Platelet transfusion goals in oncology patients

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Despite the advances in platelet component preparation and transfusion support over the years, platelet products remain a limited resource due to their short (5 day) shelf life, and therefore their optimal use in the non-bleeding thrombocytopenic patient continue to draw much attention. There have been a number of national and international guidelines for platelet transfusion therapy in patients with hematologic diseases, some within the last 1-2 years that have incorporated key randomized controlled trials (RCTs) which address issues, such as the optimal platelet dose, the most appropriate threshold for prophylactic platelet transfusions, and whether prophylactic platelet transfusions are superior to therapeutic-only platelet transfusion practices for the prevention life-threatening bleeding in patients with hypoproliferative thrombocytopenia. This review highlights key RCTs and recent systematic reviews focused on optimal platelet transfusion therapy in adult and pediatric patients with hypoproliferative thrombocytopenia secondary to chemotherapy or hematopoietic stem cell transplant (HSCT), discuss how recent innovations in platelet component processing may affect transfusion efficiency, and introduce renewed concepts on adjuvant therapies to prevent bleeding in the hypoproliferative thrombocytopenic patient.

Learning Objectives

- Review measures of bleeding propensity, platelet transfusion efficacy, and bleeding patterns in adult and pediatric oncology patients receiving chemotherapy or hematopoietic stem cell transplant (HSCT)
- Review key randomized controlled trials (RCTs) that have influenced recent guidelines on optimal platelet dose, the most appropriate threshold for prophylactic platelet transfusions, and whether prophylactic platelet transfusions or therapeutic-only platelet transfusion practices should be used in adult and pediatric patients with hypoproliferative thrombocytopenia
- Discuss how recent innovations in platelet component processing may affect transfusion efficiency
- Introduce renewed concepts on adjuvant therapies to prevent bleeding in the hypoproliferative thrombocytopenic patient
- Highlight a practical approach to the diagnosis and management of patients with platelet transfusion refractoriness

Since the first demonstration in 1910 by W. W. Duke of hemorrhagic disease relieved by transfusion of platelets in 3 individuals with thrombocytopenia, platelet transfusions have become standard treatment for thrombocytopenic patients.[1] The invention of plastic blood bags enabled the platelet component to be separated from whole-blood collections by centrifugation and stored at room temperature with agitation in the 1950s and 1960s. This allowed for increased utilization of platelet transfusions to support the expanded use of high-dose chemotherapy regimens and hematopoietic stem cell transplantation (HSCT) in the 1970s and 1980s. Apheresis techniques introduced in the 1980s allowed for collection of apheresis platelets, which enabled much more efficient platelet yields per donor; apheresis techniques were refined in the 1990s facilitating collection of leukoreduced platelets. Most recently, advances have given rise to platelet additive solutions (PASs), and pathogen-reduced platelet products, which are designed to reduce platelet transfusion-related adverse effects.

The most common indication for platelet transfusions today is for supportive care of patients with bone marrow failure secondary to primary marrow dyscrasias, chemotherapy, or HSCT, with over one-third of platelet transfusions in the US issued to hematology/oncology patients.[2] The majority of these platelet components are issued prophylactically to prevent bleeding.[3,4] Prophylactic (and therapeutic) platelet transfusion practices have grown and continue to expand as a result of increased use of high-dose chemotherapy and HSCT, and as supportive care of these patients continue to improve.

Because platelet products are a limited resource, their optimal use in the non-bleeding thrombocytopenic patient needs to be practical yet judicious. A number of guidelines for platelet transfusion therapy in patients with oncologic diseases address issues such as the optimal platelet dose, the most appropriate threshold for prophylactic platelet transfusion, and whether prophylactic platelet transfusion practices are preferred to therapeutic-only platelet transfusions for the supportive care of patients with hypoproliferative thrombocytopenia. The majority of the data contributing to the development of these guidelines are from studies in adults with very few randomized controlled trials (RCTs) including significant numbers of children (ie, Platelet Dose "PLADO" study).[5] Inherent differences in bleeding patterns in children and adults exist, which may influence platelet transfusion management decisions and highlight the need for the development and validation of pediatric-specific bleeding scales in order to determine the incidence of and better define clinically significant bleeding in this population.[6] Adjuncts to platelet transfusions such as the lysine analogue anti-fibrinolytics

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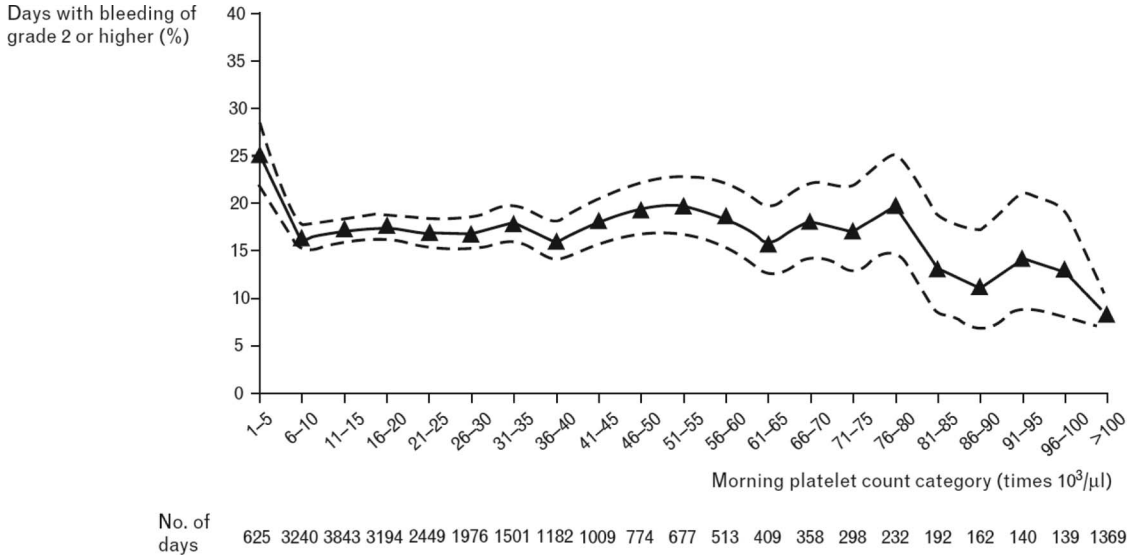

Figure 1. Relationship between morning platelet count and days with grade 2 or higher bleeding. Results of PLADO trial illustrating percentage of days with bleeding of grade 2 or higher in all 3 platelet dose groups, according to morning platelet count categories, along with the associated 95% confidence intervals (dashed lines). Reprinted from Slichter et al[5] with permission.

[tranexamic acid (TXA) and epsilon aminocaproic acid (EACA)], and recombinant human thrombopoietin (rhTPO) and thrombopoietin (TPO) agonists have been used to prevent bleeding in oncology patients, as well as in other patient groups. Although limited, the available results using these agents in this setting are promising and deserve future consideration.

Measures of platelet transfusion efficacy

Assessment of platelet transfusion efficacy may include direct measures of bleeding severity and frequency, laboratory testing of platelet increment, or indirect surrogate markers such as intervals between transfusion and red blood cell transfusion use. Although hemostatic assays, such as thromboelastography (TEG) have been shown to be valuable in implementing goal-directed transfusion therapy in bleeding surgical, trauma, and select hemophilia patients,[7] no single test has yet been validated to reliably predict impending clinically significant bleeding in the thrombocytopenic patient.

The most commonly used grading system for measuring bleeding severity in platelet transfusion trials has been the standardized 5-point grading scale proposed by the World Health Organization (WHO) in 1979, where grade 0 = no bleeding; grade 1 = petechiae; grade 2 = mild blood loss; grade 3 = severe blood loss requiring transfusion; and grade 4 = debilitating blood loss. Although the definition of "clinically significant bleeding" had been inconsistent among older studies,[8-10] it has been defined as WHO grade 2 or above in the majority of recent platelet transfusion trials. Despite this, the WHO grading system is imperfect because the grades are broad and subjective with poor inter-rater reliability. For example, more recent studies with trained bleeding assessors, detailed documentation, and expanded grading system evaluations have reported higher overall levels of bleeding than older investigations.[11] Furthermore, WHO grades 2 through 4 are grouped together to define clinically significant bleeding despite a lack of evidence that grade 2 bleeding predicts future grade 3 or 4 bleeding, or that grade 2 bleeding predicts a worse clinical outcome than grade 1 bleeding.[6,12] As such, these imperfections in grading bleeding severity make study comparisons difficult, which needs to be considered when reviewing meta-analyses on the effectiveness of different platelet transfusion strategies.

Despite limitations, the (morning) platelet count has been able to estimate the risk of clinically significant bleeding in hematology patients with hypoproliferative thrombocytopenia. The PLADO Trial, which enrolled 1272 patients (pediatric and adult) and included 24,309 days when both the morning platelet count and the bleeding severity were reported, demonstrated that the risk of WHO grade 2-4 bleeding was 25% when morning platelet counts were $<5000/\mu L$ versus 17% at platelet counts $>5000/\mu L$ which remained fairly consistent up to a platelet count of 80 000/μL (Figure 1).[5] It should be noted that although all patients received prophylactic platelet transfusions for platelet counts $<10,000/\mu L$, they were stratified into three platelet dose groups but that the morning platelet count did not differ significantly between the treatment (dose) groups. These findings are consistent with prior data which suggested that a minimum of 5000-7000 platelets/μL are critical for maintaining hemostasis and endothelial support, and with previous findings that with >10 000 platelets/μL bleeding rates are fairly consistent over a wide range of platelet counts.[13-15]

The type of disease treatment and patient age are also important factors to consider when assessing risk of clinically significant bleeding. As demonstrated in the PLADO Trial, the risk of grade 2 or greater bleeding in patients receiving an allogeneic HSCT was 79% versus 73% in those receiving chemotherapy for hematologic malignancies, and 57% in those receiving an autologous HSCT ($P < 0.001$ for the auto HSCT vs the first 2 groups).[5] Secondary analysis of the PLADO trial conducted to determine whether bleeding outcomes differed among pediatric age groups (ages 0-5, 6-12, and 13-18 years) and adults demonstrated that pediatric patients (0-18 years) had a higher incidence of grade 2-4 bleeding than adults [86% (ages 0-5), 88% (ages 6-12), 77% (ages 13-18), and 67% (age >18)]. Similarly, the percentage of days with grade 2-4 bleeding was higher in pediatric patients compared to adults given a similar morning platelet count (Figure 2A). Among patients who received HSCT, all 3 of the pediatric cohorts had significantly

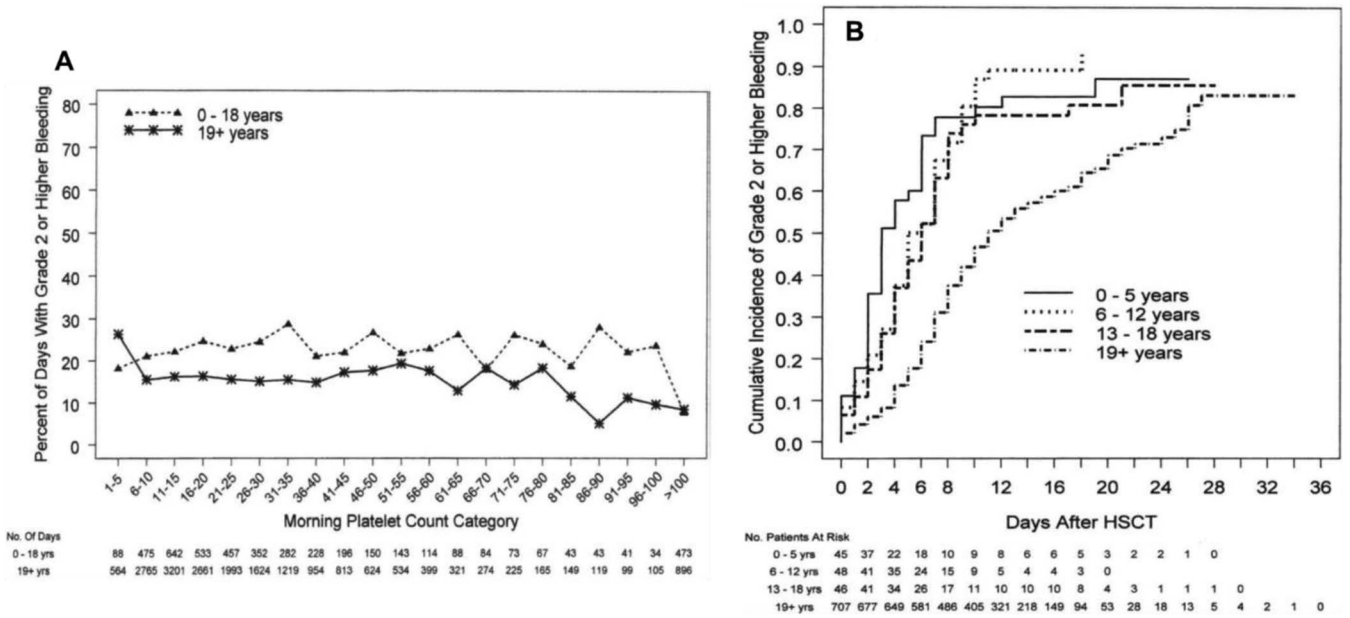

Figure 2. (A) Relationship between morning platelet count category and the occurrence of same-day grade 2 or higher bleeding. Pediatric patients had a higher incidence of bleeding at the same platelet count as their adult counterparts except at platelet counts ≤5 000/μL ($P < .001$). (B) Relationship between age and time to first bleed in HSCT patients among adult and pediatric patients. Pediatric patients (18 years of age) had a shorter time from day of HSCT to day of first bleed than adult patients ($P < .001$). Reprinted from Josephson et al[6] with permission.

shorter times from transplant to grade 2-4 bleeding than adults [median 3.0 days (ages 0-5), 5.5 days (ages 6-12), 6.0 days (ages 6-12), and 11.0 days (age >18); $P = .001$; Figure 2B). In addition, pediatric patients were more likely to have oropharyngeal and gastrointestinal bleeding and hemodynamic instability associated with bleeding compared to adults.[6,16]

Therefore, in addition to the platelet count, other factors clearly play a significant role in determining the likelihood of clinically significant bleeding such as the type of disease, the treatment used, and patient age. There are most certainly additional factors yet to be definitively proven which are likely to contribute to bleeding risk in the hypoproliferative thrombocytopenic patient. These may include intrinsic or acquired differences in various clotting factors, anemia-induced platelet axial redistribution within the vascular compartment,[17] as well as the degree of vascular endothelial integrity, which may be compromised by many disease-specific treatment perturbations (infection, graft versus host disease, veno-occlusive disease, thrombotic microangiopathy, etc). These additional factors likely influence each patient's propensity to bleed and should be considered when individual patient transfusion management decisions are made. As an example, patients with multiple myeloma and related plasma cell disorders may have platelet dysfunction due to circulating monoclonal proteins , which may warrant platelet transfusions at higher platelet counts.[18]

Prophylactic versus therapeutic platelet transfusions

A Cochrane Collaboration meta-analysis of data from 3 small RCTs conducted in the late 1970s and comprising <100 patients compared the advantage of prophylactic to therapeutic platelet transfusions. The investigation revealed that there was a non-significant trend towards an increased risk of significant bleeding in the therapeutic transfusion arm (RR 1.66; 95% CI 0.90-3.04), no difference in the number of days with bleeding, and no differences in mortality.[3]

Following the Cochrane Collaboration meta-analysis, 2 large RCTs were completed which compared prophylactic to therapeutic-only platelet transfusions in patients with hematologic malignancies receiving high-dose induction chemotherapy or undergoing HSCT.[19,20] The TOPPS Trial, which was a randomized, open-label, non-inferiority trial, randomized 600 patients, 16 years of age or older, to either no-prophylactic (therapeutic) platelet transfusions or prophylactic platelet transfusions (using a morning platelet count trigger of 10 000/μL). They found a higher rate of WHO grade 2-4 bleeding events in patients receiving therapeutic platelet transfusions (50% vs 43%; $P = .06$ for non-inferiority), and post hoc superiority analysis demonstrated that the difference in grade 2-4 bleeding was significant ($P = .04$).[20] Subsequent subgroup analysis found that the reduction in grade 2-4 bleeding seen in the prophylactic transfusion arm was of greater magnitude in patients receiving high-dose chemotherapy or allogeneic HSCT than in patients undergoing autologous HSCT (interaction $p = .04$). In fact, there were similar rates of WHO grade 2- 4 bleeding in the no-prophylaxis (47%) and prophylaxis groups (45%) in patients undergoing autologous HSCTs[21]

The RCT reported by Wandt et al entailed a similar trial design, with comparable minimum age cutoff (≥16 years of age), disease categories, and platelet count trigger in the prophylactic transfusion arm. This study reported a significant increase in the proportion of patients with grade 2-4 bleeding (42% vs 19%; $P < .0001$) and grade 4 bleeding (5% vs 1%; $P = .0159$) in patients receiving therapeutic-only platelet transfusions. In subgroup analysis, grade 2-4 bleeding in the AML and autologous HSCT groups were reported at 51% (no-prophylactic transfusion) versus 24% (prophylactic transfusion; $p < .0001$) and 28% versus 8% ($p = .0005$), respectively. The risk of grade 4 (mostly CNS) bleeding was increased in patients receiving intensive chemotherapy for AML, with 6 minor and 2 fatal intra-cerebral

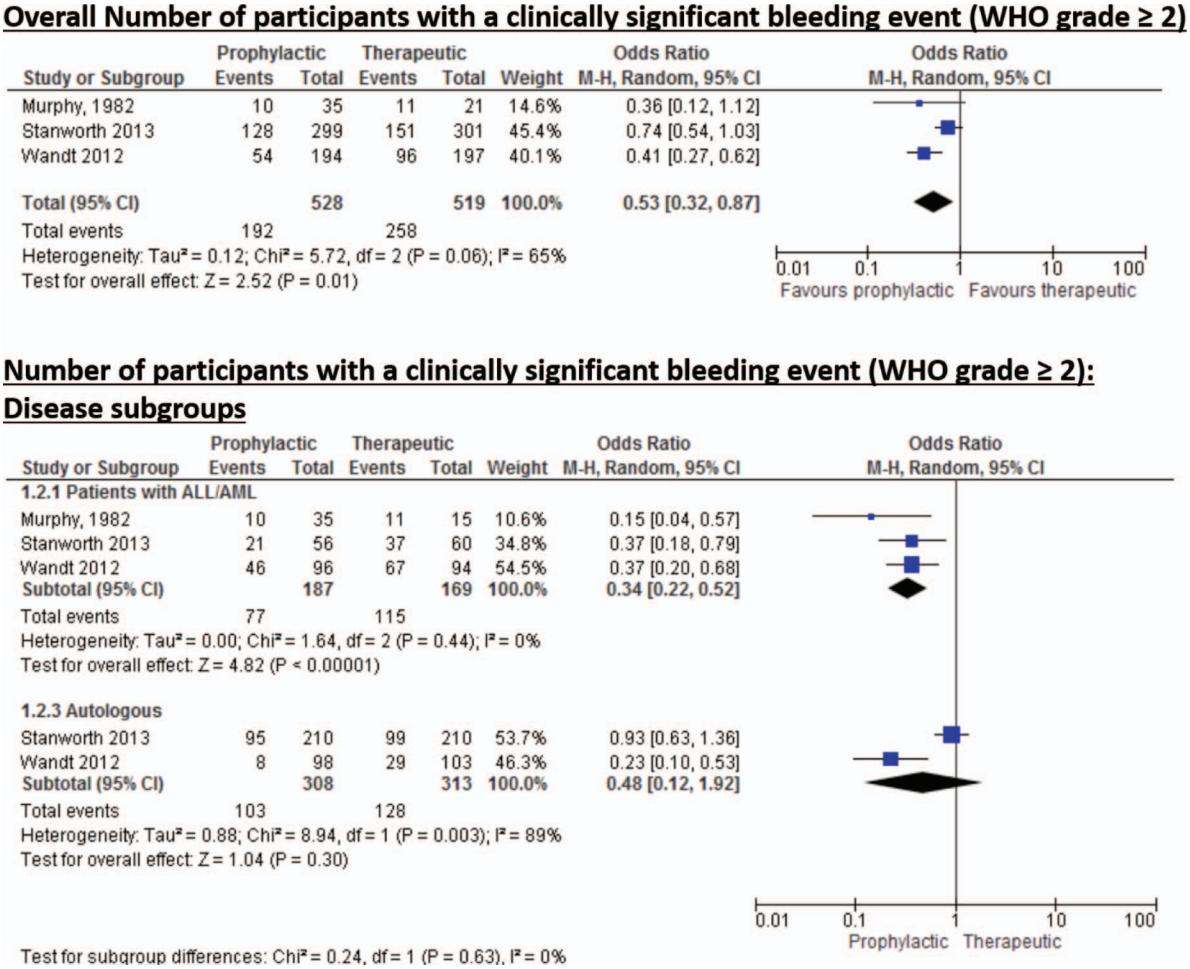

Figure 3. Relationship between number of patients with clinically significant bleeding event and prophylactic versus therapeutic-only platelet transfusions. Results of meta-analysis performed by AABB guidelines panel to address the question of whether prophylactic platelet transfusions should be used to prevent bleeding in patients with hypoproliferative thrombocytopenia. Reprinted from Kumar et al[23] with permission.

bleeds in the therapeutic-only transfusion arm and no intracerebral bleeding in the prophylactic transfusion arm. However, no increased risk of major hemorrhage was noted in patients who had undergone autologous HSCT; there was no grade 4 bleeding or significant differences in grade 3 bleeding in either the prophylactic or therapeutic transfusion groups.[19] Not surprisingly, both trials showed significant reductions in platelet transfusions with a therapeutic-only platelet transfusion strategy. The 2 trials had different time frames in which reported bleeding rates were measured (14 days for the Wandt study vs 30 days for the TOPPS trial), and slightly different bleeding grading systems and assessment methods, which may account for lower bleeding rates reported in the Wandt study.[21]

The data from both studies support that there exists a protective effect at reducing clinically significant bleeding with prophylactic transfusions, but that the effect was less compelling in patients undergoing autologous HSCT compared to patients receiving high-dose chemotherapy or allogeneic HSCT. The International Collaboration for Transfusion Medicine Guidelines (ICTMG) recommends for a transfusion policy in patients with hypoproliferative thrombocytopenia to include prophylactic platelet transfusions to decrease the risk of WHO grade 2-4 bleeding. Analogous recommendations were made for pediatric patients, although it was recognized that pediatric data are limited. Separate recommendations for patients undergoing autologous HSCT were not made because of the dissimilar bleeding rates in the Wandt study and TOPPS trial.[22]

In addition to the ICTMG report, an AABB guidelines panel performed a systematic review aimed at synthesizing the current evidence for many common situations in which platelet transfusions are considered. In this review, a meta-analysis was performed to address the question of whether prophylactic platelet transfusions should be used to prevent bleeding in patients with hypoproliferative thrombocytopenia. These results were in agreement with the ICTMG report and are illustrated in Figure 3.[23] Although the data are not shown, all-cause mortality and mortality from bleeding showed trends toward a protective effect of a prophylactic transfusion strategy; however, this effect was not significant.

The appropriate threshold for prophylactic platelet transfusion

Several studies have evaluated the appropriateness of various platelet transfusion thresholds in oncology patients with hypoproliferative thrombocytopenia. Four RCTs have evaluated 10 000/μL versus 20 000/μL,[8,9,24] or 30 000/μL.[25] These studies consistently have demonstrated no significant increases in bleeding risk or red cell transfusion requirements using the lower platelet count threshold of 10 000/μL, and 3 of the RCTs showed substantial decreases

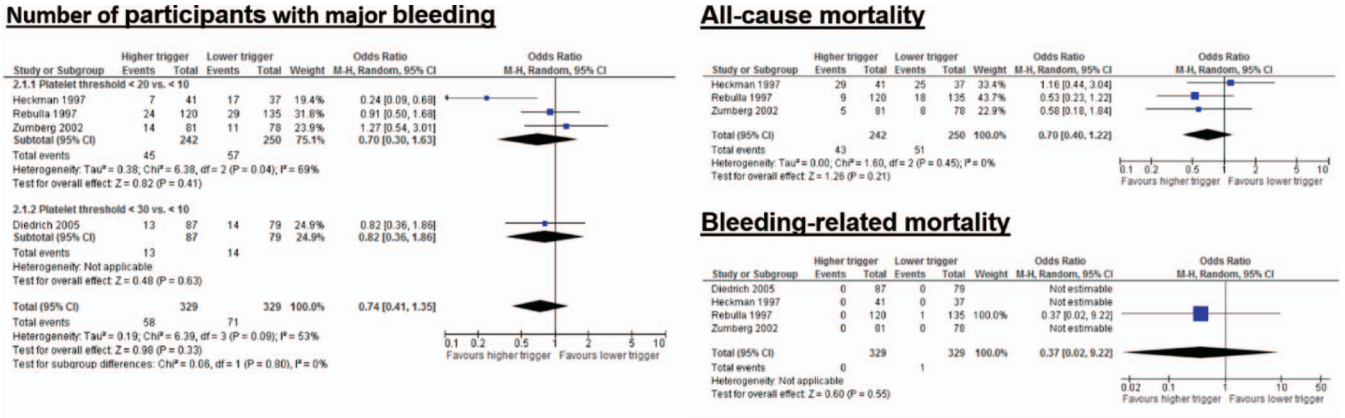

Figure 4. Relationship between number of patients with a major bleeding event and platelet count thresholds of 10 000/μL versus 20 000/μL or 30 000/μL. Results of meta-analysis performed by AABB guidelines panel to address the question of which platelet count threshold is most appropriate for prophylactic platelet transfusions. Reprinted from Kumar et al[23] with permission.

in number of platelet transfusions.[8,9,25] The AABB guidelines panel's recent meta-analysis of these four RCTs which included data on 658 patients reported that there was no significant difference in major bleeding or mortality from bleeding between a platelet count threshold of 10 000/μL versus 20 000/μL or 30 000/μL (Figure 4).[23] The ICTMG report also endorsed the platelet count threshold of 10 000/μL.[22]

Platelet thresholds of 5000/μL have been reported to be relatively safe but have not been rigorously assessed.[26,27] Although it has been suggested that this may be the critical platelet level based on earlier studies of thrombocytopenic patients not being supported by platelet transfusions,[13,15] embracing a platelet count threshold of 5000/μL is challenged by reports of lack of reliability of platelet counts at very low levels.[28] However, the data suggesting a similar hemostatic effect at 5000/μL compared with 10 000/μL should reinforce the safety of the 10 000/μL platelet-count threshold for non-bleeding patients with hypoproliferative thrombocytopenia.

The optimal platelet transfusion dose

Platelets may be prepared by 1 of 2 methods: whole blood (WB) collection and separation via centrifugation, or apheresis. WB-derived platelets (often referred to as random-donor platelets) contain at least 5.5×10^{10} platelets per unit, whereas apheresis platelets (often called single-donor platelets) contain a minimum of 3×10^{11} platelets per collection. The typical dose for prophylactic platelet transfusions in adults ranges between 4 and 8 units of WB-derived platelet units (2.2×10^{11} and 4.4×10^{11} platelets, respectively). Assuming that the average body surface area (BSA) for adult men and women is 1.9 m^2 and 1.6 m^2 respectively, the typical doses of platelets administered range between 1.1×10^{11} and 2.3×10^{11} per m^2 for the average adult male and 1.4×10^{11} to 2.8×10^{11} per m^2 for the average adult female. The 2 most common ways platelets are administered in children are based on volume (mL/kg) or based on equivalent units/kg, which is more accurate and preferred. An equivalent unit or "EU" is the volume of a platelet aliquot that has a minimum platelet content of 5.5×10^{10} (1 WB-derived platelet unit). The standard dose using this method is 1 EU per 5-10 kg, which approximates to 1.6×10^{11} to 3.3×10^{11} platelets per square meter. Based on these estimates, various RCTS have developed different platelet dosing comparisons based on the number of platelets per BSA to determine the optimal dose for prophylactic platelet transfusions in patients with hypoproliferative thrombocytopenia.

Over the past 15 years, multiple RCTs have examined the effect of different platelet doses for prophylactic platelet transfusions on bleeding outcomes in patients with hypoproliferative thrombocytopenia.[5,29-31] The PLADO study is by far the largest, and enrolled 1272 adult and pediatric patients with hypoproliferative thrombocytopenia secondary to chemotherapy for acute leukemia (25%), autologous HSCT (34%), or allogeneic HSCT (41%). In this trial, patients were randomized to receive low-dose ($1.1 - 10^{11}/m^2$), standard-dose ($2.2 - 10^{11}/m^2$), or high-dose ($4.4 - 10^{11}/m^2$) prophylactic platelet transfusions using a morning threshold platelet count of 10 000/μL. There was no significant effect of platelet dose on the incidence of WHO grade 2-4 bleeding (71%, 69%, and 70% in the low-dose, medium-dose, and high-dose group, respectively), nor was there a significant effect of dose on bleeding of any grade. However, there were statistically significant differences in days to next transfusion (1.1 days vs 1.9 days vs 2.9 days in the low-dose, medium-dose, and high-dose group; $P < .001$), number of platelet transfusion episodes (5 vs 3 vs 3 in the low-dose, medium-dose, and high-dose group; $P < .001$), and total number of platelets transfused per patient (9.25×10^{11} vs 11.25×10^{11} vs 9.63×10^{11} in the low-dose, medium-dose, and high-dose group; $P \leq .002$ for both comparisons).[5]

The AABB guidelines panel's recent meta-analysis also addressed optimal dosing of platelet transfusions for patients with hypoproliferative thrombocytopenia. The meta-analysis, which included data from 5 RCTs in 1660 patients, was heavily weighted by the PLADO study. Because platelet doses were reported differently in different studies, the panel converted different dose metrics into the number of platelets per square meter and categorized low-dose, standard-dose, and high-dose as $1.1\text{-}1.3 \times 10^{11}/m^2$, $2.2\text{-}3.0 \times 10^{11}/m^2$, and $4.4\text{-}6.0 \times 10^{11}/m^2$, respectively, to allow meaningful comparisons. The meta-analysis demonstrated no significant differences in incidence of clinically significant bleeding, all-cause mortality, or bleeding-related mortality between standard-dose and low-dose platelet groups, or between high-dose and standard-dose platelet groups (Figure 5).[23] Further, the ICTMG recommended the use of low- or standard-dose prophylactic platelet transfusion as opposed to high-dose platelet transfusion for hospitalized patients with hypoproliferative thrombocytopenia based on its independent systematic review of the same available published data.[22]

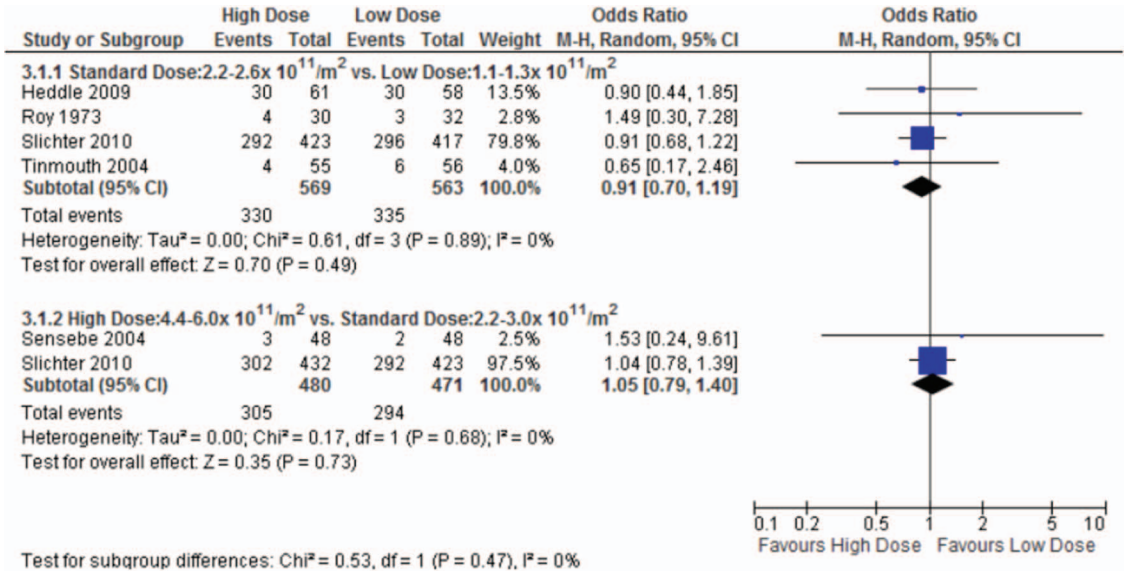

Figure 5. Relationship between number of patients with a major bleeding event and platelet transfusion dosage. Results of meta-analysis performed by AABB guidelines panel to address the question of which platelet dose is most appropriate for prophylactic platelet transfusions. Reprinted from Kumar et al[23] with permission.

New platelet products and adjuvant therapies

Blood transfusion safety has continued to improve in recent years because of improved donor screening/testing processes for transfusion-transmitted infections; however, risks remain due to both newly emerging blood-borne pathogens and bacterial contamination of blood products, especially platelet concentrates due to their higher storage temperature (22°C). Photochemical pathogen-reduction technologies, which have been developed and implemented over the past decade, inactivate or significantly reduce a wide range of infectious agents within cellular blood components, including platelet concentrates.

There are 2 pathogen-reduction systems commercially available for the treatment of platelet concentrates, which use either the synthetic psoralen amotosalen (Intercept) or riboflavin (Mirasol) in the presence of ultraviolet light. Although these pathogen-reduction technologies have proven to be very effective in reducing infectious agents in platelet concentrates, there have been uncertainties regarding the hemostatic effectiveness of pathogen-reduced platelets compared with standard platelets and how this may affect future transfusion effectiveness when using these platelet products.

Multiple trials have compared pathogen-reduced platelets with standard platelets; however, only 6 non-crossover trials have assessed both platelet response and bleeding outcomes in patients transfused numerous times (via either pathogen-reduced or standard platelets). Despite heterogeneity of their study designs including the pathogen-reduction system used (5 Intercept, 1 Mirasol), the platelet transfusion threshold applied, definitions and methods of outcome assessment, and duration of follow-up, 4 recent meta-analyses have been conducted assessing the hemostatic efficacy of pathogen-reduced platelets compared to standard platelets.[32-35] The most recent meta-analysis performed by the Cochrane Collaboration assessed various bleeding outcomes including "any bleeding" (WHO grade 1-4), "clinically significant bleeding" (WHO grade 2–4) and "severe bleeding" (WHO grade ≥3),[35] in addition to platelet response, overall platelet usage, adverse reactions, and mortality. Similar to preceding reviews, this investigation found no difference in the rates of "clinically significant" or "severe" bleeding, adverse events, or mortality between pathogen-reduced and standard platelet treatment groups. However, 1-hour, 24-hour, and corrected-count increment (CCI) were significantly less, and the rate of "any bleeding" and overall platelet usage were higher in pathogen-reduced platelets compared to standard platelets.[32-35] Recognizing that pathogen-reduction technologies may affect platelet dose, and that participants in at least 3 of the trials received a 10% lower platelet dose in the pathogen-reduced platelet arm, it remains unclear whether the inferior platelet increments observed in these trials can be overcome by issuing higher platelet doses.

The PLADO trial demonstrated that thrombocytopenic patients had fairly uniform rates of bleeding (17%) with platelet counts between 6000 to 80 000/μL[5] suggesting that a significant number of bleeding episodes are not effectively prevented by prophylactic platelet transfusions. Therefore, adjunct (or alternative) treatments to prophylactic platelet transfusions aimed at other parts of the coagulation system may therefore improve bleeding outcomes. Two large systematic reviews have recently shown anti-fibrinolytics (TXA and EACA) to be effective in decreasing both blood loss and the need for blood transfusions in surgical patients.[36,37] In addition, the CRASH-2 trial published in 2010 demonstrated that when administrated within 3 hours of injury, TXA reduced the risk of death due to bleeding in trauma patients with significant hemorrhage.[38] Based on these recent results showing a beneficial effect of anti-fibrinolytic agents in other patient groups, there has been renewed interest in using these drugs as adjuvant therapy to prevent bleeding in patients with hematological disorders.

A Cochrane Collaboration review designed to establish the efficacy and safety of anti-fibrinolytics in patients with hematologic disorders included outcome analysis of 3 trials containing 87 patients (TXA, 2 trials, 68 patients; EACA, 1 trial, 18 patients).[39] All three studies compared the drug with placebo in adults receiving chemotherapy for acute leukemia. Because of the limited sample size combined with heterogeneity of outcome measures and study design, meta-analysis was unable to be performed. However, all the studies showed a reduction in bleeding (although not for patients in

consolidation therapy), and a reduction in platelet usage. Thromboembolic events were assessed in two of the studies. Although there were no reports of thromboembolic events reported in either study (68 patients), the sample size was too small to assess thromboembolic risk of anti-fibrinolytics in this population. Relatedly, systematic review of >25 000 surgical patients did not demonstrate that the use of either TXA or EACA peri-operatively was associated with an increased risk of myocardial infarction, deep vein thrombosis, pulmonary embolism, stroke, or death.[36] Nevertheless, it should be recognized that anti-fibrinolytics may increase the risk of disseminated intravascular coagulation (DIC), and that patients with hematological malignancies are at increased risk for DIC. Ancillary analysis of the CRASH-2 trial revealed that late treatment with TXA (>3 hours from injury) seemed to increase the risk of death due to bleeding which was hypothesized to have been from evolution of DIC. Altogether, this highlights a serious need for caution in the use of anti-fibrinolytic agents in patients with hematological malignancies, and that larger trials are needed to determine whether anti-fibrinolytics can be recommended for widespread use in patients with hematological disorders.

Other adjuvant therapies aimed at decreasing the incidence of thrombocytopenic bleeding have been suggested but deserve much further clinical investigation. These include the use of pharmacologic agents that either act at different parts of the clotting cascade (recombinant factor VIIa; Desmopressin (DDAVP); fibrinogen concentrate) or hasten bone marrow recovery (rhTPO; the TPO agonists eltrombopag and romiplostim). Most noteworthy are the rhTPO/TPO agonist therapies, which particularly have shown promise in terms of minimizing platelet transfusion usage and promoting platelet engraftment in patients undergoing allogeneic (haploidentical) HSCT.[40] In addition, artificial platelet substitutes have been shown to be effective in vitro and in animal models; however, there have yet to be any preclinical studies or clinical trials assessing safety and/or efficacy of platelet substitutes for human use.

Management of patients with platelet transfusion refractoriness

Platelet transfusion refractoriness (PTR), defined as the repeated failure to achieve satisfactory responses to platelet transfusions from random donors,[41] can result from immune and/or non-immune causes. Non-immune etiologies such as ongoing infections, high fevers, consumptive processes (eg, bleeding, veno-occlusive disease, DIC, splenomegaly), and concurrent treatment with various antibiotics (eg, Vancomycin) or anti-fungal medications (eg, amphotericin B) are more common than alloimmune causes, which account for ~20% of cases of PTR. Platelet alloimmune refractoriness results from prior exposure to human leukocyte antigens (HLA) or less commonly human platelet antigens (HPA) from pregnancy, transfusions, and/or transplantation. The Trial to Reduce Alloimmunization to Platelets (TRAP) demonstrated that leukocyte reduction of blood components reduces the frequency of HLA alloimmunization and PTR. Nevertheless, chronic platelet transfusion support using leukoreduced blood products still resulted in 18% of patients becoming HLA alloimmunized, and 3% of patients developing immune-mediated PTR, defined as a 1 hour CCI of $<5 \times 10^6/\mu L$ on 2 sequential occasions.[42]

When PTR is suspected, clinical assessment and treatment of potential contributory non-immune factors, and provision of ABO-identical apheresis platelet products with 1 hour post-transfusion CCI assessment is recommended.[22,41] If 1 hour post-transfusion CCI is $<5 \times 10^6/\mu L$ on 2 sequential occasions, screening for HLA antibodies by either cell-based (complement-dependent cytotoxicity) or solid-phase (ELISA, microbead-based assays using Luminex or flow) methods is indicated. If HLA antibodies are identified, crossmatch compatible platelets, antigen-negative platelets, or HLA-matched platelets can be provided. Decisions on which product is most optimal depend on many factors including: the urgency of need for compatible platelets; whether the patient has been HLA typed (for HLA-A and HLA-B antigens); whether there is an HLA laboratory on site; the degree of alloimmunization to HLA-A and HLA-B antigens; and the availability of sufficient numbers of HLA-typed platelet donors. If HLA antibodies are not identified, consideration should be given to testing the patient for HPA antibodies.[43] Managing highly alloimmunized patients with refractory bleeding can be very challenging particularly when they do not respond to any platelets, including crossmatch compatible, antigen-negative, and HLA-matched platelets. In these cases, massive or continuous transfusion of ABO identical platelets, use of high-dose intravenous immunoglobulin, splenectomy, and plasma exchange, have been tried with limited success. However, EACA and TXA may be useful in reducing bleeding in these patients.[41]

Summary and future directions

Despite the advances in optimizing platelet transfusion therapy, platelet products remain a limited resource, and therefore their optimal use in patients with hypoproliferative thrombocytopenia is critical. Based on a number of RCTs and subsequent systematic reviews and meta-analyses, national and international guidelines have been formulated for platelet transfusion therapy in patients with hematologic diseases. As such, it is recommended that prophylactic platelet transfusions should be administered to non-bleeding adult and pediatric patients with hypoproliferative thrombocytopenia using a platelet count threshold of 10 000/μL. Low- or standard-dose ($1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$, respectively) platelet transfusions should be used in hospitalized patients; however, low-dose platelet transfusion may be inappropriate for outpatient management because it may increase the frequency of clinic visits.[22] Pathogen-reduced platelets seem to be an acceptable alternative to standard platelets based on their reducing risk of infectious complications, and their comparable efficacy of minimizing clinically significant bleeding. However, with lower platelet count increments at 1 and 24 hours post-transfusion their increased use may unfavorably impact overall platelet usage and inventory management unless their shelf life can be safely expanded beyond 5 days. Adjuvant treatments to prophylactic platelet transfusions, such as anti-fibrinolytics and rhTPO/TPO agonists may have a beneficial effect at improving bleeding outcomes in patients with hypoproliferative thrombocytopenia especially those with PTR; however, further clinical investigation is needed before recommendations can be made on their use in this population. Artificial platelet substitutes, if proven to be safe and effective in humans, would be favorable to offset the known drawbacks of standard platelet concentrates used in transfusions for patients with thrombocytopenia. Lastly, better laboratory-based assays to reliably predict bleeding propensity are needed to implement goal-directed transfusion therapy in the individuals with thrombocytopenia, especially the pediatric patient.

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