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## **rhIL-11 for the Prevention of Chemotherapy-Induced Thrombocytopenia**

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# Dose Reductions and Delays: Limitations of Myelosuppressive Chemotherapy

**T**hrombocytopenia in patients with cancer has multiple origins. Disease-related causes include reduced thrombopoiesis in cancers with bone marrow involvement and tumor-induced disseminated intravascular coagulopathy as seen in mucinous prostatic, lung, ovarian, and gastrointestinal adenocarcinomas.[1] However, the use of chemotherapy with or without radiation therapy is the most common cause of clinically significant thrombocytopenia.[1,2] The National Cancer Institute offers a grading system for determining the severity based on platelet counts (Table 1).

Data from two large, retrospective studies conducted at the Baltimore Cancer Research Center (n = 1,274) and The University of Texas M. D. Anderson Cancer Center in Houston (n = 3,682) indicate that clinically significant reductions in platelet counts to nadirs < 50,000/ $\mu$ L occur in approximately 20% to 25% of patients receiving dose-intensive myelosuppressive chemotherapy for solid tumors or lymphoma.[3,4] In approximately 10% to 15% of these patients, platelet counts fall below 20,000/ $\mu$ L.

The risk of the development of thrombocytopenia is aggravated by the

## ABSTRACT

*Thrombocytopenia occurs at various grades of severity in patients with nonmyeloid malignancies undergoing chemotherapy with myelosuppressive agents. Frequently, it is the major dose-limiting hematologic toxicity, especially in the treatment of potentially curable malignancies such as leukemia, lymphomas, and pediatric cancers. This is becoming increasingly important given the recent trend toward the use of dose-intensive combination chemotherapy regimens facilitated by supportive hematopoietic colony-stimulating factors to prevent chemotherapy-induced febrile neutropenia. The standard preventive measure against chemotherapy-induced depression of platelets in subsequent treatment cycles has been dose reduction and/or dose delay. However, follow-up data from studies in various populations of patients with cancer suggest a correlation between delivery of lower than intended doses and poor outcomes, including reduced disease-free periods and overall survival. Other consequences of thrombocytopenia include the need for platelet transfusions and subsequent exposure to the risk of numerous complications, including bacterial and viral infections; febrile, nonhemolytic transfusion reactions; and transfusion-induced immunosuppression. Furthermore, a large proportion of multitransfused patients become refractory to subsequent infusions. Refractoriness to platelet transfusions is quickly becoming more prominent. The availability of a platelet growth factor—recombinant human interleukin-11 (rhIL-11, also known as oprelvekin [Neumega])—provides an effective means of preventing chemotherapy-induced thrombocytopenia and accelerating platelet recovery, thereby facilitating the administration of full doses of chemotherapy during subsequent cycles and avoiding the need for rescue with platelet transfusions.*

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use of dose-intensive chemotherapy, with or without the support of hematopoietic colony-stimulating factors for the amelioration of chemotherapy-associated febrile neutropenia.[5-7] Providing hematopoietic support with pe-

ripheral blood stem-cell transplantation during multiple cycles of high-dose chemotherapy does not prevent cumulative thrombocytopenia or enhance platelet recovery.[8] In fact, Spitzer et al[8] reported a significant delay in platelet re-

Table 1

## National Cancer Institute Grading System for Severity of Thrombocytopenia

Adverse Event	0	1	2	3	4
Platelets	WNL	< LLN - 75.0 × 10 <sup>9</sup> /L < LLN - 75,000/μL	≥ 50.0 - < 75.0 × 10 <sup>9</sup> /L ≥ 50,000 - < 75,000/μL	≥ 10.0 - < 50.0 × 10 <sup>9</sup> /L ≥ 10,000 - < 50,000/μL	< 10.0 × 10 <sup>9</sup> /L < 10,000/μL
For BMT studies	WNL	≥ 50.0 - < 75.0 × 10 <sup>9</sup> /L ≥ 50,000 - < 75,000/μL	≥ 20.0 - < 50.0 × 10 <sup>9</sup> /L ≥ 20,000 - < 50,000/μL	≥ 10.0 - < 20.0 × 10 <sup>9</sup> /L ≥ 10,000 - < 20,000/μL	< 10.0 × 10 <sup>9</sup> /L < 10,000/μL
For leukemia studies or bone marrow infiltrative/myelophthisic process	WNL	10% - < 25% decrease from baseline	25% - < 50% decrease from baseline	50% - 75% decrease from baseline	≥ 75% decrease from baseline

BMT = bone marrow transplant; LLN = lower limit of normal; WNL = within normal limits.

covery after the second cycle compared with that seen following the first cycle of high-dose myelotoxic chemotherapy (cyclophosphamide [Cytoxan, Neosar], carmustine [BiCNU], etoposide) in patients with lymphoma, despite infusion. After cycle 2, the platelet recovery time to 100,000/μL ranged from 10 to 267 days vs 12 to 53 days after cycle 1; 8 to 267 days to 50,000/μL vs 9 to 53 days after cycle 1; and 8 to 101 days to 20,000/μL vs 8 to 28 days after cycle 1.

### Thrombocytopenia Associated With Myelosuppressive Chemotherapy

Megakaryocytic suppression and recovery occur rapidly following treatment with cell-cycle-specific chemotherapeutic agents. In contrast, with cell-cycle-nonspecific agents—such as busulfan (Myleran), nitrosourea, mitomycin (Mutamycin), and platinum complexes—suppression occurs more gradually but is more persistent. With the latter agents, recovery from myelosuppression may take up to 50 days or longer, depending on the extent of suppression.[9] These agents affect proliferating platelet precursors rather than mature platelets. Therefore, thrombocytopenia gradually develops over 7 to 10 days, and platelet counts < 20,000/μL generally occur by about day 10 after the start of myelotoxic chemotherapy.[8] It should be noted, however, that because changes in peripheral platelet counts lag behind changes in bone marrow production, at a given point in time the platelet count does not reflect the level of megakaryocytopoietic activity.

Chemotherapy-induced thrombocytopenia increases in severity with in-

creased intensity of treatment,[10] with the combined use of cycle-specific and cycle-nonspecific chemotherapeutic agents (which is often the case [Table 2]), and with the adjuvant use of radiation therapy and highly myelosuppressive drugs.[2] The combined use of cycle-specific and cycle-nonspecific agents also produces thrombocytopenia of more prolonged duration. Moreover, particular treatment regimens appear to be associated with high rates of severe thrombocytopenia. For example, World Health Organization grades 3/4 thrombocytopenia (platelet counts < 50,000/μL) have been reported at rates of 48% among patients treated with doxorubicin 20 mg/m<sup>2</sup>/d, ifosfamide (Ifex) 2,500 mg/m<sup>2</sup>/d, and dacarbazine (DTIC-Dome) 300 mg/m<sup>2</sup>/d (MAID) for advanced sarcoma;[11] > 50% with ifosfamide 5 g/m<sup>2</sup>, carboplatin (Paraplatin) 400 mg/m<sup>2</sup>, and etoposide at doses ranging from 300 to 1200 mg/m<sup>2</sup> for non-small-cell lung cancer;[5] and 24% to 33% with paclitaxel (Taxol) 135 mg/m<sup>2</sup> (one dose), ifosfamide 1,200 mg/m<sup>2</sup>/d, and cisplatin (Platinol) 30 mg/m<sup>2</sup>/d for ovarian cancer.[12]

Thrombocytopenia also interferes with other modalities of cancer treatment, such as radiation therapy. In a case-control study involving 45 patients with malignant disease, MacManus et al retrospectively evaluated risk factors for unscheduled interruptions in radiotherapy associated with platelet counts < 50,000/μL or significant neutropenia.[2] Multivariate analysis identified concurrent administration of myelotoxic chemotherapeutic agents (most commonly in this study cisplatin, methotrexate, fluorouracil, vincristine, cyclophosphamide, doxorubicin, and

etoposide) as one of the strongest risk factors for interruption of radiotherapy due to thrombocytopenia (odds ratio: 45.5; *P* < .001 vs controls).

The total cumulative percentage of bone marrow irradiated was also a strong risk factor. The relative contributions of chemotherapy and radiation therapy to thrombocytopenia depend on the amount of bone marrow in the radiation field. For example, chemotherapy would be the primary contributing factor in patients receiving small-field radiation therapy. Using the results of the multivariate analysis and regression analysis, the authors estimated that 49% (22/45) of patients would be at high risk for thrombocytopenia. They also suggested that these high-risk patients may be candidates for clinical trials of a platelet growth factor.

### **Increased Severity With Dose-Intensive Chemotherapy**

Over the past 10 to 15 years, there has been a trend toward escalation of chemotherapy dose intensity with the intent of achieving cure or prolonged remission in patients with hematologic[13] and solid tumor malignancies, including ovarian cancer,[6,14,15] small-cell lung cancer,[16] testicular cancer,[17,18] and breast cancer.[10,19,20] (For breast cancer, recent trials have suggested no benefit in clinical outcomes from such dose escalation; however, longer follow-up and subset analyses are required.) This trend has been accompanied by an increased incidence of severe, prolonged thrombocytopenia, which has now become a major dose-limiting hematologic toxicity.[5,6,15,21,22] In two studies of patients with previously untreated

ovarian cancer and residual disease after primary laparotomy, combination therapy with high-dose carboplatin and cisplatin, and ifosfamide therapy for six cycles (n = 37),[6] and cisplatin, carboplatin, and cyclophosphamide for up to eight cycles (n = 44),[15] resulted in platelet nadirs < 50,000/ $\mu$ L in 100% and 66% of patients, respectively.

Furthermore, the increasing use of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]) to reduce the risk of chemotherapy-induced severe neutropenia during dose-intensive cancer chemotherapy regimens[5,21,23] appears to be associated with more severe and protracted thrombocytopenia,[7,22] likely because the chemotherapy tolerance is improved. Whereas neutropenia would have previously been dose limiting, now it is no longer so. This is well illustrated by findings in 37 young adult and pediatric patients newly diagnosed with sarcoma who received intensive combination chemotherapy and radiation therapy either with or without GM-CSF support.[7] Patients treated concomitantly with GM-CSF had significantly lower median platelet nadirs (29,500/ $\mu$ L vs 59,000/ $\mu$ L, respectively;  $P < .0001$ ) and required a significantly longer median time to recovery to platelet count > 75,000/ $\mu$ L (16 days vs 14 days, respectively;  $P < .0001$ ), compared with patients not treated with GM-CSF.

In a study of patients with advanced breast cancer, dose-intensive chemotherapy with G-CSF support was associated with a 17% incidence of low platelet counts (< 50,000/mL) compared with 0% among patients who received a less intensive regimen without G-CSF support ( $P < .002$ ).[21] Depressed platelet counts contributed to a higher incidence of treatment delays in the higher dose-intensive group, compared with the latter group (21% vs 8%, respectively;  $P < .0001$ ).[21]

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### Treatment Delays

During the use of combination chemotherapeutic regimens for nonmyeloid malignancies, the standard response of physicians to the development of thrombocytopenia is dose reductions and/or delayed administration of the next cycle of chemotherapy (Table 2). This is also the response of treating physicians for patients receiving combined-modality therapy (chemotherapy and radiation therapy). In the study conducted by MacManus et al, thrombocytopenia forced the interruption of radiation therapy for 3 days or more in 98% (44/45) of patients, 27% (12/45) of whom had at least one measurement of platelet count < 25,000/ $\mu$ L.[2] In addition to treatment interruption, the planned radiation dose was reduced by > 10% in 51% of the cases, vs 11% of controls (radiation therapy only).

During myelosuppressive chemotherapy, the administration of subsequent cycles is routinely delayed until the platelet count has recovered to 100,000/ $\mu$ L, as mandated by almost all of the protocols for investigations of chemotherapeutic regimens seen in Table 2.[5,11,12,24-27] In these studies, treatment was delayed for 1 to 4 weeks if this platelet threshold was not reached.

Elting et al retrospectively reported that among 500 patients receiving chemotherapy for solid tumors or lymphoma, reduction in platelets to < 50,000/ $\mu$ L resulted in the delay of a chemotherapy cycle by more than 7 days in 8% of patients.[28]

### Dose Reductions

The practice of reducing doses in response to prolonged myelosuppression is demonstrated in the studies in Table 2. In the event of slow platelet recovery[11,24,26,27,29,30] or persistence of platelet counts < 50,000/ $\mu$ L [11,24,30-32] or even 75,000/ $\mu$ L to 100,000/ $\mu$ L,[22,27] chemotherapy was significantly deescalated, often by reducing drug doses by up to 50%. In the breast cancer study of Fetting et al, no chemotherapy was to be administered if the platelet count was < 50,000/ $\mu$ L.[25]

In a dose-escalation study in 24 patients with solid tumors or non-Hodgkin's lymphoma, cumulative thrombocytopenia (defined as platelet count < 25,000/ $\mu$ L) was the major dose-

limiting toxicity.[5] This study was conducted to evaluate the feasibility of escalating the dose of etoposide from 300 mg/m<sup>2</sup> to 600, 900, or 1,200 mg/m<sup>2</sup> in a dose-intensive ifosfamide, carboplatin, and etoposide (ICE) regimen with GM-CSF support. At all dose levels of etoposide, clinically significant thrombocytopenia developed after multiple treatment cycles; by cycle 3,  $\geq 50\%$  of patients required platelet transfusions to maintain a platelet count > 20,000/ $\mu$ L.

Thrombocytopenia in conjunction with neutropenia led to dose reductions in most patients who received more than three cycles of therapy. Cumulative thrombocytopenia was the major factor limiting the escalation of etoposide doses above 900 mg/m<sup>2</sup>. Continued decline in nadir platelet counts over successive cycles and subsequent dose limitation have been reported in other studies in which GM-CSF support was provided.[22] These findings support the predictability of low platelet nadirs following successive cycles in patients who develop thrombocytopenia during the first cycle.

### Clinical Consequences of Low Platelets and Thrombocytopenia

#### Compromised Chemotherapy Outcome

The standard practice of reducing the dose of chemotherapeutic drugs and/or delaying treatment to avoid the risk of clinically significant bleeding secondary to thrombocytopenia could result in suboptimal outcome, including reduced antitumor efficacy and/or reduced survival rates or shorter duration of remission.[10,13,33-35]

The study of Bonadonna et al has provided the longest follow-up data for analysis of the relationship between delivered dose and survival outcome.[33] In this study, patients received either 12 cycles of adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy or no chemotherapy after radical mastectomy for primary breast cancer with positive axillary lymph nodes. Chemotherapy doses were reduced in older patients (> 60 years) and if myelosuppression was present. A total of 386 women, including 179 who received no chemotherapy after mastectomy (control group) and 207 who received

Table 2

### Reported Occurrence of Thrombocytopenia and Subsequent Treatment Reduction in Patients Receiving Combination Chemotherapy Regimens for Nonmyeloid Malignancies

Chemotherapeutic Regimen	Cancer Type	Thrombocytopenia Grade <sup>a</sup>	Incidence	Treatment Modification	Reference
Cyclophosphamide, doxorubicin, fluorouracil (CAF)	Breast	1	45%	If day 1 platelet count < 100,000/ $\mu$ L, treatment delayed up to 2 weeks	Fetting et al[25]
		2	8%		
		3	3%		
		4	1%		
Cyclophosphamide, doxorubicin, vincristine, methotrexate, fluorouracil, leucovorin	Breast (advanced)	4	70%	If platelet count < 50,000, chemotherapy delayed	Osborne et al[22]
				If platelet counts between 50,000 and 75,000, planned doses reduced by 50%	
Ifosfamide, doxorubicin (AI)	Sarcoma	2	5%	If platelets < 40,000/ $\mu$ L, dose of both drugs reduced by 20%; if platelets < 100,000 at next scheduled treatment, further therapy delayed for 1 week; if treatment delayed for > 1 week for two consecutive courses, dose reduced by 20%	Schutte et al[24]
				If treatment delayed for > 3 weeks without hematologic recovery, treatment discontinued	
Mesna, doxorubicin, ifosfamide, dacarbazine (MAID)	Sarcoma	1/2	68%	Cycle delayed until platelets at 100,000; if platelet nadir < 50,000, dacarbazine dose reduced by 50%	Elias et al[11]
		3/4	48%		
Cisplatin, etoposide (EP)	Small-cell lung	1	12%	If platelets < 100,000, dose delayed 1 week; if platelets 75 to 100,000 at 4 weeks, doses of both drugs reduced by 50%	Boni et al[27]
		2	5%		
		3	7%		
		4	2%		
Ifosfamide, carboplatin, etoposide (ICE)	Non-small-cell lung	4	> 50%	If platelets < 100,000, treatment delayed 1 week	Krigel et al[5]
Cyclophosphamide, cisplatin or carboplatin	Ovarian	<i>Cisplatin</i>		If platelets < 100,000, treatment delayed for 2 weeks; if no recovery by day 42 but platelets > 50,000, cyclophosphamide and carboplatin dose reduced by 50%, cisplatin dose by 40%	Hannigan et al[26]
		2	9%		
		3	6%		
		4	2%		
		<i>Carboplatin</i>			
		2	21%		
3	17%				
4	7%				
Paclitaxel, carboplatin	Ovarian	1	8%	If platelet recovery required 2 weeks, next courses repeated every 4 weeks with carboplatin dose reduced by 25%; if grade III or IV thrombocytopenia occurred, dose of both drugs reduced by 25% or 50%, respectively	Skarlos et al[30]
		2	8%		
		4	4%		
Paclitaxel, ifosfamide, cisplatin	Ovarian	4	24%–33%	If platelets < 100,000, next dose postponed for up to 4 weeks; if grade IV thrombocytopenia occurred, paclitaxel and ifosfamide dose reduced	Veldhuis et al[12]
		Platelet nadir: day 12–25			

Continued

Table 2, Continued

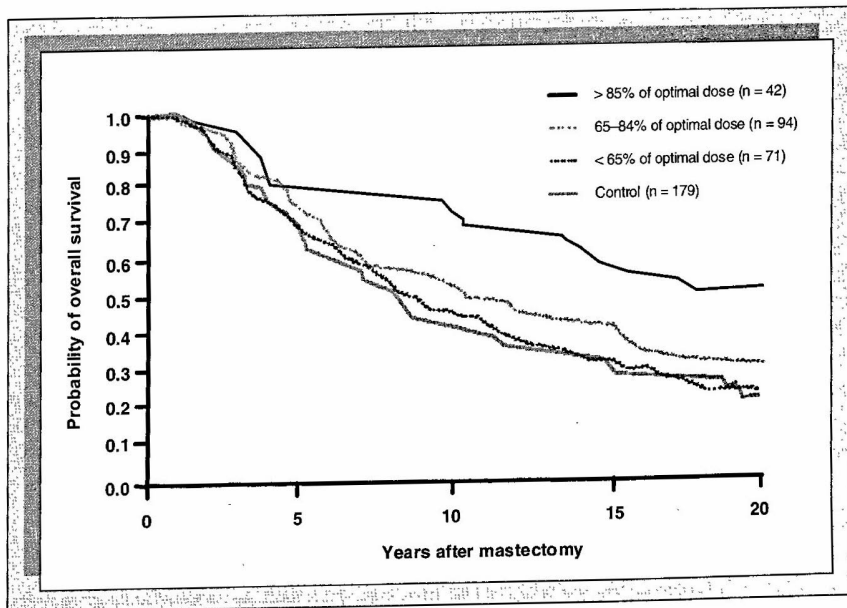
Chemotherapeutic Regimen	Cancer Type	Thrombocytopenia Grade <sup>a</sup>	Incidence	Treatment Modification	Reference
Etoposide, doxorubicin, cisplatin (EAP)	Gastric	1	36%	If platelets < 50,000/ $\mu$ L, etoposide dose reduced by 20%	Preusser et al[31]
		2	19%		
		3	21%		
		4	7%		
Etoposide, methylprednisolone, cisplatin, cytarabine (ESHAP)	Lymphoma (refractory and relapsing)	Median platelet nadir 70,000		If platelets $\leq$ 20,000, cytarabine dose reduced by 50% and etoposide dose by 20% for all future courses	Velasquez et al[29]
Prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate, leucovorin (ProMACE-CytaBOM)	Lymphoma	7% of patients required platelet transfusion		If platelets 50,000 to 99,000, etoposide and cytarabine doses reduced by 50%, cyclophosphamide and doxorubicin by 25%	Longo et al[32]
				If platelets < 50,000, methotrexate dose reduced by 50%	
Etoposide, ifosfamide, cisplatin (VIHP)	Germ-cell	4	Up to 48%	If severe myelotoxicity occurred, ifosfamide and etoposide dose reduced by 30%	Ghosn et al[33a]

<sup>a</sup> Grade of thrombocytopenia according to the World Health Organization classification system based on platelet count ( $\mu$ L): 0 = >100,000; 1 = 75,000–99,000; 2 = 50,000–74,000; 3 = 25,000–49,000; 4 = < 25,000.

adjuvant combination chemotherapy, were followed for approximately 20 years.

Survival outcomes at the 20-year analysis showed a disease (relapse)-free survival rate of 49% and an overall survival rate of 52% in 42 women who received 85% or more of the planned dose of CMF. In comparison, women who received less than 85% of the planned dose had markedly inferior survival rates (Figure 1). Disease-free and overall survival rates were 30% and 25%, respectively, among women who received < 65% of the optimal CMF dose, and 33% and 32%, respectively, among women who received 65% to 84% of the optimal dose. The overall survival rate among women who received CMF at doses reduced by 35% or more (ie, < 65% of the optimal CMF dose) was identical to the rate in the control group (25%). Myelosuppression was the main reason for dose reduction in this study. Of course, other confounding factors of comorbidity and disease severity cannot be excluded by this retrospective subset analysis.

Results consistent with Bonadonna's findings were provided by a large (n = 1,572) randomized prospective study (Cancer and Leukemia Group B [CALGB] study 8541) that evaluated outcome effects following treatment



**Figure 1: Overall Survival**—Superior 20-year overall survival rates among women with node-positive breast cancer who received 85% or more of the optimal doses of adjuvant cyclophosphamide, methotrexate, and fluorouracil following mastectomy, compared with women who received less than 85% of the optimal chemotherapy dose. Survival was estimated by Kaplan-Meier method. (Reprinted with permission from Bonadonna et al.[33])

with three different dose levels of cyclophosphamide, doxorubicin, and fluorouracil.[10] This study observed significantly ( $P \leq .05$ ) longer disease-

free survival and overall survival rates after a median of 3.4 years among women treated with "high" or "moderate" dose intensity regimens, compared



Table 3

### Potential Complications (Incidence, Where Data Are Available) of Platelet Transfusions<sup>a</sup>

Refractoriness to platelet transfusion (30%–70%)	Alloimmunization (20%–70%)
Infection	Hepatitis A
	Hepatitis B (1/200,000 units)
	Hepatitis C (1/100,000 units)
	Hepatitis non-A/B/C
	Hepatitis G/GB
	HIV [1/450,000 to 1/660,000]
	Cytomegalovirus (CMV) 30% <sup>b</sup>
	Bacterial (0.4%)
Graft-vs-host disease	
Immunomodulation of tumor biology	
Transfusion reactions (30%)	

<sup>a</sup>Data from references 1,41,42.

<sup>b</sup>Risk from unscreened blood products for CMV-seronegative recipient of a CMV-seronegative graft.[41]

with women treated with less intense doses.

However, the doses used in the study were within the conventional range, including those used in the high dose intensity regimen (cyclophosphamide 600 mg/m<sup>2</sup> and doxorubicin 60 mg/m<sup>2</sup> on day 1, and fluorouracil 600 mg/m<sup>2</sup> on days 1 and 8). This study clearly demonstrates, however, that clinical benefit is significantly reduced if administered chemotherapy doses are less than the standard doses. The 3-year disease-free survival rate associated with a low-intensity regimen (ie, 50% lower than the doses in the high-intensity regimen) was 11% less than that seen in the high-intensity regimen.

Several other studies that evaluated the outcomes of different doses of chemotherapeutic agents have shown significantly ( $P < .05$ ) superior overall survival rates at conventional doses compared with reduced doses in patients with various solid tumors. These include studies of variable doses of cisplatin and cyclophosphamide in conjunction with unchanged doses of doxorubicin and etoposide for treatment of small-cell lung cancer (43% vs 26% at 2 years;  $P = .02$ );[16] variable doses of cisplatin

and unchanged doses of cyclophosphamide (32% vs 27% at 4 years;  $P = .04$ ) for advanced ovarian cancer;[14] and variable doses of cisplatin combined with unchanged doses of vinblastine and bleomycin (83% vs 58% at 2 years;  $P = .009$ ; rates estimated from graph) for testicular cancer.[17]

A third study also showed a statistically significantly decrease in the 2-year overall survival rate among patients who received an ACVB (doxorubicin, cyclophosphamide, vindesine, bleomycin) induction regimen for aggressive lymphoma at a relative dose intensity less than 70% of the optimum dose intensity (61% vs 72%;  $P = .02$ ).[35] This study differs from the previously described studies in that the reduction in relative dose intensity was due to toxicity-dependent treatment delays rather than dose reduction.

Data from radiotherapy studies also support the importance of delivering the total planned treatment to a given patient to achieve maximum benefit. An analysis of pooled data from trials performed by the Radiation Therapy Oncology Group (RTOG) showed reduced local tumor control and reduced long-term survival rates in patients with nonresectable non-small-cell lung cancer as a result of unscheduled interruptions in treatment.[36] It is speculated that treatment interruption allows for the repopulation of tumor cells.[37]

Data from several small trials suggest improvement in survival benefit with the use of higher than standard doses of chemotherapy in patients with solid tumor malignancies, including adults with metastatic breast cancer[19] or ovarian cancer[14] and children with Burkitt's lymphoma[38] or neuroblastoma.[39] Although the benefit of higher than standard doses remains highly controversial,[13,40] the consensus regardless of the type of malignancy is that the use of lower than standard doses is associated with poorer outcomes.

Taken together, these data underline the importance of avoiding both treatment delays and dose reductions if maximum benefit is to be achieved.

### Platelet Transfusions

Platelet transfusions have been the mainstay of treatment for thrombocytopenia for decades. They are recognized as an effective short-term "rescue"

treatment for chemotherapy-induced severe thrombocytopenia and are widely used for this indication.[41] However, platelet transfusions are associated with clinically relevant risks of several immunologic and nonimmunologic complications (Table 3).[1,41,42]

### Immunologic Complications

After one or more platelet transfusions, a high percentage of patients (30% to 70%) risk becoming refractory to subsequent transfusions, the main cause being alloimmunization to class I HLA antigens on platelets and, less commonly, to platelet-specific antigens.[1,41] Approximately 20% to 70% of patients receiving random donor platelet transfusions develop alloantibodies to platelets,[42] although not all of these patients become refractory to further platelet transfusions.[1] The development of alloimmunization necessitates donor-recipient HLA matching for subsequent transfusions.[1,41] However, provision of HLA-identical platelet products is logistically difficult and costly, and products that are mismatched for cross-reactive HLA antigens are often provided. Thus, approximately 20% to 40% of platelet products that are considered "closely HLA-matched" produce unsatisfactory results; this may be due to the presence of antibodies to minor histocompatibility antigens, platelet-specific antigens, or cross-reactive HLA antigens.[41] For some alloimmunized patients, compatible platelet donors cannot be found.

Other factors that contribute to the refractory state are infusion of platelets stored for  $\geq 5$  days and underlying clinical factors leading to increased platelet consumption or sequestration (including splenomegaly, bone marrow transplantation, fever, infection, administration of amphotericin B, bleeding, and disseminated intravascular coagulopathy). In some patients, nonimmune factors, such as a combination of fever, infection, and antibiotic therapy, may be more important than immune factors as the cause of refractoriness to platelet transfusion.[41]

Transfusion-associated graft-vs-host disease is mediated by the transfusion of immunocompetent T lymphocytes contained in allogeneic blood products, resulting in significant bone marrow hypoplasia and pancytopenia, usually leading to rapid fatality.[41] Patients

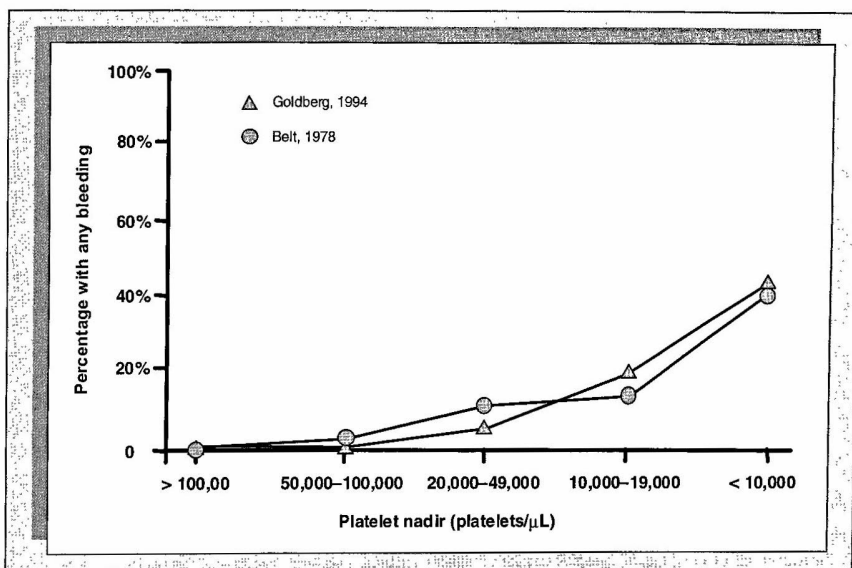
undergoing intensive chemotherapy and/or radiotherapy for malignancies, particularly those with advanced solid tumors receiving high-dose cytotoxic/immunosuppressive therapies, as well as patients receiving hematopoietic stem-cell transplants, are at increased risk for this complication.[41,42]

Transfusion-induced immunosuppression and subsequent immunomodulation of tumor biology with enhancement of tumor growth in patients with cancer is a controversial potential complication of platelet transfusion.[43] Of 7 prospective and 63 retrospective studies that examined the influence of allogeneic blood transfusions on the rate of tumor recurrence and survival among patients with a variety of solid tumors, 60% (43/70) of the studies reported a significant adverse effect.[43] The mechanism of this putative transfusion-associated immunosuppression is unknown but may be related to defects in the host immune system.[41]

Febrile nonhemolytic transfusion reactions occur frequently among recipients of random donor platelet transfusions at an incidence many times higher than the incidence with red blood cell transfusions (30% vs 0.5% to 3%, respectively).[1,42] A common cause of these reactions is alloimmunization to antigens on platelets (or leukocytes).[42] Potential causes include donor leukocytes in transfused product, cytokines (interleukin [IL]-1, IL-6, or tumor necrosis factor) released from leukocytes, histamine released from basophils, and serotonin released from stored platelets.[1] Direct infusion of pyrogens contained in the platelet-concentrate plasma may also be a cause.

### Nonimmunologic Complications

Infection secondary to transmission of viruses and bacteria via platelet transfusion is a common concern for patients, and the risk is increased in those who are immunocompromised or who receive multiple transfusions.[1] Viral hepatitis, particularly hepatitis B and hepatitis C, is the most clinically important transfusion-transmitted infection; donor testing and vaccination has reduced but not eliminated the occurrence of transfusion-associated hepatitis.[42] There is a recent report[44] of hepatitis G virus detected in 48% (29/60) of multitransfused patients with he-



**Figure 2: Bleeding With Thrombocytopenia**—Inverse relationship between risk of bleeding and platelet nadir.[46,47]

matologic malignancy. An association between testing positive for hepatitis G and hepatic dysfunction as assessed by serum aspartate transaminase (AST) levels was not apparent. However, there is concern that, like hepatitis C, hepatitis G virus infection could lead to chronic liver disease.

Cytomegalovirus (CMV) infection transmitted through transfused blood components is an important cause of morbidity and mortality among immunosuppressed patients. In CMV-seronegative recipients of CMV-seronegative grafts, the risk of primary infection from unscreened blood products is approximately 30%; this risk is reduced to < 5% by exclusive use of CMV-seronegative and, more recently, leukocyte-reduced blood components.[41] However, in CMV-seronegative recipients of CMV-seropositive grafts, the risk of CMV infection is not reduced by the use of CMV-seronegative blood components. Among CMV-seropositive recipients, the reported incidence of CMV infection is high (69%), regardless of the serostatus of the donor, possibly reflecting the reactivation of the endogenous virus.

Platelet transfusions are associated with a much higher incidence of bacterial infections and related deaths than red blood cell infusions, possibly because of the need for storage at room

temperature.[1,45] An estimated 1 in 1,000 units of platelets is contaminated. The risk, therefore, of receiving a bacterially contaminated platelet transfusion is far greater than the combined risk of receiving an HIV-, hepatitis B-, or hepatitis C-contaminated blood product.[45]

Transfusion of bacterially contaminated platelets accounted for 21 of 29 deaths due to blood products that were reported to the US Food and Drug Administration (FDA) between 1986 and 1991.[45] Both gram-negative and gram-positive organisms have been isolated in these blood products. The most common organisms implicated in platelet transfusion-related fatalities, in descending order, are *Staphylococcus*, *Klebsiella*, *Serratia*, and *Streptococcus* species.[45] Patients with cancer, who represent a large population of platelet recipients, are at high risk for transfusion-transmitted bacterial infection because of chemotherapy-induced immunosuppression.

### Bleeding Risk

The risk of bleeding is inversely related to platelet count in patients with solid tumors and lymphomas (Figure 2).[46,47] Belt et al reported bleeding in the following percentages of patients according to platelet nadir: 10% at platelet nadir between 20,000/μL and 50,000/μL over 197 cycles, 12% at

Table 4

**Proposed Platelet Transfusion Protocol for Prophylaxis**

Morning Platelet Count	Indication for Prophylactic Platelet Transfusion
≤ 5,000/μL	Always
6,000–10,000/μL	In the presence of fresh minor hemorrhage or fever (body temperature > 38°C)
11,000–20,000/μL	In the presence of coagulation disorders and/or heparin therapy; before bone marrow biopsy or lumbar puncture
> 20,000/μL	In the presence of major bleeding; before minor surgical procedures (other biopsies, central venous catheter insertion, arterial punctures)

Reprinted with permission from Gmur J et al.[51]

platelet nadir between 10,000/μL and 20,000/μL over 52 cycles, and 38% at platelet nadir < 10,000/μL over 21 cycles.[46]

Risk factors for hemorrhage due to chemotherapy-induced platelet reductions include a previous history of bleeding, poor bone marrow reserve (indicated by either a baseline platelet count of < 75,000/μL or bone marrow metastasis) presence of a potential bleeding site (such as necrotic tumor), and chemotherapy regimens with high myelosuppressive potential.[48] The presence of coagulopathy or infection may also aggravate the risk.[3]

Despite the widely held view that hemorrhage is more likely in patients with platelet counts below 20,000/μL, [49] there is great interpatient variability in the risk of bleeding at any specific platelet count.[41] For example, in a study of patients with solid tumors or lymphoma (n = 1,274), Dutcher et al found that the majority (84%, 37 of 44) of serious bleeding episodes occurred at platelet counts between 20,000/μL and 50,000/μL, not at platelet counts < 20,000/μL.[3] Only seven bleeding episodes began when platelet counts fell below 20,000/μL. Factors that increase the risk of bleeding for a given degree of thrombocytopenia and that may be relevant to patients receiving chemotherapy include mucositis or other anatomic lesions, rapidly falling platelet count, fever, and systemic infection.[41] Furthermore, in the study of Dutcher et al, 30% of bleeding episodes were related to the tumor mass and did not always respond to platelet transfusions.

**Prevention of Chemotherapy-Induced Thrombocytopenia****Platelet Transfusions**

In the United States, platelet transfusions are widely used as a rescue measure to avoid bleeding when platelet counts fall below 20,000/μL in patients receiving chemotherapy.[50] This practice is based on a study of leukemia patients conducted in the early 1960s,[49] which showed an increased risk of bleeding below this platelet threshold. However, recent data support setting lower thresholds of ≤ 10,000/μL for prophylactic platelet transfusions for most patients (Table 4).[51] Higher thresholds are appropriate for patients with concurrent coagulation disorders, major bleeding, rapidly falling platelet counts, or those undergoing invasive procedures.[3,46,51] However, platelet transfusions put recipients at risk for several complications as discussed previously.

Until the availability of platelet growth factor therapy in the form of recombinant human interleukin-11 (rhIL-11, also known as oprelvekin [Neumega]), reduction of chemotherapy doses was the only method for preventing thrombocytopenia during subsequent cycles.

**Platelet Growth Factors**

The agent rhIL-11 has been developed for the prevention of chemotherapy-induced thrombocytopenia, and is the only clinically available platelet growth factor approved by the FDA for this indication. It stimulates cells

in the megakaryocytic lineage to promote thrombopoiesis, thereby inducing an increase in peripheral platelet counts.[52] This increase results in a reduction in the depth of the platelet nadir, reduced requirement for platelet transfusions,[53,54] and shortened platelet recovery time[54] in chemotherapy-treated patients with cancer. [53,54] There is, however, evidence of an inverse relationship between platelet counts and circulating levels of IL-11.

In patients with decreased platelet counts due either to myeloablative therapy or immune thrombocytopenia purpura, there are data to suggest that the thrombocytopenia acts as a regulator for inducing the production of IL-11. However, despite platelet recovery, there remains a prolonged elevation of IL-11, which may be in part due to other inflammatory agonists produced during thrombocytopenia. Therefore, endogenous IL-11 levels may not be totally regulated by IL-11 receptor-expressing cells.[53,54]

Studies of rhIL-11 have used the requirement for platelet infusion as a surrogate measure of thrombocytopenia. In an open-label extension of a placebo-controlled trial, the use of rhIL-11 allowed 50% or more patients to receive up to four additional cycles of dose-intensive chemotherapy for breast cancer without chemotherapy dose reductions or the need for platelet transfusions.[54]

rhIL-11 has also demonstrated efficacy in enhancing myeloid and platelet recovery in clinical trials of pediatric patients following ICE chemotherapy for the treatment of recurrent or refractory solid tumors.[55-59] ICE is associated with a high incidence (92%) of severe hematopoietic toxicity despite G-CSF administration, and protracted thrombocytopenia has limited dose intensity by delaying repetitive cycles. In these studies, rhIL-11 administered in conjunction with G-CSF significantly ( $P < .05$ ) shortened the recovery time to platelet counts > 100,000/μL. No other hematopoietic growth factor regimens, including PIXY321 and IL-6 plus G-CSF, had this activity when tested in this population of patients with this regimen. Observations of significant increases in early and committed progenitor cells support the megakaryocytopoietic

activity of rhIL-11 and likely account for acceleration of platelet recovery.[55,58]

The full therapeutic effectiveness of rhIL-11 as a preventative for the development of thrombocytopenia is dependent on the practical application of knowledge regarding the involvement of rhIL-11 in megakaryocytopoiesis and thrombopoiesis. (This is discussed in more detail in this supplement by Berl and Schwertschlag.) Daily dosing with rhIL-11 produces a marked increase in platelet counts that is apparent approximately 5 to 9 days after initiation of therapy; this response time reflects the direct effect of the drug on the maturation of megakaryocytes and megakaryocyte precursors.[60] Thus, rhIL-11 should be administered within 6 to 24 hours after the last dose of the chemotherapeutic agent so that the peak increase in platelet count induced by rhIL-11 occurs when the chemotherapy-induced platelet nadir is expected to occur (approximately 10 to 14 days after the last dose of chemotherapy).

Because of the difference in maturation time between megakaryocytes and granulocytes,[61] a gradual rise in platelets occurs following treatment with rhIL-11 and other thrombopoietic agents, such as thrombopoietin (4 to 7 days),[60,62] whereas an earlier rise in neutrophils is seen after treatment with G-CSF (within 2 to 3 days).[23]

## Summary

Low platelet counts are a frequent dose-limiting toxicity of chemotherapy regimens commonly used in the treatment of patients with solid tumors or lymphomas. Until the availability of rhIL-11 the standard response of physicians to low platelets has been dose reduction and delay of subsequent chemotherapy until adequate platelet recovery has been achieved. However, undue reduction in chemotherapy dose or lengthy interruption of planned treatment schedules can reduce antitumor efficacy and thus potentially jeopardize the achievement of optimal survival benefit or remission duration. Therefore, these management strategies are undesirable and should be avoided if possible. Although effective and used extensively to treat severe thrombocy-

topenia, platelet transfusions are complicated by a high frequency of adverse transfusion reactions and alloimmunization, leading to refractoriness to platelet transfusions as well as risk of infection (viral and bacterial).

The agent rhIL-11 is the first platelet growth factor to be approved by the FDA for the prevention of severe chemotherapy-induced thrombocytopenia in patients with nonmyeloid malignancies who experience thrombocytopenia in a prior chemotherapy cycle or who are at risk of developing thrombocytopenia. In these patients, the preemptive use of rhIL-11 as a prophylactic agent for patients at high risk for developing chemotherapy-induced thrombocytopenia has been shown to be beneficial. Administering rhIL-11 as rescue therapy after chemotherapy-induced thrombocytopenia has developed is less appropriate based on our knowledge of the biological activity of rhIL-11 and, subsequently, of lower benefit.

The timing of rhIL-11 dosing is critical to obtaining optimal results. Because platelet increases begin 5 to 9 days after the start of rhIL-11 dosing, for maximum therapeutic benefit rhIL-11 must be initiated soon (6 to 24 hours) after completion of chemotherapy and administered daily for about 10 days (maximum of 21 days) depending on the platelet response, so that peak platelet increases occur when the chemotherapy-related platelet nadir is expected. Used appropriately, rhIL-11 reduces the risk of chemotherapy-induced low platelet counts that can result in dosing delays and/or dose reductions and the potential need for platelet transfusions. Thus, the administration of full doses of chemotherapy at scheduled times can be facilitated, and patient outcomes from the anti-cancer therapy can be optimized.

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