



New Strategies for the Optimal Use of Platelet Transfusions

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Patients with severe thrombocytopenia are presumed to be at increased risk for bleeding, and consequently it has been standard practice for the past four decades to give allogeneic platelet transfusions to severely thrombocytopenic patients as supportive care. Platelet transfusions may be given either prophylactically to reduce the risk of bleeding, in the absence of clinical hemorrhage (prophylactic transfusions), or to control active bleeding when present (therapeutic transfusions). While no one would argue with the need for platelet transfusions in the face of severe bleeding, important questions remain about what constitutes clinically significant bleeding and whether a strategy of prophylactic platelet transfusions is effective in reducing the risk of bleeding in clinically stable patients. It is now uncommon for patients undergoing intensive chemotherapy or bone marrow transplantation to die of hemorrhage, but it is open to debate as to what degree platelet transfusions have been responsible for this change in outcome, given the many other advances in other aspects of supportive care.

If a prophylactic strategy is followed, the optimal transfusion trigger or quantity of platelets to be transfused prophylactically per transfusion episode needs to be addressed in adequately powered clinical trials, but these remain highly controversial issues. This is because, until recently, there have been few

high-quality, prospective, randomized clinical trial (RCT) data for evaluating the relative effects of different platelet transfusion regimens or platelet doses on clinical outcomes. Moreover, most of these RCTs have not used bleeding as the primary outcome measure. Two such studies on platelet dose have now been undertaken, the PLADO (Prophylactic PLATElet DOse) and the SToP (Strategies for the Transfusion of Platelets) trials. Data from these RCTs are not contained in this overview, as these data have not yet been completely analyzed or submitted for peer review publication.

In addition to the above, several recent observational studies have raised the possibility that there is not a clear association between the occurrence of a major clinical bleeding episode and the platelet count in thrombocytopenic patients. Such findings have led to the questioning of the efficacy of prophylactic platelet transfusions in all clinically stable patients, and whether a policy of therapeutic transfusions used only when patients have clinical bleeding might be as effective and safe for selected patients. At least two RCTs evaluating the relative value of prophylactic versus therapeutic platelet transfusions have been initiated in thrombocytopenic patients with hematological malignancies. One such study, known as the TOPPS (Trial of Prophylactic Platelets Study) study, is currently underway in the U.K.

Introduction

Allogeneic platelet transfusions play a major role in the management of thrombocytopenic patients. The ready availability of platelet concentrates has made a major contribution to support the development of intensive treatment regimens for the treatment of patients with hematological and other malignancies. Although considerable advances have been made in many aspects of platelet transfusions in the last 30 years, several areas of controversy continue to exist with regard to the optimal approach to the use of platelet transfusions to further reduce the risk of clinically significant thrombocytopenic hemorrhage in patients with a hypoproliferative bone marrow and to minimize the fre-

quency and severity of adverse events. The following issues constitute the major relevant concerns:

1. What is the available evidence for the existence of an optimum prophylactic platelet dose to prevent thrombocytopenic bleeding?
2. What evidence exists that indicates that prophylactic platelet transfusions are superior to therapeutic platelet transfusions for the prevention and/or control of thrombocytopenic bleeding?

Platelets for transfusion can be prepared by three different methods: (a) the platelet-rich plasma (PRP) method; (b) the buffy coat (BC) method; and (c) the apheresis method.^{1,2}

The PRP method, which is used almost exclusively in the United States, and the BC method, which is used predominantly in Western Europe and Canada, derive platelets from units of whole blood collected from volunteer whole blood donors.² Studies comparing PRP and BC platelets have shown no difference in the *in vitro* quality of such platelet concentrates when they are stored for up to 5 days; however, few studies of direct *in vivo* head-to-head comparisons of these two methods of preparing platelet concentrates have been done.³ The third method for preparing platelets is by the process of apheresis.⁴ One of the major advantages of using apheresis platelets is that enough apheresis platelets can be derived from a single donor to provide a single clinically relevant platelet transfusion dose to an adult thrombocytopenic patient. In contrast, to obtain the equivalent number of transfused platelets required using either the PRP or BC methodology requires the pooling of platelet concentrates from 4 to 6 different donors.

Relationship Between Platelet Count and Bleeding Risk

The current thinking as to how circulating platelets control thrombocytopenic bleeding is that they provide an endothelial supportive function by plugging gaps in the endothelium of otherwise intact blood vessels.^{5,6} In experimental animals with severe thrombocytopenia, electron-microscopic studies have shown that thrombocytopenia is associated with the gradual thinning of the vessel wall endothelium over time, and that with ongoing thrombocytopenia gaps gradually occur between adjacent endothelial cells.^{7,8} This thinning and fenestration in the endothelium is accompanied with the on-going and increased use of circulating platelets to prevent the extravasation of red blood cells (RBCs) through these gaps. Relevant data from thrombocytopenic animal models show the loss of RBCs into the lymphatics of thrombocytopenic animals.⁹ Moreover, there appears to be an inverse relationship between increasing lymphatic RBC loss and decreasing platelet counts.⁹ Additional evidence that indicates that the platelet count is relevant to bleeding risk is the observation that with progressively lower platelet counts there is an increasing percentage of platelet loss from the circulation as the platelet count gradually declines.⁶ Moreover, a direct relationship exists between the platelet count and platelet survival in patients with platelet counts less than $100 \times 10^9/L$.⁶

Such studies suggest that there is a basal physiological requirement for platelets to be present in the circulation for endothelial support and thus to maintain hemostasis.¹⁰ This loss of platelets from the circulation for physiological endothelial support function has been calculated to be 7.1×10^9 platelets/L/day.⁶ It is important to note, however, that in some thrombocytopenic patients, loss of platelets from the circulation may also be associated with the presence of various underlying conditions such as sepsis, malignancy,

hypersplenism, and the use of certain types of medications, as well as the presence of other factors.¹¹ A recent study in experimental animals demonstrated that the presence of inflammation, particularly during periods of severe thrombocytopenia, was an important factor for the occurrence of life-threatening bleeding.¹² These experimental data suggest that platelet transfusions may be required for both the prevention and treatment of bleeding in thrombocytopenic patients, but that the optimal approach for their use may depend on clinical factors as well as the severity of thrombocytopenia.

Prophylactic Platelet Transfusions

A number of Clinical Practice Guidelines have been published in both Europe and North America that provide “evidence-based” recommendations for the clinical use of platelet transfusions. In general, they recommend prophylactic platelet transfusions at a transfusion trigger of $10 \times 10^9/L$.^{4,11,13,14} The use of therapeutic platelets is only recommended when there is significant bleeding or when an invasive intervention is anticipated.

It was not until the early 1970s that platelet transfusions became part of standard treatment in the management of thrombocytopenic patients with a hypoproliferative bone marrow.⁵ At that time, several observational studies were conducted to determine the possible role of prophylactic platelet transfusions to reduce the risk of clinical bleeding. Based on such studies, it became common practice to transfuse platelets prophylactically to patients with platelet counts below $20 \times 10^9/L$. It is important to note, however, that this practice was largely based on data from non-randomized studies, which indicated that bleeding was mainly evident in patients who had platelet counts of less than $5 \times 10^9/L$ compared to patients with platelet counts between 5 and $100 \times 10^9/L$.¹⁰ Thus, even though the incidence of bleeding across the range between 5 and $100 \times 10^9/L$ showed little difference, the threshold of $20 \times 10^9/L$ was widely adopted. Only in the late 1990s and early part of the twenty-first century were various studies done to try to establish an optimal prophylactic platelet count threshold for prophylactic platelet transfusions in thrombocytopenic patients.^{5,15-18}

The most widely quoted trial, which used a lower prophylactic trigger of $10 \times 10^9/L$ versus $20 \times 10^9/L$, was evaluated in a multicenter RCT.¹⁵ This group studied adult patients receiving induction therapy for newly diagnosed AML. The primary objective of this two-arm RCT was to determine the frequency and severity of hemorrhage in patients receiving prophylactic platelet transfusions. The two arms in the trial were the control arm in which the subjects were given platelets if the morning platelet count was less than $20 \times 10^9/L$ or if bleeding; and the experimental arm, which included subjects who received platelet transfusions when their morning platelet counts were less

than $10 \times 10^9/L$. Higher doses of platelets were given if study subjects were found to be actively bleeding or had a temperature higher than $38^\circ C$. The results of this trial provided data that there was no significant difference between the two arms in severe bleeding events or mortality.

Since then there have been at least 7 other studies that have evaluated the optimal threshold level for triggering prophylactic platelet transfusions at platelet counts of $10 \times 10^9/L$ versus the previously accepted trigger of $20 \times 10^9/L$ (reviewed in Slichter⁵). Overall, 4 of these studies were RCTs (including the one by Rebullá et al¹⁵) and 3 were non-randomized. Uniformly, these 7 studies showed no increase in bleeding risk or the need for more RBC transfusions when the lower transfusion trigger was used. Although 3 of the studies showed a substantial decrease in the number of platelet transfusions required in the subjects who received platelet transfusions based on the lower platelet transfusion trigger ($10 \times 10^9/L$), but it is of note that 4 studies did not. Interestingly, none of the 7 studies showed evidence of a difference in clinical outcomes in either arm, and this is a general theme across all clinical trials of platelet transfusion. It is also debatable whether these trials were adequately powered to demonstrate equivalence in outcomes.¹³

Based on such studies as well as several additional observational studies, there has been increasing interest in determining whether an even lower platelet transfusion trigger ($5 \times 10^9/L$) could provide effective hemostasis in thrombocytopenic subjects.^{5,10} The more recent studies provided evidence that it might be possible to reduce the prophylactic platelet transfusion trigger even lower than the currently accepted standard of $10 \times 10^9/L$,⁵ although several recent studies have highlighted the inaccuracies of hematology analyzers in platelet counting in patients with severe thrombocytopenia.^{19,20}

At least 5 RCTs have attempted to determine the optimal dose for prophylactic platelet transfusions. Some of these studies compared a standard platelet dose ($300\text{--}600 \times 10^9/L$) to a lower platelet dose ($150\text{--}300 \times 10^9/L$). Others compared standard dose platelets to high dose ($> 600 \times 10^9/L$) and some compared all three doses. Only one of these studies used a bleeding outcome,¹⁶⁻¹⁸ whereas the others used surrogate outcomes such as time to next transfusion and number of platelet transfusions required.²¹ Because most of these studies had small sample sizes and used surrogate outcomes, the controversy surrounding the optimal platelet dose has continued. In an attempt to resolve this long-standing controversy, two large platelet dose studies evolved—PLADO and SToP. Both studies are prospective multi-centered RCTs and are discussed in greater detail below.

Therapeutic Platelet Transfusions

As indicated above, standard practice in most hematology units in the developed world has been to use

prophylactic transfusions, and to use therapeutic transfusions only when significant clinical bleeding occurs or before an invasive intervention is undertaken. A relatively recent publication has again raised the issue about the use of therapeutic transfusions only versus the widely used threshold-defined prophylactic platelet transfusions approach.²² In a retrospective review of almost 3000 thrombocytopenic adult patients over a 10-year period Friedman et al, by using multiple logistic regression analysis, showed no relationship between the first morning platelet count, or the lowest platelet count of the day, and the risk of hemorrhage.²² This study identified several important patient-specific factors that appear to be associated with a greater risk for severe bleeding. These include a history of recent bleeding, uremia, a recent (less than 100 days) bone marrow transplant, and hypoalbuminemia.²²

Further support for the absence of a relationship between the severity of thrombocytopenia and hemorrhage came from a review of case reports of severe intracranial hemorrhage described in trials of prophylactic platelet transfusions where no clear evidence could be found for an association between the occurrence of major intracranial bleeding and absolute platelet count just prior to the onset of severe hemorrhage.¹⁴

Thus, the overall benefit of a prophylactic platelet transfusion policy over a policy to use platelets only therapeutically is not well established. It is important to note that there are now some data, albeit observational, to suggest that a treatment-based platelet transfusion strategy may indeed be safe and effective in clinical practice. This is exemplified by the results of a recent study of therapeutic platelet transfusions in hematopoietic stem cell autograft patients in Germany.²³ It is also possible that patient selection may be the key to the safety of therapeutic only-based platelet transfusion practice.

Outline of Recent Relevant Unpublished RCTs

The PLADO study

The PLADO study was designed to determine the optimal prophylactic platelet dose in patients with hypoproliferative thrombocytopenia related to patients undergoing stem cell transplants or chemotherapy.²⁴ The primary endpoint of PLADO was to compare three different platelet doses with respect to the percentage of patients in each dose arm who had at least one episode of WHO grade 2 or higher bleeding.²⁵ The most important secondary endpoints captured key data including the total number of platelets transfused, the total number of platelet transfusion events, and the highest grade of bleeding.

The PLADO trial, which has recently been completed, was a multicenter ($n = 26$) RCT sponsored by the National Heart, Lung, and Blood Institutes (NHLBI) that enrolled 1351 patients. Patients were randomized with equal allo-

cation to one of three prophylactic platelet transfusion therapy doses based on body surface area. These were a low platelet dose of 1.1×10^{11} platelets/m² (half the medium dose), a medium dose of 2.2×10^{11} /m² and a high dose of 4.4×10^{11} /m² (twice the medium dose). An acceptable platelet dose was one that was within 25%, either above or below the target dose. Patients were transfused their assigned dose prophylactically based on morning platelet counts of less than or equal to 10×10^9 /L. Additional platelet transfusions could be given for active bleeding or a planned invasive procedure.

Assessment of bleeding by study personnel was performed daily by means of a physical assessment of the patient and patient interview, as well as a review of the patient chart and laboratory data. The actual assignment of bleeding grades occurred at the data coordinating center using a computerized algorithm programmed to evaluate the data from the case report forms provided by the study sites. In addition, there was adjudication of deaths due to bleeding.

The SToP study

The SToP study which has also ended, was a multicenter prospective RCT done in association with the BEST collaborative using study sites in Canada, Norway and the US. Patients were eligible if they were thrombocytopenic and were likely to require at least 6 prophylactic platelet transfusions during their period of chemotherapy-induced thrombocytopenia. Eligible patients were randomized, using a web-based system, to one of two study arms. The subjects in the experimental arm received low-dose prophylactic platelet transfusions (1.5 to 2.9×10^{11} platelets/product) and the control arm received a standard dose of platelets in the range of 3.0 to 6.0×10^{11} platelets/product. The aim of the SToP study was to demonstrate that a low-dose prophylactic platelet transfusion strategy was not inferior to a standard-dose platelet strategy for the outcome of WHO grade 2 bleeding or greater.²⁵ Sample size calculations indicated that approximately 270 patients would be necessary for each treatment arm.

Patients were transfused prophylactically using a platelet transfusion trigger of less than or equal to 10×10^9 /L, based on their daily morning platelet count. Evidence of bleeding was assessed daily by a clinical examination, an interview of the patient, and a review of the clinical notes for the previous 24 hours using the WHO classification for bleeding. Study personnel involved in the daily hemostatic assessment of patients were blinded to a particular patient's randomization assignment. The grading of bleeds was based on an adjudication process when each patient's information was assessed by two adjudicators and graded on the WHO four-point scale. The adjudicators were also blinded as to the treatment allocation during this process. All discrepancies were then reviewed by a third adjudicator and when neces-

sary a final decision was reached through consensus.

Each patient was followed throughout their period of thrombocytopenia. A number of secondary endpoints were also determined. These were specified *a priori* and included total number of platelets transfused during a defined period of thrombocytopenia; the total number of platelet transfusion events; mean duration of thrombocytopenia; percentage of days at risk of bleeding during the period of thrombocytopenia; severity of bleeding differences between the two arms of the study; and the correlation between actual platelet dose given and evidence of bleeding on the following day.

A Data Safety Monitoring Board (DSMB) was established for the SToP study, with its primary role being that of monitoring safety. The DSMB reviewed all serious adverse events, which included bleeding WHO grades 3 and 4. Such events were reported both to the Coordinating Center at McMaster University in Hamilton and to the relevant IRB within 24 hours of such an occurrence. A pre-established safety threshold indicated that the study should be stopped by the DSMB if the cumulative incidence of Grade 4 bleeding exceeded an absolute difference of 5% between the two study arms at any time after 50 patients had been enrolled into each treatment arm. The DSMB stopped the study in March 2008, based on this stopping rule, after enrollment of a total of 130 patients.

The TOPPS study

Two new RCTs are in progress comparing the use of prophylactic versus therapeutic platelet transfusions, one in Germany²⁶ and one in the U.K. The few earlier small RCTs were undertaken and reported over 25 years ago and involved only small numbers of patients.²⁶ An interim analysis of a trial in patients who underwent autologous peripheral stem cell transplantations was reported in 2006, and found no major bleeding in the first 92 patients randomized to either prophylactic platelet transfusions or a therapeutic platelet transfusion strategy.¹⁴ The TOPPS study, which is currently underway in the U.K., is a two-stage, randomized, non-inferiority study designed to determine whether a platelet transfusion policy of no prophylactic platelet transfusions is as clinically effective and safe as a prophylactic transfusion policy, which is currently widely used and based on a prophylactic transfusion trigger of 10×10^9 /L. The primary outcome measure of TOPPS is to evaluate the proportion of patients who have a major bleeding event, defined as WHO grade 2 or higher, up to 30 days post-randomization. Secondary clinical outcome measures include time to first bleed as well as a descriptive analysis of all severe bleeds. The definitions of the original WHO grading scale were modified in light of feedback received after piloting the data collection forms for the TOPPS study.

Eligible patients are adults over the age of 16 years with a confirmed diagnosis of a hematological malignancy

undergoing myelosuppressive therapy, with or without hematopoietic stem cell support. A research nurse working with the trial team in each center will have responsibility for the collection of data on bleeding; they will not be blinded to treatment allocation, but a number of measures have been used to minimize bias in recording bleeding outcomes including repeated central training, a standardized assessment form with clear definitions for different types of bleeding, and duplication of assessments. A computer algorithm is being used to assign bleeding grades centrally.

The TOPPS trial is a two-stage RCT. Stage 1 will involve the evaluation of the first 100 patients randomized, which has now been reached. This represents an internal pilot to review both the sample size and the feasibility of the trial. It is anticipated that approximately 300 patients will be randomly allocated to each arm of the trial over the duration of the trial. Patients were initially enrolled in four U.K. centers, but it is planned that further centers both inside and outside the U.K. will be involved in the TOPPS study.

Conclusions

Patients with severe thrombocytopenia are clearly at an increased risk for bleeding, and the standard approach for treating such patients is the use of allogeneic platelets, particularly in those with a hypoproliferative marrow function (i.e., those with thrombocytopenia following chemotherapy). Thus, platelet transfusions can be given either prophylactically to reduce the risk of bleeding or to control bleeding when bleeding is actually occurring (therapeutic transfusions); however, the approach to the optimal use of platelet transfusions to reduce the risk of clinically significant bleeding in such patients is unclear. The place of therapeutic platelet transfusions and whether prophylactic are superior to therapeutic platelet transfusions for the prevention and control of thrombocytopenic bleeding

is thus a question that remains unanswered. Unfortunately, recent data on three RCTs (**Table 1**) that have recently been completed (PLADO), stopped (SToP), or on-going (TOPPS) that relate to some of these issues cannot be included in this article as they have not yet been completely analyzed nor submitted for peer-review publication.

The studies discussed during this symposium deal primarily with the treatment of patients with hypoproliferative thrombocytopenia. It is important to note that the use of platelet transfusions are generally not indicated in thrombocytopenic patients with other forms of thrombocytopenia, particularly those related to increased platelet destruction. Thus patients with thrombocytopenia due to immune thrombocytopenia, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, etc. should usually not be treated with allogeneic platelet transfusions as such transfusions are either ineffective and/or may be associated with significant risk (i.e., exacerbation of the underlying disease).

It should be emphasized that platelet number is only one part of the bleeding risk spectrum in thrombocytopenic patients. Other factors that could contribute to enhanced bleeding in such patients include altered intrinsic platelet function, alteration in platelet function due to the recent use of certain medications, or the presence of other hemostatic defects that may increase the risk for bleeding.

Thrombocytopenic patients, whether the thrombocytopenia is associated with a hypoproliferative marrow or due to increased destruction, may be treated with other interventions to decrease the degree or risk of bleeding. **Table 2** summarizes some of the other available modalities for treating thrombocytopenic patients with bleeding. A discussion of the various agents or approaches that are highlighted in **Table 2** is beyond the scope of this article and the interested reader should consult Lee and Blajchman,²⁷ Poon,²⁸ and Kuter²⁹ for further information as to their clinical

Table 1. Summary of the main features of the use of platelet transfusions in three multicenter RCTs that have either recently been completed (PLADO), stopped (SToP), or is ongoing (TOPPS) evaluating different strategies for use in thrombocytopenic patients with a hypoproliferative marrow.

	PLADO	SToP	TOPPS
Type of platelet transfusion intervention	Prophylactic	Prophylactic	Therapeutic vs prophylactic
Primary Endpoint	WHO Bleeding (grade 2 or greater)	WHO Bleeding (grade 2 or greater)	WHO Bleeding (grade 2 or greater)
Projected sample size, n	1350 (3 arms)	270 (2 arms)	300 (2 arms)
Arm 1 intervention	1.1×10^{11} platelets/m ²	1.5 to 2.9×10^{11} platelets	Prophylactic platelet transfusions with a trigger of $10 \times 10^9/L$
Arm 2 intervention	2.2×10^{11} platelets/m ²	3.0 to 6.0×10^{11} platelets	Therapeutic platelet transfusions only
Arm 3 intervention	4.4×10^{11} platelets/m ²	N/A	N/A
Study Status	Concluded; data being analyzed	Stopped by DSMB (n = 130)	Ongoing

Abbreviations: PLADO, Prophylactic PLAtelet Dose study; SToP, Strategies for the Transfusion of Platelets study; TOPPS, Trial Of Prophylactic Platelets Study; N/A, not applicable; DSMB, data safety monitoring board; WHO, World Health Organization.

Table 2. Summary of some of the approaches available for the treatment of bleeding in patients with thrombocytopenia.

- Prophylactic platelet transfusions
- Therapeutic platelet transfusions
- HLA-matched platelets for platelet transfusion-refractory patients
- Pharmacologic agents that potentially can enhance intrinsic hemostatic function:
 - Corticosteroids
 - Estrogens
 - DDAVP
 - Aprotinin
 - Tranexamic acid
 - Epsilon amino caproic acid (EACA)
- Biologic Agents that can enhance hemostatic function:
 - Platelet substitutes²⁷
 - Factor VIIa²⁸
- Agents that can improve the intrinsic platelet count:
 - Thrombopoietic growth factors²⁹
 - Other chemokines (e.g., IL-11)

effectiveness and current status. Importantly, the use of thrombopoietic growth factors represents a potentially effective new modality for increasing platelet counts in patients with thrombocytopenia, particularly in those with significant marrow reserve.²⁹

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