Managing Thrombocytopenia Associated With Cancer Chemotherapy

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This review will focus on the general approach to, and treatment of, thrombocytopenia in cancer patients, including thrombopoietin treatment in patients receiving non-myeloablative chemotherapy.

Introduction

Thrombocytopenia is a common problem in patients with cancer. It can result from chemotherapy or radiation treatment, or from the underlying disease itself.

Thrombocytopenia creates a number of problems in the care of a cancer patient. At platelet counts < 10,000/µL, spontaneous bleeding is increased. At platelet counts < 50,000/µL, surgical procedures are often complicated by bleeding. At platelet counts < 100,000/µL, chemotherapy and radiation therapy are administered with caution for fear of worsening the thrombocytopenia and increasing the risk of bleeding.[1] Therapeutic and prophylactic platelet transfusions create the additional risk of infusion complications. Thrombocytopenia can also occur with any infection or adverse drug reaction associated with cancer treatment. Finally, a diagnosis of thrombocytopenia exacerbates the patient's sense of anxiety and fear beyond that associated with the cancer diagnosis itself.

Clinicians’ responses to thrombocytopenia in a cancer patient vary. Reduction of the dose intensity of chemotherapy or radiation is common; more effective regimens with thrombocytopenic toxicity may be avoided; and treatment may even be precluded. For some patients, treatment of the underlying cause of thrombocytopenia (eg, stopping therapy with the offending antiviral drug) may work. Platelet transfusion is often the only readily available treatment.

With the discovery of thrombopoietin in 1994, great expectations were generated that it would play a role in preventing or treating thrombocytopenia in cancer patients, just as erythropoietin and granulocyte colony-stimulating factor (G-CSF) have played roles in reducing anemia and neutropenia, respectively.[2] The first-generation recombinant thrombopoietins reduced chemotherapy-related thrombocytopenia in early clinical trials, but their subsequent development was halted due to antibody formation against endogenous thrombopoietin.[3] While two second-generation thrombopoietin receptor agonists have now been developed that are potent stimulators of platelet production, neither has yet been tailored for treating thrombocytopenia in patients with cancer.[2,4]

This review will focus on the general approach to, and treatment of, thrombocytopenia in cancer patients, including thrombopoietin treatment in patients receiving non-myeloablative chemotherapy. The use of thrombopoietin in myeloablative settings (stem cell transplantation and induction therapy for acute myeloid leukemia) has recently been discussed.[5]

Clinical Approach to Thrombocytopenia in Patients With Cancer

Although chemotherapy and radiation are the major causes of thrombocytopenia in patients with cancer, other etiologies should be considered in all patients. In general, the following evaluation should be considered when platelet counts are < 100,000/µL.

Is the underlying disease the cause of the thrombocytopenia? Tumor metastatic to bone marrow is common in patients with breast and lung cancer, as well as in those with primary hematologic malignancies such as lymphoma. Many such patients also demonstrate pancytopenia, and these cytopenias generally occur when over 80% of the bone marrow is infiltrated.

Is there an associated immune thrombocytopenia (ITP)? Up to 1% of Hodgkin disease patients,[6,7] 2% to 10% of patients with chronic lymphocytic leukemia,[8-10] and 0.76% (range, 0–1.8%) of patients with other non-Hodgkin lymphomas (NHLs)[7] develop a secondary ITP. These patients respond to steroids, rituximab, splenectomy, and thrombopoietin receptor agonists in the same way.
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As patients with primary ITP, although treatment of the underlying lymphoma may be more effective.[7]

Has there been a recent infection? While infection may produce consumptive coagulopathies (e.g., disseminated intravascular coagulation [DIC]), some bacteria release neuraminidase that actually reduces platelet survival by removing the sialic acids coating platelets and thereby increasing their clearance by the Ashwell-Morell receptor in the liver.[11,12] Viral infection (e.g., with 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. Antibiotics (e.g., vancomycin,[13] linezolid[14]) and antiviral agents (e.g., ganciclovir[15,16]) commonly induce thrombocytopenia by direct bone marrow toxicity or drug-dependent antibody clearance.[13,17]

Has there been a recent transfusion? Post-transfusion purpura (PTP) is a rare complication of transfusion of red blood cells (RBCs) and platelets, with the platelet count usually dropping below 10,000/µL. PTP occurs in the 1% of patients who lack the common platelet antigen PLA1, also known as human platelet antigen (HPA)-1a, and in this group, PTP usually is observed 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 a still unclear mechanism also destroys the patient’s own HPA-1a-negative platelets. This under-recognized complication of transfusion responds readily to intravenous immunoglobulin (IVIG).

Does the patient have a coagulopathy? In addition to infection, some tumors (e.g., gastric and pancreatic adenocarcinomas) can produce chronic DIC.[18,19] Such thrombocytopenic patients usually have elevated D-dimer and low fibrinogen levels, but often have minimally prolonged prothrombin time and partial thromboplastin time.[20] Treatment of chronic DIC 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 gemicabine have been found to induce endothelial injury, with a resultant thrombotic microangiopathy whose major manifestation is renal failure and thrombocytopenia; this is best referred to as a chemotherapy-related hemolytic uremic syndrome.[21] These patients usually have normal activity levels of the protein ADAMTS13 but have abundant schistocytes in the peripheral blood smear and an elevated lactate dehydrogenase level; most improve with supportive care and discontinuation of the chemotherapy. Plasma exchange, rituximab, or steroids are not indicated.[22]

It is unclear whether complement inhibition with eculizumab is of benefit.[23]

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 (Figure 1). [24] Depending upon the dose and duration of radiation therapy, the onset of thrombocytopenia is generally at days 7 through 10. The duration of thrombocytopenia is longer, and sometimes continues for 30 to 60 days.

What chemotherapy was given? 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. Thus, most standard regimens are associated with relatively low rates of dose-limiting thrombocytopenia; when thrombocytopenia occurs, it is often of short duration (4 to 6 days). Most patients respond well to platelet transfusion. In a recent review of different chemotherapy regimens in 614 patients with solid tumors, a platelet count < 100,000/µL was seen in 21.8% of all subjects; these were unaccompanied by other cytopenias in 6.2%.[25] Grade III thrombocytopenia (platelet count, 25,000–49,000/µL) was seen in 3.6% and grade IV thrombocytopenia (platelet count, < 25,000/µL) in 3.3%. Thrombocytopenia 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 an analysis of 43,995 patients receiving 62,071 chemotherapy regimens,[26] 6.5% had grade III and 4.1% had grade IV thrombocytopenia with platinum-based regimens; 3.0% had grade III and 2.2% grade IV thrombocytopenia with anthracycline-based regimens; 7.8% had grade III and 3.4% grade IV thrombocytopenia with gemcitabine-based regimens; and 1.4% had grade III and 0.5% grade IV thrombocytopenia with taxane-based regimens. Among the 10,582 regimens for which data were available, platelet transfusions occurred in 2.5% of patients (in 1.0% of those treated with platinum-based regimens, 0.6% of those who received anthracycline-based treatment, 1.8% of patients treated with gemcitabine-based therapy, and 0.3% of those who received taxane-based...
The Table provides an overview of the reported frequencies of thrombocytopenia associated with various current chemotherapy regimens.

Pathophysiology of Chemotherapy-Induced Thrombocytopenia

Not all chemotherapy drugs cause thrombocytopenia in the same way. In reviewing the mechanism of thrombocytopenia, it is helpful to understand how platelets are made (Figure 2). Stem cells differentiate into cells committed to megakaryocyte differentiation (megakaryocyte colony-forming cells [Mk-CFCs]). At some stage, these cells stop their mitotic divisions and enter a process called “endomitosis,” in which DNA replication occurs without 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 DNA synthesis and mature into large, morphologically identifiable megakaryocytes.

Mature megakaryocytes then produce platelets by a mechanism that is still poorly defined. In its simplest iteration, 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.[27] If not consumed in hemostasis, the mature platelet undergoes programmed cell death (apoptosis), determined by a “platelet clock.”[28] This platelet clock depends on the presence of an anti-apoptotic protein called Bcl-x(L), a protein that restraints the pro-apoptotic proteins Bax and Bak.[28-31] When levels of Bcl-x(L) decline, Bax and Bak activity increase and trigger platelet apoptosis. The apoptotic platelets are cleared by the reticuloendothelial cell system; the spleen plays only a limited role in normal platelet homeostasis.[32]

Different chemotherapy drugs affect the megakaryocyte and platelet production pathway at different steps (see Figure 2). Alkylating agents such as busulfan affect pluripotent stem cells.[33,34] Cyclophosphamide spares hematopoietic stem cells because of their abundant levels of aldehyde dehydrogenase, but affects later megakaryocyte progenitors.[35] Bortezomib has no effect on stem cells[36] or megakaryocyte maturation but does inhibit nuclear factor kappa B, a critical regulator of platelet shedding.[37] This probably explains the relatively short duration of thrombocytopenia following its administration.[37]

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 agents. The experimental chemotherapy agent ABT-737 reduces the activity of the platelet clock Bcl-x(L) and rapidly induces platelets to undergo apoptosis.[29,38] After a single dose of ABT-737, platelet levels dropped to 30% of baseline by 2 hours, dropped to 5% of baseline by 6 hours, started to recover to 10% of baseline by 24 hours, and returned to baseline after 72 hours.[38] This was not due to platelet activation; rather, caspase-mediated apoptosis was induced, with a rapid appearance of phosphatidylserine on the platelet surface and clearance of these cells from the circulation by the reticuloendothelial system in the liver. Although this mechanism has not been evaluated for most standard chemotherapy drugs, etoposide also increases platelet apoptosis by reducing Bcl-x(L) activity.[38]

Finally, chemotherapy may enhance platelet clearance by immune mechanisms. In the treatment of many lymphomas, administration of single-agent fludarabine has been noted to produce an immune thrombocytopenia in up to 4.5% of patients.[39] This ITP typically responds to rituximab.[40] Platelet destruction is also increased when chemotherapy drugs produce a drug-dependent secondary immune thrombocytopenia, but this effect is uncommon.

The Role of Thrombopoietin in Platelet Production

The hematopoietic growth factor thrombopoietin is the key regulator of platelet production. In animals or humans deficient in thrombopoietin or its receptor, the platelet count is 10% to 15% of normal values.[41,42] Megakaryocyte, erythroid, and myeloid precursor cells are all reduced in such knock-out animals, but the white blood cell (WBC) and RBC counts are normal.[43] Thrombopoietin is usually made in a constant (“constitutive”) rate in the liver, lacks a storage form, and is released into the circulation. At non-physiological levels in animals, large quantities of desialylated platelets may slightly increase hepatic thrombopoietin production.[44] Once in the circulation, most thrombopoietin is cleared by avid thrombopoietin receptors on platelets and possibly on bone marrow megakaryocytes. These cells bind, internalize, and then degrade thrombopoietin. The small residual amount of thrombopoietin in the circulation accounts for the basal rate of platelet production. Thrombocytopenia does not increase the hepatic thrombopoietin
production rate, and no other physiologic stimulus has been shown to alter the rate of thrombopoietin production. With severe thrombocytopenia caused by chemotherapy, hepatic thrombopoietin mRNA levels are unchanged despite a 10- to 20-fold increase in the concentration of thrombopoietin.[45] Hepatic damage results in a proportional decrease in thrombopoietin production.[46] Circulating thrombopoietin levels are inversely related to the rate of platelet production.[47] With the reduction in platelet production as a result of chemotherapy, thrombopoietin clearance is reduced and levels rise (see Figure 1). There is a log-linear relationship between the rise in thrombopoietin concentration and the fall in the platelet count after chemotherapy.[48] In contrast, in most ITP patients, the platelet production rate is not reduced,[49,50] thrombopoietin clearance is normal, and levels do not rise. This primitive form of regulation of a hematopoietic growth factor is similar to that by which the basal levels of G-CSF and macrophage colony-stimulating factor are directly maintained by the circulating mass of neutrophils and monocytes, respectively. The only exception seems to be erythropoietin, levels of which are determined by a hypoxia-induced factor-mediated renal sensor of the hemoglobin concentration.[51] There is no such sensor of the platelet count.

Thrombopoietin binds to its receptor on many hematopoietic cells and exerts its effect on most stages of megakaryocyte growth (see Figure 2). Thrombopoietin is necessary for the viability of hematopoietic stem cells; when the thrombopoietin receptor is absent, humans are born with thrombocytopenia and develop pancytopenia over subsequent years.[52-54] Thrombopoietin stimulates mitosis of Mk-CFCs. Its major effect (at exceedingly low concentrations) is to increase megakaryocyte endomitosis and increase megakaryocyte ploidy, greatly expanding the megakaryocyte pool. Thrombopoietin then stimulates megakaryocyte maturation. It is unclear whether thrombopoietin plays any role in platelet shedding.[55] An underappreciated property of thrombopoietin is that it prevents apoptosis of early and late megakaryocytes,[56] an effect that may play a major protective role in patients receiving radiation and chemotherapy (as discussed below).

Inflammatory cytokines such as interleukin (IL)-6 and IL-11 may also stimulate platelet production by mechanisms independent of thrombopoietin.[57,58]

**Clinical Development of Thrombopoietin Molecules**

The development of clinically relevant thrombopoietin molecules has occurred in two phases: creation of the early recombinant thrombopoietins and then development of the recent thrombopoietin receptor agonists.[2] With the discovery of thrombopoietin in 1994, two recombinant thrombopoietin molecules were developed (Figure 3). Recombinant human thrombopoietin (rhTPO) was a fully glycosylated thrombopoietin protein made in CHO (Chinese hamster ovary) cells. The other, pegylated recombinant human megakaryocyte growth and development factor (PEG-rhMGDF), was a non-glycosylated protein comprising the first 163 amino acids of thrombopoietin coupled to polyethylene glycol. Both molecules were potent stimulators of platelet production, with half-lives of about 40 hours. In healthy volunteers, both agents 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 through 14, a peak platelet count was obtained; and by day 28, platelet counts returned to their baseline values.

Between 1995 and 2000, both recombinant thrombopoietins underwent extensive clinical development in oncology settings.[3] Development of both was stopped due to concerns over neutralizing antibody formation against PEG-rhMGDF.[59] Despite differences between the structure of PEG-rhMGDF and that of rhTPO, antibody formation against PEG-rhMGDF might have been due to the route of administration. After early studies suggested that rhTPO might induce antibody formation when given by a subcutaneous route, rhTPO was thereafter given intravenously, with no subsequent antibody formation. In contrast, PEG-rhMGDF was given only subcutaneously, and in several studies patients developed neutralizing antibody to the recombinant protein.[60,61] 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 thrombopoietin, creating thrombopoietin deficiency and thrombocytopenia. All subjects recovered, but some required immunosuppressive treatment.[60,61] Despite the failure of one of these recombinant thrombopoietin molecules, interest turned to developing newer thrombopoietin molecules (now called thrombopoietin receptor agonists) with
novel properties and less risk of antibody formation. In 1997, a 14-amino-acid peptide was identified that had no sequence homology to thrombopoietin but bound to the thrombopoietin receptor; when dimerized, it had the same activity as rhTPO.[62] To overcome its short half-life in the circulation, this peptide was inserted into an IgG4 heavy chain to produce romiplostim, a “peptibody” with a half-life of 120 hours (see Figure 3).[63] When injected into healthy volunteers, romiplostim produced a dose-dependent platelet count rise that began at day 5 and peaked by day 14.[64] Single doses of 10 µg/kg produced peak platelet counts of 1,600,000/µL in healthy volunteers, an eightfold increase over baseline. There was no effect on the number of WBCs or RBCs.

A separate approach identified small molecules that bound and activated the thrombopoietin receptor. One of these, eltrombogag, bound the thrombopoietin receptor in the transmembrane region, an area different from where thrombopoietin or romiplostim bound, and activated the thrombopoietin receptor in a different fashion.[65-67] When given to healthy volunteers for 10 days, eltrombogag produced a 50% increase in the platelet count with no effect on the WBC or RBC count. Both of these thrombopoietin receptor agonists have undergone extensive clinical development, and both increased the platelet count in over 85% of patients with ITP.[1,4,68-71] Both have been approved in many countries for the treatment of ITP; prolonged use of both has produced sustained increases in platelet counts for years, with minimal or no adverse events.[69,72] Additionally, eltrombogag is now approved for the treatment of thrombocytopenia in patients with hepatitis C infection requiring antiviral treatment.[73] In patients with aplastic anemia in whom immunosuppressive therapy has failed.[74,75] In the latter disease, treatment was also associated with an increase in WBCs and RBCs.

**Effect of rhTPO and PEG-rhMGDF in Cancer Patients Receiving Chemotherapy**

Before considering the use of thrombopoietin agents in patients with cancer, it is important to note that solid tumors appear not to possess functional thrombopoietin receptors.[76,77] In one study using reverse-transcription polymerase chain reaction (RT-PCR) on 39 human cell lines and 20 primary normal and malignant human tissues, thrombopoietin receptor (c-mpl) transcripts were found in all megakaryocytic cell lines tested (DAMI, CMK, CMK-2B, CMK-2D, SO), in the CD34-positive leukemia cell line KMT-2, and in the hepatocellular carcinoma cell line Hep3B.[77] 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 testing detected thrombopoietin receptor mRNA in 0 of 118 breast tumors and at very low levels in 14 of 29 lung tumors.[76] Low but detectable thrombopoietin receptor mRNA was found by quantitative real-time PCR (QT-PCR) in some normal (14%-43%) and malignant (3%-17%) breast, lung, and ovarian tissues, but none of these tissues showed detectable thrombopoietin receptor protein by immunohistochemistry. Culture of breast, lung, and ovarian carcinoma cell lines with thrombopoietin receptor agonists 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 the recombinant thrombopoietins.

The recombinant thrombopoietins were studied in a wide variety of non-myeloablative settings. Unfortunately, the results of many of these studies have never been reported other than in abstract form. In general, thrombopoietin produced an earlier but higher nadir platelet count, shortened the duration of thrombocytopenia, reduced platelet transfusions, and enabled chemotherapy to be given on schedule.

When PEG-rhMGDF was administered to lung cancer patients for up to 16 days after treatment with carboplatin and paclitaxel, the median platelet count nadir was 188,000/µL (range, 68,000–373,000/µL) vs 111,000/µL (range, 21,000–307,000/µL; P = .013) in the placebo group (Figure 4). The nadir platelet count occurred earlier in the patients treated with PEG-rhMGDF; median time to nadir was 7 days vs 15 days (P < .001). The platelet count recovered to baseline in a median of 14 days in the PEG-rhMGDF patients as compared with > 21 days in those receiving placebo (P < .001).[78] There was no effect on platelet transfusions or bleeding; only one patient in the placebo group required a platelet transfusion. The incidence of thrombosis was not increased.

In another study, rhTPO was administered on days 2, 4, 6, and 8 after a second cycle of carboplatin chemotherapy for patients with gynecologic malignancy (Figure 5). Compared with the first cycle, during which no rhTPO was administered, the median platelet count nadir was higher (44,000/µL vs 20,000/µL; P = .002); the number of days with platelet count < 20,000/µL was lower (1 vs 4 days; P = .002); and the number of days with a platelet count < 50,000/µL was lower (4 vs 7 days; P = .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 = .013). Administration of rhTPO improved recovery to a platelet count ≥ 100,000/µL (20 days for rhTPO in cycle 2 vs 23 days without rhTPO in cycle 1; P < .001).[79]

In the third major study,[80] patients with advanced malignancy were treated with carboplatin at 600 mg/m² and cyclophosphamide at 1,200 mg/m² in their first cycle. In subsequent cycles they also received PEG-rhMGDF for 1, 3, or 7 days after chemotherapy. Compared with cycle 1, those receiving the same chemotherapy dose on a subsequent cycle had a significantly higher platelet nadir (47,500/µL vs 35,500/µL; P = .003), and the duration of grade III or IV thrombocytopenia was significantly shorter (0 vs 3 days; P = .004). However, there was no difference in the time to platelet recovery. Administration of PEG-rhMGDF prior to chemotherapy did not show any benefit.

One study has suggested a possible survival benefit from treatment with PEG-rhMGDF.[81] In the treatment of patients with relapsed NHL with ifosfamide, carboplatin, and etoposide (ICE) chemotherapy, maintenance of dose intensity and dose density correlates with improved survival. In a study of 38 NHL patients randomized to placebo (n = 16) or PEG-rhMGDF (n = 22), ICE was given on schedule to 42% of those on placebo and to 75% of those on PEG-rhMGDF (P = .008) with overall survivals of 31% and 59% (P = .06), respectively, after a median follow-up of 8.5 years. Patients on placebo were 4.4 times more likely to have a dose delay; in 83% of cases, the dose delay was due to thrombocytopenia. Grade IV thrombocytopenia was seen in 35% of the placebo group vs 15% of PEG-rhMGDF patients (P = .02), with platelet count nadirs of 20,000/µL and 49,000/µL (P = .008), respectively. Platelet transfusions were administered in 23% of placebo cycles and in 8% of PEG-rhMGDF cycles (P = .04).

There were no human radiotherapy studies with PEG-rhMGDF or rhTPO, but one important series of primate studies suggested that thrombopoietin might have a radioprotective effect.[82-86] When rhesus monkeys were sublethally irradiated, all blood lines were reduced 10 days later. Administration of rhTPO in a critical time period anywhere from 2 hours before until 4 hours after the irradiation markedly ameliorated the pancytopenia; in the study, platelet counts were 1,123,000/µL ± 89,000/µL without radiation therapy or thrombopoietin, 144,000/µL ± 62,000/µL with radiation therapy but without thrombopoietin, and 739,000/µL ± 165,000/µL with both radiation therapy and thrombopoietin. Assays for precursor cells of all lineages showed marked increases in viability when rhTPO was administered.

**Effects of Thrombopoietin Receptor Agonists in Cancer Patients Receiving Chemotherapy**

Although 6 years have elapsed since the approval of thrombopoietin receptor agonists for treatment of ITP, surprisingly few studies of these agents have been conducted in cancer patients undergoing chemotherapy. Only a small number of case reports[87] and small series of patients with cancer have been published in this area.[88-91]

In one retrospective study, cancer patients were selected who had a platelet count < 100,000/µL and who had > 4-week delay in their chemotherapy or had dose reductions/modification in > 2 prior cycles.[88] These patients were treated with romiplostim at 2 µg/kg weekly. Platelet counts improved in all of them, and 19 of 20 had platelet counts ≥ 100,000/µL. A total of 15 patients resumed chemotherapy, and all but one continued for 2 or more cycles without dose modifications. Three of 20 patients developed deep vein thrombosis (DVT).

In another blinded, placebo-controlled study, patients with solid tumors and a platelet count ≤ 300,000/µL receiving either gemcitabine alone (14 patients) or gemcitabine plus either cisplatin or carboplatin (12 patients) were randomized to receive eltrombopag or placebo on days –5 to –1 and days 2 through 6, starting from cycle 2; no study drug was administered for cycle 1.[89] For patients receiving gemcitabine alone, the nadir platelet count for cycles 2 through 6 was 143,000/µL for eltrombopag vs 103,000/µL for placebo; for those receiving gemcitabine plus cisplatin or carboplatin, the nadir was 115,000/µL vs 53,000/µL for placebo. A total of 14% of all eltrombopag patients and 50% of placebo patients required dose reductions or delays in cycles 3 through 6. No DVTs were reported, but 16 of 19 patients treated with eltrombopag developed platelet counts > 400,000/µL.

Although this author anticipates that the thrombopoietin receptor agonists will have the same beneficial effects in chemotherapy treatment as did the recombinant thrombopoietins, studies are challenging in this area for many reasons, namely:

- Most standard chemotherapy regimens do not produce very high rates of thrombocytopenia, and when thrombocytopenia occurs, it is often short-lived.
- Platelet transfusions often resolve the thrombocytopenia and are usually needed for only 3 to 4
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days.

- Chemotherapy regimens commonly associated with increased rates of thrombocytopenia are usually experimental; it remains unclear whether platelet production support with a thrombopoietin receptor agonist during chemotherapy is beneficial for the overall cancer outcome, which may be more limited by the chemotherapy than by the supportive care.

- Study design in this setting is also a concern. Although it is unlikely that concurrent administration of a thrombopoietic agent during chemotherapy would have any adverse effect, the doses and schedules for these agents have certainly not been established. It is unclear whether treatment with a thrombopoietin receptor agonist before or after chemotherapy is superior or whether administration of thrombopoietin at both times is required.

- Animal chemotherapy models would be of help to assess the dose and schedule of treatment with thrombopoietin receptor agonists. Unfortunately, eltrombopag is only active in chimpanzees and humans; romiplostim is active in most species, but there are no animal studies to inform human treatment.

Good clinical studies that address the dose and schedule for the thrombopoietin receptor agonists are essential. These should probably be conducted in patients who have developed significant thrombocytopenia during prior chemotherapy cycles. Pharmacokinetic/pharmacodynamic modeling suggests that the ideal schedule for eltrombopag might be 5 days before and 5 days after chemotherapy.[92] The relevant endpoints for such studies would be:

- Avoid nadir platelet counts < 50,000/µL.
- Avoid platelet transfusions.
- Avoid bleeding events.
- Avoid chemotherapy dose reductions.
- Avoid chemotherapy delays.

**Treatment of Chemotherapy-Induced Thrombocytopenia**

The response to significant chemotherapy-induced thrombocytopenia has not been codified in guidelines, and there are no studies to guide the appropriate approach to management of patients with this condition. Much depends upon the underlying treatment goals of the individual cancer patient; different levels of risk assessment need to be brought into play for patients being treated for cure vs those being treated for palliation. Overall, it is reasonable when confronted with chemotherapy-induced thrombocytopenia 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 a synthesis of the data and the author's personal experiences over the past 4 decades.

- If possible, treat any other underlying cause of thrombocytopenia: stop antibiotics, treat infection, and control coagulopathy.

- Reduce chemotherapy dose and/or frequency or alter the chemotherapy regimen, especially if chemotherapy is not standard or not of curative intent.

- Platelet transfusion support should be used if maintenance of dose intensity is vital for response or survival. Prophylactic platelet transfusions are indicated if bleeding occurs or if platelet counts are < 10,000/µL (or with platelet counts < 20,000/µL if the patient is febrile).[93,94] In the outpatient setting, however, 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 epsilon-aminocaproic acid or tranexamic acid have been used in some thrombocytic cancer patients to decrease the bleeding risk when platelet transfusions did not work.[95-97] Total daily doses of 2–24 g (mean, 6 g) of epsilon-aminocaproic acid given in 3 or 4 divided doses have been used.[96] Tranexamic acid doses of 4–6 g/d given as 3 or 4 divided doses have also been studied.[97] However, the use of such agents in cancer patients is fraught with difficulty because antifibrinolytic agents can exacerbate the underlying increased risk of thrombosis.

- Despite the lack of US Food and Drug Administration (FDA) approval for these agents, thrombopoietin receptor agonists can be considered in patients who cannot be supported by platelet transfusions and for whom the maintenance of dose intensity is crucial for remission or survival. In this setting, this author has used romiplostim at 2–3 µg/kg weekly, or 50–75 mg of eltrombopag daily to maintain platelet counts over 100,000/µL, in order to allow continuation of chemotherapy (Figure 6). Thrombopoietin receptor agonists would be started only when the patient’s platelet count had failed to recover to levels > 100,000/µL before the next scheduled chemotherapy.
• Thrombopoietin receptor agonists should not be used in lieu of platelet transfusions. Since the platelet count only begins to rise 5 days after TPO administration, with maximal effect 10–14 days later, platelet transfusions should not be withheld if they are indicated.
• The use of vincristine, rituximab, prednisone, IVIG, splenectomy, or anti-D immunoglobulin is rarely justified in patients with chemotherapy-induced thrombocytopenia, despite their widespread use and efficacy in ITP.
• The use of IL-11 is rarely justified, given its significant side effects. Recombinant IL-11 (oprelvekin) has been 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. This drug has been FDA-approved for the prevention of thrombocytopenia with chemotherapy, but it has too many adverse effects to make it an acceptable treatment for most patients.

**Thrombocytopenia in the Cancer Patient: Costs of Treatment**

The direct costs of treating thrombocytopenia in the cancer patient can be readily assessed. For example, a platelet transfusion costs about $3,000 per event (calculated as the cost of a single apheresis product or a pool of six random donor concentrates) and a transfused unit of RBCs costs about $1,300–$3,500. A week of antifibrinolytic treatment with epsilon aminocaproic acid (6 g/d) is $280, and with tranexamic acid (6 g/d) is $290. A week of thrombopoietin receptor agonist treatment with romiplostim (2 µg/kg/wk) is about $1,400, and with eltrombopag (75 mg/d) is about $2,000. (Data are from Partners Healthcare Center for Drug Policy.) Oprelvekin at 50 µg/kg daily costs $2,366 (average wholesale price) for a week of treatment.

However, no attempt has been made to address the overall costs of thrombocytopenia and its treatment in patients with cancer. The simple issues of chemotherapy delay and dose reduction carry with them costs in material and space utilization, while the larger issue of reduced dose intensity in some settings translates into the costs of life lost.

While guidelines exist to guide the rational administration of platelet transfusions, there are few data and no established guidelines to guide rational reduction in chemotherapy dose or frequency, which is often the first response to treating thrombocytopenia in the setting of cancer.

**Conclusions**

Treatment of the thrombocytopenic cancer patient remains a challenge. If no other underlying factor can be modified, the only treatments are platelet transfusion and dose modification of chemotherapy or radiation therapy. Future studies should target methods to mitigate thrombocytopenia by protection of the bone marrow or the rational use of thrombopoietic agents. Guidelines need to be developed that carefully assess the risks and benefits of current and future treatments for our patients with thrombocytopenia.

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Table: Frequencies of Thrombocytopenia With Selected Chemotherapy Regimens

Figure 2: The Production of Platelets From Bone Marrow Stem Cells

Figure 3: Structures of the Recombinant Thrombopoietin (TPO) Molecules...

Figure 4: PEG-rhMGDF Increases the Platelet Count in Patients Undergoi...

Figure 5: rhTPO Reduces the Need for Platelet Transfusions in Patients...
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