ASCO SPECIAL ARTICLE

Platelet Transfusion for Patients With Cancer: Clinical Practice Guidelines of the American Society of Clinical Oncology*

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**Objective**: To determine the most effective, evidence-based approach to the use of platelet transfusions in patients with cancer.

**Outcomes**: Outcomes of interest included prevention of morbidity and mortality from hemorrhage, effects on survival, quality of life, toxicity reduction, and cost-effectiveness.

**Evidence**: A complete MedLine search was performed of the past 20 years of the medical literature. Keywords included platelet transfusion, alloimmunization, hemorrhage, threshold and thrombocytopenia. The search was broadened by articles from the bibliographies of selected articles.

**Values**: Levels of evidence and guideline grades were rated by a standard process. More weight was given to studies that tested a hypothesis directly related to one of the primary outcomes in a randomized design.

**Benefits/Harms/Cost**: The possible consequences of different approaches to the use of platelet transfusion were considered in evaluating a preference for one or another technique producing similar outcomes. Cost alone was not a determining factor.

**Recommendations**: Appendix A summarizes the recommendations concerning the choice of particular platelet preparations, the use of prophylactic platelet transfusions, indications for transfusion in selected clinical situations, and the diagnosis, prevention, and management of refractoriness to platelet transfusion.

**Validation**: Five outside reviewers, the ASCO Health Services Research Committee, and the ASCO Board reviewed this document.

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INTENSIVE THERAPIES producing severe and sustained thrombocytopenia are used routinely in patients with hematologic malignancies and are being applied to many patients with solid tumors as well. Advances in platelet collection, storage, and transfusion have decreased the morbidity of such therapies, and death from hemorrhage is now an unusual occurrence, despite the larger number of patients being treated aggressively. Platelet transfusions are expensive, however, and are associated with a number of side effects including febrile or allergic transfusion reactions, transmission of bacterial and viral infections, circulatory congestion, transfusion-related acute lung injury and alloimmunization. The ASCO Health Services Research Committee elected to convene an Expert Panel to design guidelines for platelet transfusion because of perceived wide variation in platelet transfusion practices. This paper will first describe the types of platelet products available for transfusion and then provide evidence-based guidelines for use in different clinical situations.

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.[1] Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence and documentation. Guidelines may be useful in producing better care and decreasing its cost. Specifically, use of clinical guidelines may provide the following:

1. improvements in outcomes,
2. improvements in medical practice,
3. a means for minimizing inappropriate practice variation,
4. decision support tools for practitioners,
5. points of reference for medical orientation and education,
6. criteria for self-evaluation,
7. indicators and criteria for external quality review,
8. assistance with reimbursement and coverage decisions, and
9. criteria for use in credentialing decisions.

In formulating recommendations for platelet transfusion, ASCO considered these tenets of guideline development, emphasizing review of data from controlled clinical trials. **However, it is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease for which better therapy is needed. In these guidelines, development involves a review and synthesis of the latest literature; a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.**

METHODS

Panel Composition

The Panel was composed of experts in clinical medicine, clinical research, health services research, and related disciplines. The clinical experts represented all relevant medical disciplines, including medical oncology, transfusion medicine, and hematologic malignancies. Both academic and community practitioners were included. A steering committee under the auspices of the Health Services Research Committee chose Panel participants for the clinical practice guideline development process. Panel participants are listed in Appendix B.

Process Overview

In evaluating the evidence regarding the management of platelet transfusions, the Panel followed the process for guideline development established by the American College of Chest Physicians.[2,3] The process included a systematic weighting of the level of the evidence and a systematic grading of the evidence for making a recommendation (Table 1).[2,3]

Literature Review and Data Collection

Pertinent information from the published literature as of mid-1999 was retrieved and reviewed for the creation of these guidelines. Searches were performed in MedLine (National Library of Medicine, Bethesda, MD) and other databases for pertinent articles. Directed searches were made of the primary articles.

Table 1. Levels of Evidence and Grade of Evidence for Recommendations[2,3]

Type of evidence	
Level	
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II	Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.
V	Evidence from case reports and clinical examples.
Grade for recommendation	
Grade	
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.
B	There is evidence of types II, III, or IV, and findings are generally consistent.
C	There is evidence of types II, III, or IV, but findings are inconsistent.
D	There is little or no systematic empirical evidence.

Consensus Development Based on Evidence

The entire Panel met twice. The first meeting was intended to identify topics to be addressed by the guidelines, to develop a strategy for completion of the guidelines, and to do a preliminary review of the initial literature search; the second meeting was intended to review the developed guidelines and to evaluate more critically the recommendations and supporting evidence. The guidelines were circulated in draft form, and all members of the Panel had an opportunity to comment on the levels of evidence as well as the systematic grading of the data supporting each recommendation. Final text editing was performed by Drs Schiffer and Anderson.

Guidelines and Conflict of Interest

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Research

Committee and by the ASCO Board of Directors before dissemination. All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts of interest were identified as a result of this disclosure procedure.

Revision Dates

At annual intervals, the Panel chairs and two Panel members designated by the chairs will determine the need for revisions to the guidelines on the basis of an examination of current literature. The entire Panel will be reconvened every 3 years to discuss potential changes, or more frequently, if new information suggests that more timely modifications may be warranted. When appropriate, the Panel will recommend revised guidelines to the Health Services Research Committee and the ASCO Board for review and approval.

Summary of Outcomes Assessed

The most important outcomes of cancer treatment and supportive care modalities are effects on overall survival, disease-free survival, and quality of life, balanced by cost-effectiveness and the toxicity of the intervention used. Platelet transfusions are used to reduce morbidity and death resulting from bleeding associated with thrombocytopenia or, occasionally, in patients with normal platelet counts but with abnormal, dysfunctional platelets. Mortality from hemorrhage is rare, and morbidity from bleeding is usually difficult to quantify with precision, however. These outcomes were used when available, but it was also necessary to consider issues of cost and convenience in certain of the recommendations. More research is needed in many areas, and this is pointed out in many sections of this article.

GUIDELINES FOR PLATELET TRANSFUSION

1. Platelet Products

Guideline: Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood, which are pooled before administration, or by apheresis from single donors. Comparative studies have shown that the posttransfusion increments, hemostatic benefit, and side effects are similar with either product. Thus, in routine circumstances, they can be used interchangeably. In most centers, pooled PCs are less costly. Single-donor platelets from selected donors are preferred when histocompatible platelet transfusions are needed. Both preparations can be stored for up to 5 days after collection at 20°C to 24°C with good maintenance of platelet viability.

Level of Evidence: I

Grade of Recommendation: A

PCs from Whole Blood. Often referred to as random-donor platelets, PCs are prepared by centrifugation of standard units of whole blood. There are two methods for doing this: (1) the platelet-rich plasma (PRP) method, and 2) the buffy coat (BC) method.[4] The PRP method is used in the United States, whereas the BC method is in common use in Europe. In the PRP method, an initial low G force (soft) spin produces PRP, which is separated from the red cells. The PRP is then centrifuged at a higher G force (hard) spin, and most of the platelet-poor plasma is removed.[5-8] The residual PCs contain approximately 0.5 to 0.75×10^{11} platelets/unit or approximately 60% to 75% of the platelets from the original unit of whole blood. Because some blood centers now supply units with higher numbers of platelets, clinicians should be aware of the average dose provided by their particular center. One drawback to this method is that the resulting PCs also contain 10^8 to 10^9 WBCs or approximately 50% or more of the leukocytes from the original unit of whole blood.

Platelets are stored at 20°C to 24°C using continuous gentle horizontal agitation in storage bags specifically designed to permit O_2 and CO_2 exchange to optimize platelet quality.[9-14] This combination of storage container, agitation, preservative solution, temperature, and the use of approximately 50 mL of plasma permits satisfactory preservation of platelets for up to 7 days.[15,16] However, several instances of bacterial contamination of PCs stored for this period have been reported,[17,18] and the storage time from collection to transfusion is now limited to 5 days.[19]

PCs can also be obtained from 40- to 50-mL BCs collected at the red cell/plasma interface after high-speed centrifugation of 450 mL whole-blood donations.[20-22] After gentle resuspension in a satellite bag, the BC is centrifuged at low speed and the platelets collected in the supernatant.[21] Alternatively, four to six BCs are pooled, diluted in plasma, and centrifuged at low speed to suspend the platelets in the supernatant, which is then transferred into a large-volume storage bag. Plasma can be replaced with a crystalloid platelet additive solution, thus reducing the amount of plasma that might be infused to plasma-incompatible recipients.[22,23] The BC-PCs must be used within 6 hours of preparation if the bags have been entered during pooling.

Storage can be extended to 5 days if the whole procedure is performed in closed systems. A number of studies indicate that BC-PCs produce comparable in vivo platelet survival and contain similar numbers of less-activated platelets and fewer white cells compared with PCs prepared with the PRP method.[24-26]

Most patients require a dose of platelets larger than can be provided by platelets from one unit of whole blood, and several PCs are usually pooled to obtain an appropriate dose for most patients. If the volume of plasma in the final pooled component is too large, as might be the case for some pediatric recipients, some of the plasma can be removed before transfusion. From 15% to 55% of platelets are lost during this additional centrifugation step.[27,28] Volume reduction should therefore be limited to patients who require severe volume restriction or situations where ABO incompatible platelets are the only available PC for a neonate or child.

Single-Donor Platelets Produced by Apheresis. Although the Food and Drug Administration term for this component is "platelets, apheresis," the component is usually called single-donor platelets. Donors usually undergo two venipunctures. Blood pumped from one vein passes through a blood-cell separator centrifugation system with removal of the platelets or other cellular components and return of the plasma and RBCs to the donor's other arm. Plateletpheresis usually requires approximately 11/2 to 2 hours and involves processing 4,000 to 5,000 mL of the donor's blood.[29-35] This results in a plateletpheresis product that contains the number of platelets equivalent to six to nine units of PC prepared from whole blood. However, many centers have recently begun to split their apheresis collections into two products so that the dose may actually be more equivalent to four to five units of PC. Clinicians are therefore advised to check on the policies of their local blood supplier so as to best determine the appropriate number of units or apheresis products to transfuse in particular clinical situations. Current standards require that a bag of apheresis platelets must contain at least 3×10^{11} platelets in at least 75% of the products tested.[36]

Platelets obtained by plateletpheresis are processed, tested, and labeled similar to whole blood. This includes ABO and Rh typing and testing for all required transfusion-transmitted diseases. The plateletpheresis product is stored for up to 5 days at 20°C to 24°C[29,37-40] in the same manner as platelets prepared from whole blood. The number of platelets contained in each bag is determined, although this information may not be recorded on the label. Each apheresis product has a volume of approximately 200 mL and contains few red cells, so that red cell crossmatching is not necessary. The WBC content varies, depending on the instrument and technique used for collection, but most

plateletpheresis products now contain less than 5×10^6 leukocytes and can be considered to be leukocyte reduced (see below).

Platelet Use. During the 1980s and most of the 1990s, the use of platelets increased more than the use of other blood components.[41] There was a brief decrease of 5.6% in platelet use between 1992 and 1994,[42] but between 1994 and 1997, platelet use in the United States resumed its upward trend, increasing from a total (whole blood plus single donor) of 7,866,000 units in 1994 to 9,037,000 in 1997. During this period, an increasing proportion of the platelets was produced by apheresis, such that single-donor platelets represented 62.4% of the platelets transfused in 1997.

Clinical Use of Random Donor Whole-Blood or Single-Donor Platelets. The mix of random-donor whole-blood and single-donor apheresis platelets provided to different medical centers varies considerably, depending on local philosophy, patient mix, blood supply availability, cost, and transfusion-transmitted disease risk. Because several units of PC are pooled to obtain a dose for one transfusion, one reason to use single-donor apheresis platelets is to minimize the number of donors to which the patient is exposed and, theoretically, to minimize the likelihood of disease transmission. Although this may be a relevant consideration in patients who receive only a few transfusions in total, there is no evidence, particularly with contemporary screening and testing techniques, that there is any difference in the incidence of transfusion-transmitted infections in oncology patients who often require dozens of donor exposures to RBC and platelet donors during their lifetime.

Comparative studies have shown comparable posttransfusion increments, platelet survival, and hemostatic effect using the two types of platelet components.[38,39,43,44] When histocompatible platelets are required for patients refractory to random donor transfusions, platelets for subsequent transfusions should be from selected donors and, thus, single-donor platelets are the only platelet product that is available for these transfusions.

In general, single-donor platelets cost 50% to 100% more than an equivalent dose of pooled PCs. However, whole-blood platelets must be pooled at the time of transfusion, which adds staff time and costs. In addition, most current plateletpheresis procedures produce a leukodepleted platelet product,[35,45] whereas whole-blood platelets are not usually leukoreduced at the time of collection and must be subsequently filtered to remove leukocytes either in the blood bank or at the bedside.[44] Even when these additional steps of pooling and filtering are considered, however, the cost of whole-blood platelets remains less than single-donor platelets.[46-48]

2. Prophylactic Versus Therapeutic Platelet Transfusion

Guideline: The Panel recommends that prophylactic platelet transfusion be administered to patients with thrombocytopenia resulting from impaired bone marrow function to reduce the risk of hemorrhage when the platelet count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality.

Level of Evidence: IV and expert consensus

Grade of Recommendation: B

Platelet transfusions should be given to treat patients with clinically significant hemorrhage and severe thrombocytopenia. A prophylactic platelet transfusion approach to prevent bleeding, as opposed to a therapeutic approach, in which platelet transfusion is given after a certain degree of hemorrhage has occurred, is followed by approximately 80% of clinicians.[49] Nonetheless, the choice between the two policies is based on a limited number of older studies. In 1966, Han et al[50] reported that the 63% incidence of hemorrhagic deaths occurring in leukemia patients in the year before the implementation of a prophylactic platelet transfusion policy decreased to 15% in the following year. A similar reduction was observed in a small double-blinded randomized clinical trial performed by Higby et al[51] in 21 patients with acute leukemia. Of interest, this study showed that fever preceded hemorrhage in 10 of the 13 patients who experienced bleeding.

In 1982, Murphy et al[52] published a prospective randomized trial comparing prophylactic and therapeutic transfusion policies in 56 pediatric leukemia patients treated from 1972 to 1976. The prophylactic threshold was set at 20,000 platelets/μL. Although patient survival was not significantly different in the two groups, the prophylactic policy was associated with a significant reduction in the number of days with hemorrhage. However, patients in the prophylactic arm suffered from more prolonged hemorrhagic episodes during their last month of life, possibly as a result of the development of HLA alloimmunization and refractoriness to random-donor platelet support.

Other data supporting a prophylactic policy were published by Gaydos et al[53] and by Slichter and Harker.[54] In a study dating from the early 1960s, Gaydos et al showed that hemorrhage was more frequent and severe at platelet counts below 5,000/μL, whereas it occurred in 8% and 4% of hospital days at counts exceeding 10,000/μL and 20,000/μL, respectively. These observations were made in an era when aspirin was frequently used as an antipyretic and when antibiotic coverage for Gram-negative organisms was inadequate by contemporary standards. Of note, these authors could not identify a threshold at which the rate of bleeding increased, and they emphasized the importance of other factors predisposing to bleeding. Slichter and Harker

found that daily blood losses in stools from patients with aplastic anemia were 9 $\pm$ 7 mL at platelet counts of 5,000/μL to 10,000/μL but increased to 50 $\pm$ 20 mL at counts below 5,000/μL.

Thus, although there are no contemporary randomized studies comparing the incidence of serious bleeding and patient survival in patients receiving prophylactic versus therapeutic platelet transfusions, the prophylactic approach has become standard practice.[49,55,56] Fatal hemorrhage is now an unusual event, even in patients with bone marrow failure or in those receiving intensive antineoplastic therapy. However, it should be emphasized that not all thrombocytopenic patients require or benefit from platelet transfusion and that the decision to administer transfusion is not based solely on the platelet count but should be individualized for specific clinical settings, as discussed below. Platelet transfusion is generally reserved for patients with impaired marrow production of platelets, is rarely needed in patients with increased platelet destruction such as autoimmune or drug-associated immune thrombocytopenia, and is relatively contraindicated in patients with thrombotic thrombocytopenic purpura because of concerns about the risk of precipitating thromboses.[55,56]

3. Platelet Count Threshold for Prophylactic Platelet Transfusion: Acute Leukemia

Guideline: The Panel recommends a threshold of 10,000/μL for prophylactic platelet transfusion in adult patients receiving therapy for acute leukemia, on the basis of the results of multiple randomized trials that demonstrate that this approach is equivalent to the use of a 20,000/μL threshold. Transfusion at higher levels may be necessary in newborns or in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities (for example, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which platelet transfusions may not be readily available in case of emergencies. The studies that form the basis of this recommendation (as well as the other recommendations in this section) have included adolescents but not younger children or infants. Nevertheless, it is probably reasonable to use similar guidelines for children and older infants. Although modern automated cell counters are quite accurate at low platelet counts, there can be modest variations in count because of limitations of the counting technology. The decision to transfuse at a precise trigger level should therefore consider the clinical context and the pattern of recent platelet counts.

Level of Evidence: I

Grade of Recommendation: A

The appropriateness of decreasing the threshold of prophylactic platelet transfusion in patients with leukemia from

the traditional level of 20,000 to 10,000 platelets/μL is supported by one observational study and three comparative studies published between 1991 and 1998. In 1991, Gmür et al[57] reported their 10-year experience in 103 patients with leukemia who received transfusions at the following levels: 0 to 5,000 platelets/μL in every case; 6,000 to 10,000/μL in the presence of fresh minor hemorrhage or body temperature greater than 38°C; 11,000/μL to 20,000/μL in the presence of coagulopathy and/or heparin therapy and before bone marrow biopsy or lumbar puncture; and greater than 20,000/μL in the presence of (and until control of) major bleeding complications and before minor surgical procedures. Three fatal hemorrhages occurred, similar to the 3.2% incidence reported from another study of 31 patients who received transfusion prophylaxis with a threshold at 15,000 platelets/μL.[58] Of note is that the serious episodes of hemorrhage often occurred at relatively high platelet counts, greater than 40,000/μL, emphasizing the importance of clinical factors other than the platelet count in the cause of bleeding. Gmür and Schaffner[59] reported that their protocol could also be applied using random-donor platelets rather than single-donor, apheresis platelets.

Two prospective randomized clinical trials comparing the 20,000/μL and the 10,000/μL thresholds were published in 1997. A single-center study of 72 patients with acute leukemia performed in Iowa City by Heckman et al[60] showed a reduction from 11 to seven platelet transfusions per patient using thresholds of 20,000/μL and 10,000/μL, respectively. There were no statistically significant differences between the groups with regard to red cell transfusion requirements, febrile days, days hospitalized, days thrombocytopenic, need for HLA-matched platelets, remission rate, or death during induction chemotherapy. Moreover, no patient in either group died from hemorrhage or underwent major surgery for bleeding complications.

A large multicenter trial was performed by the Gruppo Italiano Malattie Ematologiche dell'Adulto, which enrolled 255 assessable patients in 21 Italian centers.[61] This study focused on platelet support during the first remission induction in patients with adult acute leukemia, excluding individuals with the French-American-British M3 subtype. A total of 7,336 patient-days were evaluated. Patients were randomized to the traditional 20,000/μL threshold (controls) or to a threshold of 10,000/μL when in stable condition and less than 20,000/μL in the presence of fresh hemorrhage, fever greater than 38°C, or invasive procedures. The 10,000/μL threshold was associated with a 21.5% reduction in platelet requirements. There were no significant differences in the number of red cell transfusions, patients with severe bleeding episodes, or deaths

during induction. Overall, clinically significant hemorrhages occurred in 3.1% and 2% of the days in the 10,000/μL and 20,000/μL arms, respectively.

The most recently published evidence supporting the safety of the 10,000/μL threshold was reported in 1998 by Wandt et al,[62] who studied 105 leukemia patients undergoing 216 remission-induction or consolidation treatment cycles in 17 centers in Germany. Individual participating centers had previously chosen to adopt either a 20,000/μL or a 10,000/μL threshold level for their prophylactic transfusion policy. In this study, there were 20 bleeding complications (18%) in 110 chemotherapy cycles in the 10,000/μL group and 18 (17%) in 106 cycles in the 20,000/μL group. Hemorrhagic deaths occurred in two patients at platelet counts of 36,000/μL and 50,000/μL treated in hospitals using the 20,000/μL threshold. Mean platelet consumption per cycle was one third lower in the 10,000/μL group.

It should be reiterated that all of these studies had provisions for transfusion at counts greater than 10,000/μL in patients with clinical conditions believed to be associated with increased risks of bleeding. In addition, although contemporary blood cell counters are quite accurate at low platelet counts, small variations in count can result from limitations of the technology, and the decision to transfuse should therefore be based on the clinical situation and the pattern of recent platelet counts as well as the absolute platelet count at a given moment[63]

As emphasized earlier, it is important that clinicians are aware of the average number of platelets provided in pooled PC and apheresis products in their community so as to be able to order an appropriate number of units in specific clinical situations. A typical interval between prophylactic transfusions in patients with acute leukemia is every 2 to 4 days depending on other clinical factors. This can usually be accomplished with doses of 4 to 6 units of PC/transfusions in adults of average size. Larger doses may be needed to achieve higher counts in patients who are bleeding or who require invasive procedures (see below).

4. Hematopoietic Cell Transplantation

Guideline: Fewer studies have been performed in recipients of high-dose therapy with stem-cell support. Although such patients may experience more mucosal injury than patients receiving conventional antileukemic chemotherapy, clinical experience and the available data suggest that guidelines for prophylactic transfusion similar to those for patients with acute leukemia can be used in transplant recipients, with similar caveats about transfusion at higher counts in patients with complicating clinical conditions. The recent increased use of peripheral-blood stem cells with shorter durations of thrombocytopenia should further decrease the hemorrhagic risk.

Level of Evidence: III

Grade of Recommendation: B

Observations in leukemia patients encouraged the Department of Hematology at the University Hospital de la Princesa in Madrid to decrease the platelet transfusion trigger at the end of 1992 from 20,000/μL to 10,000/μL in stable bone marrow transplant recipients.[64] Among the 87 control patients who underwent transplantation in 1990 to 1991 and received transfusion with a threshold at 20,000/μL, there were 12 patients with 14 episodes of severe hemorrhage, three of which were fatal. Similar outcomes were found among the 103 patients who underwent transplantation in 1993 to 1994; 12 patients experienced 14 hemorrhages, which were fatal in four cases. Platelet use during the first 100 posttransplantation days decreased from a median of 73 to 54 units of PC per patient (*P* < .01). A similar study with 124 patients, reported in 1994, showed similar outcomes.[65] The thresholds of 20,000/μL and 10,000/μL were associated with transfusion of 3.34 and 2.68 platelet units/patient/d, respectively, with associated cost savings for platelet usage.

In a recent survey of transfusion practices at United States transplantation centers in 1995, Bernstein et al[66] reported that five of 18 centers used thresholds of less than 10,000/μL to 15,000/μL, with the majority using a 20,000/μL cutoff. Bleeding was more common in recipients of allogeneic transplants. Eleven percent of patients had a severe hemorrhagic event, usually related to genitourinary tract bleeding, with 2% of patients having hemorrhagic deaths. Most bleeding events occurred at platelet counts of greater than 20,000/μL, however, and therefore would not have been preventable using this level as the transfusion trigger. Virtually identical data were reported from an analysis of 1,402 bone marrow transplantations performed at Johns Hopkins Hospital.[67] Gastrointestinal and hemorrhagic cystitis were the most common bleeding sites, and only 2% of patients had intracranial bleeding. Although bleeding was more common in seriously ill patients who eventually died, hemorrhage was rarely an isolated cause of death.

These data were largely derived from transplantations using bone marrow as the source of stem cells. The use of stem cells mobilized from peripheral blood base substantially shorten the duration of thrombocytopenia and decrease the need for platelet transfusions in both the autologous and allogeneic transplantation settings.[68] Expanded use of nonmyeloablative regimens, so-called allogeneic minitransplantations will possibly further decrease the need for platelet transfusions in the future.[69]

5. Patients With Chronic, Stable, Severe Thrombocytopenia

Guideline: No randomized studies have been performed in patients with sustained, severe thrombocytopenia such as can be seen in individuals with myelodysplasia and aplastic anemia. Many such patients have minimal or no significant bleeding for long periods of time despite low platelet counts. On the basis of clinical experience and limited retrospective studies, the Panel suggests that many of these patients can be observed without prophylactic transfusion, reserving platelet transfusions for episodes of hemorrhage or during times of active treatment.

Level of Evidence: IV

Grade of Recommendation: C

A recently published study from Switzerland described 25 patients with aplastic anemia observed for more than 18,000 days, who received transfusions prophylactically at counts of less than 5,000/μL when clinically stable, at 6,000/μL to 10,000/μL if febrile or experiencing recent bleeding, and at higher counts if active bleeding was present.[70] Only three episodes of nonfatal hemorrhage occurred using this approach, and the majority of transfusions were given at counts less than 5,000/μL. The interval between transfusions in outpatients increased to more than 7 days with greater experience with this more restrictive transfusion approach, which suggests that patients had many days at counts less than 5,000/μL without developing clinically important bleeding that required medical attention and earlier transfusion.

6. Prophylactic Platelet Transfusion in Patients With Solid Tumors

Guideline: The risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth of the platelet nadir, although other factors contribute as well. Evidence obtained from observational studies supports the clinical benefit of prophylactic transfusion at a threshold of 10,000/μL platelets or less. The Panel suggests, however, on the basis of expert clinical opinion, that prophylactic transfusion at a threshold of 20,000/μL be considered for patients receiving aggressive therapy for bladder tumors as well as those with demonstrated necrotic tumors, owing to their presumed increased risk of bleeding at these sites.

Level of Evidence: IV

Grade of Recommendation: B

Because the relationship between platelet count and the risk of bleeding was first described in leukemia patients, the relevance of these findings for patients with solid tumors receiving modern chemotherapeutic agents has been considered. Although only a small minority of patients treated with conventional solid tumor regimens experience severe, sustained thrombocytopenia, the need for platelet transfusion is not uncommon with some newer, more aggressive experimental regimens. Five retrospective studies of solid tumor patients have been reported to date.[71-75] No prospective or controlled trials in this population have been re-

Table 2. Thrombocytopenia and Bleeding in Patients With Solid Tumors

Reference	20,000-50,000/µL		10,000-20,000/µL		< 10,000/µL	
	%	95% CI	%	95% CI	%	95% CI
Belt[71]						
Total cycles of therapy	197		52		21	
All bleeding	9.6	6-15	11.5	4-23	38.1	18-62
Major bleeding	2.5	1-6	7.7	2-19	14.3	3-36
Dutcher[72]						
Days at risk	4,393		576*			
All bleeding	8 episodes/ 1,000 days	6-12	10 episodes/ 1,000 days	4-21		
Goldberg[73]						
Total cycles of therapy	347		142		49	
All bleeding	2.3	1-4	17.6	12-25	40.1	18-45
Major bleeding	< 1	< 1-2	2.1	< 1-6	10.2	3-22
Fanning[74]						
Total cycles of therapy	79		62		38†	
All bleeding	0	0-5	17.7	9-30	18.4	8-34
Major bleeding	0	0-5	0	0-6	0	0-9
Elting[75]						
Total cycles of therapy	700		365		197	
All bleeding	4.7	3-7	10.1	7-14	20.1	15-27
Major bleeding	2.3	1-4	3.6	2-6	7.1	4-12

Abbreviation: CI, confidence interval.
*Data available for 10,000-20,000/µL and < 10,000/µL combined.
†Data available for 5,000-10,000/µL; data for < 5,000/µL not provided.

ported. Four of these studies confirm the findings in leukemic patients, ie, the rate of bleeding increased as the platelet count decreased and no clear threshold could be demonstrated (Table 2). For each sequential decrease in platelet nadir, the rate of bleeding increased by 50% to 100%.

These studies report a relatively low overall rate (< 5% in the three largest studies) of major or life-threatening episodes of bleeding except when the platelet count fell below 10,000/µL. These observational data also demonstrate that hemorrhage at necrotic tumor sites, including fatal hemorrhages, can occur at platelet counts well above 20,000/µL. Belt et al[71] reported three fatal hemorrhages resulting from thrombocytopenia, one at a platelet count of 60,000/µL. Dutcher et al[72] did not demonstrate any clear relationship between platelet count and the risk of bleeding because the majority of cases of serious bleeding (37 of 44 cases) occurred at platelet counts exceeding 20,000/µL, often at necrotic tumor sites. Elting et al[75] reported 32 episodes of bleeding during 700 cycles of chemotherapy in which platelet counts never fell below 20,000/µL. Eleven (34%) of these episodes were related to necrotic tumors or metastases.

Given these observations, it is extremely difficult to recommend a single threshold below which prophylactic transfusion should be prescribed to all patients with solid tumors, although thresholds have been suggested by some authors. On the basis of their findings, Belt et al[71] and Goldberg et al[73] proposed a threshold of 10,000/µL plate-

lets for bleeding prophylaxis, whereas Fanning et al[74] proposed a threshold of 5,000/µL. None of these thresholds has been tested in prospective randomized trials. However, considered together, these five observational studies provide reasonably consistent, level IV, grade B evidence supporting the advisability of providing transfusions to patients with solid tumors at a threshold of 10,000/µL platelets or less.

Because of the heterogeneity of this population, several subgroups may require special consideration. Because patients with gynecologic, colorectal, melanoma, or bladder tumors bleed from necrotic tumor sites, sometimes after these sites have been irradiated, consideration should be given to transfusion at a higher threshold, perhaps 20,000/µL. It should be noted, however, that because hemorrhage often occurs at much higher counts, it is unknown whether more liberal use of transfusions would decrease bleeding from such necrotic sites. Second, there are some patients for whom a risk of major bleeding of 2% to 5% may be considered clinically unacceptable. Included in this group are patients with poor performance status or physiologic reserve as well as those with limited access to health care facilities during thrombocytopenia that is expected to be profound and prolonged. Depending on their tumor type and the presence of a necrotic site, these patients can also be considered for prophylactic transfusion at a threshold of

20,000/μL platelets. Further clinical research in this area is desirable.

7. Surgical or Invasive Procedures in Thrombocytopenic Patients

Guideline: Thrombocytopenic patients frequently require invasive diagnostic or therapeutic procedures. Common procedures include placement of permanent or temporary central venous catheters, transbronchial and esophageal endoscopic biopsies, paranasal sinus aspirations, bone marrow biopsies, and occasionally even major surgery. The Panel suggests, on the basis of accumulated clinical experience, as attested to by a variety of consensus conference statements,[55,56] that a platelet count of 40,000/μL to 50,000/μL is sufficient to perform major invasive procedures with safety, in the absence of associated coagulation abnormalities. Certain procedures, such as bone marrow aspirations and biopsies, clearly can be performed safely at counts of less than 20,000/μL. There are sparse data (summarized below) about the safety of other invasive procedures at much lower count levels. If platelet transfusions are administered before a procedure, it is critical that a posttransfusion platelet count be obtained to prove that the desired platelet count level has been reached. Platelet transfusions should also be available on short notice, in case intraoperative or postoperative bleeding occurs. For alloimmunized patients, histocompatible platelets must be available in these circumstances.

Level of Evidence: IV

Grade of Recommendation: C

Thrombocytopenic patients frequently require invasive diagnostic or therapeutic procedures. A platelet count of 50,000/μL is often stated as a standard for the level at which major surgery can be performed safely. The largest recorded series was a retrospective review of 167 operations in 95 patients with acute leukemia.[76] Preoperative platelet transfusions were given to achieve platelet counts of greater than 50,000/μL. Seventy percent of the procedures were major operations, including laparotomy and craniotomies; the remainder were procedures such as tracheotomy, catheter insertion, and tooth extractions. There were no deaths caused by surgery-related hemorrhage, and intraoperative blood loss was greater than 500 mL in only 7% of the operations. Patients with concurrent coagulation abnormalities were more likely to have significant bleeding.

There are few systematic studies describing the outcome and safety of specific invasive procedures in thrombocytopenic patients:

Lumbar Puncture (LP). In 1974, Edelson et al described eight thrombocytopenic patients seen over a 4-year period who developed spinal subdural hematomas after LP[77] The authors point out the rarity of subdural spinal hematomas, as opposed to the more common epidural hematoma. In the 4-year period of study, no patient with a normal platelet count had this adverse outcome. Five of the eight patients had platelet counts less than 20,000/μL. The authors suggest that thrombocytopenia plays a major role in this complication and that the level of the platelet count, its rapidity of decline, and the skill of the person performing the procedure are important factors in determining the safety of the procedure. Platelet transfusions were recommended just before the LP if the count was below 20,000/μL.

In 1982, Breuer et al[78] demonstrated that the radicular vessels are the most likely source of bleeding rather than Batson's plexus, as proposed by Edelson et al.[77] After reviewing a large number of cerebrospinal fluid examinations and demonstrating the frequency of finding RBCs as well as the frequency of nerve root irritation, they emphasized the recommendations of Edelson et al, ie, that platelet transfusions be used for platelet counts less than 20,000/μL, with the most skilled person performing the test. Of their 20 patients who had LPs with platelet counts less than 20,000/μL, only seven received platelet transfusions before the procedure. Of those who did not undergo transfusion, two developed significant spinal subarachnoid hematomas.

Lastly, Howard et al[79] reviewed the outcomes of 4,309 LPs performed on 959 children treated for acute lymphocytic leukemia between 1984 and 1998 at St Jude Children's Research Hospital. Although the frequency of traumatic LPs ($>$ 10 RBC/mL of CSF) increased as platelet counts decreased, no significant iatrogenic complications were noted in this large series, which included 378 LPs in patients with platelet counts less than 25,000/μL. It is unclear whether such an exemplary safety record could be duplicated in adults, in whom the procedure is often more technically difficult.

Liver Biopsy. McVay and Toy reviewed 291 liver biopsies performed during 56 consecutive months. In patients with mild thrombocytopenia (platelet counts of 50,000/μL to 99,000/μL), the incidence of bleeding was 3.4%, with no difference when compared with patients with normal platelet counts.[80] An underlying diagnosis of malignancy was noted to be a risk factor for bleeding. There are no systematic data concerning more contemporary approaches with computed tomography–guided fine-needle biopsies.

Gastrointestinal Endoscopy. Chu et al[81] examined the results of 187 upper and lower endoscopies performed on 173 thrombocytopenic patients. These patients were subdivided into three groups by level of platelet count (group A $<$ 20,000/μL, group B 20,000/μL to 40,000/μL, and group C $>$ 40,000/μL). Diffuse oozing occurred mainly in group A and was rare in patients in the other groups, in whom

unifocal bleeding sources were demonstrated. The diagnostic yield was 92% for upper endoscopies and 60% for colonoscopy. No major complication was noted in any group, and it was concluded that endoscopy with a cooperative patient could be safely performed in thrombocytopenic patients by experienced operators without prophylactic platelet transfusion. No endoscopic biopsies were performed, however.

Fiber-Optic Bronchoscopy (FOB) and Bronchoalveolar Lavage (BAL). Weiss et al[82] examined prospectively all bone marrow transplant recipients undergoing diagnostic FOB with BAL in a 6-month period. A total of 66 FOBs with BAL were performed. As part of the general care of transplantation patients, they received platelet transfusions to maintain a platelet count of greater than 20,000/μL. However, no transfusions were given specifically for the procedure. Sixty-seven percent of patients had platelet counts of less than 50,000/μL and 20% less than 20,000/μL. Complications occurred in 12% of cases and were usually minor and self-limited. The level of platelet count did not correlate with the rate of complications.

Transbronchial Biopsy. Papin et al[83] reported their results in 24 severely thrombocytopenic patients. Twenty-five procedures were performed, and there were three self-limited episodes of endobronchial bleeding and a single death from massive hemorrhage. Although preprocedure platelet transfusions were used in 20 of the 24 patients, no posttransfusion platelet counts were obtained. The one fatality occurred in a patient whose prebiopsy platelet count was 23,000/μL and who had received 6 units of platelets before the procedure and 12 units after the procedure. The authors suggested that if the platelet count remains in the 10,000/μL to 20,000/μL range despite platelet transfusion, transbronchial biopsy should not be performed. Others have emphasized the role of other coagulation abnormalities in increasing bleeding risk.[84]

The accumulated data demonstrate that platelet counts of approximately 50,000/μL suffice to perform the procedures described above, as well as dental extractions[85,86] and central venous catheter insertions,[87-89] with acceptable risk of side effects.

Although strong opinions abound, it is difficult to draw firm data-driven conclusions as to the lower level of platelet count that is safe for these various procedures, and more systematic research in this area is clearly needed. It must be emphasized that it is critical to determine the posttransfusion platelet count in patients about to undergo invasive procedures. It is inappropriate to assume that a hemostatic platelet count level has been achieved simply because a platelet transfusion was administered. Posttransfusion counts obtained 10 minutes after transfusion can be helpful in this regard.[90] The platelet transfusion must therefore be closely coordinated with the timing of the planned surgical intervention.

8. Prevention of Alloimmunization to RhD Antigens

Guideline: Prevention of RhD alloimmunization resulting from RBCs contaminating platelet transfusions, either through the exclusive use of platelets from RhD negative donors or via anti-D immunoprophylaxis, should be considered for RhD-negative children (particularly girls) and for women of child-bearing age.

Level of Evidence: IV

Grade of Recommendation: D

Platelets do not express Rh antigens on their surface,[91] but the quantity of RBCs in platelet preparations is sufficient to induce Rh sensitization, even in immunosuppressed cancer patients.[92-95] Different studies have documented that anti-D antibodies can be detected in 7.8% to 19% of heterogeneous groups of RhD-negative cancer patients exposed to RhD antigens via transfusion.[92-95] Two small studies have demonstrated that RhD immunoprophylaxis can prevent the development of anti-D in this setting.[96,97] Taken together, these studies report on 57 RhD-negative oncology patients who received anti-D immunoglobulin simultaneously with platelet transfusions. None of the patients developed endogenous anti-D. Prevention of RhD alloimmunization resulting from platelet transfusions, either through the exclusive use of platelets from RhD-negative donors or via anti-D immunoprophylaxis, should be considered for RhD-negative children (particularly girls) and women of child-bearing age.

Thus, if platelets from an Rh-positive donor or platelets from a donor of unknown Rh phenotype are given to an Rh-negative recipient, administration of Rh immunoprophylaxis should be considered, especially for younger female patients who might become pregnant after successful treatment.[56,98,99] Because of the thrombocytopenia, it is preferable to use a preparation of anti-D that can be administered intravenously (IV). In Canada and the United States, WinRho SDF, a licensed IV preparation, is available. The amount of anti-D immunoglobulin necessary to prevent sensitization depends on the number of contaminating RBCs in the PCs. Extrapolating from guidelines used to prevent maternal sensitization after fetal-maternal hemorrhage, a dose of 25 μg (125 IU) of anti-D immunoglobulin will protect against 1 mL of RBCs.[98,99] If possible, the immunoglobulin should be given before or immediately after the transfusion, although, as in the obstetrical setting, it may still be efficacious if given within 72 hours of exposure to the RhD-positive RBCs.

9. Prevention of Alloimmunization Using Leukoreduced Blood Products

Guideline: The incidence of alloantibody mediated refractoriness to platelet transfusion can be decreased in patients with acute myeloid leukemia (AML) receiving induction chemotherapy when both platelet and RBC products are leukoreduced by filtration before transfusion (level I evidence). It is therefore appropriate to provide leukoreduced blood products to patients with AML from the time of diagnosis to ameliorate this important clinical problem. Although randomized trials have not been conducted in other patient groups, it is likely that alloimmunization can also be decreased in patients with other types of leukemia and in other cancer patients receiving chemotherapy. There are no data in patients who are not receiving chemotherapy in the same time periods that the transfusions are being administered (for example, aplastic anemia, myelodysplasia), although the consensus of opinion would favor its use in these patients as well. Because leukoreduction adds appreciably to the costs of transfusion, it should be used only for patients expected to require multiple platelet transfusions during their treatment courses and is not indicated for patients with cancer receiving RBCs or therapies that do not produce significant and sustained thrombocytopenia. In some countries, all blood products are now leukoreduced at the time of blood collection and component preparation. Should such prestorage leukoreduction become a routine in the United States, it would alleviate the need for additional filtration at the time of transfusion.

Level of Evidence: I

Grade of Recommendation: A

Alloimmunization against histocompatibility antigens occurs in many recipients of multiple random donor platelet transfusions and is the most important long-term complication of platelet transfusion. Estimates of the frequency of alloimmunization after platelet transfusion vary widely, depending in part on the patient population being studied and the intensity of cytotoxic and immunosuppressive therapy administered. Recent experience suggests that between 25% and 35% of newly diagnosed patients with AML will produce lymphocytotoxic antibody and become alloimmunized and refractory to nonhistocompatible platelet transfusions.[44,100,101]

Despite greater understanding of factors that influence the results of transfusion from HLA-selected donors, as many as 40% to 60% of apparently histocompatible platelet transfusions administered to alloimmunized patients are unsuccessful.[102] In addition to the costs of such transfusions, recipients of transfusions that do not produce satisfactory increments remain at risk of hemorrhagic morbidity

and mortality. When histocompatible donors are not available, the management of alloimmunized patients is difficult. The elimination of alloimmunization would greatly simplify platelet transfusion therapy, and in particular, would increase the safety of intensive postremission therapy administered to patients with leukemia. There is substantial in vitro and preclinical evidence from murine and canine models, which suggests that the leukocytes contaminating platelet preparations are the primary stimulus for alloimmunization.[103-106] It seems that presentation of class I and class II antigens by intact leukocytes is required for initial processing by the immune system. Because platelets do not express class II histocompatibility antigens, it is likely that it is the leukocyte that serves as the costimulus. Therefore, there has been considerable interest in the use of different methods of removal of leukocytes by filtration or modification of the antigen presenting capacity of the leukocyte to reduce the incidence of alloimmunization. With regard to the latter approach, it has been shown that ultraviolet B (UVB) irradiation can abolish reactivity in mixed lymphocyte reactions and that doses of UVB irradiation can be identified that do not affect platelet function in vitro.[107-109]

A large number of clinical trials have been reported over the past 10 to 15 years, most of which focused on filtration of platelets before transfusion to remove leukocytes.[110-120] These filters are capable of relatively reliable, 3 to 4 log reduction in leukocyte contamination of platelets obtained either by apheresis or prepared as PCs. Most, but not all, of these studies were positive and demonstrated reduction of alloantibody production in patients receiving filtered products. There are, however, a number of problems with these older trials.[121,122] In general, the studies were small with low statistical power, contained patients with a variety of different diagnoses receiving heterogeneous chemotherapy regimens, used different end points for refractoriness and criteria for alloantibody production, did not appropriately stratify for predisposing factors such as prior transfusion or pregnancy, had discrepant policies with regard to leukocyte depletion of RBC transfusions, and achieved variable degrees of leukocyte depletion, with little data reported about quality control of the transfused product. There have been fewer trials published evaluating UVB irradiation, but these same criticisms apply.[108,123] In addition, two recently published small trials failed to show benefit from leukocyte filtration, including one in which filtration was performed at the bedside, rather than at the blood bank.[115,117] All of these manipulations increase the cost of transfusion. There can be an appreciable loss of platelets after filtration (up to 25% to 35%, and sometimes greater when fresh apheresis platelets are filtered), with a potential to increase the number of transfusion products required.[124] All RBC transfusions also

have to be adequately leukoreduced, further adding to the cost of this treatment.

To help address these concerns, a large, randomized multi-institutional trial (Trial to Reduce Alloimmunization to Platelets [TRAP]), which involved eight institutions in the United States, was recently completed.[44] Six hundred three patients with newly diagnosed AML receiving initial induction therapy with anthracycline/cytarabine-based chemotherapy were randomized to receive the following: pooled PC (control group); filtered PC (leukoreduced); single donor, filtered platelets collected by apheresis; or pooled PC that had been UVB irradiated. All manipulations were performed at the blood bank, not at the patient bedside. Patients were monitored for 8 weeks after the initiation of therapy, with randomization stratified for prior exposure to histocompatibility antigens by pregnancy or prior transfusion. All RBC transfusions were leukodepleted by filtration. A target level of less than 5×10^6 leukocytes per transfusion was used in this study, although there are virtually no data about the minimum number of leukocytes that suffice to serve as an immunologic stimulus.[106]

There was a statistically significant reduction in the formation of lymphocytotoxic antibody (anti-HLA antibody) in all three groups receiving modified platelets (17% to 21%), compared with the control group (45%) receiving standard PCs.[44] This reduction was noted in all patients, including women with prior pregnancies. Filtration and UVB irradiation also produced a significant reduction in the incidence of immune-mediated platelet refractoriness during induction (3% to 5% v 13% in controls). The overall incidence of refractoriness was relatively low, probably because antibody formation tended to occur in the third to fourth week of induction, often when patients were no longer requiring platelet transfusions. All of the platelet product manipulations produced the same degree of benefit with similar posttransfusion increments. Thus, there was no additional advantage from the use of single-donor platelets compared with filtered, pooled PCs.

On the basis of these results, the accumulated conclusions of the earlier trials and a recent metanalysis,[125] it is appropriate to provide leukoreduced RBC and platelet products to newly diagnosed patients with AML and probably to patients with other types of acute leukemia. Although these conclusions most likely also apply to the use of UVB-irradiated platelets, there is no Food and Drug Administration–approved irradiation device available at this time. It should also be noted that only a subfraction of patients benefit from any successful approach to reduce the rate of alloimmunization. Only 30% to 40% of patients become alloimmunized using standard, nonleukocyte-reduced platelets and RBCs.[44] Not all of these 30% to 40% of

patients achieve complete remission and receive intensive postremission therapy. This is of importance because there was only a modest reduction in the incidence of refractoriness to transfusion in the TRAP study, because the antibodies often developed after 3 to 4 weeks, at a time when the patients may no longer have required platelet transfusion during induction. Thus, the major impact of prevention of alloimmunization may be noted in patients receiving intensive consolidation. It has been estimated that only 10% to 15% of patients with newly diagnosed AML might actually benefit clinically from any successful method of reducing alloimmunization.[121]

The TRAP trial only evaluated adult patients with AML, but it is likely, albeit unproved, that filtration would have similar benefits for patients being treated for other cancers as well. There are, however, relatively few groups of patients who require repetitive, prolonged courses of therapy with the need for repeated multiple platelet transfusions. For example, there is no compelling rationale for routine filtration of platelets for patients undergoing high-dose chemotherapy with peripheral-blood stem-cell transplantation. These patients generally only require a few platelet transfusions for the transplantation and usually do not have further planned chemotherapy afterward.[66] Therefore, the use of these expensive filters should be monitored and restricted to patients likely to require long-term transfusion support.

As in the case for the studies evaluating the indications for platelet transfusion, most of the studies addressing the issue of prevention of alloimmunization/platelet refractoriness have been performed in adult patients with AML. Nevertheless, the conclusions from the adult studies are likely generalizable to children particularly because most pediatric patients with AML (or any other malignant diseases requiring platelet transfusion support) have not had previous pregnancies or transfusions. In both the TRAP study and the meta-analysis, these subgroups benefited more than the study group as a whole from interventions to prevent HLA alloimmunization. With respect to decisions about leukocyte-reduced blood components for children with malignancies other than AML, considerations similar to those discussed above for adult patients apply. However, chemotherapeutic regimens are often more aggressive for children than adults so that children may more often be candidates for long-term platelet support than are adult oncology patients. Three descriptive comparative reports in pediatric patients of current versus older transfusion practices support these conclusions.[120,126,127]

As an alternative to filtration of platelets or RBCs after storage, there is now ample evidence indicating that removal of leukocytes just after blood collection (so-called prestorage leukocyte depletion) is advantageous because of

accumulating evidence that most transfusion reactions are a consequence of cytokines elaborated by leukocytes and released into the plasma during storage.[128] Other than alloimmunization, it is these febrile reactions that are most disturbing and dangerous to the patient. Although economic issues presently determine the fraction of RBC collections which are leukocyte depleted before storage or fractionation, it is expected that this practice will increase in the future, given its multiple clinical advantages, which also include a reduction in the incidence of transfusion-associated cytomegalovirus infections.[129] Lastly, newer modifications of apheresis techniques permit reliable collections of platelets with leukocyte contamination well below the 5×10^6 cutoff, presumably obviating the need for further leukocyte filtration of these products.[35,130] Leukoreduction of RBCs would still be required, however.

10. Diagnosis of Refractoriness to Platelet Transfusion

Guideline: Although there are no empirical data to suggest that monitoring and acting on the postplatelet transfusion count decreases the incidence of hemorrhagic events, the Panel consensus is that posttransfusion platelet counts should be obtained after all transfusions, whenever possible. The Panel further recommends that additional transfusions be administered if the posttransfusion count is less than the platelet trigger appropriate for that clinical situation. Because patients may have a poor increment to a single transfusion yet have excellent platelet increments with subsequent transfusions, a diagnosis of refractoriness to platelet transfusion should only be made when at least two ABO-compatible transfusions, stored less than 72 hours, result in poor increments, as defined in the supporting text of the recommendation.

Level of Evidence: V

Grade of Recommendation: D, panel consensus

No formal study has been performed to document the effectiveness of monitoring and acting on posttransfusion platelet counts. However, it is the consensus of the Panel that patients remain at risk for hemorrhagic events if the posttransfusion counts are still below the platelet value used to trigger the initial transfusion. Therefore, additional platelet transfusions are believed to be indicated to achieve a platelet count above the trigger level. In addition, monitoring the posttransfusion count allows the practitioner to determine the adequacy of platelet transfusion therapy. If patients fail to achieve an adequate platelet increment after transfusion, investigations as to the cause of platelet transfusion refractoriness should be initiated. The practitioner should then work with the blood bank to determine a rational transfusion program for such patients.

The platelet increment is determined by subtracting the pretransfusion platelet count from the count determined 1 hour after transfusion. Identical results are obtained, however, using a 10-minute posttransfusion count, which is simple to obtain because the patient must be seen when the transfusion is completed to switch the IV bags.[90] Although it would be desirable to obtain immediate posttransfusion increments after all platelet transfusions, it is reasonable to obtain such increments in nonbleeding hospitalized patients if the day-to-day increments are not satisfactory and after all transfusions to outpatients.

The percentage of platelet recovery, or the corrected count increment (CCI), is determined using a formula based on the estimated blood volume or size of the patient as well as the number of platelets in the infused product. Although different values of the CCI have been used to define an adequate transfusion response, the recently completed TRAP study used a CCI of $\geq 5,000$ to define a satisfactory response, and this definition is endorsed by the Panel.[44] The $CCI = $ absolute increment $\times$ body-surface area $(m^2)/$ number of platelets transfused $\times 10^{11}$. Thus, if transfusion of 4×10^{11} platelets produced an increment of $40,000/\mu L$ in a 2-m^2 recipient, the CCI $= 40,000 \times 2/4 = 20,000$.

As an alternative, Because most centers do not routinely obtain platelet counts of the infused product, the Panel suggests using a rough estimate of an absolute increment of 2000/per unit of PC to be equivalent to a CCI of 5,000. This is based on the assumption that an average-sized adult has a body-surface area of 1.76 m^2 and the average platelet count in a unit of PC is 0.7×10^{11}. For children, an approximate equivalent calculation for the absolute increment is 3,500/m^2/unit

Because patients may have a poor increment to a single transfusion yet have excellent platelet increments with subsequent transfusions, a diagnosis of refractoriness to platelet transfusion should only be made when at least two ABO-compatible transfusions, stored less than 72 hours, result in poor increments as defined above.[44] It is suggested that the transfusions be ABO-compatible because of evidence that ABO incompatibility (eg, A platelets to group O recipients) can sometimes compromise posttransfusion increments.[131] Once these criteria are fulfilled, the most likely diagnosis is alloimmunization, although immune platelet destruction as a result of drug-related antibodies, as well as hypersplenism, severe disseminated intravascular coagulation, shock, and massive hemorrhage, may also result in poor platelet increments.[132] Therefore, it is critical to first document that the patient is in fact alloimmunized, because such patients are managed differently than patients with other causes of refractoriness to transfusion. Approximately 90% of patients who are alloimmunized will have alloantibody to HLA antigens detectable by lymphocytotoxicity

assays or platelet antibody testing.[44,133,134] It is the consensus of the Panel that all patients who are refractory to platelet transfusions as defined above have such antibody studies performed to confirm a diagnosis of alloimmunity.

11. Management of Refractoriness to Platelet Transfusion

Guideline: Patients with alloimmune refractory thrombocytopenia, as defined above, are best managed with platelet transfusions from donors who are HLA-A and HLA-B antigen selected. Most blood centers have access to computerized lists of such donors. For patients (a) whose HLA type cannot be determined, (b) who have uncommon HLA types for which suitable donors cannot be identified, or (c) who do not respond to HLA matched platelets, histocompatible platelet donors can often be identified using platelet cross-matching techniques. In many patients, these two techniques are complementary. There is no evidence that alloimmunized patients benefit from nonmatched prophylactic platelet transfusions that do not produce posttransfusion increments, and the Panel recommends that such patients be transfused only for hemorrhagic events.

Level of Evidence: III

Grade of Recommendation: B, panel consensus

The transfusion of HLA-matched platelets results in adequate increments in approximately 50% to 60% of transfusion events and, if available, are generally used as the initial management for patients with alloimmune refractory thrombocytopenia.[102,132] When choosing HLA-matched products, one should consider the fact that HLA antigens can have variable expression on leukocytes (used to determine the HLA type of the patient/donor pair) and platelets. For example, platelets mismatched for HLA B44 or B45 can still produce satisfactory increments approximately 75% of the time.[133] Other single-antigen mismatched platelets can also produce adequate increments in many patients.[135] HLA-matched platelets are not available for all patients, however. For example, leukemia patients who present with low leukocyte counts may be unable to be HLA typed except by molecular techniques. Also, patients with less common HLA phenotypes may have few compatible donors available. Finally, approximately 40% to 50% of HLA-matched platelet transfusion events do not result in adequate increments. For such patients, histocompatible platelet donors are best identified using platelet cross-matching techniques that are available at many blood banks.[136,137] In addition, potential donors not identified by HLA matching may be selected by cross-matching. This may be because such recipients have platelet rather than HLA alloantibodies and therefore would not respond to HLA-matched platelets.

Repeated transfusions of large numbers of units (n = 10+) of pooled random-donor platelets may benefit patients with active bleeding. This may be related to a transient decrease in the alloantibody titer or the possibility that such random donor platelet products may fortuitously include some histocompatible units.[136,138] Therapies used for the treatment of idiopathic thrombocytopenia purpura have also been tried for patients with alloimmune refractory thrombocytopenia with little success. Perhaps the best studied is IV gamma globulin (IVIG). Most nonrandomized studies fail to show the benefit of IVIG for patients with alloimmune-refractory thrombocytopenia.[139,140] In addition, a small randomized placebo-controlled study (level II evidence), failed to show a significant benefit of IVIG for such patients.[141] Corticosteroids and splenectomy,[142] the mainstays of treatment for ITP, have also not been shown to be of benefit for patients with alloimmune thrombocytopenia (level III evidence), nor has the use of plasma exchange[143] (level III evidence).

APPENDIX A: SUMMARY OF GUIDELINES

1. Platelet Products

Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood, which are pooled before administration, or by apheresis from single donors. Comparative studies have shown that the posttransfusion increments, hemostatic benefit, and side effects are similar with either product. Thus, in routine circumstances, they can be used interchangeably. In most centers, pooled PCs are less costly. Single-donor platelets from selected donors are preferred when histocompatible platelet transfusions are needed. Both preparations can be stored for up to 5 days after collection at 20°C to 24°C with good maintenance of platelet viability.

2. Prophylactic Versus Therapeutic Platelet Transfusion

The Panel recommends that prophylactic platelet transfusion be administered to patients with thrombocytopenia resulting from impaired bone marrow function to reduce the risk of hemorrhage when the platelet count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality.

APPENDIX A: (Cont'd)

3. Platelet Count Threshold for Prophylactic Platelet Transfusion: Acute Leukemia

The Panel recommends a threshold of 10,000/μL for prophylactic platelet transfusion in adult patients receiving therapy for acute leukemia, on the basis of the results of multiple randomized trials that demonstrate that this approach is equivalent to the use of a 20,000/μL threshold. Transfusion at higher levels may be necessary in newborns or in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities (for example, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which platelet transfusions may not be readily available in case of emergencies. The studies that form the basis of this recommendation (as well as the other recommendations in this section) have included adolescents but not younger children or infants. Nevertheless, it is probably reasonable to use similar guidelines for children and older infants. Although modern automated cell counters are quite accurate at low platelet counts, there can be modest variations in count because of limitations of the counting technology. The decision to transfuse at a precise trigger level should therefore consider the clinical context and the pattern of recent platelet counts.

4. Hematopoietic Cell Transplantation

Fewer studies have been performed in recipients of high-dose therapy with stem-cell support. Although such patients may experience more mucosal injury than patients receiving conventional antileukemic chemotherapy, clinical experience and the available data suggest that guidelines for prophylactic transfusion similar to those for patients with acute leukemia can be used in transplant recipients, with similar caveats about transfusion at higher counts in patients with complicating clinical conditions. The recent increased use of peripheral-blood stem cells with shorter durations of thrombocytopenia should further decrease the hemorrhagic risk.

5. Patients With Chronic, Stable, Severe Thrombocytopenia

No randomized studies have been performed in patients with sustained, severe thrombocytopenia such as can be seen in individuals with myelodysplasia and aplastic anemia. Many such patients have minimal or no significant bleeding for long periods of time despite low platelet counts. On the basis of clinical experience and limited retrospective studies, the Panel suggests that many of these patients can be observed without prophylactic transfusion, reserving platelet transfusions for episodes of hemorrhage or during times of active treatment.

6. Prophylactic Platelet Transfusion in Patients With Solid Tumors

The risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth of the platelet nadir, although other factors contribute as well. Evidence obtained from observational studies supports the clinical benefit of prophylactic transfusion at a threshold of 10,000/μL platelets or less. The Panel suggests, however, on the basis of expert clinical opinion, that prophylactic transfusion at a threshold of 20,000/μL be considered for patients receiving aggressive therapy for bladder tumors as well as those with demonstrated necrotic tumors, owing to their presumed increased risk of bleeding at these sites.

7. Surgical or Invasive Procedures in Thrombocytopenic Patients

Thrombocytopenic patients frequently require invasive diagnostic or therapeutic procedures. Common procedures include placement of permanent or temporary central venous catheters, transbronchial and esophageal endoscopic biopsies, paranasal sinus aspirations, bone marrow biopsies, and occasionally even major surgery. The Panel suggests, on the basis of accumulated clinical experience, as attested to by a variety of consensus conference statements,[55,56] that a platelet count of 40,000/μL to 50,000/μL is sufficient to perform major invasive procedures with safety, in the absence of associated coagulation abnormalities. Certain procedures, such as bone marrow aspirations and biopsies, clearly can be performed safely at counts of less than 20,000/μL. There are sparse data (summarized below) about the safety of other invasive procedures at much lower count levels. If platelet transfusions are administered before a procedure, it is critical that a posttransfusion platelet count be obtained to prove that the desired platelet count level has been reached. Platelet transfusions should also be available on short notice, in case intraoperative or postoperative bleeding occurs. For alloimmunized patients, histocompatible platelets must be available in these circumstances.

8. Prevention of Alloimmunization to RhD Antigens

Prevention of RhD alloimmunization resulting from RBCs contaminating platelet transfusions, either through the exclusive use of platelets from RhD negative donors or via anti-D immunoprophylaxis, should be considered for RhD-negative children (particularly girls) and for women of child-bearing age.

9. Prevention of Alloimmunization Using Leukoreduced Blood Products

The incidence of alloantibody mediated refractoriness to platelet transfusion can be decreased in patients with AML receiving induction chemotherapy when both platelet and RBC products are leukoreduced by filtration before transfusion (level I evidence). It is therefore appropriate to provide leukoreduced blood products to patients with AML from the time of diagnosis to ameliorate this important clinical problem. Although randomized trials have not been conducted in other patient groups, it is likely that alloimmunization can also be decreased in patients with other types of leukemia and in other cancer patients receiving chemotherapy. There are no data in patients who are not receiving chemotherapy in the same time periods that the transfusions are being administered (for example, aplastic anemia, myelodysplasia), although the consensus of opinion would favor its use in these patients as well. Because leukoreduction adds appreciably to the costs of transfusion, it should be used only for patients expected to require multiple platelet transfusions during their treatment courses and is not indicated for patients with cancer receiving RBCs or therapies that do not produce significant and sustained thrombocytopenia. In some countries, all blood products are now leukoreduced at the time of blood collection and component preparation. Should such prestorage leukoreduction become a routine in the United States, it would alleviate the need for additional filtration at the time of transfusion.

10. Diagnosis of Refractoriness to Platelet Transfusion

Although there are no empirical data to suggest that monitoring and acting on the postplatelet transfusion count decreases the incidence of hemorrhagic events, the Panel consensus is that posttransfusion platelet counts should be obtained after all transfusions, whenever possible. The Panel further recommends that additional transfusions be administered if the posttransfusion count is less than the platelet trigger appropriate for that clinical situation. Because patients may have a poor increment to a single transfusion yet have excellent platelet increments with subsequent transfusions, a diagnosis of refractoriness to platelet transfusion should only be made when at least two ABO-compatible transfusions, stored less than 72 hours, result in poor increments, as defined in the supporting text of the recommendation.

APPENDIX A: (Cont'd)

11. Management of Refractoriness to Platelet Transfusion

Patients with alloimmune refractory thrombocytopenia, as defined above, are best managed with platelet transfusions from donors who are HLA-A and HLA-B antigen selected. Most blood centers have access to computerized lists of such donors. For patients (a) whose HLA type cannot be determined, (b) who have uncommon HLA types for which suitable donors cannot be identified, or (c) who do not respond to HLA matched platelets, histocompatible platelet donors can often be identified using platelet cross-matching techniques. In many patients, these two techniques are complementary. There is no evidence that alloimmunized patients benefit from nonmatched prophylactic platelet transfusions that do not produce posttransfusion increments, and the Panel recommends that such patients be transfused only for hemorrhagic events.

APPENDIX B: ASCO PLATELET TRANSFUSION EXPERT PANEL

Investigator	Institution	Specialty
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Linda S. Elting, PhD	University of Texas M.D. Anderson Cancer Center, Houston, TX	
Miriam Goldsmith	Rite of Passage Cancer Project, Newport, RI	Patient Representative
Michael Goldstein, MD	Harvard Medical School, Brookline, MA	Community Oncologist
Heather Hume, MD, FRCPC	Hopital Sainte-Justine, Montreal, Canada	Hematology Oncology
Jeffrey J. McCullough, MD	University of Minnesota, Minneapolis, MN	Laboratory Medicine/Pathology
Rosemary E. McIntyre, MD	Venture Co Hematology/Oncology Specialists, Oxnard, CA	Community Oncologist
Bayard L. Powell, MD	Wake Forest University Comprehensive Cancer Center, Winston Salem, NC	Medical Oncology/Hematology
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Paolo Rebulla, MD	Centro Transfusionale e di Immunologia dei Trapianti, IRCCS Ospedale Maggiore, Milan, Italy	Hematology/Oncology
Scott D. Rowley, MD	Fred Hutchinson Cancer Research Center, Seattle, WA	Medical Oncology/Hematology
Michael B. Troner, MD	Oncology Radiation Association, Miami, FL	Medical Oncology/Hematology
Alton H. Wagnon, MD	Society of Utah Oncologists, Ogden, UT	Medical Oncology/Hematology

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