The Incidence and Impact of Thrombocytopenia in Myelodysplastic Syndromes

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Thrombocytopenia and platelet dysfunction contribute to hemorrhagic complications in the myelodysplastic syndromes (MDS). Reliable data regarding the frequency and consequences of thrombocytopenia in MDS are lacking. An extensive literature review indicated that the prevalence of thrombocytopenia (platelets $<100 \times 10^9$/L) in MDS ranged from 40% to 65%; the median frequency of thrombocytopenia prior to any MDS therapy was 65% (range, 23–93%). A retrospective review of patients who were referred to the University of Texas M. D. Anderson Cancer Center (MDACC) identified 1605 of 2410 patients (67%) with thrombocytopenia at referral. Of these, 1756 patients were classified using the International Prognostic Scoring System (IPSS), and 896 patients (51%) had intermediate-2 or high-risk disease. Treatment-related thrombocytopenia was observed in studies that involved azacitidine, tipifarnib, decitabine, lenalidomide, sirolimus, and combination chemotherapy with idarubicin, cytarabine, and topotecan. 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%. At MDACC, 460 patients had a coded cause of death: hemorrhage as a contributory cause of death, 20%; hemorrhage as the only cause of death, 10%. Thrombocytopenia was common in MDS, and there was an increased prevalence in higher risk IPSS categories. Many approved and investigational MDS therapies caused or exacerbated preexisting thrombocytopenia. The incidence of severe bleeding in MDS was greater than reported in current guidelines. ***Cancer* 2007;109:1705–14.** © *2007 American Cancer Society.*

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The myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal bone marrow disorders characterized by ineffective hematopoiesis, morphologic and functional abnormalities of hematopoietic cells, and an increased risk of transformation to acute myeloid leukemia (AML), particularly in more advanced forms of MDS.[1,2] Patients with MDS most commonly have peripheral blood cytopenias coupled with hypercellular bone marrow and dysplastic changes.[3] Patients may have pancytopenia or single cytopenias of individual cell lines.[2,3] Typical complications associated with cytopenias include fatigue, an increased risk of infection, bleeding, and confusion in the diagnosis leading to costly and risky studies.[2] Approximately 50% of individuals are asymptomatic at the time of

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their diagnosis,[3] underlining the difficulties of recognizing and diagnosing MDS.

Epidemiologic data on MDS are limited. This is partly because MDS was not recognized previously as a specific hematologic condition[4] and because the definition, classification, and diagnostic criteria for MDS have not been consistent.[1] Based on regional cancer surveys or hospital-based statistics, the incidence rates for MDS have been estimated at 1.0 to 12.6 per 100,000 individuals, which would translate to between 4000 and 50,000 new diagnoses in the United States each year.[5–11] The incidence of MDS increases with age, particularly after age 60 years.[7,10] The annual incidence rates range from 15.0 to 49.0 per 100,000 in individuals aged ≥70 years.[8,9,11] The risk of MDS also appears to be greater in men than in women and is associated positively with age. In a nationwide Japanese study, the point prevalence of MDS per 100,000 individuals was 1.6 times greater for men than for women (3.4 per 100,000 vs 2.1 per 100,000).[5] In other studies, the incidence of MDS was approximately 1.9 times greater in men than in women.[7,9] The 2007 International Classification of Diseases, Ninth Revision-Clinical Modification Oncology-related Coding Update separates myelodysplasia into low-grade, high-grade, 5q−, and unspecified groups with the expectation that better epidemiologic data will become available in the United States over the next few years.

MDS can be either primary or secondary. Primary MDS has no obvious cause. Secondary MDS often refers to MDS after chemotherapy or therapeutic irradiation exposure for a primary malignancy.[1,12–15] Other factors, such as benzene or benzene derivatives,[13] occupational/environmental carcinogens,[13] inherited causes,[13] autoimmune disorders,[16] and alcohol or tobacco use,[16] have been associated with secondary MDS.

The diagnosis and classification of MDS depends on the morphologic assessment of blood and bone marrow cells.[17] The most commonly used classification system was developed by the French-American-British (FAB) group.[18,19] The World Health Organization has recently introduced a new classification system based on morphologic, genetic/karyotypic, and clinical features.[20,21] Although this new system was created to enhance and supersede the FAB classification, it has yet to be endorsed and adopted universally.[22,23]

The course of MDS varies. In some patients, it behaves like an indolent disease, akin to the chronic leukemias; in others, it can be more aggressive and is comparable to the acute leukemias.[2,24] The International Prognostic Scoring System (IPSS) is used widely to predict survival and progression to AML in patients with MDS. This system combines cytogenetic, morphologic, and clinical data to give a composite score indicating a patient's risk category (Table 1).[22,25] Median survival ranges from approximately 6 years to 6 months according to the IPSS classification, depending on whether patients are considered to have low-risk or high-risk disease.[3] The proportion of patients who have MDS that transforms to AML also varies, ranging from 5% to 15% for those classified as low risk and from 40% to 50% for those classified as high risk, in whom the disease often will either evolve to AML, or they will die from infection or bleeding complications of their MDS.[2] Even low-risk MDS is associated with poor survival rates as a consequence of the complications related to bone marrow dysfunction and cytopenias.[24,26,27] Patients with secondary, treatment-related MDS tend to have a higher IPSS score, a worse prognosis, and a greater risk of evolution to AML than patients with primary MDS.[28,29]

TABLE 1
International Prognostic Scoring System Point Values for Myelodysplastic Syndromes*

	Score value†				
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**
Bone marrow blasts, %	<5	5–10	—	11–20	21–30
Karyotype‡	Good	Intermediate	Poor		
Cytopenias (no. of lineages affected)§	0/1	2/3			

* See Greenberg et al., 1997.[25]

† Composite score = bone marrow blast score + karyotype score + cytopenia score (low risk = 0, intermediate-1 risk = 0.5–1, intermediate-2 risk = 1.5–2, high risk = ≥2.5).

‡ Good indicates normal (−Y, del[5q], del[20q]); poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate, other abnormalities.

§ Cytopenias refer to hemoglobin <10 g/dL, granulocytes <1.5 × 10^9/L, and platelet count <100 × 10^9/L.

Thrombocytopenia and platelet dysfunction contribute to hemorrhagic complications observed in MDS.[24,30,31] Reliable data regarding the frequency and clinical consequences of thrombocytopenia in MDS are lacking. Currently, there is little consensus regarding its optimal treatment. Using data from a literature review and retrospective chart review, we have assessed the burden of disease and treatment-related thrombocytopenia in patients with MDS and reviewed the current and potential treatment options for this condition.

A systematic review of the MDS literature published between January 1980 and November 2005 was performed. Articles and abstracts were identified using the MEDLINE, EMBASE, and Cochrane databases; and searches of key society Web sites, such as

the American Society of Hematology, American Society of Clinical Oncology (ASCO), and European Hematology Association, were performed. Searches of bibliographies from relevant articles and abstracts also were used to identify additional references. MEDLINE and Internet searches were used to identify guidelines for the management of MDS.

Relevant articles and abstracts on MDS were identified using the following Medical Subject Heading (MeSH) terms and keywords: myelodysplastic syndrome, preleukemia, refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and refractory anemia with excess blasts in transformation. Separate search strategies, using specific MeSH terms, keywords, and inclusion criteria, were used for each topic of interest. To identify articles and abstracts on the clinical consequences of thrombocytopenia in MDS, the following MeSH terms and keywords were used: thrombocytopenia, thrombopenia, platelet, platelet count, blood platelets, blood platelet disorder, hemorrhage, bleed, and bleeding. Articles were rejected if only the clinical consequences of AML were reported. The following MeSH terms and keywords were used to identify articles and abstracts on MDS-related treatments and the impact these have on thrombocytopenia: therapy, therapeutic, treatment, thrombopoietic agents, platelet transfusion, hematopoietic stem cell transplantation, cord blood stem cell transplantation, bone marrow transplantation, chemotherapy, androgens, immunosuppressive agents, platelet-derived growth factor, thrombopoietin, megakaryocyte growth and development factor, interleukin-11, interleukin-3, azacitidine, decitabine, danazol, antithymocyte globulin, all-trans retinoic acid, and 13-cis retinoic acid. Articles and abstracts were accepted based on the following inclusion criteria: included only human subjects with MDS, examined interventions used to treat thrombocytopenia, reported outcomes such as platelet response and changes in platelet count. Articles and abstracts were rejected if patients were age <18 years; included patients with AML; evaluated the efficacy of splenectomy; were published letters, editorials, news, comments, or case reports; or had a sample size <10 patients.

Two reviewers independently assessed a 10% sample of randomly selected articles and abstracts. Agreement between the reviewers regarding which articles to include was excellent ($\kappa > 0.7$), and discrepancies were resolved by consensus. The remaining 90% of articles and abstracts were divided equally between the reviewers and were assessed independently.

The accepted definition of thrombocytopenia is a platelet count $<100 \times 10^9$/L, therefore this was applied as the threshold point in the literature analysis.[25] Thrombocytopenia has been classified as mild ($50–100 \times 10^9$/L), moderate ($20–50 \times 10^9$/L), or severe ($<20 \times 10^9$/L).

In addition, a retrospective review of all patients referred to the University of Texas M. D. Anderson Cancer Center (MDACC) with MDS since 1980 was performed. This allowed us to compare the published data with the MDACC experience.

In total, 85 references were identified that addressed the clinical consequences of thrombocytopenia (n = 16), the efficacy and safety of MDS therapies (n = 60), and guidelines (n = 9).

Thrombocytopenia in MDS

The estimated prevalence of thrombocytopenia in MDS ranged from 40% to 65%.[2,24,32] Data on the exact incidence of thrombocytopenia in MDS are lacking. Based on a platelet count threshold of $<100 \times 10^9$/L, the results from a cohort analysis of 816 untreated patients with primary MDS indicated that 37% were thrombocytopenic.[25] However, in the 18 clinical studies of treatment for MDS identified by the literature review that did not specifically use thrombocytopenia or dependency on platelet transfusions as inclusion criteria, the incidence of thrombocytopenia at baseline was 65% (range, 23–93%).[33–50] The definition of thrombocytopenia varied in those studies (although the most common cut-off point was a platelet count $<100 \times 10^9$/L or equivalent), and 9 studies had a sample size of ≤ 20 patients. These estimates of incidence also were based on patients with MDS who were enrolled in clinical trials, who may not represent the wider population of individuals with the condition.

In the MDACC chart review, 2410 patients were included. Of these, 1903 patients were diagnosed with primary MDS, and 507 patients were diagnosed with secondary MDS. The distribution by extent of prior therapy is shown in Table 2. The majority of patients were referred with primary disease and no prior therapy. Using a platelet count $<100 \times 10^9$/L to define thrombocytopenia, the analysis identified 1605 patients (67%) with thrombocytopenia at referral. Severe thrombocytopenia was observed in 415 patients (17%), and 618 patients (26%) had moderate thrombocytopenia. The incidence of thrombocytopenia varied with the MDS subtypes of the FAB classification (Table 3) and was greater in patients who had refractory anemia (RA) with excess blasts (RAEB) and RAEB in transformation. The incidence of thrombocytopenia in patients who were categorized according to IPSS risk classification (1756 of 2410 patients; 507 patients with secondary MDS and 76 patients who had received prior chemotherapy were excluded) is shown in Table 4. The incidence of thrombocytopenia and

TABLE 2
Distribution of Patients with Myelodysplastic Syndromes Referred to the University of Texas M. D. Anderson Cancer Center Since 1980

Disease category	No. of patients	Median MDS duration, m
Primary MDS*	1903	4
No prior therapy	1827	4
Prior chemotherapy† plus supportive care	76	14
Secondary MDS*	507	3

MDS indicates myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; MDACC, The University of Texas M. D. Anderson Cancer Center.
* Included CMML with white blood cells $<12 \times 10^9$/L (nonproliferative CMML) (see Greenberg et al., 1997[25]).
† Chemotherapy for MDS only prior to referral to MDACC.

TABLE 3
Incidence of Thrombocytopenia and Severe Thrombocytopenia in 2410 Patients with Myelodysplastic Syndrome Referred to The University of Texas M. D. Anderson Cancer Center Since 1980 According to the French-American-British Classification

	No. of patients (%)		
FAB classification	Total no.	Thrombocytopenia*	Severe thrombocytopenia†
Refractory anemia	577	336 (58)	89 (15)
Refractory anemia with ringed sideroblasts	175	75 (43)	22 (13)
Refractory anemia with excess of blasts	804	574 (71)	137 (17)
Refractory anemia with excess of blasts in transformation	680	525 (77)	150 (22)
Chronic myelomonocytic leukemia	174	95 (55)	17 (10)

FAB indicates French-American-British.
* Platelet count $<100 \times 10^9$/L.
† Platelet count $<20 \times 10^9$/L.

severe thrombocytopenia, as expected, increased with IPSS risk classification. Using the IPSS, 896 of 1756 patients (51%) patients had intermediate-2 or high-risk disease; 77% had thrombocytopenia, and 20% had severe thrombocytopenia. Among the patients with low-risk or intermediate-1 risk MDS, 51% had thrombocytopenia, and 12% had severe thrombocytopenia.

Therefore, current evidence suggests that approximately 66% of patients with MDS develop thrombocytopenia. The incidence appears to be greater in individuals with certain subtypes of MDS, increases with IPSS risk group, and increases with prior therapy and longer duration of MDS.

TABLE 4
Incidence of Thrombocytopenia and Severe Thrombocytopenia in Patients with Myelodysplastic Syndrome Referred to The University of Texas M. D. Anderson Cancer Center Since 1980 by International Prognostic Scoring System Classification

	No. of patients (%)		
IPSS group	Total no.	Thrombocytopenia*	Severe thrombocytopenia†
Primary, untreated			
Low risk	257	52 (20)	6 (2)
Intermediate-1 risk	603	387 (64)	93 (15)
Intermediate-2 risk	514	371 (72)	83 (16)
High risk	382	316 (82)	95 (25)
Secondary MDS‡	507	378 (75)	106 (21)
Prior chemotherapy‡	76	56 (73)	17 (22)

IPSS indicates International Prognostic Scoring System; MDS, myelodysplastic syndromes.
* Platelet count $<100 \times 10^9$/L.
† Platelet count $<20 \times 10^9$/L.
‡ Patients in these groups could not be categorized by using the IPSS, because the system excludes secondary MDS and prior chemotherapy.

Clinical Consequences of Thrombocytopenia

Individuals with thrombocytopenia are at an increased risk of bleeding. In the general population, bleeding outcomes are stratified based on the degree of thrombocytopenia (mild, longer bleeding time; moderate, bleeding with minor trauma; severe, possible spontaneous bleeding). The increased risk of bleeding in patients with MDS typically is attributed to both low platelet counts and abnormalities of platelet morphology and function (ie, platelet aggregation defects).[24] However, the platelet levels at which patients with MDS and thrombocytopenia become at risk of hemorrhage have not been defined well.[51] The literature review identified no studies that assessed the risk of bleeding based on platelet counts exclusively in an MDS population.

Bleeding complications that occur in patients with MDS and thrombocytopenia range from relatively minor events, such as petechiae, gingival bleeding, and hematoma after injury, to serious complications, such as gastrointestinal, intracranial, pulmonary, or retinal hemorrhages.[3] It has been suggested that <10% of patients with MDS will present initially with serious bleeding.[3]

The results from 1 study of patients with MDS indicated that 26% had spontaneous mild bleeding; all of those patients had $\geq$1 abnormal platelet function on platelet aggregometry.[52] Results from a retrospective study of ocular complications in patients with MDS indicated that 24% of patients had developed retinal hemorrhage and that retinal hemorrhages were associated with significantly reduced

platelet counts ($P = .006$).[53] In a study of patients with platelet counts $<50 \times 10^9$/L, bleeding was reported in 50% of the population at baseline.[54] In 2 additional studies, active bleeding was reported in 18% to 23% of all patients at baseline, irrespective of platelet count.[55,56] In studies of a variety of treatments for MDS, rates of moderate-to-severe hemorrhage of 18%,[57] gastrointestinal hemorrhage of 6% to 7%,[58,59] and intracranial hemorrhage of 3% to 5%[42,60] have been observed. In patients with AML and MDS who were receiving combination *salvage* chemotherapy, 15% of patients had a mild-to-moderate hemorrhage, and 4% of patients had a severe hemorrhage.[33]

Hemorrhagic complications can have serious outcomes in patients with MDS and are among the major causes of death in this population, particularly in patients who progress to AML. In a retrospective chart review of 99 patients with MDS at a single hospital, major bleeding (gastrointestinal or intracranial hemorrhage) was a contributing cause of death in 16% of patients.[61] Autopsy findings for 32 patients provided evidence of major gastrointestinal bleeding in 25% of patients with MDS and intracranial bleeding in 6% of patients with MDS.[61] In the MDACC chart review, 968 patients with MDS died without progression to AML. Of these, 460 patients had a coded cause of death: hemorrhage was a contributory cause death in 90 patients (20%) and was listed as the only cause of death in 48 patients (10%).

An analysis of treated and untreated patients with MDS indicated that 24% had evidence of bleeding at presentation; and, of those untreated patients who died, infection and/or hemorrhage was the cause of death in 30% of patients.[62] An additional retrospective review indicated that 24% of deaths were the result of hemorrhage.[63] In 1 case series that followed the clinical course of patients with MDS, 45% of patients died as a result of infections and bleeding.[64] In another series, bleeding was the cause of death in 21% of patients, and the most common bleeding site was the gastrointestinal tract.[65] A long-term study of patients with MDS who registered between 1975 and 1990 indicated that 14% of patients died as a result of hemorrhage.[9] Finally, various small clinical trials of patients with MDS have reported death rates from 5% to 9% as a result of hemorrhage after treatment.[35,40,49,66,67] Although the rates of serious outcomes because of bleeding events vary across studies, it is clear that bleeding is a problem in patients with MDS.

Treatment of Thrombocytopenia in MDS

A range of treatment strategies are used in MDS; some focus on a specific cytopenia, whereas others are more general regimens. Therapy may include transfusions, allogeneic bone marrow transplantation or peripheral blood progenitor cell transplantation,[3] or pharmacologic treatment. Drug treatments that have been studied in MDS are summarized in Table 5.

TABLE 5
Summary of Treatments for Thrombocytopenia in Myelodysplastic Syndromes

Regimen class/drug category	Drug name
Platelet focused	
Androgens	Danazol
Thrombopoietic growth factors	IL-11; IL-6; PEG-rHuMGDF
General	
Differentiation agents	Azacitidine; decitabine
Anti-TNFα factors	Amifostine; etanercept; pentoxifylline
Hematopoietic growth factors	IL-3
Immunosuppressive agents	Cyclosporine; ATG
Retinoids	ATRA; 13-cis retinoic acid
Angiogenic inhibitors	Arsenic trioxide; sirolimus
Immunomodulatory agents	Lenalidomide; thalidomide
Chemotherapy	Cytosine arabinoside; Combination of topotecan, cytarabine, and idarubicin
Farnesyl-transferase inhibitors	Tipifarnib; lofarnib
Vitamin D compounds	Calcitriol
Vitamin K2	Menatetrenone

IL-11 indicates interleukin-11; IL-6, interleukin-6; PEG-rHuMGDF, pegylated recombinant megakaryocyte growth and development factor; TNF, tumor necrosis factor; IL-3, interleukin-3; ATG, antithymocyte globulin; ATRA, all-trans retinoic acid.

Platelet transfusions

Platelet transfusions are used widely in the treatment of thrombocytopenia. In the United States, approximately 9 million platelet units were transfused in 1999,[68] and there is an increasing trend toward the use of platelets from single-donor apheresis.[69] 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.[69,70]

There is a risk of infection with platelet transfusion. Although the risk of transmission of viral agents is reduced now because of improved screening methods, there remains a risk of infection from the bacterial contamination of platelet units during collection and room temperature storage.[71] A prospective surveillance program of 3141 random-donor platelet pools indicated that 0.19% were contaminated with *Staphylococcus epidermis*, *Bacillus cereus*, or *Staphylococcus aureus*.[72] The risk of a transfusion-transmitted infection appears to be higher with platelet transfusions than with red blood cell (RBC) transfusions. During the period from 1998 to 2000,

the rate of transfusion-transmitted bacteremia in the United States was estimated at 9.98 events per 1 million units for single-donor platelets, 10.64 events per 1 million units for pooled platelets, and 0.21 events per 1 million units for RBC units.[71] This pattern was also observed in the rate of fatal transfusion-transmitted bacteremia, which was estimated at 1.94 events per 1 million units for single-donor platelets, 2.22 events per 1 million units for pooled platelets, and 0.13 events per 1 million units for RBC units.[71]

Platelet alloimmunization occurs when antibodies are formed in response to the foreign antigens on donor platelets.[73] It is estimated that 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 posttransfusion) and posttransfusion purpura. Although estimates vary, approximately 20% to 70% of patients with thrombocytopenia who receive multiple transfusions become refractory to donor platelet transfusions;[73] this is a particular problem in patients with hematologic malignancies.[74] In 16-month study that analyzed the length of hospital stay and inpatient hospital costs for patients receiving platelet transfusions, significant increases in both measures were reported for refractory patients compared with nonrefractory patients (35.0 days vs 14.4 days and $103,956 vs $37,817; both $P < .001$).[75] Febrile nonhemolytic reactions also occurred in 5% to 30% of patients who were receiving platelet transfusions.[69] In a study of patients with MDS who received both RBC and/or platelet transfusions, 46% had a febrile transfusion reaction, and 15% had an allergic reaction.[63]

Platelets for transfusion are often in short supply, because recruiting platelet donors can be difficult: Platelets have a shelf-life of only 5 days in the United States and generally are administered in a hospital setting.[76] Taken together, the risks and issues associated with platelet transfusions suggest a need for alternative treatments for thrombocytopenia in patients with MDS.

Pharmacologic treatment

Pharmacologic treatment options for thrombocytopenia in MDS typically suppress the immune response or remove the major site of platelet destruction. The literature review identified 60 studies that investigated the efficacy and safety of drug treatment in MDS. Only 4 of those were randomized controlled trials; most were single-arm studies. Fourteen studies focused on treating thrombocytopenia, whereas the other studies addressed all cytopenias. More than 20 agents have been investigated for the treatment of thrombocytopenia in MDS (Table 5). Most treatments for MDS cause at least transient cytopenias if they are to be effective; thus, it is difficult to interpret the effect of these drugs on platelet counts. Immunosuppressive agents, such as cyclosporine and antithymocyte globulin (ATG), increase the platelet count by blocking the abnormal immune response that otherwise would lead to clonal progression and apoptosis of hematopoietic cells. Complete remission was reported in 26% of patients who received cyclosporine[77] and in 14% of patients who received ATG.[78] Azacitidine and decitabine are both differentiation agents and have received United States Food and Drug Administration (FDA) approval for the treatment of MDS. Response rates of 40% to 60% have been observed with azacitidine; however only 7% to 17% were complete responses, and myelosuppression was reported in 33% to 78% of patients.[55,56,79] In a recent study of decitabine, a response rate of 17% with 9% complete responses and a grade 4 thrombocytopenia incidence of 63% were reported.[80]

It is noteworthy that many of the other treatments explored for use in MDS also can cause or exacerbate thrombocytopenia. Based on evidence from the studies reviewed, tipifarnib,[81] linomide,[58] lenalidomide,[47] sirolimus,[66] and combination chemotherapy with idarubicin, cytarabine, and topotecan[33] also can result in posttreatment thrombocytopenia. Thrombopoietic growth factors, which correct thrombocytopenia by stimulating the production of platelets, usually are not associated with this side effect. Thrombopoietic growth factors investigated in MDS include recombinant forms of interleukin (IL)-11, IL-6, and thrombopoietin (TPO).

Oprelvekin, which is a recombinant human IL-11, stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitors and induces increased platelet production through megakaryocyte maturation.[82] It is approved by the FDA for the prevention of severe thrombocytopenia after myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at high risk for this toxicity.[82] Two small, single-arm studies have explored its use in patients with bone marrow failure, including those with bone marrow failure caused by MDS.[82,83] In the pilot study, median platelet counts at baseline were 12×10^9/L, and 38% of patients showed a platelet response.[83] Of the 6 responders in that study, 1 patient had RA, 1 patient had RA with ringed sideroblasts (RARS), and 3 patients had RAEB; the other responder had aplastic anemia. The duration of platelet response ranged from 12 weeks to >30 weeks.[83] 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).[82] Of the responders, 4 patients had RAEB, 1 patient had RARS, and the remaining patients had chronic myelomonocytic leukemia or aplastic anemia. The duration of response ranged from 1.4 months to $\geq$34.5 months. Most of the toxicities observed in those trials were mild (peripheral edema, conjunctival infection, fatigue, arthralgia, and myalgia). However, 1 patient in the second study had a transient ischemic attack after completing treatment, and 1 patient developed atrial fibrillation/supraventricular tachycardia.[82,83] Other cardiovascular events, such as arrhythmias and pulmonary edema, also have been observed.[84] Oprelvekin also has been associated with allergic and hypersensitivity reactions, including anaphylaxis, and serious fluid retention, which has been fatal in some patients.[84] Papilledema also has been reported and is more common in children; therefore, oprelvekin is not indicated for use in the pediatric population.[81] It also is not indicated for use after myeloablative chemotherapy, because a clinical study reported a significant increase in side effects in this population relative to a group that received placebo.[84]

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 this population.[85] 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.[85] 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.[82,86] A small trial in patients with MDS assessed the efficacy of PEG-rHuMGDF in treating thrombocytopenia (baseline platelet count $<30 \times 10^9$/L) over 4 weeks.[87] The mean time to achieving an increase in average weekly platelet count of $\geq 10 \times 10^9$/L was 2 weeks. In both healthy volunteers and patients undergoing intensive nonmyeloablative chemotherapy, PEG-rHuMGDF was associated with episodes of persistent thrombocytopenia caused by the development of antibodies to PEG-rHuMGDF that cross-reacted with, and neutralized, endogenous TPO.[86,88] 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, nonneutralizing antibodies have been observed after subcutaneous injection).[89,90] 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.

Guidelines

In total, 9 MDS guidelines were identified. Five guidelines were developed in the United States by the National Comprehensive Cancer Network, National Oncology Alliance, ASCO, MDACC, and the National Institute of Health Consensus Development Program. Four international guidelines were identified; 2 in the United Kingdom (British Committee for Standards in Haematology), 1 in Canada (British Columbia Provincial Blood Coordinating Office), and 1 in Italy (Italian Society of Hematology). The guidelines were not clear or were not in agreement regarding the treatment of thrombocytopenia. Based on the evidence available, ASCO and the British Committee for Standards in Haematology guidelines for platelet transfusions concluded that patients with MDS may have minimal or no serious hemorrhages, even at very low platelet counts of $<10 \times 10^9$/L or $<5 \times 10^9$/L.[91,92] However, our review of the literature and the MDACC experience indicated that bleeding complications in patients with MDS may be more common than current opinion would suggest.

Conclusion

This systematic literature and chart review demonstrated that thrombocytopenia is common in patients with MDS, with a greater prevalence in higher risk IPSS categories. The incidence of severe bleeding in MDS is greater than reported in current guidelines. Many approved and investigational MDS therapies cause or exacerbate preexisting thrombocytopenia, and the development of novel agents that specifically target thrombocytopenia is warranted in anticipation of the increased frequency and treatment of MDS in our aging population.

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