Treatment of chemotherapy-induced thrombocytopenia in patients with non-hematologic malignancies

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Abstract

Chemotherapy-induced thrombocytopenia (CIT) is a common complication of the treatment of non-hematologic malignancies. Many patient-related variables (e.g., age, tumor type, number of prior chemotherapy cycles, amount of bone marrow tumor involvement) determine the extent of CIT. CIT is related to the type and dose of chemotherapy, with regimens containing gemcitabine, platinum, or temozolomide producing it most commonly. Bleeding and the need for platelet transfusions in CIT are rather uncommon except in patients with platelet counts below 25×10^9/L in whom bleeding rates increase significantly and platelet transfusions are the only treatment. Nonetheless, platelet counts below 70×10^9/L present a challenge. In patients with such counts, it is important to exclude other causes of thrombocytopenia (medications, infection, thrombotic microangiopathy, post-transfusion purpura, coagulopathy and immune thrombocytopenia). If these are not present, the common approach is to reduce chemotherapy dose intensity or switch to other agents. Unfortunately decreasing relative dose intensity is associated with reduced tumor response and remission rates. Thrombopoietic growth factors (recombinant human thrombopoietin, pegylated human megakaryocyte growth and development factor, romiplostim, eltrombopag, avatrombopag and hetrombopag) improve pretreatment and nadir platelet counts, reduce the need for platelet transfusions, and enable chemotherapy dose intensity to be maintained. National Comprehensive Cancer Network guidelines permit their use but their widespread adoption awaits adequate phase III randomized, placebo-controlled studies demonstrating maintenance of relative dose intensity, reduction of platelet transfusions and bleeding, and possibly improved survival. Their potential appropriate use also depends on consensus by the oncology community as to what constitutes an appropriate pretreatment platelet count as well as identification of patient-related and treatment variables that might predict bleeding.

Introduction

Thrombocytopenia is a common problem in patients with cancer, whether due to the underlying disease, infection, other medications or cancer treatment with chemotherapy or radiation. Thrombocytopenia creates a number of problems in the care of the cancer patient. At platelet counts less than 10×10^9/L, spontaneous bleeding may be increased. At platelet counts less than 50×10^9/L, surgical procedures are often complicated by bleeding. At platelet counts under 100×10^9/L, chemotherapy and radiation therapy may be administered with caution thereby decreasing dose intensity and clinical outcome.[1] Therapeutic and prophylactic platelet transfusions create the additional risk of infusion-related complications and might be immunosuppressive.[2] Finally, thrombocytopenia instills in the patient a sense of anxiety and fear of bleeding which exacerbates that due to the cancer diagnosis itself.

The clinician's response to thrombocytopenia in a cancer patient is varied. Reduction of relative dose intensity (RDI) of chemotherapy or radiation is common; less effective regimens may be chosen; treatment may even be precluded. For some, treatment of another cause of thrombocytopenia (e.g., stopping the offending antiviral agent) may be effective. Platelet transfusion is often the only immediately available treatment. There is increasing interest in using recombinant human thrombopoietin (rhTPO) or thrombopoietin receptor agonists (TPO-RA) such as romi-

plostim, eltrombopag, avatrombopag, lusutrombopag, and hetrombopag to enhance platelet production and platelet counts.[3]

Recognizing that chemotherapy creates other hematologic problems (e.g., neutropenia) that may also limit the ability to administer chemotherapy, the focus here will be primarily on situations in which thrombocytopenia is a major limiting variable. This review will discuss the general approach to the patient with a non-hematologic malignancy receiving non-myeloablative chemotherapy, the pathophysiology of chemotherapy-induced thrombocytopenia (CIT), and options for treating CIT including TPO-RA. The use of TPO-RA therapy in myeloablative settings (stem cell transplantation and acute myeloid leukemia induction) has been discussed separately.[4] A discussion of thrombocytopenia secondary to therapeutic irradiation or treatment of hematologic malignancies is beyond the scope of this review.

CIT is here defined as a platelet count less than 100×10^9/L and divided into grades as follows; grade 1: 75×10^9/L to less than 100×10^9/L; grade 2: 50×10^9/L to less than 75×10^9/L; grade 3: 25×10^9/L to less than 50×10^9/L; and grade 4: less than 25×10^9/L.[5,6]

The platelet count is an imprecise predictor of bleeding risk in cancer patients

The main reason to check the platelet count in a cancer patient receiving chemotherapy is to attempt to predict the bleeding risk. A biological estimate of the lowest effective platelet count for effective hemostasis comes from the work of Slichter and colleagues,[7-9] who used chromium-51 labeled red blood cells to quantify fecal blood loss in stable thrombocytopenic aplastic patients treated only with anabolic steroids. At platelet counts above 10×10^9/L, blood loss was normal at less than 5 mL/day. At platelet counts of 5×10^9/L to 10×10^9/L, blood loss rose slightly to 9 ± 7 mL/day; however at platelet counts below 5×10^9/L, the loss was markedly elevated to 50 ± 20 mL/day. Subsequent platelet kinetic studies[10] found a fixed minimum requirement for 7.1×10^9 platelets/L/day to maintain vascular integrity; 18% of the normal daily turnover of 41.2×10^9 platelets/L/day. This is consistent with *in vitro* data showing that thrombin generation appears to be maximal as long as the platelet count is above 10×10^9/L; below that value thrombin generation declines in direct proportion to the platelet count.[11,12]

A recent trial assessed the relation of platelet count to bleeding (using a validated bleeding scale[6]) in thrombocytopenic patients undergoing myeloablative chemotherapy for leukemia or stem cell transplantation (Figure 1).[13]

It clearly showed bleeding of grade 2 or higher on 25% of days with platelet counts of 5×10^9/L or less, on 17% of days with platelet counts from $6-80 \times 10^9$/L ($P<0.001$ for platelet counts $\leq 5 \times 10^9$/L *vs.* counts of $6-80 \times 10^9$/L), on 13% of days with platelet counts of $81-100 \times 10^9$/L ($P=0.001$ for platelet counts of $81-100 \times 10^9$/L *vs.* counts of $6-80 \times 10^9$/L), and on 8% of days with platelet counts above 100×10^9/L ($P<0.001$ for platelet counts $>100 \times 10^9$/L *vs.* counts of $6-80 \times 10^9$/L).

In cancer patients undergoing chemotherapy, thrombocytopenic bleeding and bleeding grade have been inadequately studied; in general both increase once the platelet count drops below 75×10^9/L (odds ratio=3.1; 95% confidence interval [95% CI]: 1.9–5.1).[14] Roughly, when the platelet count falls below 50×10^9/L the probability of bleeding is 0–9.6%; rises to 10.1–17.7% when the count is below 20×10^9/L; and rises again to 18.4–40.1% when below 10×10^9/L.[15] The incidence of CIT rises with each subsequent cycle of chemotherapy.[16]

Unfortunately, using just the platelet count to predict bleeding risk for the cancer patient is an over simplification. Platelet function may be altered by other medications, antipyretics, chemotherapy drugs themselves, and renal insufficiency. Platelets in patients with CIT lack the increased size and function of the "young" platelets in immune thrombocytopenia (ITP) which tends to mitigate the bleeding risk seen at comparably low platelet counts in ITP.[17] Other patient-related variables markedly affect the hemostatic risk (Table 1). The bleeding risk for each patient needs to be personalized

The importance of maintaining chemotherapy dose intensity

Most chemotherapy regimens have been developed to provide the greatest therapeutic benefit with acceptable toxicity. As demonstrated in Table 2, in patients with metastatic breast cancer, chemotherapy dose intensity is important; when cyclophosphamide/methotrexate/5-fluorouracil dose intensity was decreased by 50%, there was less thrombocytopenia but there was also a significant decrease in median survival.[18]

Reductions in RDI (due to either reductions in dose or dosing frequency) decrease response rate and survival. In a retrospective study of patients with metastatic colorectal disease being treated with FOLFIRI (folinic acid, fluorouracil, irinotecan) or modified FOLFOX6 (folinic acid, fluorauracil, oxaliplatin), patients receiving a high RDI of irinotecan had a median performance-free survival of 9.9 months compared with 5.6 months for those receiving a low RDI of irinotecan (hazard ratio [HR]=3.18; 95% CI: 1.47–6.88; $P<0.01$); median overall survival was also reduced from 26.7 months down to 12.9 months for
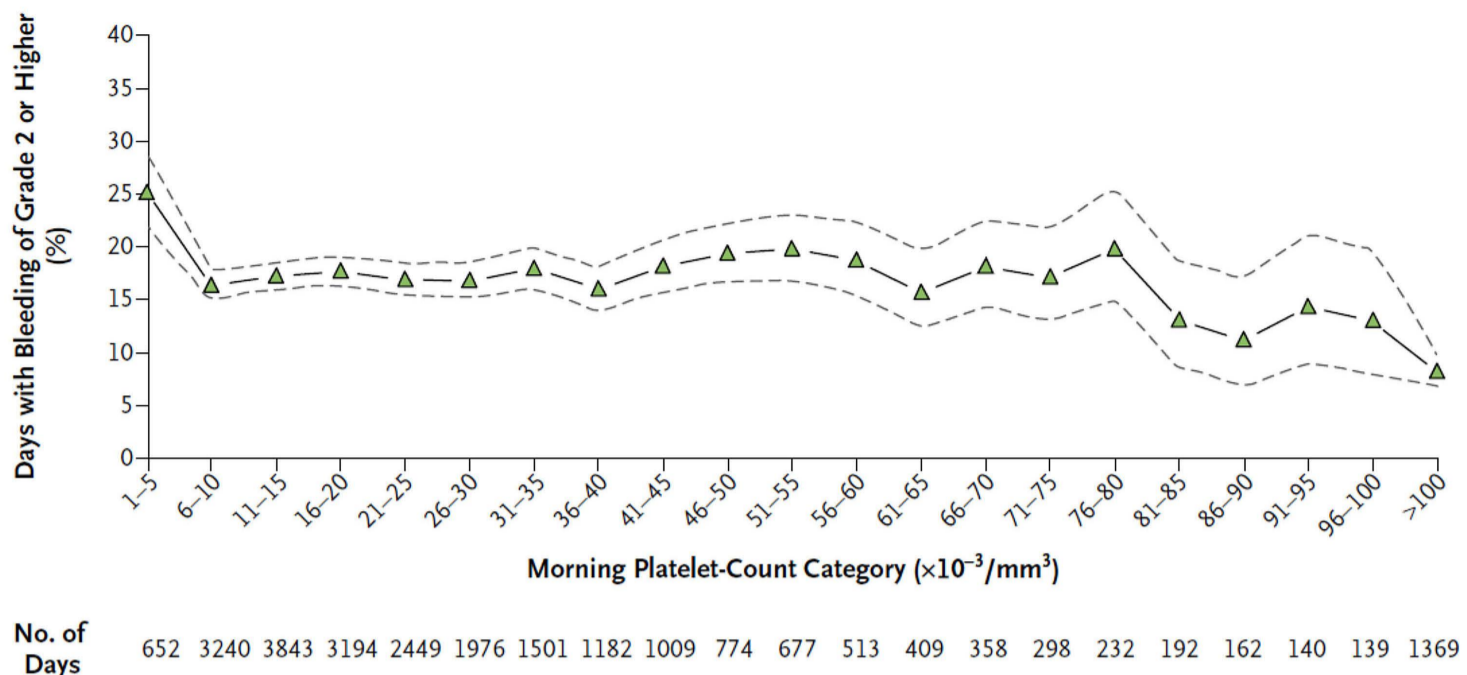
Figure 1. Relation between bleeding (measured using the World Health Organization bleeding scale) and the platelet count in patients with hypoproliferative thrombocytopenia. The percentage of days on which patients had bleeding of grade 2 or greater is shown, along with the associated 95% confidence intervals (dashed lines), according to the morning platelet count category. (From Slichter *et al.*[13] and reproduced with the permission of the Massachusetts Medical Society.)

the same two groups (HR=2.72; 95% CI: 1.22–6.04; P=0.01].[19]

Similar effects of reduction in RDI leading to decreased overall survival have been demonstrated in the adjuvant treatment of non-small cell lung cancer,[20,21] breast cancer,[22] ovarian cancer,[22] and non-Hodgkin lymphoma.[23] In elderly patients with advanced non-small cell lung cancer, those receiving a RDI of 80% or more had a higher response rate (55.2% *vs.* 33.3%) and overall survival than those who received a RDI less than 80%.[24] In advanced epithelial ovarian cancer[25] and metastatic breast cancer[26] improved survival was associated with a RDI of 85% or more.

Many factors other than thrombocytopenia determine the feasibility of delivering an adequate RDI for any particular cancer patient: anemia, neutropenia, mucositis, nausea, intravenous access, need for concurrent radiation therapy, and performance status. However, for a significant number of chemotherapy recipients, thrombocytopenia is the major limiting variable, as discussed below.

So, for the cancer patient whose chemotherapy regimen is primarily limited by thrombocytopenia, the potential bleeding risk with chemotherapy becomes a complex calculation in which the platelet count and other hemostatic variables need to be weighed in the context of potential benefit from maintaining chemotherapy RDI. Furthermore, there is no reliable predictor of the degree of nadir thrombocytopenia (and hence risk of bleeding) based on pretreatment platelet count or other patient-related or chemotherapy regimen variables. In general, chemotherapy is administered at pretreatment platelet counts over 100x10⁹/L with many chemotherapy regimens and physicians challenged when platelet counts are below 70x10⁹/L, in particular below 50x10⁹/L. There is no evi-

dence as to what constitutes an "adequate pretreatment platelet count" for any specific chemotherapy for solid tumors; although 70x10⁹/L or higher is widely accepted.

Not all cases of thrombocytopenia in chemotherapy recipients are due to chemotherapy: the clinical approach to thrombocytopenia in the cancer patient

Although chemotherapy and radiation are by far the major causes of thrombocytopenia in the cancer patient, other etiologies should be considered in all patients. In general, the following "checklist" should be considered in cancer patients with platelet counts less than 100x10⁹/L.

• *Is the underlying disease the cause of the thrombocytopenia?*

Tumor that metastasizes to bone marrow is common in patients with breast and lung cancer as well as in those with primary hematologic malignancies such as lymphoma. Most such patients also demonstrate pancytopenia and these cytopenias generally occur when over 80% of the bone marrow is infiltrated. As discussed below, patients with infiltrated bone marrow respond poorly to TPO-RA.[27]

• *Is there an associated immune thrombocytopenia?*

Up to 1% of patients with Hodgkin disease,[28,29] 2 to 10% of patients with chronic lymphocytic leukemia,[30-32] and 0.76% (range, 0–1.8%) of patients with other non-Hodgkin lymphomas[29] develop a secondary ITP. These patients respond to steroids, rituximab, splenectomy, and TPO-RA just like pa-

tients with primary ITP,[33] although treatment of the underlying lymphoma may be effective.[29]

• *Has there been a recent infection?*
While infection may produce consumptive coagulopathies (e.g., disseminated intravascular coagulation), some bacteria release neuraminidase that actually reduces platelet survival by removing the sialic acids coating platelets and thereby increasing their clearance by the liver Küpffer cell type C lectin receptor (CLEC4F) or hepatic Ashwell-Morell receptor.[34-36] Viral infections (e.g., cytomegalovirus) in compromised patients may inhibit bone marrow production of platelets. Such thrombocytopenias improve with adequate treatment of the infection.

• *Has the patient received a new medication?*
Heparin-induced thrombocytopenia should be considered.[37] Antibiotics (e.g., vancomycin,[38] linezolid[39]) and antiviral agents (e.g., ganciclovir[40,41]) commonly induce thrombocytopenia either by direct bone marrow toxicity or by immune drug-dependent antibody clearance.[38,42]

• *Has there been a recent transfusion?*
Post-transfusion purpura is a rare complication of transfusion of red blood cells and platelets with the platelet count usually dropping below 10×10^9/L.[43,44] Post-transfusion purpura occurs in the 1% of patients who lack the common platelet antigen PLA-1 (HPA-1a) and is usually seen in women previously sensitized by pregnancy. Upon transfusion of HPA-1a-positive platelets into sensitized HPA-1a-negative patients, antibody destroys the transfused platelets and by an as yet unclear mechanism also destroys the patient's own HPA-1a-negative platelets. This under-recognized complication of transfusion responds readily to intravenous immunoglobulin.

• *Does the patient have a coagulopathy?*
In addition to infections, some tumors (e.g., gastric and pancreatic adenocarcinomas) can cause chronic disseminated intravascular coagulation.[45,46] Such thrombocytopenic patients usually have elevated D-dimer and prothrombin fragment 1.2[47] with a low fibrinogen, but often have minimally prolonged prothrombin time and partial thromboplastin time.[48] Treatment of this is often difficult. Heparin may improve the coagulopathy, but most patients do not improve without effective treatment of the underlying tumor.

• *Is there a chemotherapy- or transplant-related thrombotic microangiopathy?*
Mitomycin-C and gemcitabine induce endothelial injury with a resultant thrombotic microangiopathy whose major manifestation is renal failure and thrombocytopenia, best referred to as a chemotherapy-related hemolytic uremic syndrome.[49] Patients with such a microangiopathy usually have thrombocytopenia, microangiopathic hemolytic anemia, and organ dysfunction with a normal level of ADAMTS13;[50] most improve with supportive care and discontinuation of the chemotherapy. Plasma exchange, rituximab, or steroids are not indicated.[51] It is unclear whether complement inhibition with eculizumab or ravulizumab will help.[52]

• *Is the thrombocytopenia temporally related to chemotherapy or radiation therapy?*
When was the last chemotherapy or radiation therapy administered? The platelet has a normal lifespan of 8 to 10 days. After many types of chemotherapy, the platelet count generally starts to drop by day 7 and reaches its nadir at day 14 with a gradual return back to baseline by day 28 to 35.[53]

Table 1. Variables potentially increasing bleeding risk in cancer patients.

Platelet count	Platelet function	Patient-specific variables
Liver disease	Antibiotics	Fever
Splenomegaly	Renal insufficiency.	Infection
	Antipyretics	Procedures
	Chemotherapy drugs	Age
	Anticoagulants	Coagulation factor abnormalities
		Indwelling catheters
		Surgery
		Malignant lesions
		Mucositis/esophagitis

Table 2. The effect of dose intensity on platelet count and chemotherapy response.

	Low dose	High dose	*P*-value
Mean (SEM) dose intensity for cyclophosphamide*	46 (1)	80 (2)	
Mean (SD) nadir absolute neutrophil count, $\times 10^9$/L	2.850 (0.180)	0.760 (0.080)	<0.001
Mean (SEM) nadir platelet count, $\times 10^9$/L	240 (10)	180 (8)	<0.001
Median survival (months)	12.8	15.6	0.009

Low dose intensity: cyclophosphamide 300 mg/m², methotrexate 20 mg/m², 5-fluorouracil 300 mg/m²; high dose intensity: cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m². *Expressed as percentage of cyclophosphamide prescribed for the higher dose arm and averaged over the entire course of treatment. Dose intensity for the other drugs was similar to that of cyclophosphamide. Table based on data from Tannock *et al.*[18] SEM: standard error of mean; SD: standard deviation.

Depending upon the dose and duration of radiation therapy, the onset of thrombocytopenia is generally at day 7 to day 10 with a longer duration of thrombocytopenia, sometimes lasting for 30 to 60 days.

• *What dose and type of chemotherapy was given?*

As reviewed next, the incidence, severity, and duration of thrombocytopenia vary with the chemotherapy regimen. Most non-myeloablative chemotherapy regimens were developed to minimize thrombocytopenia and the need for platelet transfusions. As such, most standard regimens have relatively low rates of dose-limiting thrombocytopenia; when thrombocytopenia occurs, it is often of short duration (4 to 6 days). Most cases respond well to platelet transfusion.

The incidence of thrombocytopenia and the use of platelet transfusions vary with the type of chemotherapy

Although many factors may lead to reduction of chemotherapy RDI, it is difficult to identify how much is attributed to thrombocytopenia. In a review of different chemotherapy regimens in 614 patients with solid tumors, CIT (a platelet count <100x10^9/L) was seen in 21.8% of all subjects; thrombocytopenia was unaccompanied by other cytopenias in 6.2%.[54] Grade 3 thrombocytopenia was seen in 3.6% and grade 4 thrombocytopenia in 3.3%. CIT occurred in 82% of those receiving only carboplatin, and in 58%, 64% and 59% of those receiving combination therapies with carboplatin, gemcitabine or paclitaxel, respectively.

In a retrospective analysis of 43,995 patients (including those with solid tumors or hematologic malignancies) who received 62,071 chemotherapy regimens in the USA between 2000 and 2007,[55] CIT occurred in 13,304 (21.4%) regimens. Grade 3 and grade 4 thrombocytopenia occurred in 2,660 (4.3%) and 2,087 (3.4%) regimens, respectively: 7.8% and 3.4% of gemcitabine-based regimens; 6.5% and 4.1% of platinum-based regimens; 3.0% and 2.2% of anthracycline-based regimens; and 1.4% and 0.5% of taxane-based regimens.

In a more recent analysis of 15,521 patients with solid tumors,[56] 12.8% (95% CI: 12.3–13.4%) had CIT: grade 2 in 6.4%; grade 3 in 4.2% and grade 4 in 1.9%. CIT was more common in patients with solid tumors who received gemcitabine- and platinum-based regimens (14.8% and 13.5%, respectively) than in patients treated with anthracycline- or taxane-based regimens (9.3% and 6.5%, respectively). With regard to tumor type, CIT occurred in 21.4% of melanoma patients, 14.3% of lung cancer patients, 13.5% of colorectal cancer patients, 12.9% of pancreatic cancer patients, and 9.6% of breast cancer patients. Grade 3 (13.3%) and 4 (5.0%) thrombocytopenia occurred most commonly in melanoma patients. The median time to the first decline in platelet count was about 1 to 2 weeks after starting chemotherapy, except for platinum-based regimens which was usually longer than 2 weeks. As expected, other cytopenias also occurred in most patients but 17.7% of CIT patients had only thrombocytopenia. In comparison, CIT was much more common in patients with hematologic malignancies (28% of 2,537 patients) with grade 3 and grade 4 thrombocytopenia in 16.3% and 12.4%, respectively.

The incidence of thrombocytopenia-related bleeding and platelet transfusions has been very poorly studied in CIT. Bleeding events were not measured for the 62,071 chemotherapy regimens described above, but platelet transfusion data were available for 10,582; transfusions occurred in 2.5% of patients (1.0% for platinum-based regimens, 0.6% for anthracycline-based regimens, 1.8% for gemcitabine-based regimens, and 0.3% for taxane-based regimens). Table 3 provides an overview of the reported frequencies of thrombocytopenia and platelet transfusions with various chemotherapy regimens.

Pathophysiology of chemotherapy-induced thrombocytopenia

Not all chemotherapy drugs cause thrombocytopenia in the same way. In reviewing the mechanism of CIT, it is helpful to understand how platelets are made (Figure 2). Stem cells differentiate into cells committed to megakaryocyte differentiation (megakaryocyte colony-forming cells). At some stage, these cells stop their mitotic divisions and enter a process called endomitosis, in which DNA replication occurs but with no subsequent division of the nucleus or the cell. This gives rise to polyploid precursor cells with 2, 4, 8, 16, or 32 times the normal diploid DNA content. These polyploid megakaryocyte precursor cells then stop synthesizing DNA and mature into large, morphologically identifiable megakaryocytes. Mature megakaryocytes then produce platelets by a mechanism that is still poorly defined. In its simplest iteration, portions of the megakaryocyte membrane bud off into the bone marrow sinusoid to produce platelets.[57-59] Other models suggest that mature megakaryocytes extrude long cytoplasmic processes through endothelial cells and large strands of platelet material (proplatelets) are released into the circulation, eventually becoming mature platelets, possibly through fragmentation in the lung.[60] More recently it has been suggested that some intact megakaryocytes migrate to the lung where they may account for up to 50% of platelet production.[61] If not consumed in hemostasis, the mature platelet undergoes programmed cell death (apoptosis) determined by a "platelet clock".[62] This platelet

clock depends upon the presence of the anti-apoptotic protein Bcl-x(L), a protein that restrains the pro-apoptotic proteins Bax and Bak.[62-65] When Bcl-x(L) declines, the activity of Bax and Bak increases, which triggers platelet apoptosis. The apoptotic platelets are cleared by the reticuloendothelial cell system, probably in the liver; the spleen plays little role in normal platelet homeostasis.[66] Different chemotherapy drugs affect the megakaryocyte and platelet production pathway at different steps (Figure 2). Alkylating agents such as busulfan and carboplatin affect pluripotential stem cells.[67,68] Cyclophosphamide spares hematopoietic stem cells because of their abundant levels of aldehyde dehydrogenase, but affects later megakaryocyte progenitors.[69] The antibody-drug conjugate T-DM1 (trastuzumab [T] coupled to the microtubule toxin emtansine [DM1]) causes grade 3 or higher thrombocytopenia within 1 week in about 13% of patients by inhibiting megakaryocyte growth and differentiation. T-DM1 is internalized into megakaryocytes via the FcγRIIa receptor or by pinocytosis where it releases DM1, which inhibits megakaryocyte polyploidization and growth.[70] Bortezomib has no effect on stem cells[71] or megakaryocyte maturation but does inhibit NF-κB, a critical regulator of platelet shedding.[72] This probably explains the relatively short duration of thrombocytopenia following its administration.[72] Not all chemotherapy drugs reduce platelet production; some can actually increase the rate of platelet destruction. Indeed, platelet survival itself may be altered by some chemotherapy agents. The experimental chemotherapy agent ABT-737 reduces the activity of the platelet clock Bcl-xL and rapidly induces platelets to undergo apoptosis.[63,73] After a single dose of ABT-737, platelets dropped to 30% of baseline by 2 h, to 5% of baseline by 6 h, started to recover to 10% of baseline by 24 h, and returned to baseline after 72 h.[73] This was not due to platelet activation. Rather, caspase-mediated apoptosis was induced with rapid appearance of phosphatidylserine on the platelet surface and clearance of these cells from the circulation by the reticuloendothelial system in the liver. Although not evaluated for most standard chemotherapy drugs, etoposide also increases platelet apoptosis by reducing Bcl-x(L) activity.[73]

The antibody-drug conjugates gemtuzumab ozogamicin and inotuzumab ozogamicin are both associated with acute thrombocytopenia (platelet counts dropping by 86% in 3–4 days in monkeys) and sinusoidal obliteration syndrome due to acute hepatic sequestration of platelets.[74] Finally, chemotherapy may enhance platelet clearance by immune mechanisms. In the treatment of many lymphomas, the administration of single-agent fludarabine has been noted to produce an antiplatelet antibody-mediated ITP in up to 4.5% of patients.[75] This ITP is commonly responsive to rituximab.[76] Platelet destruction is also increased when chemotherapy drugs produce a drug-dependent antiplatelet antibody-mediated secondary ITP, but this effect is uncommon.

Current approaches to the treatment of chemotherapy-induced thrombocytopenia

The response to significant CIT has not been codified in guidelines and there are few studies to describe the appropriate approach to CIT. Much depends upon the underlying goals of the treatment of the cancer patient; different levels of risk assessment need to be brought into play for those being treated for a cure compared to those being treated for palliation. Overall, it is reasonable when confronted with CIT first to assess the underlying need for chemotherapy and the goals of treatment for that particular patient. A clinical assessment of bleeding risk for patients is also important to undertake, especially if patients are receiving anticoagulant drugs or other therapies that might increase bleeding. What follows is the synthesis of the data and the author's personal experience over the past four decades:
• If possible, treat any other underlying cause of thrombocytopenia: stop antibiotics, treat infections, and control coagulopathy.
• Reduce chemotherapy dose, frequency or alter the chemotherapy regimen, especially if chemotherapy is not standard or not of curative intent.
• Platelet transfusion support can be used if maintenance of dose intensity is vital for response or survival. Platelet transfusions are indicated if the patient is bleeding or to prevent major bleeding if platelet counts are less than 10×10^9/L ($<20 \times 10^9$/L if febrile).[13,77] However, in the outpatient setting, this transfusion trigger needs to be reconsidered; transfusing at higher platelet counts on the Friday before a long weekend has its advantages.
• Antifibrinolytic agents such as ε-aminocaproic acid (Amicar®) or tranexamic acid (Lysteda®) have been used in some thrombocytopenic cancer patients to improve hemostasis when platelet transfusions do not work, but are of unproven benefit.[78-80] Total daily doses of 2–24 g (mean: 6 g) of ε-aminocaproic acid given in three or four divided doses have been used.[79] Tranexamic acid doses of 4–6 g/day given as three or four divided doses have also been studied.[80] However, the use of antifibrinolytic agents in cancer patients might exacerbate the underlying increased risk of thrombosis. A recent randomized, prospective, blinded study reported that addition of tranexamic acid (1,000–1,300 mg every 8 h) had no benefit in reducing grade ≥2 bleeding, platelet transfusions, or days without grade ≥2 bleeding in thrombocytopenic (platelets $<30 \times 10^9$/L) patients undergoing treatment for hematologic malignancies. Of interest, while there was no increase in non-catheter thromboses, an increased inci-

Table 2. Thrombocytopenia and platelet transfusions in commonly used chemotherapy regimens.

Regimen	Cancer	Thrombocytopenia		Platelet transfusion
		Grade 3	Grade 4	
Ibritumomab tiuxetan[a]	NHL[139]	87% (est)	13%	30%
Bortezomib[b]	Myeloma[140]	28%	3%	
Carboplatin[c]	Various[141]	23%		
Cisplatin[d]	Unknown primary[142]	4%		
Cisplatin/etoposide[e]	SCLC[143]	4%		
Cisplatin/etoposide[f]	SCLC[144]	17%	6%	
Cisplatin/tegafur[g]	Gastric[145]	5%	3%	
Gemcitabine[h]	Pancreas[146]	3.4%	1.7%	
Gemcitabin[i]	Pancreas[147]	3.7%		
Gemcitabine[j]	Pancreas[148]	12%	1%	
Docetaxel[k]	Breast[149]	1.9%		
Docetaxel/doublet[l]	NSCLC[150]	7.5%		
Temozolomide[m]	Glioblastoma[151]	11%		
Gemcitabine/cisplatin[n]	Unknown primary[142]	37%		15%
Gemcitabine/cisplatin[o]	NSCLC[152]	21.2%		
Gemcitabine/cisplatin[p]	Pancreas[147]	2.1%		
Gemcitabine/cisplatin[q]	NSCLC[153]	4.5%		4.5%
Gemcitabine/oxaliplatin[r]	Pancreas[148]	10%	1%	
Gemcitabine/carboplatin[s]	NSCLC[154]	32%	24%	9%
Gemcitabine/carboplatin[t]	SCLC[143]	22%		
Pemetrexate/cisplatin[u]	NSCLC[153]	4.1%		1.8%
Pemetrexate/carboplatin[v]	NSCLC[154]	13%	11%	3%
R-CHOP 21[w]	NHL[155]	5%		
R-CHOP 14[x]	NHL[155]	9%		
ICE[y]	NHL[125]	35%		23%
MAID[z]	Sarcoma[156]	52%		
MAID[aa]	Sarcoma[157]	34%		
MAID-Intensive[ab]	Sarcoma[157]	79%		
5FU/doxorubicin/cyclophosphamidac[ac]	Breast[158]		10%	
FOLFOX[ad]	Colon[159]	3.4%		
FOLFOX4[ae]	Colorectal[160]	2.0%	1.0%	
FOLFIRI[af]	Colorectal[160]	0.5%	0%	
Lapatinib/capecitabine[ag]	Breast[161]	0.2%		
T-DM1[ah]	Breas[161]	12.9%		
T-DM1[ai]	Breast[162]	4.2%	8.3%	4%
T-DM1[aj]	Breast[163]	7.3%	1.8%	
T-DM1[ak]	Breast[164]	5%		
Palbociclib/fulvestrant[al]	Breast[165]	1.7%	0.6%	
Topotecan[am]	SCLC[166]	28.8%	9.8%	5.8%
Topotecan/cisplatin[an]	SCLC[144]	29%	9%	
Cyclophosphamide/adriamycin/vincristine[ao]	SCLC[166]	4.9%	1.4%	1.9%
Oxaliplatin/tegafur[ap]	Gastric[145]	10%	3%	
Capcitabine/oxaliplatin[aq]	Colorectal[167]	9%	0%	

Table updated from that previously published.[168] [a]Ibritumomab tiuxetan (11 MBq/kg) x 1. [b]Bortezomib 1.3 mg/m^2 IV days 1, 4, 8 and 11; repeated every 21 days. [c]Carboplatin 500 mg/m^2 IV every 4 weeks. [d]Cisplatin 100 mg/m^2 IV every 3 weeks. [e]Cisplatin 60 mg/m^2 IV day 1, etoposide 120 mg/m^2 IV day 1 and 100 mg PO BID days 2 and 3; 21-day cycle. [f]Cisplatin 80 mg/m^2 IV day 1, etoposide 100 mg/m^2 IV days 1-3; 21-day cycle. [g]Cisplatin 60 mg/m^2 IV day 1, tegafur potassium oxonate 40 mg/m^2 PO BID days 1-14; 21-day cycle. [h]Gemcitabine 1,000 mg/m^2 IV on days 1, 8, and 15, repeated every 4 weeks. [i]Gemcitabine 1,000 mg/m^2 IV on days 1 and 8, repeated every 3 weeks. [j]Gemcitabine 1,000 mg/m^2 IV weekly. [k]Docetaxel 75 mg/m^2 IV every 3 weeks. [l]Docetaxel 75 mg/m^2 IV q3weeks with either IV cetuximab, vandetanib, apecitabine, gemcitabine, oxaliplatin, carboplatin, or iri-

notecan. [mm]Temozolomide 75 mg/m^2/d PO during radiotherapy; thereafter 150-200 mg/m^2 PO days 1-5 of each 28-day cycle. [n]Gemcitabine 1,250 mg/m^2 IV on days 1 and 8 and cisplatin 100 mg/m^2 IV on day 1, repeated every 3 weeks. [o]Gemcitabine 1,000 mg/m^2 IV on days 1 and 8 and cisplatin 75 mg/m^2 IV on day 1, repeated every 3 weeks. [p]Gemcitabine 1,000 mg/m^2 IV on days 1 and 8; cisplatin 60 mg/m^2 IV on day 1, repeated every 3 weeks. [q]Cisplatin 75 mg/m^2 IV on day 1 and gemcitabine 1,250 mg/m^2 IV on days 1 and 8, repeated every 3 weeks. [r]Gemcitabine 1,000 mg/m^2 IV on day 1 plus oxaliplatin 100 mg/m^2 IV on day 2, repeated every 14 days. [s]Gemcitabine 1,000 mg/m^2 IV on days 1 and 8 plus carboplatin IV (AUC= 5) on day 1, repeated every 3 weeks. [t]Gemcitabine 1200 mg/m^2 IV on days 1 and 8; carboplatin (AUC 5) IV on day 1. [u]Cisplatin 75 mg/m^2 IV and pemetrexed 500 mg/m^2 IV on day 1, repeated every 3 weeks. [v]Pemetrexed 500 mg/m^2 IV plus carboplatin (AUC= 5) IV on day 1, repeated every 3 weeks. [w]Cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV, rituximab 375 mg/m^2 IV on day 1; prednisone 40 mg/m^2 PO days 1-5; repeated every 21 days. [x]Cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV, rituximab 375 mg/m^2 IV on day 1; prednisone 40 mg/m^2 PO days 1-5; repeated every 14 days. [y]Etoposide 100 mg/m^2/day IV on days 1 to 3; carboplatin (AUC=5) IV on day 2; ifosfamide 5 g/m^2 via continuous infusion for 24 hours beginning on day 2; repeated every 2 weeks. [z]Ifosfamide 2,500 mg/m^2 IV, adriamycin 20 mg/m^2 IV, and dacarbazine 300 mg/m^2 IV on days 1-3; repeated every 4 weeks. [aa]Ifosfamide 2,500 mg/m^2 IV, adriamycin 20 mg/m^2 IV, and dacarbazine 300 mg/m^2 IV on days 1-3; repeated every 3 weeks. [ab]Ifosfamide 3,000 mg/m^2 IV, adriamycin 25 mg/m^2 IV, and dacarbazine 400 mg/m^2 IV on days 1-3; repeated every 4 weeks. [ac]Fluorouracil 600 mg/m^2 IV, doxorubicin 60 mg/m^2 IV, and cyclophosphamide 750 mg/m^2 IV on day 1; repeated every 21 days. [ad]Leucovorin 400 mg/m^2 IV, flourauracil 400 mg/m^2 IV, oxaliplatin 85mg/m^2 IV all on day 1 followed by 2,400 mg/m^2 IV over 46 hours; administered every 2 weeks. [ae]Fluorouracil 400 mg/m^2 IV bolus with 600 mg/m^2 continuous infusion for 2 days; leucovorin 200 mg/m^2 IV on day 1; oxaliplatin 85 mg/m^2 IV on day 1. [af]Fluorouracil 400 mg/m^2 IV bolus with 2400 mg/m^2 continuous infusion for 2 days; leucovorin 400 mg/m^2 IV on day 1; irinotecan 180 IV mg/m^2 on day 1. [ag]Lapatninb 1250 mg PO qd and capecitabine 1000 mg/m^2 PO BID days 1 to 14, every 21 days. [ah]Trastuzumab emtansine (T-DM1) 3.6 mg/kg IV every 21 days. [ai]T-DM1 0.3-4.8 mg/kg IV every 21 days. [aj]T-DM1 3.6 mg/kg IV every 21 days. [ak]T-DM1 3.6 mg/kg IV every 21 days. [al]Palbociclib 125 mg/day PO days 1-21; fulvestrant 500 mg IM every 2 weeks; 28-day cycle. [am]Topotecan 1.5 mg/m^2 IV days 1-5 every 21 days. [an]Topotecan 1.75 mg/m^2 PO days 1-5; cisplatin 60 mg/m^2 IV day 5. [ao]Cyclophosphamide 1000 mg/m^2 IV, doxorubicin 45 mg/m^2 IV, vincristine 2 mg IV all on day 1; every 21 days. [ap]Oxliplatin 130 mg/m^2 IV day 1; tegafur potassium oxonate 40 mg/m^2 PO BID days 1-14; 21-day cycle. [aq]Capecitabine 900 mg/m^2 PO BID days 1-14; oxaliplatin 130 mg/m^2 IV day 1; 21-day cycle. NHL: non-Hodgkin lymphoma; SCLC: small-cell lung cancer; NSCLC: non-small cell lung cancer; est: estimated; PO: *per os*; IV: intravenous; AUC: area under the curve; BID: *bis in die.*
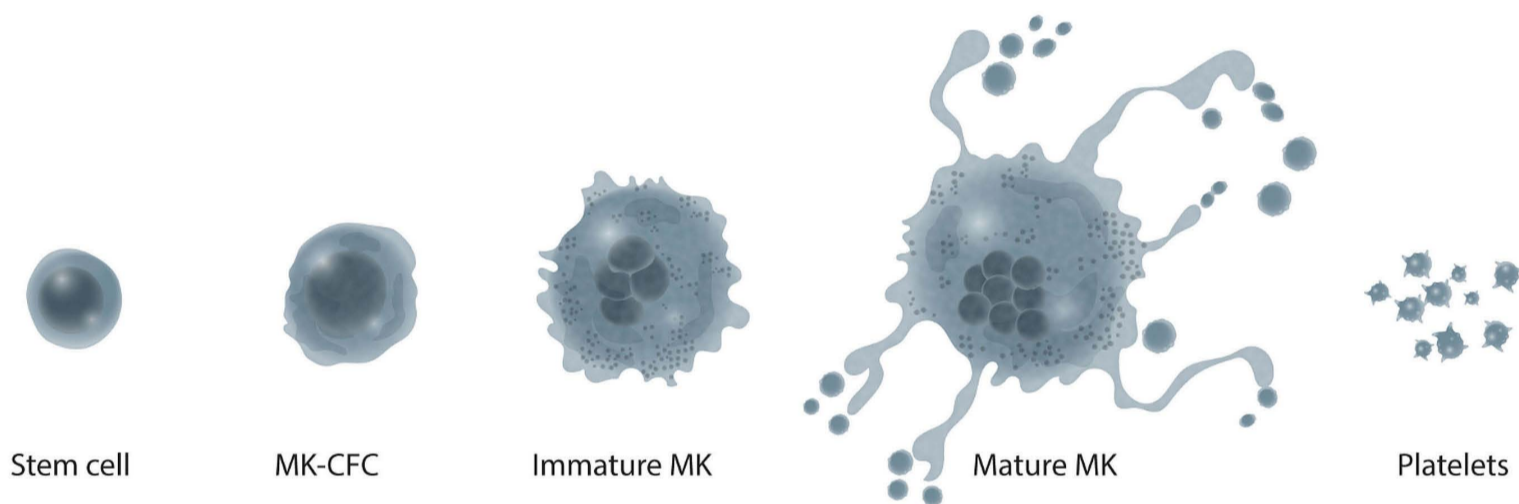
Figure 2. The production of platelets from bone marrow stem cells. Stem cells differentiate into cells committed to megakaryocyte differentiation (megakaryocyte colony-forming cells, MK-CFC) which are mitotically active. MK-CFC then stop mitosis and start endomitosis producing immature megakaryocytes (MK) with polyploid nuclei. The immature MK then stop their endomitosis and mature into large, morphologically identifiable MK that then migrate to the bone marrow sinusoids and produce platelets.

dence of central line occlusion requiring clearing with tissue plasminogen activator was observed.[81]

• Recombinant interleukin 11 (oprelvekin, Neumega®) was shown to reduce the need for platelet transfusions from 96% to 70% of patients who had been transfused with platelets in a prior cycle and who then received additional chemotherapy; but it has significant adverse effects.[82] This drug was approved by the Food and Drug Administration for the prevention of thrombocytopenia with chemotherapy but is no longer manufactured for use in North America; it is still available in other parts of the world.

• Despite the lack of Food and Drug Administration approval for these agents, rhTPO and TPO-RA might be considered in patients for whom thrombocytopenia prevents maintenance of dose intensity crucial for remission or survival, and who cannot be supported by platelet transfusions. Recently the National Comprehensive Cancer Network endorsed the use of TPO-RA, notably romiplostim, for treatment of CIT. They recommended initiation of TPO-RA for platelet counts 30–50x10^9/L with discontinuation when the platelet count recovers to 50–100x10^9/L based on an unsupported concern over thrombosis.[83]

The use of thrombopoietin and thrombopoietin receptor agonists in chemotherapy-induced thrombocytopenia

The pathophysiology of thrombopoietin in chemotherapy-induced thrombocytopenia

Thrombopoietin (TPO) is the major regulator of platelet production. In animals or humans deficient in TPO or its receptor, the platelet count is 10–15% of normal.[84,85] Megakaryocyte, erythroid, and myeloid precursor cells are

all reduced in such knock-out animals but their white blood cell and red blood cell counts are normal.[86] TPO is produced by the liver usually at a constant rate and its production is decreased by liver disease[87] and increased by interleukin-6 in rare conditions such as that associated with ovarian cancer.[88,89] TPO has no storage form and is secreted into the circulation and cleared by TPO receptors on platelets. In disorders such as in CIT, TPO levels are inversely related to the rate of platelet production and rise in a log-linear fashion (Figure 3).[90-93]

TPO binds to its receptor on many hematopoietic cells (Figure 4) and exerts its effects on most stages of megakaryocyte growth (Figure 2). It is necessary for the viability of hematopoietic stem cells; when the TPO receptor is absent, humans are born with thrombocytopenia and develop pancytopenia over subsequent years.[94-96] TPO stimulates mitosis of megakaryocyte colony-forming cells. Its major effect (at exceedingly low concentrations) is to increase megakaryocyte endomitosis and increase megakaryocyte ploidy, greatly expanding the megakaryocyte mass. It then stimulates megakaryocyte maturation. It is unclear whether TPO plays any role in platelet shedding.[97] An under-appreciated effect of TPO is that it prevents apoptosis of early and late megakaryocytes,[98] an effect that may play a major protective role in patients receiving radiation and chemotherapy.

Before considering the use of TPO agents in patients with cancer, it is important to note that solid tumors appear not to possess functional TPO receptors.[99,100] In one study using reverse transcriptase polymerase chain reaction on 39 human cell lines and 20 primary normal and malignant human tissues, TPO receptor (c-mpl) transcripts were found in all megakaryocytic cell lines tested (DAMI, CMK, CMK-2B, CMK-2D, SO), the CD34+ leukemia cell line KMT-2, and the hepatocellular carcinoma cell line Hep3B.[100] While fetal liver and brain cells had detectable levels of c-mpl mRNA, none was found in primary tumors. In a more extensive study, microarray detected TPO receptor mRNA in 0/118 breast tumors and at very low levels in 14/29 lung tumors.[99] Low but detectable levels of TPO receptor mRNA were found by quantitative polymerase chain reaction in some normal (14−43%) and malignant (3−17%) breast, lung, and ovarian tissues but in none of these tissues was TPO receptor protein detectable by immunohistochemistry. Culture of breast, lung, and ovarian carcinoma cell lines with TPO-RA showed no stimulation of growth. Finally, in none of the human clinical studies described next was there any stimulation of tumor growth by the administration of rhTPO or TPO-RA.

Development of recombinant thrombopoietin and thrombopoietin receptor agonists

The development of clinically relevant TPO molecules has occurred in two phases: the early recombinant TPO molecules and the recent TPO-RA.[3,101]

With the discovery of TPO in 1994, two recombinant TPO molecules were developed (Table 4). rhTPO is a fully glycosylated TPO protein made in Chinese hamster ovary cells. The other, pegylated recombinant human megakaryocyte growth and development factor (PEG-rhMGDF), is a non-glycosylated protein comprising the first 153 amino acids of TPO coupled to polyethylene glycol. Both molecules are potent stimulators of platelet production with half-lives of about 40 h. In healthy volunteers both demonstrated the same time course of platelet response after a single dose: by day 3 megakaryocyte ploidy increased, by day 5 platelet counts started to rise, by days 10−14 a peak platelet count was obtained, and by day 28 platelet counts returned to their baseline.[102]
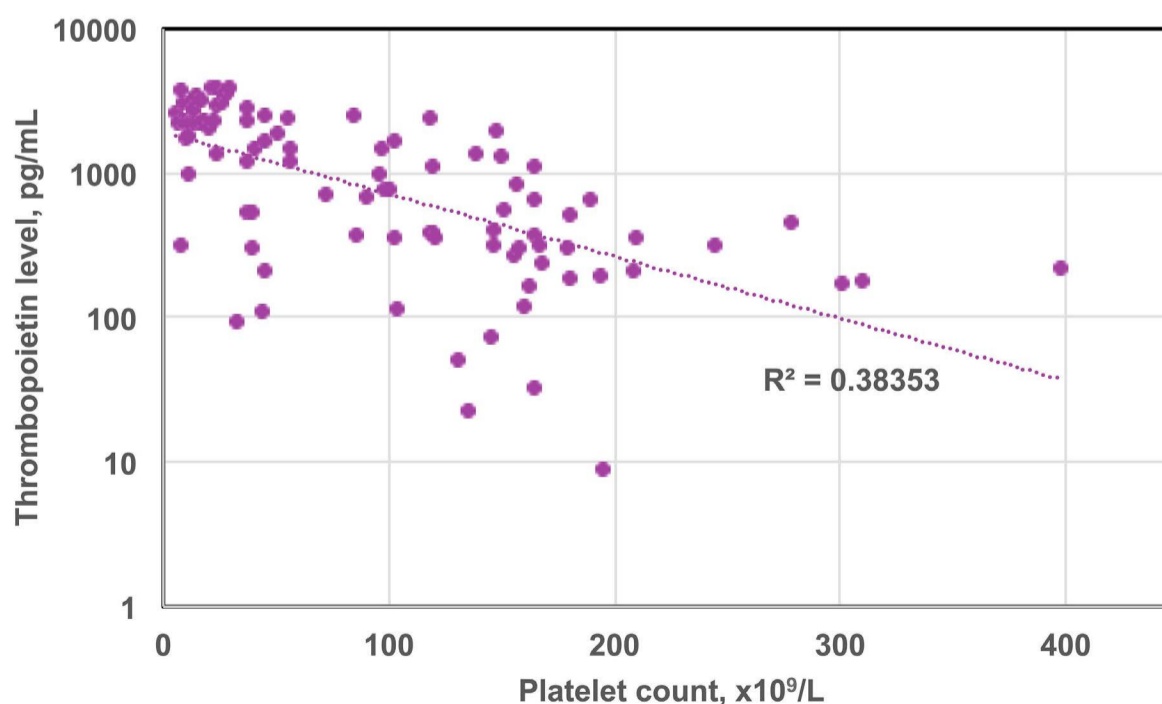
Figure 3. Log-linear correlation of thrombopoietin level with platelet counts. Patients undergoing double umbilical cord blood transplantation had serial platelet counts and thrombopoietin levels determined over their hospital course. As platelet counts declined, thrombopoietin levels rose. Figure created from data in the study by deFilipp *et al.*[91]

Between 1995 and 2000, both recombinant TPO underwent extensive clinical development in CIT.[103] As discussed more below, both produced an earlier and higher nadir platelet count, shortened the duration of thrombocytopenia, re-

duced platelet transfusions, and enabled non-myeloablative chemotherapy to be given on schedule.

Development of both was stopped in the West around 2000 because of concerns over neutralizing antibody formation
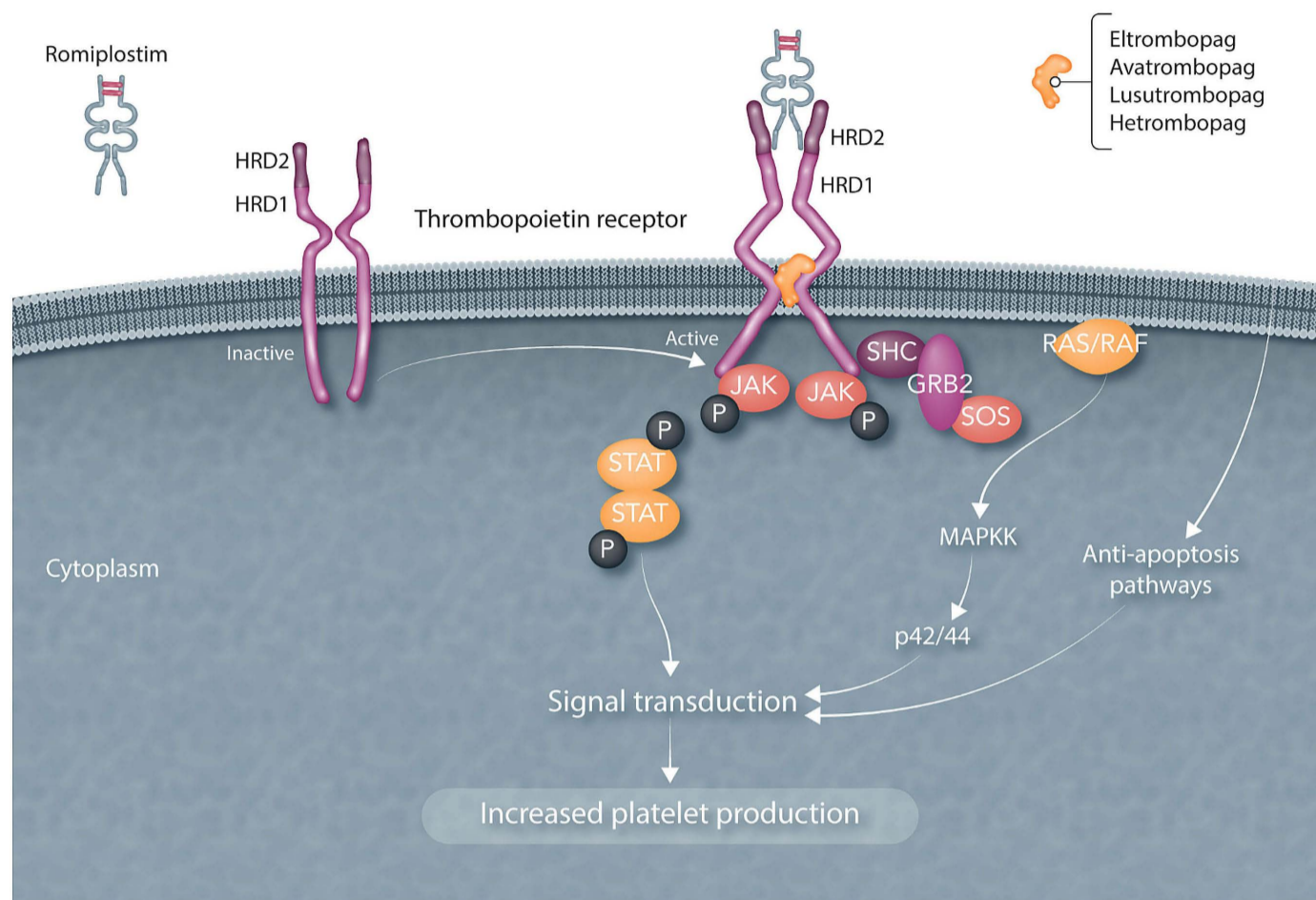
Figure 4. Recombinant human thrombopoietin and the thrombopoietin receptor agonists bind to and activate the thrombopoietin receptor in different ways. The thrombopoietin (TPO) receptor has been proposed to exist as an inactive preformed dimer (left side) with a proximal and distal hematopoietic receptor domain (HRD1 and HRD2, respectively). Upon binding of romiplostim or recombinant human TPO (not pictured) to the distal HRD2, the conformation of the receptor changes (right side) and a number of signal transduction pathways are activated which increase platelet production. The other TPO receptor agonists bind to the transmembrane region of the receptor and activate many of the same signal transduction pathways. TPO: thrombopoietin; HRD: hematopoietic receptor domain protein; STAT: signal transducer and activator of transcription; JAK: Janus kinase; GRP2: growth receptor bound protein 2; SOS: son of sevenless (a guanine nucleotide exchange factor); RAS: rat sarcoma virus (a small GTP-ase); RAF: rapidly accelerated fibrosarcoma (a serine/threonine kinase); MAPK: mitogen-activated protein kinase.

Table 4. Thrombopoietic therapies under development for treating chemotherapy-induced thrombocytopenia.

	rhTPO	Romiplostim	Eltrombopag	Avatrombopag	Hetrombopag
TPO-R binding	Distal	Distal	Transmembrane	Transmembrane	Transmembrane
Chelates iron	No	No	+	?	No
Off-target effects	?+	?+	+++	?	?
Potency in healthy subjects	++++++++	++++++++	+	++++	+++
Route	SC	SC	Oral	Oral	Oral
Dietary effect	No	No	Yes	No	Yes
Interacts with cations	No	No	++	No	?
Decrease dose if East Asian	No	No	Yes	No	Yes
Decrease dose if liver dysfunction	No	No	Yes	No	Yes
Increases liver function tests	No	No	+	No	?
Use in renal failure	OK	OK	Probably OK	Probably OK	No data
Use in pregnancy	OK	No	No	No	No
Regulatory approval for CIT	Yes, China and 7 other countries	No	No	No	No

rhTPO: recombinant human thrombopoietin; TPO-R: thrombopoietin receptor; SC: subcutaneous; CIT: chemotherapy-induced thrombocytopenia.

against PEG-rhMGDF.[104] In 525 healthy volunteers given up to three monthly doses of PEG-rhMGDF, 13 (2.5%) developed thrombocytopenia due to the formation of antibodies to PEG-rhMGDF that cross-reacted with endogenous TPO, creating TPO deficiency and thrombocytopenia. All subjects recovered, but some required immunosuppressive treatment.[105,106] Development of rhTPO (TPIAO®) continued in China where it is now licensed for treatment of CIT (*https://www.mims.com/thailand/drug/info/tpiao*) and ITP.[107] Despite the failure of one of the recombinant TPO molecules, interest turned to developing newer TPO molecules (now called TPO-RA) with novel properties and less risk of antibody formation.[1,3] Romiplostim is a "peptibody" created by inserting a 14 amino acid peptide that activates the TPO receptor into an IgG4 heavy chain (Table 4).[108] Romiplostim is approved in many countries for the treatment of ITP and in Japan for the treatment of aplastic anemia.

A separate approach identified a number of small molecules (eltrombopag, avatrombopag, lusutrombopag, hetrombopag) that bind and activate the TPO receptor (Table 4).[109] All of these small molecule TPO-RA bind the TPO receptor in the transmembrane region, an area different from where TPO or romiplostim binds, and activate the TPO receptor in a different fashion (Figure 4).[110-112] All of these small molecules have undergone extensive clinical development and most (eltrombopag, avatrombopag, hetrombopag) are licensed for treating patients with ITP, of whom they increase the platelet count in over 85%.[113-119] Eltrombopag is also approved for the treatment of thrombocytopenia in patients with hepatitis C infection requiring anti-viral treatment[120] and in patients with aplastic anemia in whom immunosuppressive therapy has failed.[121,122] In the latter disease, treatment was also associated with an increase in white blood cells and red blood cells. Avatrombopag and lusutrombopag are both approved for treating thrombocytopenic patients with chronic liver disease about to undergo procedures.[109]

PEG-rhMGDF, rhTPO, romiplostim, eltrombopag, avatrombo-pag and hetrombopag have all been studied in patients with CIT. Although a 2017 meta-analysis stated that there was insufficient evidence to support their use in CIT,[15] considerable new evidence has emerged since then which challenges that conclusion. Clearly all TPO increase the platelet count in CIT patients but the question is whether that translates into clinical benefit in maintaining RDI, reducing bleeding, and improving response or survival. What follows is a summary of current data.

Treatment of chemotherapy-induced thrombocytopenia with pegylated recombinant human growth and development factor

When PEG-rhMGDF was administered for up to 16 days after treatment of lung cancer patients with carboplatin and paclitaxel, the median platelet count nadir was 188×10^9/L (range, $68–373 \times 10^9$/L) *versus* the count in the placebo-treated group of 111×10^9/L (range, $21–307 \times 10^9$/L; $P=0.013$) (Figure 5). The nadir platelet count occurred earlier in the patients treated with PEG-rhMGDF; the median time to nadir was 7 *versus* 15 days ($P<0.001$). The platelet count recovered to baseline in 14 days in the patients given PEG-rhMGDF as compared with more than 21 days in those receiving placebo ($P<0.001$).[123] There was no effect on platelet transfusions or bleeding; only one patient in the placebo group required a platelet transfusion. Thromboses were not increased and the patients' survival was not affected.

In a second major study,[124] patients with advanced malignancy were treated with intravenous carboplatin 600 mg/m² and cyclophosphamide 1,200 mg/m² in their first cycle. In subsequent cycles they received, in addition, PEG-rhMGDF for 1, 3 or 7 days after chemotherapy. Those receiving the same chemotherapy dose on a subsequent cycle had a significantly higher platelet nadir than in cycle 1, (48×10^9/L *vs.* 36×10^9/L; $P=0.003$) and the duration of grade 3 or 4 thrombocytopenia was significantly shorter (0 *vs.* 3 days; $P=0.004$). However, there was no difference
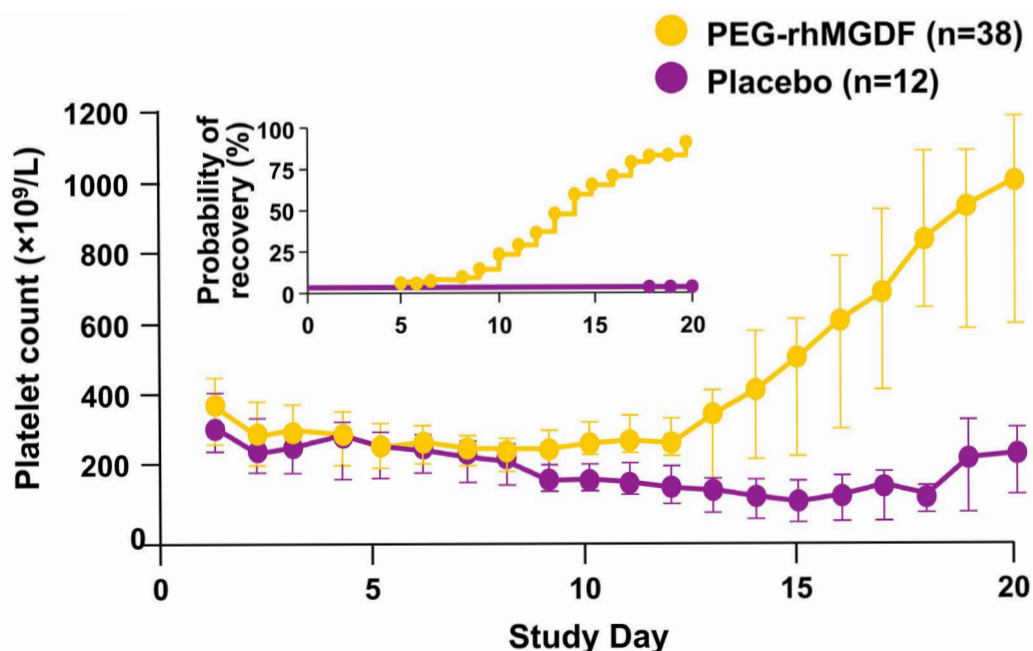

Figure 5. Pegylated recombinant human megakaryocyte growth and development factor increases the platelet count in patients undergoing chemotherapy. Lung cancer patients being treated with carboplatin and paclitaxel were also given either placebo (purple circles) or pegylated recombinant human megakaryocyte growth and development factor (yellow circles) in a double-blind, randomized study.[123] Platelet counts were measured daily. The inset shows the probability of recovery of the platelet count back to baseline in the two treatment groups. Figure adapted from published data.[123] PEG-rhMGDF: pegylated recombinant human megakaryocyte growth and development factor.

in the time to platelet recovery. Administration of PEG-rhMGDF prior to chemotherapy did not show any benefit. A third study has suggested a possible survival benefit from treatment with PEG-rhMGDF.[125] In the treatment of patients with relapsed non-Hodgkin lymphoma with ifosfamide, carboplatin, and etoposide (ICE) chemotherapy, maintenance of RDI correlates with improved survival. In a study of 38 non-Hodgkin lymphoma patients randomized to placebo (n=16) or PEG-rhMGDF (n=22), ICE was given on schedule to 42% of those on placebo and 75% of those on PEG-rhMGDF (P=0.008) with overall survival of 21% and 31%, respectively (P=0.06), after a median follow-up of 8.5 years. Patients on placebo were 4.4 times more likely to have a dose delay, which was due to thrombocytopenia in 83%. Grade 4 thrombocytopenia was seen in 35% of placebo recipients *versus* 15% of patients given PEG-rhMGDF (P=0.02) with platelet nadirs of 20×10^9/L and 49×10^9/L (P=0.008), respectively. Platelet transfusions were administered in 23% of placebo cycles and 8% of PEG-rhMGDF cycles (P=0.04).

As described above, PEG-rhMGDF development stopped in 2000 due to the appearance of antibodies against PEG-rhMGDF which cross-reacted with endogenous TPO and caused thrombocytopenia.[105]

Treatment of chemotherapy-induced thrombocytopenia with recombinant human thrombopoietin

In an early study, rhTPO was administered on days 2, 4, 6, and 8 after a second cycle of carboplatin chemotherapy for patients with a gynecological malignancy (Figure 6). The mean platelet count nadir in the second cycle was higher than that in the first cycle, during which no rhTPO was administered (44×10^9/L *vs.* 20×10^9/L; P=0.002); the number of days with platelet count less than 20×10^9/L was lower (1 *vs.* 4 days, P=0.002); the number of days with a platelet count less than 50×10^9/L was lower (4 *vs.* 7 days; P=0.006). The need for platelet transfusion in the group receiving rhTPO was reduced from 75% of patients in cycle 1 to 25% of patients in cycle 2 (P=0.013). Recovery to a platelet count 100×10^9/L or greater was faster (20 days for
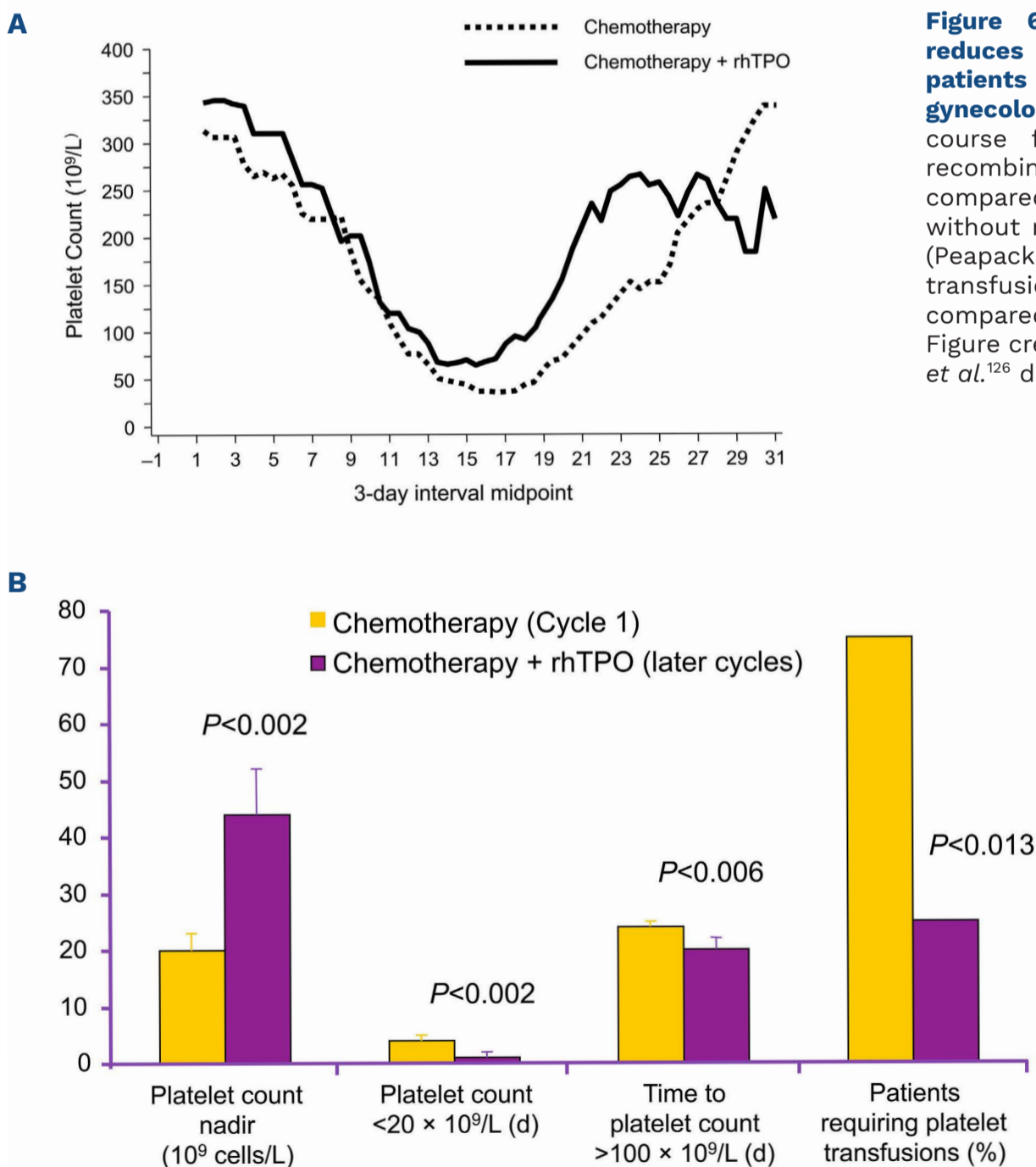
Figure 6. Recombinant human thrombopoietin reduces the need for platelet transfusions in patients undergoing carboplatin chemotherapy for gynecological malignancy. (A) Platelet count time course for patients in cycle 2 (treated with recombinant human thrombopoietin [rhTPO]) compared to that in patients in cycle 1 (treated without rhTPO). Figure provided by Pharmacia, Inc. (Peapack, NJ, USA). (B) Platelet counts and platelet transfusions in cycle 2 (treated with rhTPO) compared with cycle 1 (treated without rhTPO). Figure created from data in the study by Vadhan-Raj *et al.*[126] d: days.

Table 5. Outcomes of 62 patients with chemotherapy-induced thrombocytopenia in a cross-over study who received placebo in one chemotherapy cycle and recombinant human thrombopoietin in an adjacent cycle. Study data on file at 3sBIO Inc, Shenyang, China.

	Placebo	rhTPO	*P* value
Nadir platelet count (x10⁹/L), mean (SD)	49 (35)	61 (51)	0.015
Highest recovery platelet count (x10⁹/L), mean (SD)	153 (82)	261 (164)	<0.001
Platelet count difference (x10⁹/L), mean (SD)	104 (74)	199 (158)	<0.001
Duration platelets <50x10⁹/L post-chemotherapy, mean (SD) days	4.7 (6.9)	3.1 (4.4)	<0.05
Time for platelets to rise >75x10⁹/L, mean (SD) days	17.2 (10.9)	12.0 (9.7)	<0.001
Time for platelets to rise >100x10⁹/L, mean (SD) days	21.2 (10.6)	15.8 (9.7)	<0.001
Platelet transfusion events, mean (SD)	0.6 (1.3)	0.3 (0.7)	<0.05
Platelet units transfused, mean (SD)	3.0 (6.6)	1.5 (4.4)	<0.05

rhTPO: recombinant human thrombopoietin; SD: standard deviation.

rhTPO in cycle 2; 23 days without rhTPO in cycle 1; $P<0.001$).[126]

Numerous CIT studies have been conducted in China with rhTPO but with few results published in non-Asian medical journals.[127,128] In one study (Study 005) made available to this author in English, 62 cancer patients (42% with lymphoma and the rest with solid tumors) with a platelet count less than 75x10⁹/L on a prior cycle and requiring two more chemotherapy cycles at the same dose were randomly treated in a crossover study of CIT prophylaxis. Twenty-eight patients in group A (n=28) received rhTPO treatment (1 µg/kg rhTPO subcutaneously daily for 14 days starting 6–24 h after chemotherapy) during cycle 1 and received no rhTPO during cycle 2. Group B (n=34) received no rhTPO in the first cycle but received rhTPO treatment during cycle 2. As shown in Table 5 there was a modest improvement in nadir platelet count, with a shorter duration of platelet count below 50x10⁹/L, a much higher recovery platelet count by day 24, and fewer transfusion events. No data were provided regarding maintenance of RDI, bleeding, or whether platelet transfusions were standardized. Similar improvements in platelet counts were obtained in an additional crossover study (Study 006) done in 213 cancer patients.

In a study of 58 lymphoma patients undergoing high-dose cytarabine therapy, two different forms of prophylactic rhTPO were prospectively evaluated. A group that was given rhTPO daily for 10 days after chemotherapy was compared to a group that was given two doses prior to chemotherapy and eight doses after. Those receiving rhTPO before the chemotherapy were less likely to have grade 4 thrombocytopenia (26.9% *vs.* 48.1%), experienced a shorter duration of grade 4 thrombocytopenia (0.58 days *vs.* 1.23 days), and required fewer transfusions (13.5% *vs.* 25%).[129]

In a small study of rhTPO in 30 patients undergoing adjuvant chemotherapy for gastric or colorectal cancer with regimens containing gemcitabine and capecitabine, patients were randomized to receive either prophylactic treatment with rhTPO 15,000 U/day beginning 4 days before chemotherapy or to receive treatment only when platelet counts after chemotherapy dropped below 75x10⁹/L. Those receiving prophylactic rhTPO experienced better outcomes in terms of a higher mean [standard deviation, SD] nadir platelet count (76x10⁹/L [27x10⁹/L] *vs.* 53x10⁹/L [17x10⁹/L]; $P<0.001$], fewer days of dose interruption (1.72 [2.78] *vs.* 3.72 [3.38]; $P=0.002$), and a shorter recovery to platelet counts over 100x10⁹/L (4.6 [4.7] *vs.* 8.9 [2.3] days; $P<0.001$).[130]

In a recent meta-analysis[131] of 12 CIT studies, mostly in China, when compared with patients treated with placebo or interleukin-11, those treated with rhTPO had modest decreases in the duration of days with platelet counts under 50x10⁹/L and 75x10⁹/L but no difference in days with platelet counts under 100x10⁹/L. Other clinical endpoints were not reported.

Although rhTPO is approved for CIT in China, the studies above document a modest increase in platelet count with treatment but it is hard to assess from published data whether any clinical endpoints such as RDI, remission rate, bleeding or survival were affected.

Treatment of chemotherapy-induced thrombocytopenia with romiplostim

In one retrospective study, cancer patients were selected who had a platelet count less than 100x10⁹/L and who had a more than 4-week delay in their chemotherapy or had dose reductions/modifications in two or more prior cycles of chemotherapy.[132] These patients were treated with 2 µg/kg of romiplostim weekly. Platelet counts improved in all and 19/20 had platelet counts of 100x10⁹/L or more. Fifteen patients resumed chemotherapy and all but one of these continued for two or more further cycles without dose modifications. Three of 20 patients developed deep vein thrombosis.

In a phase II, randomized prospective trial (NCT02052882: An Open Label Phase II Study of Romiplostim for Chemotherapy Induced Thrombocytopenia) in solid tumor patients with CIT, patients with platelet counts below 100x10⁹/L for more than 4 weeks despite dose reduction or delay were randomized to receive either romiplostim weekly or observation.[133] The primary endpoint was attain-

ing a platelet count of 100x10⁹/L or more by week 3. After enrolling 23 patients, it was found that 14/15 (93%) patients who received romiplostim attained the primary endpoint, whereas only 1/8 (12.5%) of those on observation did so (*P*<0.001). After 2–3 weeks of treatment, those receiving romiplostim had a mean platelet count of 141x10⁹/L *versus* 57x10⁹/L for those on observation. The randomized portion of the study was discontinued and 37 subsequent patients all received romiplostim. Of the 52 patients who received romiplostim, 44 (85%) met the primary endpoint. All of these 44 patients resumed chemotherapy supported with romiplostim and only three (6.8%) developed subsequent CIT. Twenty-eight patients continued on romiplostim for more than 6 months at a mean dose of 3.3 µg/kg. Six of the 59 patients (10.2%) developed a venous thromboembolism during the first year of romiplostim therapy; none discontinued romiplostim.

At four Boston cancer centers, supportive care with romiplostim has been utilized for almost 10 years for CIT patients.[27,134] Patients eligible for this program had to have a platelet count below 100x10⁹/L for at least 3 weeks after their last chemotherapy treatment or a dose delay of longer than 1 week. Overall, 173 CIT patients (153 with solid tumors, 20 with lymphoma or myeloma) were treated, with 170 (90%) undergoing a median of four (range, 1–36) chemotherapy cycles on romiplostim. The primary outcome was a platelet response defined as a median on-romiplostim platelet count of 75x10⁹/L or more and at least 30x10⁹/L higher than pretreatment

baseline. Among all the solid tumor patients 71% had a platelet response, 79% avoided chemotherapy dose reductions/delays and 89% avoided platelet transfusions. The median baseline platelet count of 60x10⁹/L rose to 116x10⁹/L (*P*=0.001). The median weekly romiplostim dose was 3 µg/kg (interquartile range, 3–5 µg/kg). Solid tumor patients who failed to respond were characterized by extensive bone marrow involvement by tumor, prior pelvic radiotherapy or treatment with temozolomide and their low response rate (<10%) was comparable to that of patients with lymphoma and myeloma (Figure 7). Bleeding rates (7.1/100 patient-years on romiplostim) were less than those of historical controls and there was no apparent increase in thrombosis (11/100 patient-years on romiplostim). Two different dosing algorithms were explored: weekly romiplostim dosing including on days of chemotherapy administration *versus* a less intense regimen with weekly dosing except on days of chemotherapy administration. Patients on weekly dosing had a significantly higher median platelet count (143x10⁹/L *vs.* 106x10⁹/L; *P*<0.001) and a higher rate of achieving a platelet response (81% *vs.* 63%; *P*=0.006). Other clinical outcomes including the extent of chemotherapy RDI reduction and bleeding were better in patients receiving weekly treatment.

There are two ongoing trials of romiplostim in CIT with the primary endpoint being the incidence of either a chemotherapy dose delay or reduction (defined as "no thrombocytopenia-induced modification [dose delay, reduction,
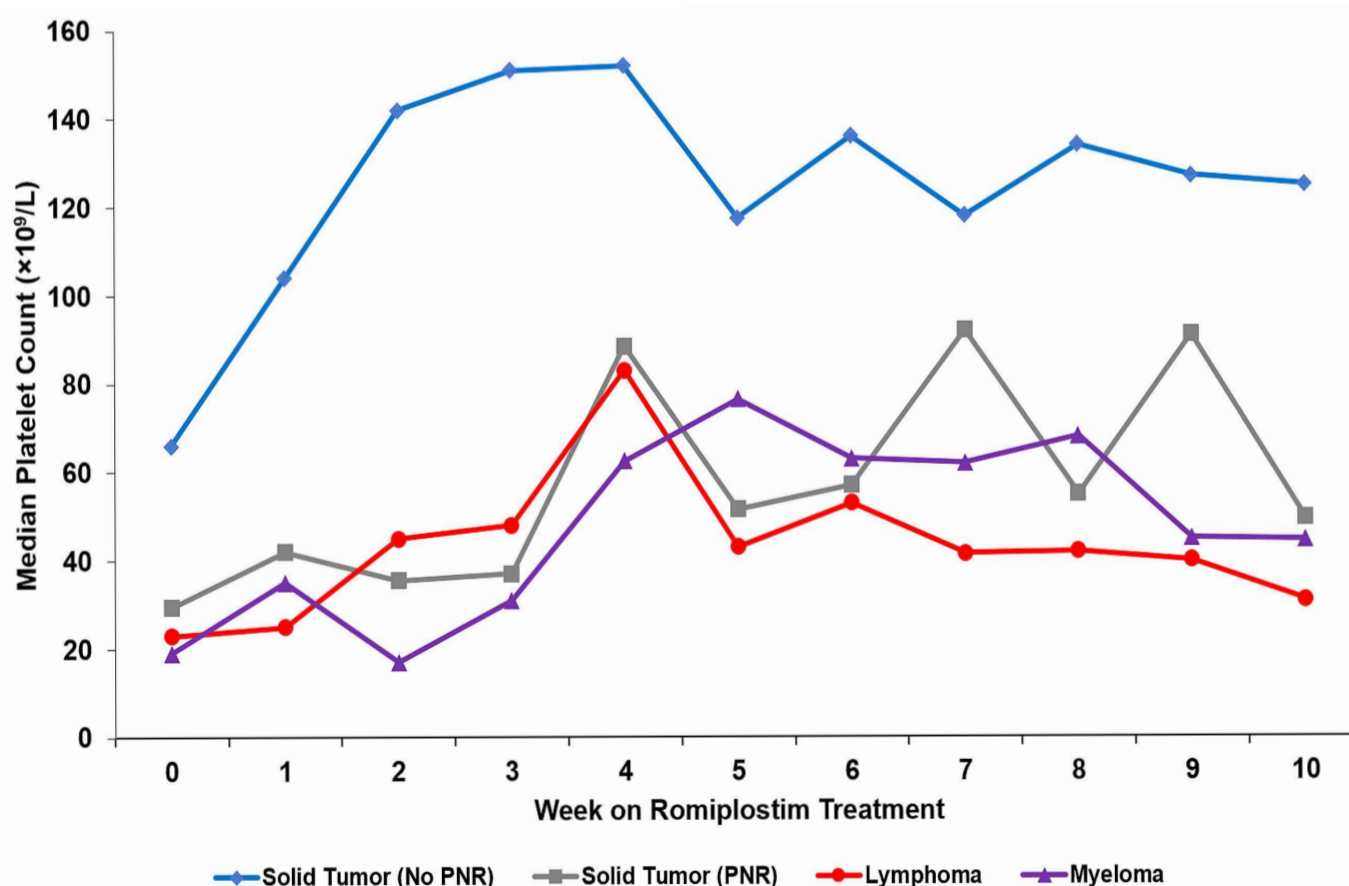
Figure 7. Platelet counts of patients with chemotherapy-induced thrombocytopenia treated with romiplostim. Median weekly platelet counts for solid tumor patients (n=122, blue) with no predictors of non-response (no PNR); solid tumor patients (n=31, gray) with predictors of non-response (PNR: bone marrow invasion by tumor, prior pelvic irradiation, or prior temozolomide treatment); aggressive lymphoma patients (n=13, red); and myeloma patients (n=7, purple). Data reproduced with permission from Al-Samkari H *et al.*[27]

omission or chemotherapy treatment discontinuation due to platelet counts <100 x 10^9/L] of any myelosuppressive agent in the second and third cycles of the planned on-study chemotherapy regimen"): NCT03937154: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving Chemotherapy for Treatment of Non-small Cell Lung Cancer (NSCLC), Ovarian Cancer, or Breast Cancer; and NCT03362177: A Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-Induced Thrombocytopenia in Patients Receiving Oxaliplatin-based Chemotherapy for Treatment of Gastrointestinal, Pancreatic, or Colorectal Cancer.

Treatment of chemotherapy-induced thrombocytopenia with eltrombopag

In a CIT prophylaxis study (NCT00102726), 183 patients received either placebo or eltrombopag 50 mg, 75 mg or 100 mg on days 2 through 11 for at least two 21-day chemotherapy cycles. Eltrombopag was well tolerated. The primary endpoint (the difference in platelet count from day 1 in cycle 2 to the platelet nadir in cycle 2) was not met but post-nadir platelet counts were higher for cycles 1 and 2 than in patients in the placebo group.[135]

In an early but informative blinded, placebo-controlled phase I study to prevent CIT, patients with solid tumors and a platelet count 300x10^9/L or below receiving up to six cycles of either gemcitabine alone (9 patients) or gemcitabine plus either cisplatin or carboplatin (10 patients) were randomized (3:1) to receive eltrombopag 100 mg or placebo on days -5 to -1 and days 2-6 starting from cycle 2; no study drug was administered for cycle 1.[136] For patients receiving gemcitabine alone, the mean (SD) nadir platelet count for cycles 2-6 was 143x10^9/L (82x10^9/L) for eltrombopag *versus* 103x10^9/L (64x10^9/L) for placebo; for those receiving gemcitabine plus cisplatin or carboplatin the nadir was 115x10^9/L (83x10^9/L) *versus* 53x10^9/L (7x10^9/L) for placebo; 14% of all eltrombopag patients and 50% of placebo patients required dose reductions or delays in cycles 3-6. Three thromboembolic events were reported and felt to be related to other disease characteristics. Platelet counts greater than 400x10^9/L were reported more frequently in eltrombopag-treated *versus* control patients (92/19 [4.8 events/patient] *vs*. 18/7 [2.6 events/patient]) and the decision was made not to increase the dose of eltrombopag above 100 mg/day.

A larger phase II study investigated eltrombopag prophylaxis for the prevention of CIT in patients receiving either gemcitabine alone (42 patients) or gemcitabine with carboplatin or cisplatin (32 patients) over six cycles of chemotherapy. Patients were randomized (1:2) to receive either placebo or eltrombopag 100 mg/day for 5 days before and again daily for 5 days after the chemotherapy.[137] The primary endpoint

was the mean pretreatment platelet count over six cycles of chemotherapy. The treatment was well tolerated with no increased risk of thrombosis (5/52 [9.6%] on eltrombopag and 2/23 [8.7%] on placebo) but was complicated by a 65% withdrawal rate. The geometric mean platelet count of the 48 eltrombopag–treated patients was 246x10^9/L compared with 193x10^9/L for the 23 placebo patients, but the difference did not attain statistical significance (*P*=0.103). Patients receiving eltrombopag had a slightly lower rate of grade 3/4 thrombocytopenia (27/50 [54%] *vs*. 16/23 [70%]) and slightly higher nadir platelet counts than patients receiving placebo. There were fewer dose reductions, dose delays and missed doses due to thrombocytopenia in cycles 2-6 for eltrombopag (15/38 [39%]) than for placebo (10/19 [53%]).

A real-world retrospective observational study assessed the response of lymphoma patients whose platelet counts dropped below 30x10^9/L and who were then treated with eltrombopag (n=51), rhTPO (n=50) or no platelet growth factor support (n=52).[138] The baseline platelet counts for all three groups was 24x10^9/L. After 10 days there was a significantly higher median [SD] platelet count in those on eltrombopag and rhTPO than the untreated patients (131x10^9/L [71x10^9/L], 147x10^9/L [68x10^9/L], and 76x10^9/L [40x10^9/L], respectively; *P*<0.001); the median (SD) duration of platelet counts <50x10^9/L was 6.25 (2.61), 5.48 (2.62), and 8.33 (3.98) days, respectively (*P*=0.036); the mean (SD) days required for recovery to greater than 50x10^9/L was 6.33 (2.31), 5.44 (2.57), and 8.32 (2.53) days, respectively (*P*=0.001). Patients receiving eltrombopag or rhTPO were less likely to have grade 2/3 bleeding (5.9% and 4.0%) compared with untreated patients (11.5%); with fewer platelet transfusions (55% and 50%) compared with untreated patients (75%).

One eltrombopag CIT study is currently being conducted: NCT04600960: Eltrombopag for Chemotherapy-induced Thrombocytopenia: A Prospective Single-center One-arm Study.

Treatment of chemotherapy-induced thrombocytopenia with avatrombopag

Avatrombopag has been studied in patients with CIT: NCT03471078: Randomized, Double-blind, Placebo-controlled Study With Open-label Extension to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Chemotherapy-induced Thrombocytopenia in Subjects With Active Non-Hematological Cancers. This was a double-blind, placebo-controlled phase III prospective study assessing the safety and efficacy of avatrombopag in patients with CIT (grade ≥2 in a prior cycle) who were receiving chemotherapy for ovarian cancer, small cell lung cancer, non-small cell lung cancer, or bladder cancer. One hundred twenty-two patients were enrolled who had developed grade 3 or 4 thrombocytopenia following treatment with chemotherapy in a prior cycle. Preliminary results of the study showed that avatrombopag failed to

meet the composite primary endpoint (avoiding platelet transfusions, chemotherapy dose reductions by ≥15%, and chemotherapy dose delays by ≥4 days). In the intent-to-treat population, 69.5% of patients who received avatrombopag and 72.5% of those who received placebo were responders for the primary endpoint (P=0.72). In the per-protocol population, these rates were 85.0% and 84.4% for avatrombopag and placebo, respectively, (P=0.96). Other avatrombopag CIT studies are being planned with different entry requirements.

Treatment of chemotherapy-induced thrombocytopenia with hetrombopag

CIT studies are ongoing in China and will soon be started in the West. The current ongoing study is: NCT03976882: A Randomized, Double-blind, Placebo-controlled Multi-centre Study With an Open-label Extension to Evaluate the Efficacy and Safety of Hetrombopag for the Treatment of Chemotherapy-induced Thrombocytopenia in Subjects With Malignancy.

Conclusion

CIT is a common complication of non-myeloablative chemotherapy in patients with solid tumors and its incidence varies with the chemotherapy regimen used. Bleeding is generally associated with the degree of thrombocytopenia. Studies that include other variables in addition to the platelet count are needed to predict bleeding in chemotherapy patients; artificial intelligence predictive algorithms may help here.

Other non-chemotherapy-related causes for thrombocytopenia should be assessed and treated in all patients. Platelet transfusions are the main therapy for bleeding in CIT patients. Chemotherapy dose or frequency reductions are the mainstay of CIT treatment but may compromise RDI and therapeutic effect. rhTPO and TPO-RA increase the pretreatment and nadir platelet counts in most patients with CIT but their beneficial effect on RDI, tumor response, transfusion, bleeding or survival have not yet been adequately demonstrated. It is too early to assess the cost-effectiveness of this form of supportive care. There remains a need for consensus as to what is an adequate pretreatment platelet count in patients being given chemotherapy; such a count will certainly vary with the chemotherapy regimen and patient's pretreatment variables. This reviewer feels that in most situations, a pretreatment platelet count over 50×10^9/L is usually adequate.

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