Treatment of Iron Overload in Myelodysplastic Syndrome
Guest Editor: Alan F. List, MD

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TREATMENT OF IRON OVERLOAD IN MYELODYSPLASTIC SYNDROME

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TREATMENT OF IRON OVERLOAD IN MYELODYSPLASTIC SYNDROME

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TREATMENT OF IRON OVERLOAD IN MYELODYSPLASTIC SYNDROME

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INTENDED AUDIENCE
This activity has been developed for hematologists and oncologists who provide care to patients diagnosed with myelodysplastic syndrome (MDS).
PROGRAM GOAL
To increase awareness of clinical considerations in monitoring and treating iron overload in patients with MDS.

EDUCATIONAL OBJECTIVES
After reading this Supplement to Hematology/Oncology Clinics and taking the test, participants should be able to:
• Describe the usefulness of applying the International Prognostic Scoring System to patients with MDS.
• Identify key factors in considering donor stem cell transplant for patients with MDS.
• Identify the advantages and disadvantages of iron chelating agents.
• Describe study findings regarding the association between transfusion-dependent patients with MDS and survival rates.

FINANCIAL SUPPORT
This CME activity is supported by an educational grant from Novartis Pharma AG.

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SPECIAL NEEDS
We encourage participation by all individuals. If you have any special needs, please contact Sherrilyn Chiu at (908) 547-2086 or v.fendt@elsevier.com for assistance.
For patients with transfusion-dependent myelodysplastic syndrome (MDS), regular blood transfusions may improve both symptoms and quality of life; however, long-term use of blood transfusions may also lead to iron overload. This is especially true for patients at lower risk for whom survival is expected to be prolonged, as they will likely be receiving blood transfusions for an extended period. Additionally, older patients with MDS who have comorbid cardiac and hepatic conditions may likely suffer from morbidity and mortality associated with iron overload. Although supportive interventions and chelation therapy have been considered the standard of care for patients with MDS and iron overload, patients and clinicians may be reluctant to initiate chelation therapy, as many are uninformed about the need for and the long-term benefits of this treatment option. Although there are drawbacks inherent to chelation therapy, maximum benefit may be seen when treatment is initiated early in the course of the disease.

This article addresses the characteristics of MDS; current treatment options, including 2 new pharmacologic agents; and the clinical impact of iron overload and chelation therapy in patients with transfusion-dependent MDS. Best practices in treating iron overload in MDS based on the National Comprehensive Cancer Network guidelines for supportive care are summarized. In addition, the characteristics of patients with MDS who are most likely to benefit from chelation therapy are reviewed.

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**Preface**

Identifying best practices in the monitoring and treatment of iron overload in myelodysplastic syndrome

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The myelodysplastic syndrome (MDS) comprises a diverse group of hematopoietic stem cell disorders that are characterized by ineffective blood production with consequent cytopenias, cytologic dysplasia, and variable risk for leukemia transformation [1,2]. Although affected individuals with lower-risk disease may survive for years, most patients eventually succumb either to infectious complications, complications from blood cell deficiencies, or acute leukemia [3,4].

In this article we review the characteristics and treatment of MDS, and discuss the clinical impact of iron overload and chelation therapy in patients with transfusion-dependent MDS. Best practices in treating iron overload in MDS are summarized based on current National Comprehensive Cancer Network (NCCN) guidelines for supportive care of patients with MDS [5]. Finally, we highlight the characteristics of patients with MDS who are most likely to benefit from chelation therapy during treatment of transfusion-dependent MDS.

Incidence and epidemiology of myelodysplastic syndrome

MDS is a relatively common hematologic malignancy. The annual incidence rate in all age groups is estimated at 3 to 4 per 100,000 people [6,7]; however, these patients are typically elderly with a male predominance, and a median age at onset of 65 years. The rising incidence of MDS in recent years is probably not due to changes in etiologic factors, but rather may reflect increased awareness on the part of clinicians and more extended use of diagnostic procedures in elderly patients [6,7].

Morphologic categorization of myelodysplastic syndrome subtypes

MDS is currently described and categorized according to the World Health Organization (WHO) classification (Table 1) [8].

The French-American-British (FAB) criteria identified the following 5 subtypes of MDS: refractory anemia (RA); refractory anemia with ringed sideroblasts (RARS); refractory anemia with excess blasts (RAEB); RAEB in transformation (RAEB-T); and chronic myelomonocytic leukemia (CMML) [9].

The current WHO classification differs from the FAB system in that blood or bone marrow threshold for acute myeloid leukemia (AML) is reduced to 20% blast cells, thereby eliminating the FAB category of RAEB-T [8]. This newer classification also refines the definitions of RA and RARS to refer to erythroid-limited dysplasia, and introduces the category of refractory cytopenia with multilineage dysplasia. Furthermore, the RAEB category is divided into 2 subgroups, RAEB-1 and RAEB-2, depending on the number of blast cells present in blood and bone marrow [8].

A new MDS subtype in the WHO classification is characterized by a specific cytogenetic abnormality, MDS with deletion 5q [8]. Although deletions of chromosome 5q represent the most common chromosome abnormality in MDS [10], this category is defined narrowly as de novo MDS with the presence of an isolated cytogenetic deletion involving band q31 of chromosome 5, abundant atypical marrow megakaryocytes with a normal or elevated platelet count, and a low blast percentage [8].

Finally, in the WHO classification [8], CMML is eliminated from the category of MDS and placed in a separate group of disorders with features of both myelodysplasia and myeloproliferative diseases.

As a result of these changes in classification, the WHO criteria delineate 8 subtypes of MDS, in contrast to the 5 subtypes characterized in the FAB classification [8,9].

Pharmacologic treatment of myelodysplastic syndrome

Until recently, supportive interventions have been the accepted standard of care for patients with MDS. Two
pharmacologic agents now show promise for patients with this condition.

Azacitidine (Vidaza®, Pharmion Corporation, Boulder, Colorado) is the first agent approved for the treatment of MDS by the US Food and Drug Administration (FDA) [11]. This agent is approved for the treatment of all 5 subtypes of MDS, as originally categorized by the FAB classification criteria, and is appropriate for treatment of both low- and high-risk patients. Azacitidine is believed to exert antineoplastic effects through hypomethylation of DNA and direct cytotoxicity to the myelodysplastic clone [11]. Azacitidine is administered by daily SC injection for a minimum of 4 treatment cycles, each cycle consisting of a daily dose for 7 days every 4 weeks.

The second agent to receive FDA approval in MDS is lenalidomide (Revlimid®, Celgene Corporation, Summit,

Table 1
World Health Organization classification and criteria for myelodysplastic syndrome

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>&lt;15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td></td>
<td>No blasts</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>≥15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenias (bicytopenia or pancytopenia)</td>
<td>Dysplasia in ≥10% of cells in ≥2 myeloid cell lines</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt;1 × 10⁹/L monocytes</td>
<td>&lt;15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)</td>
<td>Cytopenias (bicytopenia or pancytopenia)</td>
<td>Dysplasia in ≥10% of cells in ≥2 myeloid cell lines</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt;5% blasts</td>
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<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt;1 × 10⁹/L monocytes</td>
<td>≥15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>&lt;5% blasts</td>
<td>5% to 9% blasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt;1 × 10⁹/L monocytes</td>
<td>–</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>5% to 19% blasts</td>
<td>10% to 19% blasts</td>
</tr>
<tr>
<td></td>
<td>Auer rods ±</td>
<td>Auer rods ±</td>
</tr>
<tr>
<td></td>
<td>&lt;1 × 10⁹/L monocytes</td>
<td>–</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia in granulocytes or megakaryocytes</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td>MDS associated with isolated del (5q)</td>
<td>Anemia</td>
<td>Normal to increased megakaryocytes with hypolobated nuclei</td>
</tr>
<tr>
<td></td>
<td>&lt;5% blasts</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>Platelets normal or increased</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>Isolated del (5q)</td>
</tr>
</tbody>
</table>

New Jersey), an immunomodulatory agent that is structurally related to thalidomide. This agent has significant erythropoietic and cytogenetic remitting activity in MDS with the chromosome 5q deletion [12], the precise indication for which FDA approval was granted. In a Phase II study of 148 patients with confirmed transfusion-dependent MDS and 5q deletion [13], 99 (67%) of patients achieved red blood cell transfusion independence after treatment with lenalidomide, and 73% of responders experienced a cytogenetic response. Nearly half (45%) of responders had a complete cytogenetic response, and more than a third (36%) of evaluable patients achieved complete pathologic response. Responses were durable and the median duration of transfusion independence had not been reached after a mean follow-up of 24 months (range, <8.6 to >89 weeks). Moderate to severe myelosuppression was the most common adverse event, necessitating close laboratory monitoring during the initial 8 weeks of clonal suppression.

Recombinant human erythropoietin has assumed a primary role in the initial management of anemia in MDS patients with inappropriately low endogenous erythropoietin levels and infrequent transfusion requirements [5,14]. Other agents—including antithymocyte globulin, darbepoetin alpha, cyclosporine, sirolimus, and a tumor necrosis factor receptor inhibitor—have recently demonstrated encouraging results in preliminary clinical trials [15–19].

Selection of treatment is based on the disease risk category (applying the International Prognostic Scoring System [IPSS]), age, and comorbid conditions. The IPSS is a widely applied prognostic system that classifies patients with MDS into 4 distinct risk groups (low, intermediate-1, intermediate-2, and high) that segregate according to differences in both overall survival and progression to AML based on 3 major variables: percentage of bone marrow blasts, cytogenetic pattern, and number of cytopenias (Table 2) [20]. For example, patients with fewer bone marrow blasts (0%–4%), fewer cytopenias, and near-normal cytogenetics may have a prolonged median survival measured in years, whereas patients with excess bone marrow blasts (≥5%), a greater number of cytopenias, and an unfavorable karyotype have a survival expectation of <1 year [20] and a high frequency of AML evolution. Consequently, more aggressive treatment may be warranted for patients with MDS who are determined to be at high risk using the IPSS criteria, as compared with patients with MDS who are determined to be at low risk and may be managed with supportive care and intensive therapy.

### Allogeneic stem cell transplant as a treatment for myelodysplastic syndrome

Allogeneic stem cell transplant is a potentially curative treatment for MDS; however, it is generally regarded as a realistic option for only a small number of younger patients (mean age, 30–45 years) at earlier stages of the disease [20]. Key factors in considering donor stem cell transplant for a patient with MDS are the availability of a donor, the patient’s age, the patient’s IPSS score, the patient’s general health, the type of MDS that has been diagnosed, and the time interval between the diagnosis of MDS and transplant [21].

A recent study by Cutler et al [22] examined the clinical outcomes of 260 patients with MDS (≤60 years of age) who received allogeneic bone marrow transplants from sibling donors compared with a cohort of 184 patients with MDS (≤60 years of age) who did not receive transplants. Using decision analysis and prospectively collected registry data, these researchers found that transplantation at the time of MDS diagnosis is associated with maximization of discounted life-years for patients classified in the IPSS intermediate-2 and high-risk groups.

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**Table 2**

**International prognostic scoring system (IPSS)**

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score</th>
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<tbody>
<tr>
<td>Prognostic variable</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow blast percentage</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostic score</th>
<th>IPSS subgroup</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>Intermediate-1</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>Intermediate-2</td>
<td>1.2</td>
</tr>
<tr>
<td>≥2.5</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Iron overload may complicate the outcome of allogeneic hematopoietic stem cell transplantation. In one study of bone marrow transplant recipients [23], 67 (88%) of 76 1-year survivors were found to have iron overload with high ferritin levels and high liver iron content. In another study, 20 (91%) of 22 liver biopsies performed 15 to 110 days posttransplant showed histologic evidence of siderosis [24]. Blood transfusion, prolonged dyserythropoiesis, and increased iron absorption also contribute to the accumulation of iron which predisposes to hepatic dysfunction [25]. Although further studies on the clinical consequences of iron overload and therapeutic iron depletion in transplant recipients are needed, iron accumulation may contribute to the development of chronic liver disease [26]. In some patients, phlebotomy therapy after transplant or adequate chelation therapy can help minimize these risks and improve liver function [27].

Iron overload in patients with myelodysplastic syndrome

For patients with transfusion-dependent MDS, regular blood transfusions ameliorate symptoms and possibly improve quality of life. Unfortunately, long-term use of blood transfusions may eventually lead to iron overload, a problem that commonly affects lower-risk patients with MDS in whom prolonged survival is expected [28,29]. MDS patients and others with refractory anemias requiring long-term blood transfusions develop iron overload at a rate of ~0.5 mg/kg of body weight per day [30]. This iron accumulation ultimately leads to organ complications that affect the liver, endocrine glands, and, most importantly, the heart. Complications of the heart cause cardiac failure and arrhythmias that account for ~70% of deaths among patients with iron overload due to thalassemia major [30].

Studies of transfusion-dependent patients with thalassemia or MDS have revealed the pathophysiology and adverse effects of chronic iron overload on the hepatic, endocrine, and cardiac systems. Specifically, when plasma iron content exceeds the binding capacity of available plasma transferrin levels, non-transferrin-bound iron combines with oxygen to form hydroxyl and oxygen radicals, both of which are toxic to cells and tissues. The results are lipid peroxidation and damage to cell membranes, protein, DNA, and organs [5,31,32].

The survival of patients with MDS worsens with the development of transfusion dependency. A study by Malcovati et al [33] found that although most clinical features at diagnosis are similar between transfusion-dependent and transfusion-independent patients within defined subgroups, the effect of cytogenetics may suggest the severity of bone marrow failure. Furthermore, the development of secondary iron overload (defined as serum ferritin >1000 ng/mL) adversely affects survival: a 30% increase in hazard was found for every 500 ng/mL increase in serum ferritin above the threshold. The authors concluded that therapeutic approaches that reduce transfusion needs or mitigate iron loading may impact survival in lower-risk patients. Treatment with iron chelating agents such as deferoxamine can reduce total body iron load. With prolonged treatment, sporadic reports suggest that chelation may improve hematopoiesis [34].

Despite the importance of iron chelation therapy in avoiding iron toxicity in transfusion-dependent patients with MDS, several factors may discourage patients and clinicians from pursuing this option. Patients with MDS are typically elderly. Although many elderly patients with MDS receive blood transfusions, only a relatively small percentage of these patients receive iron chelation therapy. Unlike patients with thalassemia major—who are younger and have demonstrated benefits from chelation therapy—little, if any, data are available on the benefits of iron chelation in this older MDS population.

In addition, iron overload is widely underrecognized among patients with MDS, partly because of the insidious nature of iron overload in light of the potentially devastating long-term effects of MDS. Furthermore, iron chelation therapy may not be initiated by clinicians because of the typically advanced age of many patients with MDS; a reduced life expectancy and high rate of medical fragility may apply for many of these patients. Patients and clinicians also may be uninformed about the need for chelation therapy, as well as the potential long-term benefits of this treatment.

Estimating and monitoring iron overload

Serum ferritin levels are often used for estimating iron burden, because these markers rise as iron stores increase and fall as iron stores decrease, providing a rough estimate of total body iron stores over time [35]. Monitoring serum ferritin concentration at the time of diagnosis and at least every 3 months in patients receiving regular blood transfusions is prudent to help monitor iron overload [35]. However, such measurements should be evaluated in the context of overall MDS progression, based on the understanding that serum ferritin levels may fluctuate owing to many factors, including inflammation, infection, hepatitis, hemolysis, or vitamin C deficiency [35,36]. It is appropriate, therefore, to consider threshold levels of serum ferritin within a wide range to allow for short-term fluctuations and to provide flexibility with respect to a patient’s transfusional status, as it may be the rate of infusion rather than the actual number of infusions that may be more relevant to the decision to initiate chelation therapy [35]. Depending on a patient’s transfusion rate, chelation therapy should be considered when
serum ferritin levels reach 1000 to 2000 ng/mL and should be ongoing as long as transfusions continue and iron overload remains a risk [35].

Magnetic resonance imaging (MRI) is a noninvasive method of estimating organ iron load. Although in principle MRI can be used to quantify iron stores wherever they exist in the body, current variability in its quantitative accuracy limits its usefulness as a definitive diagnostic test. Furthermore, lack of availability and poor accessibility of MRI, as well as cost factors, can be barriers to the widespread use of MRI for patients with MDS. Nevertheless, MRI can be used to detect iron overload and monitor iron chelation therapy. Other imaging modalities that may become more available to assess iron overload include computed tomography, nuclear resonance imaging, and the superconducting quantum interference device (SQUID).

Encouraging best practices for chelation therapy of iron overload in myelodysplastic syndrome

Chelation therapy is considered the standard of care for patients with iron overload. In fact, current guidelines from the NCCN regarding the care of patients with MDS recommend iron chelation therapy for those who receive >20 units of packed red blood cells [5]. Barriers to chelation therapy remain, however, because of the drawbacks inherent in the chelation treatment options currently available in the United States. Those patients most likely to suffer from morbidity and mortality related to MDS and problems associated with iron overload are the elderly, who often have comorbid conditions such as heart disease and liver damage. This vulnerable population may benefit from iron chelation therapy, despite its drawbacks, with maximum benefit occurring when treatment is initiated early in the course of the disease.

NCCN guidelines on supportive care for patients with myelodysplastic syndrome

NCCN practice guidelines describe supportive care for patients with MDS that involves observation, clinical monitoring, psychosocial support, and quality-of-life assessment [5]. Supportive care includes the administration of red blood cell transfusions, as needed, for treatment of symptomatic anemia, as well as platelet transfusions for severe thrombocytopenia or thrombocytopenic bleeding. These recommendations and other supportive measures are summarized in Table 3 [5].

Treatments that may ameliorate anemia should be considered for patients in the IPSS low-risk or intermediate-1 risk categories. The benefit of recombinant erythropoietin is greater in patients with low serum erythropoietin levels (≤500 mU/mL) and low transfusion requirements (<2 units/month). In suboptimal responders, the addition of granulocyte colony-stimulating factor may augment response in some patients. Immunosuppressive therapy with antilymphocyte globulin or cyclosporine should be considered for younger patients (<60 years) with a DR15 class II human leukocyte antigen phenotype and short transfusion duration. For patients with a chromosome 5q deletion, lenalidomide may be particularly effective [5,37]. For others, investigational therapy may be the most hopeful therapeutic option.

NCCN guidelines recommend the use of daily iron chelation therapy, generally with SC injection of deferoxamine, to manage iron overload [5]. Deferoxamine therapy is recommended for patients who have received 20 to 30 units of red blood cells, for patients in whom ongoing red blood cell transfusions are anticipated, and for patients with serum ferritin levels >2500 ng/mL. Deferoxamine treatment is typically used for patients with relatively lower-risk MDS whose clinical course suggests an ongoing red blood cell transfusion require-

<table>
<thead>
<tr>
<th>Table 3 National Comprehensive Cancer Network clinical practice guidelines for supportive care of patients with myelodysplastic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation</strong></td>
</tr>
<tr>
<td>- Clinical monitoring</td>
</tr>
<tr>
<td>- Psychosocial support</td>
</tr>
<tr>
<td>- Quality-of-life assessment</td>
</tr>
<tr>
<td><strong>Transfusions</strong></td>
</tr>
<tr>
<td>- Red blood cell transfusions (leuko-reduced) for symptomatic anemia</td>
</tr>
<tr>
<td>- Platelet transfusions for thrombocytopenic bleeding</td>
</tr>
<tr>
<td>- Irradiated blood products suggested for transplant candidates</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
</tr>
<tr>
<td>- For bacterial infections</td>
</tr>
<tr>
<td>- Aminocaproic acid or other antifibrinolytic agents</td>
</tr>
<tr>
<td>- May be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia</td>
</tr>
</tbody>
</table>

Iron chelation

- If >20–30 red blood cell transfusions received
  - Strongly consider daily chelation with SC deferoxamine or oral deferasirox to decrease iron overload, particularly for low-risk and intermediate-1 risk patients

Cytokines

- Epoetin alfa
- Granulocyte colony-stimulating factor (G-CSF) or granulocyte-monocyte colony-stimulating factor (GM-CSF)
  - Not recommended for routine infection prophylaxis
  - Consider if recurrent or resistant infections present in a neutropenic patient
  - Combine with epoetin alfa for anemia, when indicated
  - Platelet count should be monitored

Iron chelating agents: advantages and disadvantages

Two iron chelating agents are currently approved by the FDA for the treatment of iron overload: parenteral deferoxamine (Desferal®, Novartis Pharmaceutical Corporation, East Hanover, New Jersey) [38] and oral deferasirox (Exjade®, Novartis) [39]. A third agent, oral deferiprone (Ferriprox™, ApoPharma, Piding, Germany) [40], is currently undergoing Phase III clinical trials in the United States. The oral availability of these newer agents may offer greater compliance and better outcomes in the treatment of iron overload. Clinical trials in patients with MDS are under way to determine the role of deferasirox and deferiprone, alone and in combination with deferoxamine, for treating iron overload.

Deferoxamine

Deferoxamine (also known as desferrioxamine B) is derived from ferroxamine B, a sideramine isolated in 1960 from Streptomyces pilosus. Whereas its high binding affinity for trivalent iron is clinically effective in removing excess iron from blood and tissue [41], the mechanism of action of this agent is not fully understood [34].

The use of deferoxamine is supported by clinical evidence that optimal therapy with this agent can arrest progression of iron overload and prevent early death from this condition [42–44]. However, deferoxamine treatment requires parenteral administration because of its large molecular size, poor oral bioavailability, and short plasma half-life, making it necessary for patients to receive lengthy infusions several times per week [38,45]. According to NCCN guidelines [5], deferoxamine can be administered in 1- to 2-g doses by overnight SC infusion 5 to 7 nights per week, or as 1- to 2-g SC bolus infusion BID. This agent also may be given IM at intervals of 4 to 12 hours [38]. Careful monitoring of eye, ear, and renal function is necessary during treatment with deferoxamine. Toxicities associated with deferoxamine therapy include (1) retinal and optic nerve disturbances (risk may be higher in patients with diabetes or other factors affecting the blood-retinal barrier); (2) high-frequency sensorineural hearing loss; (3) effects on growth and bone (including growth retardation and bone abnormalities); (4) localized reactions (such as skin reddening and soreness at the SC infusion site); and (5) increased risk of infection (eg, Yersinia infection can occur in patients with iron overload who receive deferoxamine therapy) [46]. When using deferoxamine therapy, ensure that doses do not exceed 40 mg/kg per day; be aware of concerns regarding the introduction of deferoxamine therapy to very young patients (<3 years of age); and follow guidelines to reduce the dose of deferoxamine as iron loading falls [46].

Because of the demanding regimen of parenteral infusions, many patients with iron overload succumb to organ complications as a consequence of poor compliance with deferoxamine maintenance therapy [44]. Furthermore, because of the practical difficulties of repeatedly administering lengthy SC infusions of deferoxamine to MDS patients who generally are older and who may have a variety of comorbidities, initiation of parenteral chelation therapy is often delayed owing to reservations on the part of the patient and physician. Undertreatment of iron overload may occur due to the lack of therapeutic options that are determined to be tolerable for a particular patient. Consequently, compliance with parenteral deferoxamine regimens represents a major clinical challenge.

Deferasirox

Deferasirox is an oral iron chelator that is rapidly absorbed and can be administered QD. It is a tridentate iron chelator, requiring 2 molecules to stabilize and chelate each molecule of iron [44]. In clinical trials, treatment with deferasirox achieved a negative iron balance in patients with iron overload at rates comparable to those achieved in patients receiving deferoxamine [44,47]. Investigations to date indicate that deferasirox is effective in patients with various chronic anemias, including MDS, and its pharmacokinetic, tolerability, and safety profiles are suitable for long-term use [44,48–51]. This agent is well tolerated in children as young as 2 years of age, with only 3% of subjects in this age group withdrawing from clinical studies due to adverse effects [52]. Deferasirox was recently approved by the FDA for the treatment of all forms of iron overload. Given its safety and efficacy profile, this agent is expected to offer greater compliance for patients with lower-risk MDS and, as a consequence, possibly mitigate the adverse effect of transfusion dependence on survival expectations. Phase II studies are under way to evaluate the possible hematopoietic-promoting effect of deferasirox in patients with MDS with prolonged daily administration.

Deferiprone

Deferiprone is an orally active iron chelator licensed in 43 countries for the treatment of iron overload in patients for whom deferoxamine treatment has proved intolerant or inadequate. Deferiprone has a less efficient iron-binding profile than deferoxamine, with 3 molecules of deferiprone required to bind 1 molecule of triva-
lent iron; therefore, relatively large doses are necessary to achieve a negative iron balance in most patients [44].

Recent data suggest that this agent may be better than deferoxamine in extracting iron from cardiac and endocrine tissue because of improved intracellular penetration that protects these tissues from toxicity related to iron overload [30]. Large, well-designed studies are needed to clarify the comparative utility of deferoxamine versus deferiprone. Deferiprone may also prove useful in combination with deferasirox [30,44]. Patients receiving deferiprone, especially those with diabetes, are at increased risk for agranulocytosis and arthropathy, as well as zinc deficiency [30]. These adverse effects may lead to discontinuation of the drug in 5% to 10% of patients [30].

Conclusions

Despite the ability of iron chelation therapy to lessen or delay the complications of iron overload in transfusion-dependent patients with MDS, several factors have discouraged patients and clinicians from pursuing this option. Clinicians may not initiate iron chelation therapy because of the advanced age and medical fragility of many of their MDS patients. Patients and clinicians also may be uninformed about the need for chelation therapy and the long-term benefits of this treatment. Other barriers relate to potential side effects and the practical drawbacks inherent in parenteral chelation treatment.

Because of the potential toxic effects of iron on the heart, liver, and other organs, the patients most likely to suffer from the morbidity and mortality associated with iron overload in MDS are elderly patients with comorbid cardiac and hepatic conditions. This vulnerable population will benefit most from the development of new iron chelation agents that are safe, effective, and orally available. The introduction of the oral chelators deferasirox in the United States and deferiprone in Europe offers more convenient and effective iron chelation therapy. Clinical trials in MDS are under way to determine the role of these agents, alone and in combination with deferoxamine, for treating iron overload in MDS. Nonetheless, early intervention appears appropriate to maximize clinical benefit and mitigate the negative effects of iron overload on survival expectation in lower-risk patients.

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References


[21] Hematology/Oncology Clinics • Supplement 1


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Iron overload is a serious concern in addressing the needs of patients with myelodysplastic syndrome (MDS). Although blood transfusions are an effective intervention that often restores some measure of function and improves the quality of life for many of these patients during the course of their care, multiple transfusions over time may lead to iron overload. For some patients, iron overload can result in damage to the heart, endocrine glands, and/or liver, as well as contribute to the morbidity and mortality of patients with MDS. Yet, iron overload is often underdiagnosed in clinical practice. Widespread awareness of the potential impact of iron overload in patients with MDS is clearly warranted.

Physicians around the globe face a number of challenges in determining “best practices” to assess and treat iron overload in patients with MDS. A series of meetings with leading experts in the field and physicians who treat patients with MDS was recently convened; one meeting held in Japan during May 2005 included participants from Europe, Latin America, and Asia-Pacific, and one meeting held in the United States during November 2005 included physicians from various health care facilities who collectively have provided care to thousands of patients with MDS over the years. Participants’ opinions expressed during these meetings reflected a diversity of perspectives on many issues. This commentary attempts to highlight some of the key discussion points of these meetings, serving as a communications tool to encourage further conversations in the physician community about the need to take a close look at clinical issues relating to iron overload in this population.

The primary focus of each meeting was to share information about various aspects relating to the diagnosis, monitoring, and management of iron overload in patients with MDS. Topics included discussion on the implications of iron overload in MDS; the use of chelation agents in the treatment of iron overload in patients with transfusion-dependent MDS; the basic criteria to determine how this patient population can benefit from chelation therapy; the utility of applying guidelines established by the National Comprehensive Cancer Network in clinical practice; and the need to raise awareness about the role of iron overload and chelation therapy among physicians who provide care to patients with MDS.

The following statements summarize the key discussion points generated from the meeting held in Japan [1].

- The clinical consequences of untreated or inadequately managed iron overload in MDS are potential cardiac, hepatic, and endocrine complications.
- The goal of chelation therapy in MDS patients with iron overload is to prevent complications of iron overload and to improve survival.
- Chelation therapy is highly likely to be clinically important in a subgroup of patients with MDS.
- Body iron stores should be assessed at diagnosis of MDS and at regular intervals thereafter, depending on transfusion rate.
- The tools used for diagnosis and monitoring of iron overload should be serum ferritin, transferrin saturation, and liver magnetic resonance imaging (MRI).
- Iron overload should be monitored at least every 3 months in patients receiving transfusions.
- The initiation of chelation therapy should be considered in MDS patients when serum ferritin levels reach 1000 to 2000 ng/mL, depending on the transfusion rate.
- Chelation therapy should continue as long as transfusion therapy continues and as long as iron overload remains clinically relevant.
- MDS patients likely to benefit most from treatment of iron overload include: transfusion-dependent patients; patients with serum ferritin levels >1000 to 2000 ng/mL or other evidence of significant tissue iron overload; patients with low-risk MDS (as defined by the International Prognostic Scoring System as low or intermediate-1 or as defined by the World Health Organization [WHO] classification system as refractory anemia, refractory anemia with ringed sideroblast, or 5q-syndrome [which is a cytogenetic abnormality that occurs in only
a small proportion of the MDS patient population); patients with documented stable MDS; patients free of comorbidities that severely limit prognosis; and candidates for allograft.

Participants also acknowledged that the current knowledge base about iron overload in MDS is inadequate. Further research using clinical trials and/or patient registries is needed to make advances in this area. Specific areas of research were identified to address a range of unanswered questions in the minds of these participants. These areas include improved methods for assessing iron burden in particular organs; objective evidence regarding the effect of iron overload in MDS; and further clarification on the efficacy and safety of iron chelators in the MDS population, as well as studies on the compatibility of iron chelation therapy with other therapies that are administered to patients with MDS.

Participants in the meeting held in the United States expressed a wide range of opinions on similar discussion points. As background, it is useful to point out that MDS affects between 12,000 and 20,000 people each year in the United States, which translates to a rate of 22 to 45 people per 100,000 >70 years of age [2]. An estimated 30,000 to 40,000 people are living with MDS in this country, with a majority of these patients determined to have indolent MDS (which is generally defined as having <5% myeloblasts in the bone marrow) [2]. MDS is as prevalent as other common hematologic malignancies of older adults, such as multiple myeloma and chronic lymphocytic leukemia [3].

Discussion points among the participants in the US meeting included the need for objective data that clearly define the role of chelation therapy in MDS. This group identified 4 treatment goals of chelation therapy in MDS patients with iron overload: prevention of complications; treatment of complications; improvement of cytopenia; and improvement of survival. Potential cardiac, hepatic, and endocrine complications are regarded as the clinical consequences of not using iron chelation in MDS.

While noting the limitations of using serum ferritin measurements alone to make clinical decisions, many of the participants consider the need to assess serum ferritin in patients with MDS at the time of diagnosis and at follow-up visits, as clinically indicated. Both serum ferritin testing and noninvasive imaging modalities (for example, T2-MRI when accessible) are identified as potentially useful in the diagnosis and monitoring of iron overload; tissue biopsy and serum ferritin testing are the most frequently used biomarkers in clinical practice among these physicians. For many participants, the decision to start chelation therapy is based on the presence of organ dysfunction that is documented as related to iron overload, with continuation of chelation therapy depending on how long iron overload continues to be a clinical problem. Evidence of iron-related end-organ dysfunction is an important factor—along with other individualized considerations such as the perceived life expectancy—that helps these physicians determine the potential benefits from chelation therapy for their patients with MDS.

A number of specific areas for further research of special interest to this US group were identified. More studies are needed to provide objective evidence on the impact of iron chelation on MDS-related disease complications including survival; the role of chelation before and after allogeneic transplant; the impact of iron overload on survival and quality of life; and the impact of iron chelation on MDS-related cytopenias. In addition, further studies can provide a better understanding of any potential impact when patients with MDS receive both iron chelation therapy and other concomitantly administered drugs, as well as more data on any adverse events relating to various combinations of therapies. Other areas of interest include optimal methods of assessing end-organ damage from iron overload; the role of additional agents in optimizing iron mobilization; the impact of infectious complications; and the impact from concomitantly chelated trace elements.

Findings from 2 studies have been useful in addressing the need for additional information in caring for patients with MDS who have iron overload. A study by Jensen et al [4] examined the long-term (defined as up to 60 months) follow-up data of 11 patients with MDS with transfusional iron overload (before and after iron chelation therapy); this data included an assessment of peripheral blood counts and hemoglobin requirements of these patients and included the morphological and cytogenetical bone marrow changes observed during iron chelation, as well as erythroid marrow activity. Researchers concluded that iron chelation therapy in MDS patients with transfusional iron overload may induce blood transfusion independence if the patients are treated for a sufficiently long period of time.

An important study by Malcovati et al [5] was designed to evaluate the prognostic value of the new World Health Organization (WHO) classification system for MDS and assess the role of primary prognostic factors in MDS according to WHO subgroups, as well as estimate mortality and life expectancy in these groups of patients with MDS. In this retrospective study, a total of 467 patients who were diagnosed with MDS between 1992 and 2002 were evaluated for clinical and hematologic features at time of diagnosis, overall survival, and progression to leukemia. Researchers found that transfusion-dependent patients experienced a significantly shorter survival rate as compared with patients who did not require transfusions ($P < 0.001$). Furthermore, researchers observed that the development of secondary iron overload significantly worsened the survival of transfusion-dependent patients ($P = 0.003$). These findings suggest
that efforts to reduce transfusion needs using various therapeutic approaches—as well as interventions that can help prevent iron overload—may lead to improved outcomes in patients with MDS.

Clinical decision making among physicians who provide care for patients with MDS continues to be a daunting challenge. The availability of effective therapeutic modalities and the timing of specific interventions are critical factors to consider. Complexities are inherent in caring for these patients, given the natural history of MDS that can range from indolent conditions spanning over a number of years to forms that rapidly progress to leukemia. Widespread awareness of the potential impact of iron overload in patients with MDS—in combination with more research in this area—will help physicians in clinical practice as they make decisions on an individualized basis.

References
1. The myelodysplastic syndrome (MDS) refers to a group of hematologic stem cell disorders that are characterized by _______.
   a. ineffective blood production
   b. cytopenias and cytologic dysplasia
   c. variable risk for leukemia transformation
   d. both a and c
   e. all of the above

2. Most patients with MDS eventually develop which of the following morbidities?
   a. Infectious complications
   b. Complications from blood cell deficiencies
   c. Cardiovascular disease
   d. Acute leukemia
   e. Either a, b, or d

3. The annual incidence rate of MDS for all age groups is approximately ______ per 100,000 people.
   a. 1 to 2
   b. 3 to 4
   c. 9 to 10
   d. 14 to 15

4. The International Prognostic Scoring System (IPSS) classifies patients with MDS in risk groups for both overall survival and progression to acute myeloid leukemia based on which of the following variable(s)?
   a. Percentage of bone marrow blasts
   b. Cytogenetic pattern
   c. Number of cytopenias
   d. Both a and c
   e. All of the above

5. What are the key factors in considering a donor stem cell transplant for patients with MDS?
   a. Availability of a donor and the time interval between the diagnosis of MDS and transplant
   b. The patient’s age and general health
   c. The patient’s IPSS score
   d. The type of MDS diagnosed
   e. Only a, b, and c
   f. All of the above

6. Long-term use of blood transfusions may eventually lead to iron overload.
   a. True
   b. False

7. Patients with MDS who receive regular blood transfusions should have their serum ferritin concentration monitored for iron overload how often?
   a. At time of diagnosis of MDS and at least every 3 months
   b. At time of diagnosis of MDS and every month if serum ferritin concentration >1000 ng/mL
   c. At time of diagnosis of MDS and every 6 months
   d. At time of diagnosis of MDS and when serum ferritin levels reach 1000 to 2000 ng/mL

8. MDS is as prevalent as other common hematologic malignancies of older adults, such as multiple myeloma and chronic lymphocytic leukemia.
   a. True
   b. False

9. Which of the following are potential clinical consequences of not using iron chelation in patients with MDS?
   a. Cardiac complications
   b. Hepatic complications
   c. Endocrine complications
   d. All of the above

10. A study by Malcovati et al on 467 patients who were diagnosed with MDS between 1992 and 2002 found that transfusion-dependent patients experienced a ______ survival rate as compared with patients who did not require transfusions.
    a. longer
    b. shorter
    c. equal
    d. none of the above
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PRETEST ASSESSMENT: Please rate your current knowledge of treatment of iron overload in myelodysplastic syndrome on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

1 2 3 4 5

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2. a b c d e
3. a b c d

1. a b c d e
2. a b c d e f
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1. a b c d e
2. a b c d e
3. a b

1. a b c d e
2. a b c d e
3. a b

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1 2 3 4 5

1. Did the material adequately discuss the usefulness of applying the International Prognostic Scoring System to patients with myelodysplastic syndrome (MDS)?

2. Did the material identify key factors in considering donor stem cell transplant for patients with MDS?

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1. e.
MDS refers to a group of hematologic stem cell disorders that are characterized by ineffective blood production, cytopenias and cytologic dysplasia, and variable risk for leukemia transformation.

2. e.
Most patients with MDS eventually develop infectious complications, complications from blood cell deficiencies, or acute leukemia.

3. b.
The annual incidence rate of MDS for all age groups is approximately 3 to 4 per 100,000 people, typically found in elderly men at a median age at onset of 65 years.

4. e.
The IPSS classifies patients with MDS in risk groups for both overall survival and progression to acute myeloid leukemia based on percentage of bone marrow blasts, cytogenetic pattern, and number of cytopenias.

5. f.
Key factors in considering a donor stem cell transplant for patients with MDS include availability of a donor, the time interval between the diagnosis of MDS and transplant, the patient’s age, the patient’s general health, the patient’s IPSS score, and the type of MDS diagnosed.

6. a.
True. Long-term use of blood transfusions may eventually lead to iron overload.

7. a.
Patients with MDS who receive regular blood transfusions should have their serum ferritin concentration monitored for iron overload at time of diagnosis of MDS and at least every 3 months.

8. a.
True. MDS is as prevalent as other common hematologic malignancies of older adults, such as multiple myeloma and chronic lymphocytic leukemia.

9. d.
Potential clinical consequences of not using iron chelation in patients with MDS include cardiac complications, hepatic complications, and endocrine complications.

10. b.
A study by Malcovati et al on 467 patients who were diagnosed with MDS between 1992 and 2002 found that transfusion-dependent patients experienced a significantly shorter survival rate as compared with patients who did not require transfusions ($P < 0.001$).