Issues in the Management of Cancer-Related Thrombocytopenia

By Lawrence T. Goodnough, MD and John F. D. Dipersio, MD, PhD

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The evolving use of intensive chemotherapy regimens in oncology and bone marrow/stem cell transplantation programs has increased the demand for platelet products, particularly for patients with severe thrombocytopenia or bleeding complications. The use of apheresis platelet transfusions has also increased substantially, from 352,000 units in 1989 to 1,003,000 units in 1999 (Table 1)[1-3]; this increase is being driven partly by the need for alternative platelet inventories to support cardiac surgery and peripheral blood stem cell (PBSC) transplantation programs, and partly by the use of leukoreduced platelet products.[4]

Emerging issues are renewing interest in platelet transfusion practices.[5] This review discusses the current risks associated with platelet transfusion and the results of recent studies of alternative strategies in platelet transfusion therapy, including: (1) reevaluation of the platelet threshold for prophylactic transfusion, (2) modification of the platelet transfusion dose, (3) the potential role of thrombopoietin therapy, and (4) current investigational and pharmacologic options for the treatment of cancer-related thrombocytopenia.

Current Risks of Platelet Transfusion

The risk of acquiring transfusion-transmitted diseases is estimated to be lower than ever (Table 2).[3,6] Nucleic acid testing has decreased the risk of viral infection by shortening the window of infectivity, and thus reducing the risk of posttransfusion infection with the hepatitis C virus and human immunodeficiency virus (HIV).

HIV Transmission

Transfusion-associated HIV infection was first reported in late 1982 and early 1983. HIV antibody testing was implemented in March 1985, and over the next 5 years, only about five cases of transfusion-associated HIV infection were reported annually. In the year before testing began, 714 cases had been reported.[7] In late 1995, blood banks began testing donors for the p24 antigen to further decrease the risk of transfusion-transmitted HIV disease. In 1999, nucleic acid testing was introduced to close the window of infectivity (from infection to detection) by at least 50%, lowering the estimated risk of HIV transmission by transfusion to approximately 1 in 2 million units.[8]

Posttransfusion Hepatitis

Labeling of blood from paid donors (a practice initiated in 1972) and the implementation of third-generation screening tests for the hepatitis B surface antigen markedly reduced transfusion-transmitted hepatitis B. By 1995, however, these measures were found to eliminate only about 10% of all posttransfusion hepatitis cases.[6]

The incidence of non-A, non-B posttransfusion hepatitis was further reduced when potential HIV-positive donors were excluded and was reduced again when donors were tested for the surrogate markers alanine aminotransferase (a marker for acute liver inflammation) and antibody to hepatitis B core antigen (evidence of previous hepatitis B infection).[9] Even greater reductions in the risk of transmission of non-A, non-B hepatitis were described after implementation of a test for antibody to the hepatitis C virus (Table 2).[3,10] Finally, implementation of nucleic acid testing reduced the current estimated risk of hepatitis C transmission to approximately 1 in 2,000,000 units.[8]

Platelet Product Contamination

The estimated risk of sepsis related to apheresis platelets is 1:2,000. This risk is greater with transfusions of pooled platelet concentrates from multiple donors. Because the risk of bacterial overgrowth increases with time, the shelf life of platelets stored at 20°C to 24°C is limited to 5 days. The organisms most commonly implicated in fatalities, in descending order, are Staphylococcus
Clinical presentation of infection with bacterially contaminated platelets can range from mild fever (potentially indistinguishable from febrile, nonhemolytic transfusion reactions) to acute sepsis, hypotension, and death. Sepsis caused by transfusion of contaminated platelets is unrecognized, in part, because the organisms found in platelet contamination are often the same as those implicated in catheter-related sepsis. The overall mortality rate of identified platelet-associated sepsis is 26%.[6]

No widely accepted test is available to detect bacterially contaminated blood products. Currently, the most promising approach is the use of psoralen and ultraviolet (UV) light to sterilize blood products.[11] In the clinical setting, any patient who develops fever within 6 hours of receiving platelets should be evaluated, and empiric antibiotic therapy should be considered.

**Cytomegalovirus Infection**

Cytomegalovirus (CMV) infection caused by platelet transfusions has been associated with substantial morbidity and mortality in immunocompromised oncology patients. Patients who undergo allogeneic bone marrow/stem cell transplantation are at risk of contracting the virus present in blood products due to their use of cytotoxic preparative regimens or immunosuppressive therapy (cyclosporine and corticosteroid), or graft-vs-host disease.[12] Up to 60% of this patient population will become infected with CMV, and 50% will develop CMV disease if no preemptive therapy is administered.

The risk of developing CMV infection ranges from 28% to 57% for seronegative bone marrow transplant patients who receive standard blood products.[13] Even with the use of CMV-negative blood products, CMV seroconversion has been reported in 1% to 4% of CMV-negative donor-recipient transplant patients.[14]

A recent analysis of our program at Washington University identified CMV viremia in only 1 (2.5%) of 39 CMV-negative donor-recipient pairs undergoing allogeneic PBSC transplantation.[15] Our analysis included 59 patients who had undergone allogeneic PBSC transplantation in an investigational study of prophylactic granulocyte infusions from stem cell donors. Notably, results showed that CMV-positive granulocytes did not alter the risk of viremia compared with CMV-negative granulocytes; the incidence of CMV viremia was 34.5% vs 26.6%, respectively (95% confidence interval [CI] = 0.47-4.41).

CMV infection and CMV disease occur much less commonly than other virally transmitted diseases in patients receiving conventional chemotherapy or autologous bone marrow/stem cell transplantation[16] and are not a significant clinical problem except in CD34-selected or T-cell-depleted stem cell transplantations.[17]

A randomized, controlled clinical trial[13] in allogeneic bone marrow transplantation patients compared the value of CMV-seronegative blood products vs unscreened blood products subjected to bedside leukofiltration. Of 252 patients in the CMV-seronegative cohort, 4 (1.3%) developed CMV infection, with no CMV disease or fatalities; 6 (2.4%) of 250 patients in the leukoreduced cohort developed CMV disease, and 5 of these patients died. The leukoreduced cohort had an increased probability of developing CMV disease by day 100 (2.4% vs 0%, \( P = .03 \)). Even when investigators eliminated the CMV infections that occurred within 21 days of transplantation, two patients in the leukoreduced arm and none in the seronegative arm died of CMV disease.[18] The investigators’ conclusions that leukoreduced blood products are "CMV safe" remain controversial.[19]

In a consensus conference held by the Canadian Blood Service,[18] 7 of 10 panelists concluded that patients considered at risk for CMV disease should receive CMV-negative products, even when blood components are leukoreduced.

**Universal Leukoreduction**

Debate over the merits of "universal" leukoreduction (cellular components with \(< 5 \times 10^6\) leukocytes) has focused on several potentially important clinical effects, including transfusion-related alloimmunization to platelets, febrile-associated transfusion reactions, and transfusion-related immunomodulation. Use of both leukoreduced and nonleukoreduced blood components is currently approved by the US Food and Drug Administration (FDA).[20]

Table 3 summarizes the number of leukoreduced blood units collected in the United States from 1994 to 1999.[2,3] While the percentages of red cell transfusions remained static, the generation of leukoreduced apheresis platelets, especially by blood centers, increased substantially.[3] For the first 9 months of 1999, 13% of all red cells transfused at our hospital were leukoreduced. Our indications for leukoreduction reflect those published previously (Table 4).[21]

Febrile Reactions

Febrile-associated transfusion reactions occur in only 0.5% of patients transfused with red cells, and of these, 18% and 8% experience a second and third event,
Approximately 18% of all platelet transfusions are associated with febrile-associated transfusion reactions,[22] although the prevalence of these responses can be as high as 30% in frequently transfused populations, such as oncology patients. Reactions characterized as severe occur in only 2% of platelet transfusions,[23] and bedside leukofiltration has not reduced the overall prevalence of such effects.[22,23] Moreover, bedside leukoreduction filters can cause significant hypotensive events by activating the bradykinin/kininogen systems, particularly in patients who are receiving angiotensin-converting enzyme inhibitors.[24]

**Transfusion-related alloimmunization to platelets** was studied in a multicenter trial in newly diagnosed leukemia patients.[23] The study found that clinical platelet refractoriness associated with human leukocyte antigen seropositivity was reduced from 13% in patients transfused with unprocessed platelet concentrates to from 3% to 5% in patients receiving leukoreduced apheresis platelets, leukoreduced platelet concentrates, or psoralen/UV-B-treated platelets. Although this difference is statistically significant, no clinically important differences were found between patient cohorts in prevalence of transfusion reactions, hemorrhagic events, length of hospital stay, number of platelet transfusions, number of red cell transfusions, or mortality.

**Transfusion-related immunomodulation** has been cited as clinically important in patients undergoing renal transplantation and in women who have had multiple miscarriages.[25] However, a multicenter, controlled study found no evidence of such an effect, and the authors recommended against the use of allogeneic mononuclear infusions as treatment for unexplained recurrent miscarriages.[26] Similarly, patients who received transfusions before renal transplantation had a superior 1-year renal allograft survival rate compared with untransfused patients.[27]

Nevertheless, among patients who did not receive a transfusion prior to surgery, blood transfused at the time of transplantation had no effect on 1-year renal allograft survival. Only a few prospective studies have attempted to clarify the potential immunomodulatory effects of allogeneic transfusion in other settings.[28] Table 4 lists the indications for leukoreduction published in a review in 1992.[21] These guidelines continue to be applicable, pending future controlled, prospective clinical trials.[20]

**Platelet Transfusion Practices**

**Threshold for Transfusion**

Several studies have evaluated prophylactic platelet transfusion thresholds for patients with thrombocytopenia due to myelosuppressive therapy. Bernstein et al.[29] found that most patients who underwent stem cell transplantation received prophylactic platelet transfusions when their platelet counts measured 10,000 to 20,000 cells/µL, indicating that a threshold of 20,000 cells/µL was most common (Figure 1).[29] Only 9% of hemorrhagic events reported in this study occurred when platelet counts were < 10,000 cells/µL.

Two prospective, randomized studies evaluated the relative merits of platelet transfusion thresholds of 10,000 or 20,000 cells/µL for leukemia patients undergoing chemotherapy.[30,31] Rebulla et al.[30] found that the lower transfusion threshold was associated with 22% fewer platelet transfusions. In an analysis of hemorrhagic complications, number of red cell transfusions, duration of hospital stay, and mortality, no differences were seen between the two thresholds. In the second study, Wandt et al.[31] showed that a platelet threshold of 10,000 cells/µL was safe and effective vs the 20,000 cells/µL threshold. Of 105 patients in this study, 2 (1.9%) died of hemorrhagic complications, each with a platelet count > 30,000 cells/µL at the time of death.

**Dose**

Standards of the American Association of Blood Banks require that 75% of apheresis products contain > 3 × 10^{11} platelets and that 75% of platelet concentrates contain > 5.5 × 10^{10} platelets.[32] However, no consensus exists as to a standardized platelet transfusion dose. Table 5 lists the broad range of platelet doses used in several recent studies.[23,30,33] In an evaluation of our own hospital-based apheresis program, 32% of products contained 3 to 4 × 10^{11} platelets, and another 32% contained 4 to 5 × 10^{11} platelets.[33] Leukoreduction of apheresis platelets or platelet concentrates results in approximately a 20% loss of platelets.[23]

**Low-Dose Therapy** Mathematical modeling has suggested that low-dose platelet therapy would be more beneficial in thrombocytopenic patients receiving prophylactic platelet transfusions.[34] The relationship between patient platelet count and in vivo platelet survival is illustrated in Figure 2.[34,35] The fixed platelet requirement for hemostasis is estimated to be 7,100/µL/d, and platelet consumption above this threshold is mainly a result of platelet senescence. Among patients who become thrombocytopenic due to myeloablative therapy, platelet survival decreases with increasing...
severity of thrombocytopenia. Thus, platelet survival is 5 to 7 days in patients with platelet counts in the normal range, but only 1 to 2 days in patients with platelet counts of 10,000 to 20,000 cells/µL, levels at which most thrombocytopenic patients are maintained to prevent hemorrhage.

A mathematical model predicts that low-dose platelet therapy provides a 22% decrease in the number of donor exposures (and the total number of platelets) while maintaining patients at a platelet threshold > 10,000 cells/µL.[34] This is achieved despite a shorter transfusion-free interval and a greater daily relative risk of receiving additional transfusions.[36]

**High-Dose Therapy** A randomized clinical trial was conducted to address the issue of high-dose platelet therapy.[37] Standard, high, and very high platelet doses (4.6 × 10^{11}, 6.5 × 10^{11}, and 8.9 × 10^{11} platelets, respectively) were administered to patients receiving prophylactic platelet transfusions. The high- and very high-dose cohorts showed greater incremental increases in platelet count and prolonged time to next transfusion than the standard-dose cohort. Interestingly, platelet half-life estimates (ie, slopes) were similar among patient cohorts for posttransfusion platelet counts ranging from approximately 50,000 to 110,000 cells/µL (Figure 3).[37] These data suggest that the in vivo life span of transfused platelets cannot be normalized in this setting, even at higher platelet counts. Further studies of platelet transfusion dosage strategies are needed.

**Patient Response**

Patient response to platelet transfusion varies. When thrombocytopenic patients who were undergoing hematopoietic stem cell transplantation were analyzed for platelet corrected count increment after transfusion, a bell-shaped or polynomial distribution was found (Figure 4), and patient-specific factors accounted for this distribution.[38] Factors usually associated with response to platelets (eg, history of previous transfusion, pregnancy, presence of the human leukocyte antigen or platelet-specific antibodies) did not significantly correlate with corrected count increment. These findings suggest that administration of leukoreduced platelets is not clinically important in the prevention of refractoriness to platelet transfusion. Rather, patient-specific variables such as disease status (advanced vs early), conditioning regimen (total body irradiation vs no radiation), progenitor cell source (bone marrow vs PBSC), and type of transplant (allogeneic vs autologous) are significant predictors of platelet refractoriness.[38]

In summary, platelet transfusion dose and patient response to transfusion vary. Moreover, thrombocytopenic patients can be maintained safely at prophylactic transfusion thresholds of 10,000 cells/µL. The likelihood of hemorrhagic complications correlates poorly with the degree of thrombocytopenia in patients receiving myeloablative chemotherapy. These findings, the results of the TRAP study,[23] and our observations indicate that the use of specialized products (apheresis platelets and leukodepleted platelets) needs to be reassessed in the context of emerging technologies.[39]

**Pharmacologic Options forTreating Cancer-Related Thrombocytopenia**

The biologic nature of platelet products, the need for available donors, and the problems associated with platelet use create a need for pharmacologic options to manage cancer-related thrombocytopenia and prevent its attendant morbidity and mortality. At the present time, the marketed and investigational treatment options include interleukin (IL)-11 (Neumega), c-Mpl ligands, and c-Mpl mimetics (Table 6).[40]

**Interleukin-11**

A variety of cytokines have been evaluated in an attempt to identify an effective treatment for chemotherapy-induced or other hypoproliferative thrombocytopenia. Of these, only IL-11 has been approved by the FDA. Although the other cytokines remain under investigation, their development for the treatment of thrombocytopenia has been discontinued.

IL-11 is a cytokine with multiple effects on hematopoietic and nonhematopoietic cells. In vivo, IL-11 stimulates megakaryocytic maturation and produces an increase in circulating platelets. After experimental myeloablation, mice treated with IL-11 exhibited accelerated recovery of trilineal hematopoiesis.[41] Because adult mice with targeted mutations of the IL-11 receptor show normal hematopoiesis, IL-11 does not appear to be essential for this process.[42] Furthermore, the residual megakaryocytopoiesis seen in c-Mpl-deficient mice does not appear to depend on the presence of IL-11.[43] These studies indicate that IL-11 plays an important but secondary role in megakaryocytopoiesis and platelet regulation.

The safety and efficacy of recombinant IL-11 for the treatment of severe chemotherapy-induced
thrombocytopenia was evaluated in a multicenter, placebo-controlled trial.[44] Patients were randomized to receive either placebo or recombinant IL-11 (25 or 50 µg/kg subcutaneously once daily for 14 to 21 days, beginning 1 day after chemotherapy). Among patients who received recombinant IL-11 at 50 µg/kg/d, 30% (8/27) required no platelet transfusions, compared with only 4% (1/27) of those who received placebo (P < .05). Adverse effects of treatment included significant fatigue and edema as well as atrial arrhythmias and syncope. Although recombinant IL-11 showed modest activity in this study and toxicities were a concern, it was the first cytokine to demonstrate efficacy in this setting.

c-Mpl Ligands
Thrombopoietin is the hematopoietic growth factor responsible for megakaryocytic growth, development, and platelet production. Although the existence of thrombopoietin has been postulated for almost half a century, it was not until the early 1990s that real progress was made in identifying this elusive factor. Vigon et al[45] cloned the human homolog of the v-Mpl oncogene transduced in the myeloproliferative leukemia retrovirus and described its striking similarities to members of the hematopoietic growth factor receptor superfamily. Platelet counts in c-Mpl knockout mice are reduced by approximately 90% as a result of reductions in megakaryocyte progenitors and megakaryocyte ploidy.[46] In 1994, cloning of the gene for the c-Mpl ligand led to the identification of thrombopoietin.[47,48] This cytokine promotes the full spectrum of megakaryocyte growth and development.[49]

Two forms of recombinant thrombopoietin were developed for human studies: pegylated recombinant human megakaryocyte growth and development factor and recombinant human thrombopoietin.

Pegylated Megakaryocyte Growth and Development Factor
The recombinant human megakaryocyte growth and development factor consists of the N-terminal 163 amino acids of thrombopoietin. The molecule has been linked covalently to polyethylene glycol to extend its half-life. Subcutaneous administration of the pegylated form of this cytokine has been studied in myelosuppression, myeloablation, and platelet mobilization in normal donors.[50,51-53] However, it was withdrawn from clinical trials after reports that neutralizing antibodies had developed in cancer patients[54] and normal subjects[51] who were receiving multiple doses.

Recombinant Human Thrombopoietin
Recombinant human thrombopoietin is the full-length glycosylated molecule, homologous to human endogenous thrombopoietin, produced in genetically modified Chinese hamster ovarian cells. In clinical studies, this agent has reduced the severity of chemotherapy-induced thrombocytopenia and the need for platelet transfusions, and exhibited a multilineage stimulatory effect on the expansion and mobilization of bone marrow progenitor cells into the peripheral blood.[55-57]

Early studies of recombinant human thrombopoietin in sarcoma patients demonstrated that a single dose (0.3 to 2.4 µg/kg) administered 3 weeks before dose-intensive chemotherapy with doxorubicin and ifosfamide (Ifex) resulted in a dose-dependent increase from baseline in the mean number of circulating platelets (61% to 213%, P = .002). This effect on platelet counts was observed as early as day 4 and peaked on day 12.[57] When given after chemotherapy with doxorubicin and ifosfamide, recombinant human thrombopoietin reduced the severity of thrombocytopenia in some patients, but the nadir platelet values for the group as a whole did not differ significantly between cycle 1 and cycle 2.[58]

The results of these studies indicate that recombinant human thrombopoietin is effective in reducing chemotherapy-induced thrombocytopenia. Moreover, the data suggest that optimizing the schedule of thrombopoietin administration is important for optimal attenuation of the cumulative thrombocytopenia associated with this regimen.

A subsequent study evaluated the effect of recombinant human thrombopoietin administered subcutaneously to patients with gynecologic malignancies who were being treated with carboplatin (Paraplatin) at an area under the concentration-time curve [AUC] of 11.[59] In this study, thrombopoietin given every other day for four doses after carboplatin administration effectively reduced the depth of the platelet nadir and the duration of severe thrombocytopenia. At the optimal biologic dose (1.2 µg/kg), recombinant human thrombopoietin doubled the platelet nadir count (20 × 10^9/L vs 44 × 10^9/L in cycles 1 and 2, respectively) and reduced the platelet transfusion requirement from 75% in cycle 1 (without recombinant thrombopoietin) to 25% in cycle 2 (with recombinant thrombopoietin).[59] In addition, thrombopoietin enhanced platelet count recovery, with 67% of thrombopoietin-treated patients recovering platelets (≥ 100 × 10^9/L) by day 21 in cycle 2, compared with only a 37% recovery in cycle 1.

Recombinant human thrombopoietin is well tolerated and exhibits a favorable safety profile. To date,
1 patient of 28 who received subcutaneous doses developed a transient, low-titer antibody that was partially inhibiting on bioassay.[55] However, no antibodies have been detected in more than 500 patients who received intravenous doses.

**c-Mpl Ligand Mimetics**

Other pharmacologic agents can be designed to mimic the activities of thrombopoietin at the c-Mpl receptor. GW395058, a potent pegylated peptide human thrombopoietin receptor agonist,[60,61] is currently being investigated in preclinical trials for the treatment of thrombocytopenia. In a canine model of carboplatin-induced thrombocytopenia, animals treated with GW395058 had a 2.7-fold reduction in the platelet nadir, compared with a vehicle-alone group.[61] Another approach is the synthesis of a monoclonal antibody (BAH-1) with agonist activity directed specifically against the human c-Mpl receptor.[62] The eventual role of c-Mpl ligand mimetics awaits further development of these and other compounds.

**Conclusions**

Thrombocytopenia remains a common problem among cancer patients. Although platelet transfusions are efficacious when administered prophylactically or for the treatment of thrombocytopenic bleeding, they are expensive and associated with a variety of adverse events. Examination of transfusion triggers suggests that the threshold for prophylactic platelet transfusion should include not only a patient’s relative risk of bleeding (as reflected in platelet count) but also the patient’s absolute risk (a function of platelet numbers, physiology, disease state, and presence or absence of comorbidities). A variety of pharmacologic options, including recombinant IL-11, recombinant thrombopoietin, and c-Mpl ligand mimetics, offer the possibility of managing thrombocytopenic bleeding in the hematology/oncology population. Although recombinant IL-11 is modestly effective in increasing platelet counts in patients with thrombocytopenia after chemotherapy, it can trigger significant adverse effects. The cloning of the c-Mpl ligand, its identification as thrombopoietin, and clinical trials of the recombinant molecule suggest that recombinant thrombopoietin may complete the hematopoietic triad that now includes recombinant erythropoietic agents and colony-stimulating factors. Ongoing trials of recombinant thrombopoietin will help determine the most effective treatment schedule and aid in targeting indications for this hematopoietic growth factor.

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