs of spontaneous bleeding even in the most severely thrombocytopenic animals, and clinical hemostasis, thrombosis and ischemic brain infarction were observed, even at unexpectedly low platelet counts.35 Only in those mice with the very lowest platelet counts (less than 2.5% of control) were animals not able to arrest bleeding. There are limitations in extrapolating from this mouse model based on anti-body mediated thrombocytopenia which destroys all platelets including younger platelets to a myeloablative mechanism of thrombocytopenia in patients with hematologic malignancies and significant endothelial disruption, but the findings are consistent with the accumulating clinical data suggesting a weak relationship between severity of thrombocytopenia and bleeding.25

Much of the bleeding documented in all clinical trials has been graded as ‘moderate’ or WHO grade 2, and this bleeding has been assumed to be clinically significant in many of the studies performed. However, the type and severity of bleeding that affects a patient’s quality of life is unknown,27 nor is it clear whether grade 1 or 2 bleeding predicts more severe and life-threatening bleeding.28,29 Severe bleeding, graded at WHO 3 or 4 is often clinically significant, but until recently, the (fortunately) uncommon occurrence of these bleed types has limited the power of individual prospective trials to provide meaningful data on risk factors for these bleeding events. The Intracranial Haemorrhage in Thrombocytopenic Haematology Patients (INCITE) study is a UK-wide case-control study nested within a prospective reporting strategy. It aims to identify clinical and laboratory factors that increase the risk of intracranial hemorrhage (ICH) in patients with hematologic malignancies (receiving myeloablative therapy with or without hematopoietic stem cell rescue), as well as providing an estimate of the incidence of ICH, and has currently collected data on over 100 cases (and controls).40 All clinicians will be aware of the need for and importance of considering alternatives to blood transfusion. For example, antifibrinolytics have been used widely in both elective and emergency surgery, and have been shown to decrease blood loss and the use of red cell transfusions. Indeed, in a recent Cochrane review, the use of lysine analogs (tranexamic acid and epsilon aminocaproic acid) and another agent, aprotinin, were assessed in over 25,000 patients on their ability to minimize peri-operative blood transfusions.41 But only a limited number of RCTs have studied the use of antifibrinolytics in patients with hematologic malignancies.42 Although tranexamic acid may be used sometimes in clinical practice, to manage refractory bleeding, their safety profile in patients with hematologic malignancies and endothelial disruption requires further evaluation.

In summary, recent clinical research has started to address fundamental issues of effectiveness of platelet transfusion prophylaxis. But it should be noted that essentially all the randomized trials described above have recruited patients with severe transient thrombocytopenia. No trials have been completed for outpatient management of chronic thrombocytopenia due to bone marrow failure, although one pilot study is currently recruiting patients (OPTIMAL study).43,44 It seems likely that future work will support more individualized or targeted use of platelet transfusions in those patients at greater risk of bleeding. Further research is necessary to establish whether a no-prophylaxis approach is non-inferior to prophylactic platelet transfusions in autoHSCT patients. Thrombopoietic growth factors are the only other specific treatment for thrombocytopenia that are currently available. They are the subject of ongoing research and a number of clinical trials have suggested they may be beneficial in myelodysplasia (MDS) and refractory severe aplastic anemia, raising platelet counts and reducing the need for platelet transfusions.45-48 In one study, multilinage responses were seen with increases in platelet, hemoglobin and neutrophil levels.48 However, there have been concerns that their use could increase the risk of clonal evolution.46,47 The only trial that has studied a larger patient group (250 MDS patients: romiplostim n=167, placebo n=83) over a more prolonged time period (21.5 weeks) was stopped early over safety concerns regarding increased blast cell counts.49

Use of red cells for transfusion

The overall changing profile of blood use has been well described in different audits. In the North East of England, the largest group of medical indications for use of red cells was hematology disorders, including myelodysplastic syndromes (MDS), lymphoma, and acute leukemia.50 Current areas of clinical controversy for the use of red cells
include the optimal hemoglobin concentration to trigger red cell transfusion, and the effects of different strategies for red cell transfusion on outcomes such as quality of life for both inpatients and outpatients.

Most MDS patients will become red blood cell transfusion-dependent during the course of the disease. Although MDS represents a large group of hematology patients receiving red cell transfusion, there are very little data on safe and effective hemoglobin concentration thresholds in transfusion-dependent MDS patients. The Cochrane collaboration recently published an update to a review: “Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.” They identified 19 RCTs comparing different transfusion strategies, but only one small (pilot) trial recruited hematology patients; these were acute leukemia patients undergoing chemotherapy or stem cell transplantation. Most of the outcomes collected related to the proportion of patients transfused, amount of transfused units, mortality, cardiac events and hospital length of stay. Quality of life was not an important outcome in any of these studies, despite recent guidelines advising that red cell transfusions should be given to maintain quality of life.

Transfusion practice for MDS appears broadly similar in many centers, with transfusions usually being given only when patients have moderately severe anemia. In a recent national audit on medical use of blood carried out in the UK, 610 of 635 patients with MDS were transfused for anemia, with a median pre-transfusion hemoglobin concentration of 78 g/L (mean pre-Hb 82.4g/L; SD13.0) (K Pendry, personal communication, 2013). The European LeukemiaNet MDS registry found the most common threshold across Europe to be approximately 80 g/L, but this varied from country to country. Outcome data in new clinical studies comparing different transfusion policies for use of red cells in MDS must consider health-related quality of life (HrQoL). A number of studies that have evaluated HrQoL in MDS, either as single measurements, or as secondary end points. Most deployed validated HrQoL instruments, including EQ-5D, EORTC QLC-C30 and FACT-An. Transfusion dependence is associated with inferior HrQoL, shortened survival, and decreased health utility, particularly in “lower-risk” MDS. Lower hemoglobin concentrations also have a significant impact on HrQoL. However, the relationship between the degree of anemia, use of red cell transfusion and HrQoL is less clear cut. A systematic review of HrQoL and use of red cell transfusion in MDS identified only small studies with heterogeneous use of HrQoL instruments, poorly defined transfusion protocols, and variable drop-out rates; there was a dearth of data on the nature of relationships between anemia, transfusion and HrQoL.

Therefore, although transfusion dependence and anemia are associated with inferior HrQoL, and a commonly used transfusion strategy is to target the hemoglobin concentration in the range of 80-90 g/L for red cell transfusion, the optimal transfusion threshold and target hemoglobin that translate into significantly improved HrQoL is unknown. It is possible that a higher hemoglobin target might lead to improvement in HrQoL, despite the negative impact that greater transfusion dependence may have on HrQoL (due to associated time commitments, expense, potential for transfusion reactions). Several groups have prospective-ly suggested that targeting hemoglobin levels of greater than 120 g/L (with hematopoietic growth factors (HGFs) and/or blood transfusions) or incremental increases of 15-20 g/L (with HGFs alone) were associated with improved HrQoL, and a hemoglobin level of 100 g/L or over may be a key threshold for improvement in function and symptom scores. But it seems likely that responses to different strategies for red cell transfusion will vary considerably between patients, for reasons including burden of comorbidities. Alongside the possible beneficial effects of different red cell transfusion strategies on HrQoL in MDS, is the potential role for enhanced use of iron chelation to also impact on quality of life.

There is a lack of current evidence to define a safe hemoglobin concentration threshold in other acute hematology patients, such as those receiving chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT). An ongoing trial in Canada (TRIST) is randomizing patients undergoing hematopoietic stem cell transplant to either a restrictive (target hemoglobin 70-90 g/L) or liberal (target hemoglobin 90-110 g/L) red cell transfusion strategy. Clinical studies such as this one should help to better define best red cell transfusion practice.

References


