Platelet Transfusions in Patients with Hypoproliferative Thrombocytopenia: Conclusions from Clinical Trials and Current Controversies

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Key points:

- One prophylactic platelet transfusion strategy for all patients with thrombocytopenia is not appropriate.
- Patients may have significant bleeding at platelet counts > 10 x 10^9/L and should be assessed and managed on clinical grounds, not on platelet count alone.
- Platelet count is not the only factor that contributes to a patient's propensity to bleed.
- Patients with acute leukemia should receive prophylactic platelet transfusions when their platelet count is < 10 x 10^9/L to prevent clinical bleeding.
- More consistency in the assessment and documentation of bleeding across transfusion trials is essential to support comparisons of outcomes between studies.

Synopsis

Patients with hematological malignancies frequently become thrombocytopenic as a result of their underlying malignancy or treatments, including cytotoxic chemotherapy and hematopoietic stem cell transplantation (HSCT) and are at increased risk of hemorrhage.

Prophylactic platelet transfusions are aimed at preventing severe or life-threatening hemorrhage. This review presents a summary of recent evidence, including the need for prophylactic platelet transfusions, the optimal dose, platelet transfusion triggers, risk factors for bleeding and discusses controversies surrounding platelet transfusions in this population.

Introduction

Duke reported the first description of bleeding in the setting of thrombocytopenia, which improved following blood transfusion and recurred when the platelet count dropped.[1] Up to 70% of patients with hematologic malignancy will have clinically significant bleeding (WHO grade 2 or higher) and up to 10% will have severe or life-threatening bleeding.[2]

Patients have a tendency to develop bleeding symptoms as their platelet counts fall, and major bleeding occurs more frequently at platelet counts < 10 x 10^9/L.[2,3] However, many patients with severe thrombocytopenia do not develop clinically significant bleeding.[4,5] Conversely, major and even fatal bleeding is well recognised to occur at platelet counts > 10 x 10^9/L.[2,4-7]

In early leukemia studies, bleeding as a result of thrombocytopenia was a major contributing factor to mortality rates.[8] Platelet transfusions helped reduce the incidence of death attributable to bleeding[8,9] and today, mortality as a result of thrombocytopenia-related bleeding is exceedingly rare.[2] (See Table 1) Platelet transfusions have become an important adjunctive therapy and led to improved patient survival. They have also supported delivery of more intensive chemotherapy regimens.[8-10]

Platelet concentrates are the second most commonly prescribed blood product after red blood cells (RBC)[11] and hemato-oncology patients are the largest users of platelet concentrates.[12-14] Platelet transfusion rates are increasing; in the United States (US), more than 2 million platelet units were transfused in 2011, a 7.3% increase compared to 2008.[14] Platelet transfusions may be given therapeutically, to treat bleeding when thrombocytopenia or abnormal platelet function are contributing factors, but are more frequently given prophylactically, in efforts to avert bleeding prior to a procedure or when the platelet count falls below a certain threshold.[12,15,16] Many patients with platelet counts < 10 x 10^9/L will not have clinically significant bleeding, and therefore many platelet transfusions may be being given unnecessarily.

Methods

This review provides an update of the literature and some of the challenges raised by a very recent update of a Cochrane systematic review.[17] The methodology of this update has been described, but in brief, searching for platelet transfusion trials multiple datasets was undertaken. Eligible trials were identified and data abstracted, alongside an assessment of risk of bias. The update of an earlier Cochrane review[18] aimed to determine whether therapeutic-only platelet transfusions were as effective and safe as prophylactic platelet transfusions in patients with haematological disorders undergoing cytotoxic chemotherapy or HSCT.[17] Seven randomized controlled trials (RCTs) met the pre-defined selection criteria (one is still ongoing), leaving a total of six eligible trials and a total of 1195 participants. These trials were conducted over a 35-year time period. Five studies contained separate data for each arm and were able to be critically appraised. Only one study was deemed to be at low risk of bias.[4]

[Insert Table 1]

Main findings for review

For the systematic review's primary outcome (number of patients with at least one bleeding episode within 30 days) significant heterogeneity was noted (I^2=88%).[17] This heterogeneity may in part reflect the different methodology and grading systems used to analyse and categorize bleeding in the individual studies. Four studies in the review[4,5,19,20] reported clinically significant bleeding events and all showed a similar effect: higher rates of bleeding in participants receiving therapeutic-only platelet transfusions. Major differences were noted between studies, including: platelet transfusion indications, RBC transfusion policy and study end-points, as well as classification of bleeding events. Individual studies also reported bleeding outcomes over different time-periods and used different units of analysis. For these reasons a meta-analysis was unable to be performed.[17]

Time to first bleeding episode was reported by two studies[4,5] and again meta-analysis was unable to be performed because of heterogeneity (I^2=90%).[17] Individually, both studies showed that time to first bleeding episode was shorter in patients receiving therapeutic-only platelet transfusions.[17] One study reported the number of days with clinically significant bleeding events per patient and this was statistically higher in the therapeutic-only transfusion group.[4]

Due to low mortality rates and rates of WHO grade 3 and 4 bleeding, there was insufficient evidence to determine whether there was any difference between platelet transfusion strategies for these outcomes.[17] Three studies[4,5,20] reported higher numbers of patients with WHO grade 3 or 4 bleeding events in the therapeutic-only transfusion group, however a significant difference was not demonstrated, reflecting the rarity of this outcome.[17]

Recent trials

The systematic review included the results of two recent, large, multi-center RCTs; the Trial of prophylactic versus no-prophylactic platelet transfusions (TOPPS) and the trial by Wandt *et al.*[4,5] Bleeding events were graded and reported differently in the trials; each trial used their own modification of the WHO bleeding scale and the same bleeding event would have been classified differently between studies.[4,5] (See Table 2) TOPPS reported that WHO grade 2 – 4 bleeding events occurred in 50% of patients in the therapeutic-only platelet transfusion group compared with 43% in the prophylaxis group; p=0.06 for non-inferiority indicating that a therapeutic-only strategy was non-inferior to prophylactic platelet transfusions.[4] Analysis of TOPPS data by the systematic review found that whilst there appeared to be an increased risk of bleeding events with a therapeutic-only transfusion policy, the 95% confidence interval (CI) crossed 1.0 (RR1.17, 95% CI 0.99 to 1.39).[17] In the study by Wandt *et al*, therapeutic-only transfusions were associated with an increased risk of WHO grade 2 – 4 bleeding events per treatment cycle ($p < 0.0001$).[5]

[Insert Table 2]

Disease and treatment category

Many factors can affect a patient's bleeding susceptibility, including disease and treatment category, genetic predisposition and concurrent medications. Different platelet RCTs have used different disease and treatment cohorts: acute leukaemia patients receiving induction or consolidation chemotherapy,[6,7,21-23] HSCT patients[21,24] and both acute leukemia or HSCT patients.[2,4,5,25,26] (See Table 3)

[Insert Table 3]

RCTs and systematic reviews have indicated that bleeding rates differ between patient disease and treatment categories.[2,4,5,18,26] Lower bleeding rates are noted in patients during autologous HSCT than during chemotherapy or allogeneic HSCT.[2,18,24,26] Tinmouth *et al* reported minor bleeding in 56% of acute leukemia patients versus 18% for autologous HSCT patients, and major bleeding in 23.5% of leukemia patients compared with 2.6% in the autologous group.[26] Slichter *et al* similarly reported lower rates of WHO grade 2 – 4 bleeding in patients receiving autologous/synergeic HSCT (57%) compared with those receiving chemotherapy for hematological malignancies (73%) or allogeneic HSCT (79%).[2] Meta-analysis performed in the 2012 Cochrane review showed a significantly lower risk of bleeding for autologous HSCT patients compared to patients receiving chemotherapy or allogeneic HSCT (RR 0.73, 95% CI 0.65 to 0.82).[18] Lower rates of bleeding in the autologous HSCT group may relate to faster platelet count recovery following autologous HSCT than after induction chemotherapy or allogeneic HSCT.[27]

The Cochrane systematic review 2015[17] identified two studies[4,5] that compared therapeutic-only versus prophylactic platelet transfusions in patients receiving autologous HSCT. As before, meta-analysis was not performed because of considerable heterogeneity (I^2 = 90%).[17] (See Table 2) Results from TOPPS showed no evidence of difference in the number of clinically significant bleeding episodes between transfusion strategies (RR 1.04; 95% CI 0.85 to 1.28).[17,28] However, the results from Wandt *et al* indicated a significant difference between transfusion protocols (RR 3.45; 95% CI 1.66 to 7.17); study authors reported p=0.0005.[5]

The systematic review found no difference in the number of patients undergoing autologous HSCT who experienced severe or life threatening bleeding, however this was a rare event and the 95% CI of the meta-analysis was wide.[17] The review concluded there was inconclusive evidence in autologous HSCT patients as to whether a therapeutic-only transfusion policy was associated with increased rates of clinically significant bleeding. Variability was noted in baseline patient characteristics between studies with regard to underlying hematological disease requiring HSCT.[17] In TOPPS, no patients received autologous HSCT for acute leukemia, whilst Wandt *et al* included 13 patients with acute leukemia. It is unknown whether the underlying disease necessitating transplantation has any impact on bleeding rates.

Ford *et al's* review of 125 Jehovah's witnesses undergoing autologous HSCT without prophylactic platelet transfusions may provide additional insight into safety of therapeutic-only platelet transfusions, with the addition of specific patient blood management strategies. Patients received anti-fibrinolytics as an alternative to platelet transfusions when the platelet count was < 30 x 10^9/L. Authors reported two WHO grade 2 bleeds, one grade 3 bleed, one grade 4 bleed and no bleeding-associated mortalities.[29]

The 2015 Cochrane systematic review[17] identified three studies[4,5,19] that compared therapeutic-only versus prophylactic platelet transfusions in patients with acute leukemia and all reported increased bleeding rates in patients receiving therapeutic-only platelet transfusions.[17] Again, meta-analysis for this outcome was unable to be performed because of the different study endpoints and units of analysis.[17] TOPPS and Wandt *et al* both reported statistically higher rates of WHO grade 2 - 4 bleeding in patients with acute leukemia using therapeutic-only platelet transfusions.[4,5] Murphy *et al* reported higher numbers of bleed/100 patient-months in the therapeutic-only group, but did not provide comparative statistical analysis for this outcome.[19] Post-hoc analysis by Wandt *et al* demonstrated higher numbers of WHO grade 3 and 4 in patients receiving induction chemotherapy compared with consolidation chemotherapy.[30] Stanworth *et al's* post-hoc analysis of TOPPS reported two WHO grade 3 bleeds in patients receiving induction chemotherapy and no grade 3 or 4 bleeds in patients receiving consolidation chemotherapy.[28] These studies suggest that patients receiving induction chemotherapy are at higher risk of bleeding with therapeutic-only platelet transfusions than those receiving consolidation chemotherapy. Neither study has reported rates of WHO grade 2 bleeding events between induction and consolidation chemotherapy groups. Available evidence supports the ongoing use of prophylactic platelet transfusions to patients with acute leukemia receiving chemotherapy.

The 2015 Cochrane systematic review[17] found one study[4] that compared therapeutic-only with prophylactic platelet transfusions in patients receiving allogeneic HSCT.[17] Whilst the number of patients with clinically significant bleeding was higher in the therapeutic-only group, this was not statistically significant and higher patient numbers would be needed to confirm or refute this finding.[17] Post hoc statistical analysis from TOPPS found that chemotherapy/allogeneic HSCT patients in the therapeutic-only arm had the highest incidence of grade 2 - 4 bleeding.[31] There is insufficient evidence to change current practice of prophylactically transfusing allogeneic HSCT patients.

In summary, the evidence indicates that the efficacy of prophylactic platelet transfusions differs between sub-groups of patients with hematological malignancies; there is little evidence that a prophylactic policy for platelet transfusion is a superior policy for patients receiving autologous HSCT. The findings also inform future research. Factors other than those addressed by administration of platelet transfusions are important in determining risk of bleeding. Since many patients continue to bleed despite prophylactic platelet transfusions, additional strategies are required to minimise bleeding in all patient groups. These issues will be addressed below.

Platelet dose

In the US, FDA Standards state that more than 75% of platelet units must have a count of $> 3.0 \times 10^{11}$ equating to a dose of 0.04×10^{11} platelets/75kg adult. [32]

The 2012 Cochrane systematic review[18] identified six RCTs that compared different platelet doses for prophylactic transfusion. A lower platelet transfusion dose did not result in an increased risk of WHO grade 2 – 4 bleeding (RR 1.02; 95% CI 0.93 to 1.11).[18] This review included the Platelet Dose (PLADO) study; a RCT in which patients undergoing HSCT or chemotherapy for malignancy were randomized to low dose (1.1×10^{11} platelets per m^2 body surface area), medium dose (2.2×10^{11}) and high dose (4.4×10^{11}) platelet transfusion when their morning platelet count was $\leq 10 \times 10^9$/L. This study found that the prophylactic platelet transfusion dose had no effect on the incidence of bleeding. Lower doses decreased the number of platelet transfusions ($p<0.001$) without comprising haemostasis.[2] However, post-transfusion platelet counts were higher in those receiving the higher platelet transfusion dose.[2] This finding has been confirmed in other trials and has been shown to translate to a longer interval between platelet transfusions.[10,33]

In the hospital in-patient setting a low-dose platelet strategy is appropriate and effective at reducing clinically significant bleeding, but will result in more frequent platelet transfusions. A single adult platelet unit should be given and the patient's clinical condition and platelet count should be reassessed. In the outpatient setting it may be desirable to have a longer period between platelet transfusions in order to reduce the frequency of hospital visits for a patient and a higher platelet transfusion dose may allow reduced transfusion frequency.

Platelet transfusion threshold

Gaydos *et* al first described the quantitative relationship between degree of thrombocytopenia and bleeding in leukemia patients receiving chemotherapy.[3] At lower platelet counts the frequency, number of bleeding days and severity of bleeding events were increased. Grossly discernible hemorrhage rarely occurred at platelet counts $> 20 \times 10^9$/L, but rates increased when the count was 5 to 20×10^9/L and a steep increase occurred at platelet counts $< 5 \times 10^9$/L. Whilst the authors concluded that a platelet threshold could not be determined; this study has frequently been cited as the origin of the platelet transfusion threshold of 20×10^9/L.[3]

The Platelet Transfusion Trigger Trial by Rebulla *et al* randomized adolescents and adults with a new diagnosis of AML receiving induction chemotherapy to a platelet transfusion threshold of $< 10 \times 10^9$/L compared with 20×10^9/L. No statistical difference ($p=0.41$) in bleeding endpoints was seen between patient groups and patients in the 10×10^9/L group received significantly fewer platelet transfusions.[6]

The 2012 Cochrane systematic review[18] included three RCTs with different platelet count triggers and found no significant difference between platelet trigger and number of participants with clinically significant bleeding (RR 1.35; 95% CI 0.95 to 1.9).[18]

Currently many hematology centres adopt the platelet transfusion trigger of 10 x 10^9/L. However, an even lower threshold of 5 x 10^9/L may be appropriate. Slichter *et al* demonstrated that bleeding occurred on 25% of study days when the platelet count was < 5 x 10^9/L and 17% of the days when it was 6 – 80 x 10^9/L; ($p<0.001$).[2] Observational studies have provided further evidence that patients may be safely managed by transfusing at a threshold of 5 x 10^9/L.[3,34-36] Ford *et al* reported their experience of performing autologous HSCT without platelet transfusions and reported no major bleeding events at platelet counts < 5 x 10^9/L.[29]

Routine hematology analysers are inaccurate at counting platelets in the setting of severe thrombocytopenia and frequently over-estimate them.[37] Over-estimation of the platelet count will potentially result in under-transfusion of platelets, particularly when the count is 5 - 10 x 10^9/L.[37] If patients are not bleeding, then a lower threshold may be appropriate. Higher thresholds of 20 x10^9/L are frequently implemented by clinicians when a patient has concurrent headache, fever, infection, coagulation disorders or prior to invasive procedures.[38]

Limitations in the interpretation of platelet transfusion trials

Caution must be had in adopting a 'one-size fits all' approach as there may be important differences between patients enrolled in platelet RCTs and the patient seen in the clinic. Trials have specific inclusion and exclusion criteria; only including certain patient cohorts and treatment groups, and therefore results may not be generalizable to other patient groups. Patients enrolled in trials are likely to receive very attentive surveillance, with close monitoring of all bleeding events, new clinical symptoms and hematological parameters. (See Table 1 and 3)

Platelet RCTs have been conducted in a variety of patient cohorts; paediatric patients,[7,19] any age patient,[2,21] and only adolescents and adults[4-6,21,23,25,26]. (See Table 3) Roy *et al* found higher rates of bleeding in patients aged 0 - 4 years of age.[7] Josephson's secondary analysis of the PLADO trial found children aged 0 - 5 years had a significantly higher risk of WHO grade 2 - 4 than those 19 years or older (86% versus 67%). Children from all age groups had more days of WHO grade 2 - 4 bleeding compared with adults.[39] Conclusions drawn from adult trials cannot be directly applied to paediatric patients.

Many trials exclude patients at highest risk of bleeding. Acute promyelocytic leukemia (APML) is associated with coagulopathy, hyperfibrinolysis and hemorrhagic complications are the most frequent cause of death in this group.[40] Countless platelet RCTs exclude patients with APML,[2,4,6,23,25,26,33] only Wandt *et al* included APML patients once in

complete remission.[5] Patients with inherited hemostatic disorders, taking antiplatelet medications or anticoagulants are commonly excluded from trials.[2,5,21,23,24,26] Patients with platelet refractoriness are excluded in a number of trials.[2,5,23,24,26]

Careful attention must be taken when comparing bleeding events between studies. Bleeding assessment tools, the analysis and grading of bleeding events differ significantly between trials. (See Table 1 and 2) The WHO 1979 bleeding scale[41] provides a very general classification system adopted for grading toxicities associated with cancer treatments; grade 0 – no bleeding, grade 1 - petechiae, grade 2 - mild blood loss, grade 3 - gross blood loss, grade 4 - debilitating blood loss.[41] These very non-specific categories allow substantial interpretation by the clinician. Several trials have adapted the WHO bleeding scale with major differences between adaptations, particularly for grading of central nervous system and retinal bleeding events.[2,4,5,25] (See Table 2) Grade 3 bleeding is frequently considered bleeding that necessitates RBC transfusion. However RBC transfusion policies differ between studies; in TOPPS an Hb of < 90g/L was used,[4] Wandt *et al* transfused to maintain Hb ≥ 80g/L, Hb threshold was not reported by Heddle *et al* [25] and Slichter *et al* reported that RBC transfusion was indicated by local practice.[2] Of platelet studies using the WHO scale or a modification; WHO grade 2 bleeding events were reported in 11- 45% of patients,[2,4,21,25] WHO grade 3 events in 0.8 - 8.5%,[2,4,5,25] and WHO grade 4 bleeding events in 0.3% - 4.5%.[2,4,5,25] (See Table 1)

Rebulla *et al* and the GIMEMA (Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto) developed their own 8-point scale for bleeding assessment.[6] RBCs were administered when the Hb was < 80g/L.[6] In platelet transfusion RCTs using the GIMEMA scale, or a modification, minor bleeding rates were reported in 8 - 30% [24,26] and major bleeding rates in 9% - 21%.[6,24,26]

To analyse and compare bleeding events between studies a reliable and reproducible bleeding assessment tool is needed. The Bleeding Severity Measurement Scale will hopefully provide a valid and reliable measurement of bleeding.[42]

Risk factors for bleeding aside from platelet count

Many patients have severe bleeding despite a platelet count of > 10 x 10^9/L and sometimes at platelet counts > 20 x 10^9/L.[4-6] Many studies have suggested that other factors contribute to a patient's tendency to bleed.[4-6]

The relationships between minor bleeding events, platelet counts and more severe bleeding events have been reviewed by a number of trials. Whilst many trials do not specifically report WHO grade 1 bleeding as a study outcome[2,4,5] this may be very important if it predicts more severe bleeding.[43] Webert *et al's* post-hoc analysis of the Platelet Transfusion Trigger trial noted that the majority of severe bleeds were associated with bleeds of lesser severity in the preceding days. Patients with WHO grade 1 bleeding were 2.6 times more likely to experience WHO grades 2 – 4 bleeding on the next day.[43] Friedmann's large retrospective review of thrombocytopenic patients, also reported a significant association between recent bleeding and

the risk of severe hemorrhage. In contrast, post-hoc statistically modelling from TOPPS found no evidence that minor bleeding predicted WHO grade 2 – 4 bleeding.[31] Stanworth *et al* did find that the number of days with a platelet count < 10 x 10^9/L was significantly associated with grade 2 - 4 bleeding and there was a significant association between platelet count on the previous day and hemorrhage.[31] Similarly Webert *et al* found that for every 1 x 10^9/L increase in platelet count there was a 4% reduction in the risk of grade 2 - 4 bleeding on the next day.[42] In contrast, Friedmann's review found no relationship between first or lowest platelet count of the day and the risk of severe hemorrhage.[44] This may be due to the retrospective nature of this study, that analysis excluded WHO grade 2 bleeding events and that the platelet count from the day before was the significant factor.

Fever has been identified by a number of studies as a potential risk factor for bleeding.[22,31,43] Early studies postulated that the association between bleeding and fever reflected the use of aspirin, which was historically given as an anti-pyretic.[44] Today aspirin and non-steroidal anti-inflammatories are withheld, if possible, in hemato-oncology patients and patients taking these medications are excluded from clinical trials.[2,4,26] Webert *et al's* post-hoc analysis found the risk of clinically significant bleeding was 3.35 times higher in the presence of clinical infection.[43] In this study, platelet transfusions were given to patients in the 10 x 10^9/L trigger group when their platelet count was 10 - 20 x 10^9/L in the presence of fever.[6] Post hoc analysis of TOPPS found that patients with temperatures of ≥ 38 degrees had the highest hazard of grade 2 - 4 bleeding.[31] In TOPPS platelets were also given at physician's discretion; 18% of transfusions in the therapeutic-only group were for infection or when the patient was unwell compared with 11% in the prophylaxis group.[4] These results support a higher platelet threshold for patients who are febrile or have an infection. Older platelet transfusion guidelines support these findings and recommend a platelet transfusion trigger of 20 x 10^9/L in the presence of risk factors,[45,46] however, newer ones have not made recommendations supporting this practice.[47,48]

The TOPPS authors also found that female sex was significantly associated with WHO grade 2 - 4 bleeding.[31] Even when the authors removed menstrual bleeding data, female patients consistently had a higher risk of bleeding. The reason for this finding remains unclear.[31] Neither the reviews by Webert *et al* or Friedmann *et al* specifically analysed sex as a risk factor for bleeding.[43,44]

There may be a relationship between Hb, RBC transfusion and risk of bleeding. *In vitro* studies by Escolar *et al* suggest that RBC are critical for maintenance of interactions between platelets and subendothelium. These interactions and bleeding times are consistently improved following RBC transfusion to patients with anemia and thrombocytopenia.[49] Valeri *et al* reported that an acute reduction in HCT in normal individuals produced reversible platelet dysfunction and increased bleeding times, which normalized following RBC transfusion.[50] In TOPPS, patients in the therapeutic-only transfusion group, who received RBC transfusion in the previous three days were at increased risk of bleeding.[31] This increased risk of bleeding associated with recent RBC transfusion may reflect a recent history of significant anemia, necessitating the

transfusion. Webert *et al* similarly reported that higher Hbs were associated with a delay in time to clinically significant bleeding. A 10g/L increase in Hb decreased the risk of clinically significant bleeding by 22% the next day.[43]

Limitations in the post hoc and investigative analyses performed by Friedmann, Stanworth and Webert include: incomplete data sets, their retrospective nature and time since the original study. However, they are still a valuable means to identify risk factors for bleeding and help stratify patients. Stable patients without risk factors may potentially be able to avoid prophylactic platelet transfusions.

Hematological disease linked with bleeding

Hematological diseases may be linked with bleeding dyscrasias. Abnormalities in platelet function may be associated with myelodysplastic syndrome (MDS) and AML.[51] Severely thrombocytopenic patients with AML or MDS may have smaller platelets, lower immature platelet fractions and substantially lower platelet surface expression of activated GPIIb/IIIa and GPIb than severely thrombocytopenic patients with immune thrombocytopenia.[52] Familial platelet disorders with predisposition to AML due to RUNX1 mutations are associated with platelet dysfunction.[53]

Acquired von Willebrand disease is a rare bleeding disorder that is associated with lymphoproliferative disorders and myeloproliferative neoplasms.[54] It is characterized by structural and functional defects in von Willebrand factor (vWF).[54] Treatment involves controlling acute bleeding with vWF-containing concentrates and attempting to obtain remission of the underlying disease by surgery, chemotherapy, radiotherapy or immunosuppression.[54]

Patients with plasma cell dyscrasia such as multiple myeloma, Waldenstr**o**m macroglobulinemia, monoclonal gammopathy of uncertain significance and amyloidosis not infrequently develop bleeding symptoms such as purpura, epistaxis or hematuria.[55] The implicated paraproteins interact with platelets and coagulation factors causing multiple hemostatic abnormalities, including prolonged coagulation assays, factor deficiencies and platelet dysfunction, resulting in bleeding.[55,56] Uremia and renal failure associated with advanced myeloma are additional risks for platelet dysfunction.

Anti-fibrinolytics

Tranexamic acid (TXA) is an anti-fibrinolytic that has been used to reduce the risk of death due to hemorrhage in the trauma setting and reduce blood loss and the need for RBCs during surgery.[57,58] Shpilberg *et al's* small RCT of patients with AML receiving chemotherapy, randomised participants to TXA or placebo and patients were only given platelets when bleeding occurred. Whilst the sample size was small, they found that during consolidation chemotherapy there was a significantly reduced bleeding tendency in the TXA group that resulted in lower platelet transfusion requirements. No difference in bleeding rates, severity or platelet transfusion requirements were noted in the induction chemotherapy group.[59]

A 2013 Cochrane systematic review[60] evaluated the use of anti-fibrinolytics in patients with hematological malignancies and found limited evidence for the use of anti-fibrinolytics in this cohort. Available data suggests that anti-fibrinolytics may reduce bleeding and therefore may be a useful adjunct to platelet transfusions.[60] TREATT (Trial to EvaluAte Tranexamic acid in Thrombocytopenia) is an RCT currently recruiting patients that aims to examine whether giving TXA to patients receiving treatment for hematological malignancies reduces the risk of bleeding or death and the need for platelet transfusions.[61]

Conclusion

Platelet transfusions are an important adjunctive therapy in the management of hematology patients with hypoproliferative thrombocytopenia secondary to chemotherapy or HSCT. The systematic review concluded that overall prophylactic platelet transfusions appeared to reduce the number of bleeding events and days with clinically significant bleeding, therefore supporting the continued use of prophylactic platelet transfusions.[17] However, recent findings challenge the basis of a uniform policy of platelet transfusion prophylaxis for all patients. Individual patient, disease and treatment characteristics increasingly need to be considered, and new guidelines need to reflect these implications. Studies report major bleeding occurs despite prophylactic platelet transfusions at platelet counts > 10 x 10^9/L indicating that patients should be managed clinically and not on the basis of platelet count alone.[4,5,20] A better understanding of risk factors will identify patients at greater or lesser risk of bleeding, and hence more or less likely to experience benefit from platelet transfusions. Patients with acute leukemia receiving chemotherapy or undergoing allogeneic HSCT should continue to receive prophylactic platelet transfusions. There is no evidence that a prophylactic policy for platelet transfusion is superior for patients receiving autologous HSCT, and risk factors such as duration of severe thrombocytopenia and fever may be more relevant. Other research gaps include understanding donor factors and changes in platelet function, which are not captured by isolated measures of platelet count.

Table 1: Rates of clinically significant bleeding and death from bleeding in the platelet transfusion RCTs.

Trial	Total patients	Bleeding scale	Bleeding assessment and rates of bleeding			Death from hemorrhage
Therapeutic-only versus prophylactic platelet transfusions						
Solomon 1978 [62]	31	Not defined	Not reported			0
Sintnicholas 1982 [63]	12	Not defined	Not reported			0
Grossman 1980 [20]	100	Study specific Mild (not requiring active intervention) versus severe	**Mild**	**Severe**		14^
			86 (86%)	74 (74%)		
Murphy 1982 [19]	56	Study specific	**Clinically significant bleeding event**			3
			21 bleeds from study enrolment until study closure (37.5%)			
			15 bleeds in the first 10 months of the study (27%)			
Wandt 2012 [5]	396	Modified WHO	**WHO grade 2**	**Grade 3**	**Grade 4**	2
			Reported per treatment cycle	10 (2.5%)	18 (4.5%)	
Stanworth 2013 [4]	600	Modified WHO	**WHO grade 2**	**Grade 3**	**Grade 4**	0
			272 (45%)	5 (0.8%)	2 (0.3%)	

Platelet dose						
Roy 1973 [7]	62	Study specific	**Minor[a]**		**Major[b]**	NR
			18 (29%)		7 (11%)	
Steffens 2002 [64]	54	Not reported	NR			NR
Senesebe 2004 [33]	101	WHO 1979 [65]	**Hemorrhaging**	**WHO grades 2 - 3**	**Grade 4**	0
			14 (14%)	5 (5%)	NR	
Tinmouth 2004 [26]	111	Modified GIMEMA	**Minor**		**Major**	0
			33 (30%)		10 (9%)	
Heddle 2009 [25]	129	Modified WHO	**WHO grade 2**	**Grade 3**	**Grade 4**	0
			56 (43%)	11 (8.5%)	3 (2.3%)	
Slichter 2010 [2]	1351	Modified WHO	**WHO grade 2**	**Grade 3**	**Grade 4**	1
			177 (13%)	24 (1.8%)	7 (0.5%)	
Platelet trigger						
Heckman 1997 [23]	78	Ajani 1990 [66]	**Any bleeding event**		**Significant bleeding event**	0
			72 (92%)		24 (31%)	

Rebulla 1997 [6]	255	Study specific GIMEMA scale	**Major**		
			53 (21%)		1
Zumberg 2002 [24]	159	Modified GIMEMA	**Minor***	**Major#**	0
			128 (8%)	25 (16%)	
Diedrich 2005 [21]	166	WHO 1979 [65]	**WHO grade 2**	**Grades 3 - 4**	1
			19 (11%)	8 (4.8%)	
Platelets versus other product					
Higby 1974 [22]	21	Study specific	**Hemorrhage**	**Serious bleeding**	0
			13 (6%)	9 (4%)	

GIMEMA – Gruppo Italiano Malattie Ematologiche Dell'Adulto, NR- Not reported, WHO – World Health Organization

[a] Skin, mucous membranes of mouth, lips, gums, epistaxis

[b] GU and GI tract

* Minor bleeding events – petechial, mucosal and microscopic bleeding, as well as melena and hematemesis not requiring RBC transfusion

Major bleeding events - gross hematuria, any bleed requiring RBC, retinal bleeding or CNS bleeding

^ Bacterial and/or fungal sepsis were a contributing factor in eight of these deaths

Table 2 - Platelet transfusion RCTs with study adaptations of the WHO bleeding scale

	WHO grade 3	**WHO grade 4**
Heddle 2009 [25]	**Oral/nasal/skin/musculoskeletal/GI/GU/pulmonary /invasive sites/other**	**Any source**

	Bleeding requiring RBC transfusion specifically for support of bleeding within 24 hours of onset.	Fatal bleeding Debilitating bleeding
	Retinal# -	**Retinal** Retinal bleeding with visual impairment
	CNS -	**CNS** Non-fatal CNS bleeding
Wandt 2012 [5]	**Oral/nasal/skin/musculoskeletal/GI/GU/pulmonary/ invasive sites/other** Bleeding necessitating RBC transfusion over routine needs within 24 hours	**Oral/nasal/skin/musculoskeletal/GI/GU/pulmonary/invasive sites/other** Bleeding necessitating RBC transfusion and associated with severe haemodynamic instability necessitating ICU
	Retinal Routine fundoscopy without visual impairment	**Retinal** Bleeding with visual impairment proven by fundoscopy
	CNS -	**CNS** Fatal or non-fatal CNS bleeding
Slichter 2010 [2]	**Oral/nasal/skin/musculoskeletal/GI/GU/pulmonary** Bleeding requiring RBC transfusion over routine transfusion needs**	**Any site** Fatal bleeding Bleeding associated with severe hemodynamic instability and requiring RBC transfusion over routine transfusion needs
	Body cavity Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate).	
	Retinal # -	**Retinal** Bleeding with visual impairment

	CNS LP with visible blood in absence of symptoms, and non-traumatic tap	**CNS** CNS symptoms with non-traumatic bloody LP CNS bleeding on imaging with or without dysfunction
Stanworth 2013 [4]	**Oral/nasal/skin/musculoskeletal/GI/GU/pulmonary/ invasive sites** Bleeding requiring RBC transfusion specifically for support of bleeding within 24 hours of onset and without hemodynamic instability	**Any site** Fatal bleeding any source Debilitating bleeding Bleeding associated with hemodynamic instability
	Body cavity Bleeding in body cavity fluids grossly visible	
	Retinal bleeding # -	**Retinal bleeding** Retinal bleeding and visual impairment
	CNS Cerebral bleeding noted on CT without neurological signs and symptoms	**CNS** Non-fatal cerebral bleeding with neurological signs and symptoms

CNS – central nervous system, CT – computer tomography, GI – gastrointestinal, GU – genitourinary, ICU – intensive care unit, RBC – red blood cell, WHO – World Health Organization.

** RBC transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding

Retinal bleeding without visual impairment classified as WHO grade 2.

Table 3: Platelet transfusion randomized controlled trials: Inclusion and exclusion criteria

Therapeutic-only versus prophylactic transfusion trials	**Inclusion criteria**	**Exclusion criteria**
Solomon 1978 [62]	Adults with AML	APML

Grossman 1980 [20]	Patients with amegakaryocytic thrombocytopenia	Refractory to platelet transfusions No longer candidate for aggressive therapy TCP not expected to last for > 7 days
Murphy 1982 [19]	Pediatric patients Untreated acute leukemia	Not reported
Sintnicholas 1982 [63]	Patients with acute leukemia and severe TCP	Not reported
Wandt 2012 [5]	<u>AML</u> Age 16 – 80 years AML trial participants, APML in complete remission <u>Auto HSCT</u> Age 16 – 65 years AML/ALL in 1st or 2nd remission, non-Hodgkin lymphoma, Hodgkin lymphoma or multiple myeloma	APML (initial diagnosis) Platelet refractoriness Major bleeding with TCP when the reason for bleeding is still ongoing Plasmatic coagulation disorder Unable to consent
Stanworth 2013 [4]	Age ≥ 16 Hematological malignancy received or receiving chemotherapy and/or HSCT Platelet count expected to be <50 for at least 5 days. Able to comply with treatment	APML WHO 3 bleeding or higher during treatment to date WHO 2 bleeding during current admission Inherited hemostatic or thrombotic disorder Antiplatelet or anticoagulants HLA antibodies Pregnant Prior randomization in this trial
Platelet dose studies	**Inclusion criteria**	**Exclusion criteria**
Roy 1973 [7]	Pediatric hospitalized patients Acute leukemia	Not reported

	Platelet count ≤ 25 x10^9/L No active bleeding in previous 5 days	
Steffens 2002 [64]	Patients > 16 years AML or undergoing an allogeneic HSCT	HLA antibodies Cardiovascular disease unable to tolerate a volume load
Senesebe 2004 [33]	Patients with acute leukemia undergoing first line treatment or autologous HSCT without criteria impairing platelet efficiency	APML
Tinmouth 2004 [26]	Patients > 16 years AML or ALL receiving induction chemotherapy or autologous HSCT	APML Active bleeding Abnormal coagulation tests (INR >1.5, APTT >5 sec above normal, fibrinogen < 1.0mg/dl History of bleeding diathesis History of ITP, platelet refractoriness, anticoagulants, antiplatelet agents, antifibrinolytics or desmopressin acetate.
Heddle 2009 [25]	Weight 40-100kg Hypoproliferative TCP Platelet count expected to be < 10 × 10^9/L for a minimum of 10 days Receiving treatment as an inpatient	APML History of ITP/TTP/HUS WHO grade 2 bleeding or higher at entry Requiring bedside leukoreduced platelets Pregnancy
Slichter 2010 [2]	Any age Weight 10-135kg HSCT or chemotherapy for hematological	APML WHO grade 2 bleeding or higher

	malignancy or solid tumours Expected to have platelet count ≤10 for 5 days PT or APTT ≤1.3 x normal Fibrinogen ≥100mg No previous platelet transfusions for TCP during the current hospital admission.	Bedside platelet leukoreduction Platelet refractoriness within past 30 days Panel reactive HLA antibody level of ≥20% ITP or TTP/HUS Planned prophylactic platelet transfusion at >10 x 10^9/L Major surgery within 2 weeks Anti-platelet medications Pregnancy Previous enrolment in PLADO trial
Platelet trigger studies	**Inclusion criteria**	**Exclusion criteria**
Heckman 1997 [23]	Age ≥ 17 years. Acute leukemia (AML, ALL in relapse, acute undifferentiated leukemia or MDS transformed to AML) Induction chemotherapy or re-induction following relapse	APML Inherited clotting disorder or history of bleeding diathesis Uncontrolled infection or DIC at randomisation Concomitant malignancy AIDS Platelet refractoriness
Rebulla 1997 [6]	Adolescents and adults (17 – 70 years) Newly diagnosed AML admitted to hospital during their first course of chemotherapy	APML or secondary AML Received a blood transfusion prior to diagnosis of AML
Zumberg 2002 [24]	Patients > 2years,	Bleeding disorder or coagulopathy

	Allogeneic, MUD or autologous BMT	Anticoagulation Acute hemorrhage within 1 week of enrolment or within 1 week of a fall in the platelet count to below 50×10^9 /L Prior bladder irradiation Planned use of cyclophosphamide Platelet alloimmunization
Diedrich 2005 [21]	All ages Allogeneic HSCT	Bleeding disorder or coagulopathy
Platelets versus other product	**Inclusion criteria**	**Exclusion criteria**
Higby 1974 [22]	Afebrile, thrombocytopenic, AML patients	Hematological remission Bleeding or haemolysis

AIDS – acquired immune deficiency syndrome, ALL – Acute lymphocytic leukemia, AML- Acute myeloid leukemia, APML – Acute promyelocytic leukemia, BMT – bone marrow transplant, HSCT – Hematopoietic stem cell transplantation, HUS – Hemolytic uraemic syndrome, ITP – immune thrombocytopenia, MDS – myelodysplastic syndrome, MUD – matched unrelated donor, TCP – thrombocytopenia, TTP – thrombotic thrombocytopenic purpura.

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