Thrombocytopenia in patients with myelodysplastic syndromes

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Abstract

Thrombocytopenia, common in leukemias and myelodysplastic syndromes (MDS), is responsible for increased risk of bleeding and delay of therapy. Platelet transfusions, although effective in increasing platelet counts, are limited by supply, are associated with risks, and result in limited and transient benefits. Successful development of an alternative treatment approach with thrombopoietin agonists was nearly thwarted when early formulations of recombinant thrombopoietin agonists elicited antibodies that cross-reacted with and neutralized endogenous thrombopoietin. The effectiveness of these recombinant agents led to the development of second generation thrombopoietin receptor agonists that do not induce cross-reacting neutralizing antibodies against thrombopoietin. Two of the novel thrombopoietin receptor agonists, romiplostim (Nplate™, Amgen, Thousand Oaks, CA) and eltrombopag (Promacta™, GlaxoSmithKline, London UK & Philadelphia, US), have established clinical activity in chronic immune (idiopathic) thrombocytopenic purpura (ITP), and are being explored for the treatment of thrombocytopenia in MDS.

Introduction

The myelodysplastic syndromes are a heterogeneous group of disorders characterized by ineffective hematopoiesis and persistent peripheral cytopenias.[1–3] The survival of patients with MDS is poor, and fatal complications of MDS-associated peripheral blood cytopenias are common. It is estimated that as many as 65% of patients with MDS die from infections occurring as a result of neutropenia.[4] Life-threatening bleeding occurs less frequently than infection in MDS, but still represents a major problem. The reported incidence of hemorrhagic complications in the literature ranged from 3% to 53%, and the frequency of hemorrhagic deaths ranged from 14% to 24%. Both thrombocytopenia and platelet dysfunction may contribute to hemorrhagic complications observed in MDS.[5] Herein we review the most current information about thrombocytopenia in MDS and focus on approaches to manage it.

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Epidemiology of Thrombocytopenia in MDS

The estimated prevalence of thrombocytopenia in MDS, defined as a platelet count < 100×10^9/L, ranged from 40% to 65%.[6] A retrospective review of patients referred to the MD Anderson Cancer Center (MDACC) identified 1605/2410 (67%) patients with thrombocytopenia at referral. In 618 patients (26%) thrombocytopenia was moderate (platelet counts 20–50×10^9/L), and 415 patients (17%) had severe thrombocytopenia (platelet count < 20×10^9/L).[6] The incidence of thrombocytopenia and its severity increased with the international prognostic scoring system (IPSS) risk classification. Of the 896 patients with intermediate-2 or high-risk MDS, 77% had thrombocytopenia (severe in 20%). In contrast, among the 860 patients with low-risk or intermediate-1 risk disease, 51% had thrombocytopenia (severe in 12%).[6]

Clinical Consequences of Thrombocytopenia in MDS

The increased risk of bleeding in patients with MDS is typically attributed to both low platelet counts and abnormalities of platelet morphology and function (ie, platelet aggregation defects).[7] However, the platelet level at which patients with MDS and thrombocytopenia become at risk of hemorrhage is not well defined.[8] The incidence of bleeding complications reported in the literature, in patients with MDS, range from 3% to 53%.[6] These complications range from relatively minor events, such as petechiae, gingival bleeding, and hematoma following injury, to serious complications, such as gastrointestinal, intracranial, pulmonary, or retinal hemorrhages.[3] In one study, 26% of patients with MDS had spontaneous mild bleeding.[9] All patients with bleeding had abnormal platelet function based on platelet aggregometry. Retinal hemorrhage was reported in 24% of patients in a retrospective study of ocular complications associated with MDS, and was associated with significant reduced platelet count (P=0.006).[10]

Data from studies of a variety of treatments for MDS provide important information about the incidence of bleeding in MDS. In a study of patients with MDS and platelet counts below 50×10^9/L, 50% of the patients had some degree of bleeding at enrollment.[11] In another study, active bleeding was reported in 18% of patients at baseline irrespective of platelet count, and 15% had required platelet transfusions during the 3 months preceding study entry.[12] Rates of moderate-to-severe hemorrhage of 18%,[13] gastrointestinal hemorrhage of 6% to 7%,[14,15] and intracranial hemorrhage of 3% to 5% have been observed in clinical trials.[16] In patients with AML and MDS receiving combination "salvage" chemotherapy, 15% of patients had a mild-to-moderate hemorrhage and 4% of patients had a severe hemorrhage.[17]

Bleeding complications are among the major cause of death in patients with MDS, particularly in patients who progress to AML.[6,18] The frequency of hemorrhagic deaths reported in the literature range from 14% to 24%.[18] In a retrospective review of 99 patients with MDS, major bleeding (gastrointestinal or intracranial hemorrhage) was a contributing cause of death in 16% of patients.[19] Autopsy findings in 32 patients found evidence of major gastrointestinal bleeding in 25% and intracranial bleeding in 6% of patients with MDS.[19] In the MDACC review, 968 patients with MDS died without progression to AML.[6] Of these,

460 patients had a coded cause of death: hemorrhage was a contributory cause of death in 20% of cases (90 patients) and was listed as the only cause of death in 10% of cases (48 patients). Although the rates of bleeding complications and deaths as a result of hemorrhage in MDS vary across studies, it is clear that thrombocytopenia influences the clinical course and outcome for many patients with MDS.

Approaches to Management of Thrombocytopenia in MDS (Table 1)

Treatment of thrombocytopenia is individualized based on MDS subtype, disease stage, patient age, and prognostic factors. Appropriate treatment options may range from supportive care with transfusions or colony-stimulating factor to intensive chemotherapy or allogeneic bone marrow transplantation or peripheral blood progenitor cell transplantation.[3]

Platelet transfusions

In the United States, approximately 9 million platelet units were transfused in 1999.[20] (see article by McCullough in this issue) There is an increasing trend towards the use of platelets from single-donor apheresis.[21] Platelet transfusions are beneficial to stop active bleeding in patients with thrombocytopenia, but the lifespan of transfused platelets is only 1 to 7 days.[22] Although they are effective in increasing platelet counts, platelet transfusions are associated with a range of risks, including viral and bacterial infections, allergic reactions, and alloimmunization.[21,23]

Platelet alloimmunization occurs when antibodies are formed in response to the foreign antigens on donor platelets.[24] Platelet alloimmunization occurs in 20% to 85% of patients who receive multiple transfusions, and can result in refractoriness to platelet transfusion (failure to achieve adequate platelet counts post-transfusion) Approximately 20% to 70% of patients with thrombocytopenia who receive multiple transfusions become refractory to donor platelet transfusions.[24] This is a particular problem in patients with hematologic malignancies.[25,26] Febrile reactions to platelet transfusions are common, occurring in 5% to 30% of patients.[21]

There is also a risk of infections with platelet transfusions. Although the risk of transmission of viral agents is now reduced due to improved screening methods, there is still a risk of infections from the bacterial contamination of platelet units during collection and room temperature storage.[27]

Other factors can complicate this form of therapy as well. Platelets for transfusion are often in short supply, have a shelf-life of only 5 days, and are generally administered in a hospital setting.[28] Taken together, the risks and issues associated with platelet transfusions suggest a need for alternative treatments for thrombocytopenia in patients with MDS.

Hypomethylating Agents

Three agents are approved by the FDA for the treatment of MDS, lenalidomide, azacitidine, and decitabine; none is specifically approved for the treatment of thrombocytopenia in MDS, and most of them cause at least transient cytopenias, making difficult the

interpretation of their effect on platelet counts. Azacitidine (Vidaza™, Pharmion Corporation, Boulder, CO) and decitabine (Dacogen™, Eisai Inc, Woodcliff Lake, NJ) are both hypomethylating agents.[29,30] Responses of 40% to 60% have been observed with azacitidine, 7% to 17% were complete responses, and myelosuppression was reported in 33% to 78% of patients.[29] In a recent study of decitabine, a response rate of 17% with 9% complete response, and a grade 4 thrombocytopenia incidence of 63% was reported.[30]

Immunomodulating Agents

Pharmacologic treatment options for thrombocytopenia in MDS typically suppress the immune response or remove the major site of platelet destruction.

Lenalidomide (Revlimid™, Clegene Corporation, Summit, NJ) is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 –risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional abnormalities.[31] This drug is associated with significant neutropenia and thrombocytopenia.

Immunosuppressive agents such as cyclosporine and anti-thymocyte globulin (ATG) increase the platelet counts by blocking the abnormal immune response that would otherwise lead to clonal progression and apoptosis of hematopoietic cells. Complete remission was reported in 26% of patients receiving cyclosporine[32] and 14% of patients receiving ATG.[33]

Oprelvekin, a recombinant human IL-11, stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitors, and induces increased platelet production through megakaryocyte maturation.[34] It is approved by the FDA for the prevention of severe thrombocytopenia following myelosuppressive chemotherapy in patients with nonmyeloid malignancies at high risk for this toxicity.[34] Two small single-arm studies have explored its use in patients with bone marrow failure, including those with bone marrow failure due to MDS.[34,35] In the pilot study, median platelet counts at baseline were 12×10^9/L; 38% of patients showed a platelet response.[35] Of the 6 responders, one had refractory anemia (RA), one had refractory anemia with ringed sideroblasts (RARS), 3 had RAEB, and 1 had aplastic anemia. The duration of platelet response ranged from 12 weeks to >30 weeks.[35] In the second study, median platelet counts were 17×10^9/L at baseline and 27% of patients responded to treatment, with either a major or minor platelet response (6 patients) or a multilineage response (3 patients).[34] Of the responders, 4 had RAEB, 1 had RARS, and 1 had chronic myelomonocytic leukemia or aplastic anemia. The duration of response ranged from 1.4 to 34.5 months. Toxicities observed were peripheral edema, conjunctival infection, fatigue, arthralgia, and myalgia. One patient in the second study had a transient ischemic attack after completing treatment and 1 patient developed atrial fibrillation/supraventricular tachycardia.[34,35] Other cardiovascular events, such as arrhythmias and pulmonary edema, have also been observed.[36] Oprelvekin has also been associated with allergic and hypersensitivity reactions, including anaphylaxis, and serious fluid retention, which has been fatal in some patients.[36] Papilledema has also been reported and is more common in children; therefore oprelvekin is not indicated for use in the pediatric population.

It is also not indicated for use following myeloablative chemotherapy, as a clinical study showed a significant increase in side effects in this population, relative to placebo.[36]

Cytokines and Growth Factors

Recombinant human IL-6 has been shown to promote thrombopoiesis in MDS, but had only limited activity and was associated with significant toxicity, making it unsuitable for use as a single-agent treatment for thrombocytopenia in MDS.[37] In a small phase I study in patients with MDS and thrombocytopenia, 36% of patients experienced some improvement in platelet counts after IL-6 therapy.[37] Treatment-related toxicities prevented most patients from receiving maintenance therapy with IL-6. Adverse events included fever, chills, and tachycardia.

Recombinant human TPO (rHuTPO) and its shorter, polyethylene glycol-conjugated form, pegylated recombinant megakaryocyte growth and development factor (PEG-rHuMGDF), stimulate platelet production by inducing the growth of megakaryocyte progenitor cells.[34,38] A small trial in patients with MDS assessed the efficacy of PEG-rHuMGDF in treating thrombocytopenia (baseline platelet count $<30\times10^9$/L) over 4 weeks.[39] The mean time to achieving an increase in average weekly platelet count of 10×10^9/L was 2 weeks. In both healthy volunteers and in patients undergoing intensive nonmyeloablative chemotherapy, PEG-rHuMGDF was associated with episodes of persistent thrombocytopenia due to the development of antibodies to PEG-rHuMGDF that cross-reacted with, and neutralized, endogenous TPO.[38,40] For this reason, clinical trials with this agent have been discontinued in the United States. Evidence to date from trials of patients with chemotherapy-induced thrombocytopenia suggest that rHuTPO, unlike PEG-rHuMGDF, is not associated with the development of neutralizing antibodies (although transient, non-neutralizing antibodies have been seen after subcutaneous injection).[41,42] rHuTPO and PEG-rHuMGDF are no longer in clinical development; therefore stimulating platelet production remains an unmet clinical need in the management of thrombocytopenia in MDS.

Thrombopoietin Receptor Agonists

Despite the setback with the first generation thrombopoietic growth factors, the clinical effectiveness of these agents has led to the development of a second generation of thrombopoietin receptor agonists that appear to be free from causing neutralizing antibodies against endogenous thrombopoietin. Romiplostim, an Fc-peptide fusion protein, and eltrombopag, a nonpeptide agonist, received FDA approval in 2008 for the treatment of patients with chronic ITP (see article by Kuter in this issue). Their mechanism of action and clinical effectiveness in chronic ITP (see article by Ghanima and Bussel in this issue) has made these agents a potential therapeutic option for patients with MDS and thrombocytopenia. Data exploring the clinical use of romiplostim in lower risk (IPSS low or intermediate −1 risk) MDS is rapidly accumulating. Recent phase 1/2 trials evaluating the use of romiplostim alone and in combination with hypomethylating agents and immunomodulating agents will be summarized.

In a small, single arm, phase 2 study, intravenous and subcutaneous administration of romiplostim were shown to be well tolerated and effective in increasing platelet counts in

patients with lower risk MDS receiving supportive care only.[43] In a recent phase 1/2 study by Kantarjian et al,[44] 44 patients with lower risk MDS with clinically significant thrombocytopenia (platelets 50×10⁹/L) were enrolled sequentially into one of four cohorts: weekly subcutaneous injections of 300, 700, 1000, and 1500 mcg romiplostim for 3 weeks (treatment phase) and could be extended for one year (extension phase). Romiplostim was shown to improve median platelet counts and maintain a durable platelet response. Contrary to first generation thrombopoetin receptor agonists, neutralizing antibodies against romiplostim and endogenous erythropoietin were not detected throughout the study. Another concern with these agents is their potential to stimulate the proliferation of leukemic cells. Four patients treated with a romiplostim dose 1,000 mcg had a transient increase in blasts which resolved within 5 weeks after discontinuation of drug with two patients progressing to AML during the extension phase of the study.

Studies evaluating romiplostim in combination with hypomethylating agents and lenalidomide are generating promising results (Table 2). In combination with azacitidine, Kantarjian et al[45] randomized forty patients with low- or intermediate risk MDS to receive placebo or romiplostim at 500μg or 750μg weekly by subcutaneous injection. Romiplostim was shown to reduce clinically significant thrombocytopenic events, and the need for platelet transfusions, and to improve platelet nadirs. Romiplostim was generally well tolerated and adverse events were similar among all three groups. Disease progression to AML occurred in one patient from each treatment group.

Another phase 2 study by Greenberg et al[46] evaluated the safety and efficacy of romiplostim in combination with decitabine in patients with low- to intermediate-1 or intermediate-2 risk MDS. This study randomized 29 patients to receive placebo or 750μg romiplostim given subcutaneously once weekly in combination with decitabine for 4 cycles. Sixty-four percent of the patients in the placebo group and 67% of the patients in the romiplostim group completed four cycles of decitabine. Compared to placebo, adding romiplostim to decitabine elicited higher median platelet counts at the beginning of each cycle of decitabine, decreased incidence rates of platelet transfusions and decreased bleeding events. Serious adverse events were comparable between the groups and one patient from each group transformed to AML. Overall response rates (complete and partial) were higher in the romiplostim group than in the placebo group, 47% and 35%, respectively.

In a phase 2 dose-finding study, the effect of romiplostim on the incidence of clinically significant thrombocytopenic events in patients with low or intermediate-1 risk MDS receiving lenalidomide was studied.[47] Thirty-nine patients were randomized to one of three groups: placebo, 500 μg or 750 μg romiplostim. Weekly subcutaneous injections of romiplostim were administered in combination with daily lenalidomide at 10 mg by mouth daily for four cycles. The overall rates of clinically significant thrombocytopenic events appeared to be greater in the placebo group than in either romiplostim group. Median platelet counts remained above 50×10⁹/L in both romiplostim groups for the treatment period and the incidence of platelet transfusions was lower in the 500 μg romiplostim group. Fewer treatment delays and adjustments to lenalidomide were observed in the romiplostim group. MDS response rates appeared higher in the romiplostim groups (36% and 15%) than in the placebo group (8%). Similar to the other studies, the incidence of adverse events was

comparable between all groups. Only one patient in the romiplostim group progressed to AML.

Similar to romiplostim, eltrombopag is being studied in patients with low and high risk MDS. Eltrombopag, an oral nonpeptide agonist of the thrombopoietin receptor, has been FDA approved for chronic ITP. Encouraging preclinical data suggests that eltrombopag increases megakaryopoiesis in MDS and AML cell lines without stimulating malignant blasts or enhancing self renewal of leukemia cells, thus providing support for exploring the use of eltrombopag for thrombocytopenia in MDS and AML.[48]

Conclusion

Thrombocytopenia is a common hematologic problem in MDS. Its clinical management remains an important challenge because bleeding complications are a major cause of morbidity and mortality, as well as delay and/or dose reduction of chemotherapeutic treatment. Platelet transfusions are the only supportive treatment option for clinically significant thrombocytopenia. Although they are effective in increasing platelet counts, platelet transfusions are expensive, inconvenient, and potentially transmit infections. The development of novel platelet stimulating agents such as romiplostim and eltrombopag is warranted for the treatment of MDS. Recent clinical data using romiplostim in MDS as monotherapy and in combination with hypomethylating agents or lenalidomide are promising. Studies evaluating eltrombopag for MDS are also ongoing.

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Table 1

Management of thrombocytopenia in MDS

Non-pharmacologic Management	Advantages	Disadvantages
Platelet Transfusions	Effective and rapid response	Response short-lived, costly, limited by availability, refractoriness, transmission of infections, inconvenient
Chemotherapy dose/delays	Allow platelets to recover	Potentially reduce antitumor effect and reduce survival
Pharmacologic Management		
Immunosuppressive agents Cyclosporin +/− Antithymocyte Globulin	*Cyclosporin*;oral formulation	*Cyclosporin*; Monitor levels, hypertension, hyperglycemia *Antithymocyte Globulin* hypersensitivity reactions, intravenous administration Immune suppression
Oprelvekin - Recombinant IL-11	FDA approved for CIT	Excessive toxicity - flu like symptoms hypersensitivity reactions, fluid retention, cardiac arrhythmias
rHuTPO and PEG-rHuMGDF	Activity in CIT and MDS that led to development of second generation TPO agonists	Potential for development of neutralizing antibodies to endogenous thrombopoietin Discontinued from trials
Romiplostim	FDA approved for chronic ITP, once weekly dosing, non-immunogenic Ongoing clinical trials	Subcutaneous administration, potential for thromboembolic events and bone marrow fibrosis Not indicated for MDS and CIT
Eltrombobag	FDA approved for chronic ITP, oral formulation, non-immunogenic Ongoing clinical trials	Potential for thromboembolic events and bone marrow fibrosis Not indicated for MDS and CIT

CIT: chemotherapy-induced thrombocytopenia; ITP: Immune thrombocytopenia; MDS: myelodysplastic syndrome; rHuTPO: recombinant human thrombopoietin; PEG-rHuMGDF: pegylated recombinant human megakaryocyte growth and development factor; FDA: Food and Drug Administration

Table 2

Trials with romiplostim in combination with hypomethylating agents and lenalidomide for MDS

Trial	Greenburg et al[46]		Kantarjian et al[45]			Lyons et al[47]		
Description	Romiplostim with Decitabine		Romiplostim with Azacitidine			Romiplostim with Lenalidomide		
Treatment	Placebo	Romiplostim 750mcg	Placebo	Romiplostim		Placebo	Romiplostim	
				500mcg	750mcg		500mcg	750mcg
IPSS Risk Category	Low, Intermediate-1, or 2 Risk		Low, Intermediate-1, or 2 Risk			Low or Intermediate-1 Risk		
No. Patients/Cohort	14	15	13	13	14	12	14	13
Incidence of CST events (%)	79	80	85	62	71	67	29	54
Incidence of Plt. Tx (%)	57	47	69	46	36	25	7	31
Overall MDS Response (%)	36	47	NR	NR	NR	8	36	25
No. Transform to AML	1	1	0	1	0	0	1	0
Incidence of Bleeding Events (%)	43	24	2†	1†	0†	NR	NR	NR
Serious Adverse Events (%)	57	53	77	46	71`	55	39	31
No. Deaths	2	2*	2	0	0	0	0	0

* Deaths not attributed to romiplostim group

† Grade 3 and above bleeding events

CST: Clinically significant thrombocytopenia; AML: Acute Myelogenous Leukemia; Plt. Tx: platelet transfusions;