FEATURE ARTICLE


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Myelodysplastic syndromes (MDSs) are a group of hematologic diseases that present unique challenges for oncology nurses, especially because patients with the disorders are being seen more often in oncology practices. An increasing array of therapeutic options are available, and the National Comprehensive Cancer Network published its first clinical practice guidelines for MDSs in 2004. This article provides oncology nurses with the most recent data on supportive care as well as emerging therapies for patients with low- to intermediate-risk MDS.

At a Glance

✦ Recent advances in the scientific understanding, classification, and risk stratification of the myelodysplastic syndromes (MDSs) are providing guidelines for individualizing treatment.
✦ Integrating supportive care with newer active therapies for the treatment of MDSs requires an understanding of the potential toxicities, nursing management, and advantages and disadvantages of each therapy.
✦ Consideration for the special needs of older patients, including management of comorbidities and polypharmacy, quality of life, and financial and social concerns, requires incorporating geriatric and oncology nursing strategies.

Patients with myelodysplastic syndromes (MDSs) are becoming a more common part of oncology practice, partly because of an aging population, improved diagnostic capabilities, and the emergence of therapeutic options. Treatment for MDSs focuses on symptom management and supportive care. MDSs present unique challenges to oncology nurses, who are usually the primary providers of supportive care for patients with the syndromes. Traditionally, the majority of symptom management was accomplished via red blood cell or platelet transfusions, and it has been expanded to the use of erythropoiesis-stimulating therapies. New agents for active treatment of MDSs have been evaluated in clinical trials with promising results. One agent, azacitidine (5-azacitidine [Vidaza®, Pharmion Corporation, Boulder, CO]), was approved by the U.S. Food and Drug Administration (FDA) in May 2004 as the first active agent for the treatment of MDSs. A second agent, Revlimid® (lenalidomide, Celgene Corporation, Summit, NJ), was approved by the FDA in December 2005 for the treatment of transfusion-dependent anemia resulting from low- or intermediate-1-risk MDS associated with the deletion of 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

The National Comprehensive Cancer Network (NCCN) published its first clinical practice guidelines for MDSs in July 2004 (NCCN, 2006). The guidelines are comprehensive and provide useful information to oncology nurses dealing with MDSs. The guidelines will require ongoing modifications because of the expansion of clinical research in the characterization and treatment of MDSs and thus do not present detailed information on the most recent advances for certain therapies. This article is intended to provide oncology nurses with the most recent data on supportive care as well as emerging therapies for patients with low- to intermediate-risk MDS.

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Overview of the Disease

MDSs are a diverse class of hematologic disorders that result from the improper development of hematopoietic stem cells in the bone marrow. The syndromes are characterized by hypoplastic or hypercellular bone marrow with dysplastic elements, cytopenias, and functional abnormalities (Bruning, Bennett, & Flandrin, 2001; Kurzrock, 2002). In a small percentage of patients with MDSs, the bone marrow is hypoplastic, resembling that of patients with aplastic anemia. Red cells, white cells, and platelets are affected in MDSs. As a result, cytopenias represent the major clinical problems encountered by patients with MDSs, and they may have profound effects on quality of life (Kurzrock). Functional abnormalities in the blood cells increase susceptibility to infection, bleeding, and hypoxia. Although neutropenia and thrombocytopenia frequently are present in MDSs, anemia is observed in 90% of patients at the beginning or during the course of the disease and often requires chronic transfusion support. Transfusion dependence may result in iron overload and end-organ damage, predisposing patients to diabetes as well as cardiac and hepatic failure. Unless permanent control is achieved, death from MDSs may result from bone marrow failure, with or without conversion to acute myeloid leukemia (AML) (List, Sandberg, & Doll, 2004; List, Vardiman, Issa, & DeWitte, 2004).

MDSs are a diverse group of stem cell malignancies that have challenged hematologists because of a varied disease course and lack of therapeutic assignment. The symptoms first were described as preleukemic conditions in the early 1930s and were not treated as a separate group of disorders until 1976. With the refinement of classification systems for MDSs, the number of diagnosed cases is increasing (Aul, Germing, Gattermann, & Minning, 1998). An estimated 15,000–20,000 new cases of MDSs are diagnosed each year in the United States (American Cancer Society, 2005; Aul et al.; List, Sandberg, et al., 2004). Although individuals of all ages (including children) are diagnosed with MDSs, the disease is most common among individuals aged 60 years or older (Williamson, Kruger, Reynolds, Hamblin, & Oscier, 1994). The annual incidence is 49 per 100,000 for individuals aged 70–79 years and 89 per 100,000 for individuals aged 80 years or older (Williamson et al.).

The exact cause of MDSs is not clearly understood; MDSs are thought to originate from the complex interaction among malignant progenitor cells, the bone marrow stroma and microenvironment, and genetic factors (List, Sandberg, et al., 2004). Nonetheless, predisposing risk factors have been implicated in the disease. The normal physiologic changes associated with aging include hematopoietic senescence; thus, age is the most common risk factor for the development of MDSs. Because the U.S. population is aging, the impact of diseases that primarily afflict older adults, such as MDSs, may have profound implications for health care in the future (Hetzel & Smith, 2001).

Relatively few studies have adequately examined a possible link between MDSs and environmental exposures. In some studies, specific occupational exposures to myelotoxic agents (e.g., pesticides, organic solvents such as benzene) were associated with an increased risk of MDSs (Nisse et al., 2001; Rigolin et al., 1998). Tobacco smoke also has been associated with a higher risk of developing MDSs (Nisse et al.). Alcohol intake has been implicated, although a study presented at the American Society of Hematology 2004 Annual Meeting suggested that wine drinkers have a decreased risk (Strom, 2004). Exposure to ionizing radiation or chemotherapeutic agents, particularly alkylating agents and topoisomerase inhibitors, is known to increase the risk of secondary MDSs.

Disease Classification

Two primary classification systems are used to describe the characteristics of the disease. The French-American-British (FAB) classification combined with the International Prognostic Scoring System (IPSS) is used more commonly by clinicians than the new World Health Organization (WHO) system, mainly because historical studies were based on the FAB classification. The major differences between FAB and WHO are that the WHO system distinguishes chronic myelomonocytic leukemia from MDSs, categorizes refractory anemia with excess blasts, and has other subcategories (see Table 1). Both FAB and WHO provide criteria for defining disease severity based on morphologic and cytogenetic characteristics.

As the percentage of blasts and the complexity of the cytogenetic changes increase, median survival decreases and the potential for transformation to AML increases. To establish a diagnosis of an MDS, careful morphologic review and correlation with a patient’s clinical features are important (see Figure 1). A number of medications and viral infections (including HIV) may cause morphologic changes similar to MDSs in marrow cells.

IPSS is used universally for risk stratification of MDSs (see Table 2). The system was developed in 1997 using cytogenetic, morphologic, and clinical data from seven large clinical studies (Greenberg et al., 1997). Three prognostic variables—percentage of bone marrow blasts, karyotype, and number of cytopenias—categorize patients’ risk as low, intermediate-1, intermediate-2, or high (Greenberg et al.). Each group is correlated to the estimated survival and time to leukemic transformation. Most patients fall into the low- to intermediate-1-risk category (Greenberg, 2000). FAB, WHO, and the IPSS score provide the basis for individualized treatment options. The recent publication of the NCCN guidelines integrates pathologic and prognostic definitions as a framework for disease management and provides a universal framework for ongoing clinical trials (NCCN, 2006).

Treatment of Myelodysplastic Syndromes

MDSs are largely a disease of older adults, who commonly have multiple medical problems, use medications to manage them, and are more likely to have more than one healthcare provider involved in their care, increasing the risk for drug interactions and treatment toxicities (Balducci, 2003; Boyle, 2003). Manifestations of common toxicities or illnesses may be more subtle in older adults because age is associated with functional deficits in multiple organ systems (Green & Hacker, 2004). Particularly important to older adults with MDSs is the age-related decline in normal bone marrow function, including diminished capacity for response to stressors such as infection or myelosuppressive treatments (Berger, 2003; VanCleave, 2003). Integrating geriatric and oncology nursing strategies results in an individualized approach for this unique population.
Managing MDSs is complicated by the generally advanced age of patients (median age ranges from 65–70), the presence of nonhematologic comorbid conditions, and the potential inability of older patients to tolerate certain intensive forms of therapy. The goals of therapy are to select the best treatment option suited for an individual patient to minimize toxicity, improve quality of life, increase blood counts, and prolong survival. Supportive care represents the mainstay of treatment, appropriate for all patients regardless of risk category, age, performance status, or concurrent active therapy (see Figure 2). Response to MDS therapy is assessed according to the International Working Group criteria for major and minor erythroid response (Cheson et al., 2000).

Geriatic assessment tools provide useful guidelines to evaluate the physical, emotional, and socioeconomic needs of older patients with MDSs (Boyle, 2003; Overcash, 2003; VanCleave, 2003). Quality-of-life indicators specific to the MDS population are lacking. Common factors associated with quality of life in patients with cancer have been identified, including independence, physical functioning and less fatigue, maintenance of activities with family and friends, and a positive response to treatment (Gotlib, Kurtin, & Thomas, 2005; Kornblith et al., 2002). Limitations in available resources specific to patients with MDSs and the uncertainty of the disease are primary concerns. As with many diseases in older adults, reliance on family members or friends to maintain prescribed treatments, including travel to appointments, may place additional stressors on patients and their support networks.

For patients with MDSs, a therapeutic goal is to improve quality of life and halt disease progression. MDSs generally progress slowly, with patients’ blood counts remaining relatively stable over several months or longer. For patients with low-to-intermediate-risk MDS (those in the IPSS low and intermediate-1 prognostic risk groups), a short period of observation is recommended to determine patients’ degree of clinical stability. Monitoring every two to four months is recommended for patients with stable disease. Persistence of an indolent versus progressive course of disease should be documented before initiating treatment. Treatment then is based on patients’ IPSS status with consideration for age and Eastern Cooperative Oncology Group (ECOG) performance status (see Figure 3).

The NCCN guidelines propose that individuals who are categorized as IPSS low and intermediate-1 risk, aged 60 years or younger, and have good performance status should receive supportive care as needed and be considered for low-intensity treatment, preferably through clinical trials. For older adults, particularly for those older than 70 years, performance status, physiologic age (taking into consideration health status), comorbid conditions, and social support systems must be considered for clinical assessment rather than their chronologic age alone. However, allogeneic bone marrow transplantation, the only curative treatment for MDSs, generally excludes patients older than 60 years (see Table 3).

### Table 1. World Health Organization Classification for Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>NUMBER OR TYPE OF CYTOPENIAS</th>
<th>BONE MARROW FINDINGS</th>
<th>PREVIOUS FAB CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>Anemia</td>
<td>Erythroid dysplasia alone, &lt; 5% blasts, &lt; 15% ringed sideroblasts</td>
<td>RA</td>
</tr>
<tr>
<td>RA with ringed sideroblasts (RARS)</td>
<td>Anemia</td>
<td>Erythroid dysplasia alone, &lt; 5% blasts, ≥ 15% ringed sideroblasts</td>
<td>RARS</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>2 or 3</td>
<td>Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines, &lt; 5% blasts, no Auer rods, &lt; 15% ringed sideroblasts</td>
<td>None</td>
</tr>
<tr>
<td>RCMD and ringed sideroblasts</td>
<td>2 or 3</td>
<td>Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines, &lt; 5% blasts, no Auer rods, ≥ 15% ringed sideroblasts</td>
<td>None</td>
</tr>
<tr>
<td>RA with excess of blasts, type 1 (RAEB 1)</td>
<td>1, 2, or 3</td>
<td>Unilineage or multilineage dysplasia, 5%–9% blasts, occasional Auer rods</td>
<td>RAEB</td>
</tr>
<tr>
<td>RA with excess blasts, type 2 (RAEB 2)</td>
<td>1, 2, or 3</td>
<td>Unilineage or multilineage dysplasia, 10%–19% blasts, occasional Auer rods</td>
<td>RAEB</td>
</tr>
<tr>
<td>Myelodysplastic syndrome (MDS), unclassified</td>
<td>1, 2, or 3</td>
<td>Unilineage dysplasia in granulocytes or megakaryocytes, &lt; 5% blasts, no Auer rods</td>
<td>None</td>
</tr>
<tr>
<td>MDS, associated with isolated del(5q)</td>
<td>Anemia, platelet count normal to increased</td>
<td>Normal to increased megakaryocytes with hypolobated nuclei, &lt; 5% blasts, no Auer rods, isolated del(5q)</td>
<td>None</td>
</tr>
</tbody>
</table>

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*Anemia (hemoglobin < 10 g/dl), neutropenia (absolute neutrophil count < 1,800/mcl), and/or thrombocytopenia (platelets < 100,000/mcl)*

*bIn World Health Organization classification, chronic myelomonocytic leukemia with a leukocyte count > 13,000/mcl was reclassified as a disorder with both myelodysplastic and myeloproliferative features, and refractory anemia with excess of blasts-1 (myelodysplastic syndrome with 21%–30% blasts) was classified as acute myeloid leukemia.*

**FAB**—French-American-British

**Table 2. Diagnostic Classification of Myelodysplastic Syndromes Using IPSS**

<table>
<thead>
<tr>
<th>PROGNOSTIC VARIABLES</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow myeloblasts</td>
<td>&lt; 5%</td>
<td>5%–10%</td>
<td>–</td>
<td>11%–20%</td>
<td>21%–30%</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Normal, or del(5q), del(Y), del(20q) as sole abnormalities</td>
<td>Other abnormalities</td>
<td>Del(7) or 3+ abnormalities</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of cytopenias</td>
<td>0, 1</td>
<td>2, 3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**IPSS RISK GROUP ASSIGNMENT**

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>MEDIAN SURVIVAL (YEARS)</th>
<th>MEDIAN YEARS TO AML EVOLUTION</th>
<th>LIFETIME AML EVOLUTION (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5–1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5–2.0</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*a* Anemia (hemoglobin < 10 g/dl), neutropenia (absolute neutrophil count < 1,800/mcl), and/or thrombocytopenia (platelets < 100,000/mcl)  

*b* Based on total prognostic variable score  

AML—acute myeloid leukemia; IPSS—International Prognostic Scoring System


**Treatment of Anemia**

Anemia is common in MDSs, affecting more than 50% of patients at presentation and as many as 90% of patients at some point during their illness. More than 80% of patients require a red blood cell transfusion during the course of their disease (Bowen & Hellstrom-Lindberg, 2001). Anemia is defined by WHO as hemoglobin levels lower than 13 g/dl for men and lower than 12 g/dl for women (WHO, 1968). However, in MDSs, anemia is defined by a hemoglobin concentration less than 10 g/dl in accordance with IPSS (Greenberg et al., 1997). This hemoglobin cut-point commonly is used as the trigger to initiate treatment and as a criterion for inclusion in clinical trials in the absence of transfusion dependence.

Anemia is usually the principal cause of symptoms associated with MDSs and the reason for referral to specialists. Historically, red blood cell transfusions were the standard of care for the treatment of anemia. As non-transferrin-bound iron levels increase in the body, they combine with oxygen to form oxygen radicals, which lead to peroxidative damage to cell membranes and proteins and result in end-organ damage and dysfunction (Farguhar & Bowen, 2003; Malcovati et al., 2005). In particular, endocrine, cardiac, or hepatic dysfunction results in increased risk for diabetes, congestive heart failure, cardiomyopathy, and hepatic failure. Iron chelation therapy is recommended for patients who previously have received 20–40 units of packed red blood cells or who have ferritin levels in excess of 2,000 ng/ml to reduce the risk of iron overload. Ferritin is a protein that stores iron in the body. Serum ferritin levels reflect the amount of stored iron in the body. Normal serum ferritin levels in men are 12–300 ng/ml and 12–150 ng/ml in women. Deferoxamine is the most commonly administered agent for iron chelation and can be given via IV or subcutaneously (SC). More recently, an oral iron chelation agent, Exjade® (deferasirox, Novartis Oncology, East Hanover, NJ), has been approved. It is a tablet that is dissolved in water and taken orally 30 minutes prior to meals (on an empty stomach), preferably at the same time each day. The most commonly reported side effects include gastrointestinal upset, abdominal pain, increased serum creatinine, and low-grade fevers. Many of these symptoms were dose related. Iron chelation therapy requires frequent monitoring and generally is continued indefinitely once started. The only strategy for reducing the risk of iron overload in patients with MDSs is to reduce requirements for transfusions.

Although erythropoietin (EPO) deficiency is not responsible for the anemia of MDS, erythropoiesis-stimulating proteins (ESPs) have been shown to be effective and recommendations for their use have been proposed by the NCCN (2006) and American Society of Hematology/American Society of Clinical Oncologists (Rizzo et al., 2002a, 2002b), as well as by European organizations (Bokemeyer et al., 2004). The NCCN guidelines recommend baseline evaluation of serum EPO levels for patients with MDS. Patients with serum EPO levels lower than 500 mU/ml may respond well to erythropoietic stimulating proteins. Patients with baseline levels higher than 500 mU/ml are not less likely to respond to ESP administration and should be evaluated for other types of active therapy. ESPs can increase hemoglobin levels, with the possibility of reducing transfusion requirements in anemic patients with MDS (Hellstrom-Lindberg, 1995; Musto et al., 2005; Oliva et al., 2004; Rose, Abels, Nelson, McCullough, & Lessin, 1995; Spiriti et al., 2004; Stasi, Brunetti, Terzoli, Abruzzese, & Amadori, 2004; Stein, 2003).

Improvements in hemoglobin levels have been correlated with improved quality of life in patients with chemotherapy-induced anemia (Demetri, Kris, Wade, Degos, & Cella, 1998; Gabriole et al., 2001; Glaspy, 1997; Littlewood, Bajetta, Nortier, Vercaemen, & Rapoport, 2001; Vansteenkiste, Pipker, et al., 2002; Vansteenkiste, Poulsen, Rossi, & Glaspy, 2002). The clinical application of ESP anemia therapy in MDSs still is evolving. The early studies of ESPs in patients with MDSs exam-
1. Observation
   • Clinical monitoring
     − Consider age-specific physiologic parameters, comorbid conditions, and concurrent medications.
     − Use geriatric assessment tools where appropriate.
   • Psychosocial support
     − Multidisciplinary involvement and inclusion of family and friends are recommended.
     − Consider financial concerns for outpatient treatment.
   • Quality-of-life assessment
     − Consider patient expectations of therapy, fears of treatment failure and death, tolerance of treatment toxicities, participation in daily activities, and time with family and friends.

2. Transfusions
   • Red blood cell (RBC) transfusions (leuko-reduced) for symptomatic anemia
   • Platelet transfusions for thrombocytopenic bleeding (irradiation suggested for directed donor products and products for transplant candidates)

3. Antibiotics for bacterial infections
4. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.

5. Iron chelation
   • If 20–40 RBC transfusions are received or serum ferritin is more than 2,000, strongly consider chelation.
     − Deferoxamine (Desferal®, Novartis Pharmaceuticals, East Hanover, NJ) daily subcutaneously or via IV three to five times per week (Subcutaneous is more effective.)
     − Deferasirox (Exjade®), an oral agent

6. Erythropoiesis-stimulating protein (ESP) therapy
   • Epoetin alfa (Procrit®)
   • Darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, CA), less frequent dosing

7. Granulocyte–colony-stimulating factor
   • Filgrastim (Neupogen®)
   • Pegfilgrastim (Neulasta®), less frequent dosing
   • Not recommended for routine infection prophylaxis
   • Consider use if infections in neutropenic patients are recurrent or resistant.
   • Combine with ESP for anemia when indicated.
   • Platelet count should be monitored.

Figure 2. Components of Supportive Care in Myelodysplastic Syndromes


Darboepoetin alfa is at least as effective and safe at treating anemia in patients with MDSs as epoetin alfa (Gabrilove et al., 2005; Mannone et al., 2004; Musto et al., 2005).

The darboepoetin alfa studies first examined treating MDS-associated anemia using different weekly doses (Gotlib et al., 2004; Mannone et al., 2004; Musto et al., 2005; Oliva et al., 2004). A large, retrospective cohort study demonstrated comparable effectiveness of darboepoetin alfa 200 mcg every two weeks (Q2W) and epoetin alfa 40,000 units weekly in clinical practice (Patton, Mun, & Wallace, 2004). A more recent phase II clinical trial of 90 patients (Gabrilove et al., 2005) presented at the Multinational Association of Supportive Care in Cancer 2005 International Symposium showed the effectiveness of darboepoetin alfa when administered as a 500 mcg dose every three weeks (Q3W). The studies support the use of darboepoetin alfa for the treatment of anemia in low- to intermediate-1-risk patients with the added convenience of less frequent dosing (see Case Study 1). The Q3W dosing interval currently is under investigation in a larger clinical trial of patients with MDSs.
Table 3. Summary of Currently Available Treatment Strategies and Nursing Management for Low- to Intermediate-1–Risk Myelodysplastic Syndrome

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLASSIFICATION</th>
<th>DOSSING AND ADMINISTRATION</th>
<th>COMMON TOXICITIES AND NURSING MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim (Neupogen®)</td>
<td>Growth factor</td>
<td>300–480 mcg subcutaneously (SC) for current infections or 150–300 mcg three times per week when given as primary therapy concurrently with erythropoietic therapy</td>
<td>Medullary bone pain: may be managed with intermittent use of antihistamines and anti-inflammatory agents. Toxicities are less common in the myelodysplastic syndrome population.</td>
</tr>
<tr>
<td>Epoetin alfa (Procrit®)</td>
<td>Growth factor</td>
<td>40,000–60,000 units SC weekly for supportive therapy</td>
<td>Injection-site burning with administration. Contraindicated in uncontrolled hypertension.</td>
</tr>
</tbody>
</table>

LOW-INTENSITY THERAPIES

- Advantages: may alter natural history of disease.
- Disadvantages: regimen-related morbidity and mortality.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLASSIFICATION</th>
<th>DOSSING AND ADMINISTRATION</th>
<th>COMMON TOXICITIES AND NURSING MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory and antiangiogenic</td>
<td>50–400 mg per day continuous</td>
<td>Myelosuppression&lt;br&gt;• Patient education for infection and bleeding prevention and reportable signs and symptoms&lt;br&gt;• Transfuse red blood cells or platelets if indicated.&lt;br&gt;• Refer to the National Comprehensive Cancer Network (NCCN) guidelines for neutropenia, thrombocytopenia, and anemia. Fatigue: may require drug holiday or dose reduction if severe Constipation: Institute aggressive bowel regimen. Neupathy&lt;br&gt;• Monitor for progressive symptoms.&lt;br&gt;• Patient teaching for safety&lt;br&gt;• Dose reduction Fluid retention: Monitor patient weight and presence of edema; may require diuretics or dose education. Teratogenicity: Drug must be prescribed using the System for Thalidomide Education and Patient Safety program, as required by the U.S. Food and Drug Administration (FDA).</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid®)</td>
<td>Immunomodulatory and antiangiogenic</td>
<td>10 mg per day continuous or days 1–21 every 28 days</td>
<td>Myelosuppression&lt;br&gt;• Generally is resolved with drug holiday and dose modification.&lt;br&gt;• Patient education for infection and bleeding prevention&lt;br&gt;• Transfuse red blood cells or platelets if indicated.&lt;br&gt;• Refer to NCCN guidelines for neutropenia, thrombocytopenia, and anemia.&lt;br&gt;• Conduct weekly complete blood count, differential, and platelet counts for the first eight weeks, monthly, or as indicated. Pruritis (grade 1): generally self-limiting Diarrhea (grade 1): may require intermittent use of antidiarrheal agent Drug must be prescribed using the Revassist program as required by the FDA.</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Anti–vascular endothelial growth factor, antiangiogenic</td>
<td>10 mg/kg per day via IV every other week</td>
<td>Myelosuppression&lt;br&gt;Hypertension&lt;br&gt;• Monitor prior to administration.&lt;br&gt;• May require treatment with antihypertensive medications Epistaxis&lt;br&gt;• Cold packs to nape of neck&lt;br&gt;• Transfuse platelets if indicated.</td>
</tr>
</tbody>
</table>

(Continued on next page)

* Agents currently being evaluated in clinical trials

*Note. Based on information from National Comprehensive Cancer Network, 2006.*
Treatment of Neutropenia

Neutropenia occurs in more than 35% of patients with MDSs. Neutropenia can be corrected with granulocyte-colony-stimulating factor (G-CSF) in more than 75% of patients (the neutrophil count decreases again once G-CSF therapy is stopped) (Cazzola & Malcovati, 2005). Patients with white blood cell counts lower than 2,500/uL may have poorer responses. The therapies generally are not used prophylactically for neutropenia but are used for treatment in the presence of active infections or as a part of a therapeutic regimen concurrently with ESPs. Filgrastim (Neupogen®, Amgen Inc., Thousand Oaks, CA) and pegfilgrastim (Neulasta®, Amgen Inc.) are the therapies of choice and may be used in combination with ESPs (Casadevall et al., 2004; Hellstrom-Lindberg et al., 2003; Stasi, Amadori, Newland, & Provan, 2004). The combination of ESP and G-CSF therapies initially was proposed for achieving higher erythroid response rates than ESPs alone in patients with MDSs who were transfusion-dependent; however, subsequent studies have not confirmed these findings (Casadevall et al.; Musto et al., 2001; Stasi, Amadori, Newland, & Provan, 2004).

Treatment of Thrombocytopenia

Thrombocytopenia can affect 25%–45% of patients with MDSs. In contrast, thrombocytosis often occurs in association with the del(5q) syndrome. The syndrome is characterized by a cluster of diagnostic findings, including normal to elevated platelets, less than 5% bone marrow blasts, anemia, a deletion of 5q, and hypolobulated megakaryocytes, and most often occurs in female patients. Platelet dysfunction is common and may manifest as prolonged bleeding time, abnormal platelet aggregation results, and bleeding unrelated to platelet count. Platelet transfusions for thrombocytopenic bleeding (irradiation suggested for directed donor products and products for transplant candidates) may be necessary, or aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia. A recombinant protein therapy is being evaluated for thrombocytopenia using a novel thrombopoietin receptor ligand that has no sequence homology to endogenous thrombopoietin but is effective at stimulating platelet production (Wang, Nichol, & Sullivan, 2004).
Nursing management of myelosuppression in patients with MDSs is similar to strategies used in patients with chemotherapy-induced cytopenias. The primary difference in patients with underlying bone marrow abnormalities, including MDSs, is the presence of functional and quantitative abnormalities. Thus, patients with borderline cytopenias may exhibit increased tendency for bleeding, infection, and symptomatic anemias.

**Emerging Therapies**

One agent, azacitidine, recently was approved by the FDA as the first active agent for the treatment of MDSs (FDA, 2004). Azacitidine is a DNA methyltransferase inhibitor that restores differentiation capacity in AML cell lines and in patients with MDSs. A randomized, controlled trial of 191 patients with MDSs demonstrated greater response (60%: 7% complete response, 16% partial response, and 37% improved) with azacitidine than with supportive care alone (5% improved) and a reduced rate of transformation to AML (15% versus 38%) (Silverman et al., 2002). The drug is administered daily SC (recommended starting dose is 75 mg/m²) for seven consecutive days and repeated every 28 days (Pharmion Inc., 2005). A minimum of four cycles is recommended. The dose-limiting toxicity reported in clinical trials was myelosuppression. Other common toxicities are injection-site erythema and nausea. Special consideration is required for underlying renal or hepatic disorders. Azacitidine is given most often in the office setting because of specific requirements for administration ("Azacitidine (Vidaza) for Myelodysplastic Syndrome," 2005). Administration of antiemetics is recommended to reduce the potential for nausea and vomiting. Rotation of injection sites and use of a 25-gauge, half-inch needle that has not been purged may reduce local irritation caused by tracking of the drug into the subcutaneous tissue. Local application of a cold compress without massage also can reduce local irritation. Particular attention must be paid to the injection site in patients with thrombocytopenia to limit the amount of subcutaneous hemorrhage (see Case Study 2).

Antiangiogenic agents currently being evaluated as potential therapies for MDS include thalidomide and related analogs (lenalidomide) and vascular endothelial growth factor receptor tyrosine kinase inhibitors. Thalidomide, a multifunctional inhibitor of angiogenesis and an immune modulator, restores erythropoiesis and reduces transfusion dependence in approximately 18% of patients who have no response to ESP therapy. However, long-term treatment and dose escalation are limited because of the drug’s sedative and neurologic effects. In a recent study, lenalidomide, a novel analog of thalidomide, exhibited hematologic activity in 43 patients with low-risk MDS who had no response to erythropoietic therapy or who were unlikely to benefit from conventional therapy (List et al., 2005). Transfusion independence was achieved in 63% and cytogenetic responses were documented in 55% of patients, indicating an effect on the underlying disease. In a subset of patients with a del(5q) abnormality, 75% had cytogenetic remission. Cytogenetic remissions have been documented rarely in therapies for MDS. Also noted was an increased sensitivity of erythroid progenitor cells to ESPs, indicating a potential role for concurrent therapy. Preliminary data from the ongoing phase II multicenter trials were presented at the American Society of Clinical Oncology meeting. Among 146 transfusion-dependent patients with the 5q chromosomal abnormality, 64% became transfusion independent after 24 weeks of treatment, 70% (81 patients) demonstrated a cytogenetic response with reduction in the number of marrow cells that had the 5q abnormality, and 44% of those (51 patients) had a complete cytogenetic remission. After a 9.3-month follow-up, 91% of the responders continued to show a response to lenalidomide. Myelosuppression was reported as the most common toxicity (List, 2005). Based on these data, the FDA approved lenalidomide for the treatment of transfusion-dependent patients with low- to intermediate-1–risk MDS who have a 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Because lenalidomide is an analog of thalidomide, a known human teratogen, the FDA has required a restricted distribution program, Revassist. The program requires prescribers to register...
Case Study 2

**Note.** This case study highlights treatment considerations for a patient with unstable intermediate-1 risk who may progress to intermediate-2.

The first undiagnosed episode of illness in this patient, a 72-year-old Caucasian woman, consisted of a visit to the emergency department because of right upper-quadrant pain of uncertain etiology and fever. Her previous medical history included chronic anemia, hypertension, cholelithiasis, gout, and surgeries (hysterectomy and left knee arthroscopy). Laboratory results confirmed anemia (hemoglobin = 7.7 g/dL), borderline neutropenia (white blood cell count = 3,100/mcL, absolute neutrophil count = 1020/mm³), normal platelet count (162,000/mcL), and serum erythropoietin of 502 mU/L. Serum erythropoietin levels less than 500 mU/L have a weak association with response rates to erythropoiesis-stimulating protein (ESP) therapy (Musto et al., 2001, 2005), although this should not be used to select or exclude patients. Bone marrow biopsy together with findings in the peripheral blood led to the diagnosis of refractory anemia with excess of blasts (RAEB) according to World Health Organization (WHO) criteria (see Table 1) and International Prognostic Scoring System (IPSS) intermediate-1 myelodysplastic syndrome (MDS) (see Table 2): 70% cellularity, 9% blasts, < 1% ringed sideroblasts, with a normal female karyotype. A red blood cell transfusion was initiated based on the substantially reduced hemoglobin levels and associated symptoms. Based on her age, good performance status (Eastern Cooperative Oncology Group = 1), and mild comorbid conditions, the patient was determined to be a good candidate for a clinical trial. She participated in a trial of bevacizumab 10 mg/kg administered every two weeks for a total of 12 weeks. Concurrent administration of ESPs was not permitted during the trial.

An initial improvement in transfusion requirements was observed (every 14 days to every 19 days) with a corresponding decrease in bone marrow blasts to < 1%. Two months after completion of the bevacizumab therapy, the patient was diagnosed with RAEB 2 according to WHO and IPSS intermediate-2 myelodysplastic syndrome: 80% cellularity, 19% blasts, and 2% circulating blasts. Her hemoglobin level at that time was 8.4 g/dL and required blood transfusion of two units every 11–14 days. ESP therapy was initiated using darbepoetin alfa (Aranesp®) 200 mcg every two weeks. She was initiated on azacitidine (Vidaza®) 75 mg/m² per day for seven days using a 28-day cycle. The injection sites for azacitidine were rotated to decrease local reactions, and antiemetics were administered prior to her treatment to reduce the incidence of nausea. Complete blood counts and a comprehensive metabolic panel were monitored weekly for cytopenias and possible hepatic or renal toxicities. Given the patient’s history of hypertension, blood pressure checks were performed before each darbepoetin alfa injection. She also was started on deferoxamine because of hemosiderosis (ferritin = 5,540 ng/mL).

Improvements in hemoglobin (11.4 g/dL) and transfusion intervals (two units every 17–19 days) as well as resolution of peripheral blasts were evident within two cycles of treatment. She required two platelet transfusions for treatment-related thrombocytopenia. Following six cycles of azacitidine, the bone marrow biopsy showed a decrease in blasts to less than 1%, accompanied by further improvements in transfusion requirements. She remains on darbepoetin alfa every three weeks concurrently with thalidomide to allow for travel and less frequent clinic visits.

This case points out challenges associated with patients with unstable intermediate-1 risk. Initially, the patient was a suitable candidate for participation in a clinical trial. Then, the patient’s disease progressed to intermediate-2 status, and therapeutic management was indicated beyond supportive care and clinical trial enrollment. She was treated with azacitidine with daily injections for seven days. Azacitidine often is associated with nausea and injection-site reactions. Because of the drug formulation, most patients require two separate injections each day. Furthermore, azacitidine may exacerbate anemia in many patients. Therefore, symptom and anemia management must continue alongside therapeutic management. The patient was treated for her MDS-associated anemia with darbepoetin alfa while concurrent, more intensive forms of therapies were administered. Regimen-related toxicities must be monitored throughout.

and provides mandatory patient safety information, including verification of pregnancy testing for women of childbearing age as well as mandatory use of contraception for four weeks prior to treatment, during treatment, and for four weeks after treatment is discontinued. No known teratogenicity related to lenalidomide has been found in clinical trials or animal studies to date. Patients with multiple myeloma treated with lenalidomide in combination with decadron have demonstrated an increased risk of thrombosis; this was not demonstrated in the MDS studies, but careful screening of patients at increased risk is recommended.

Phase II, multicenter clinical trials are ongoing to evaluate the effectiveness of an oral farnesyltransferase inhibitor (tipifarnib [Zarnestra®, Johnson and Johnson, Raritan, NJ]), in treating MDS. To date, reports showed modest hematologic improvement (Kurzrock, Albitar, et al., 2004; Kurzrock, Fenaux, & Raza, 2004). Common toxicities associated with Zarnestra include myelosuppression, fatigue, neurotoxicity, rash, and leg pain. Most toxicities were dose related and responded to dose reduction or planned interruptions. The drug most often is given using a schedule of two weeks on and two weeks off.

Other drugs with somewhat novel antiangiogenic mechanisms of action are in development, such as the vascular endothelial growth factor-receptor blocker SU5416 and the recombinant vascular endothelial growth factor-neutralizing antibody bevacinumab (Avastin®, Genentech, Inc., South San Francisco, CA). Avastin has been used commonly in patients with solid tumors. The nursing implications for administration and patient toxicities associated with the drug are similar in patients with MDSs. Nose bleeds and other bleeding tendencies, however, require particular attention in patients with MDS who have thrombocytopenia.

As newer therapies become available, oncology nurses can help patients evaluate their treatment options. The NCCN guidelines, in combination with careful evaluation of patients’ characteristics, social circumstances, and comorbidities, must be taken into consideration so that the treatment plan is individualized for each patient, minimizing the potential treatment-related toxicities while maximizing benefits. Treatment goals continue to be reduction of transfusion requirements, delay in time to leukemic transformation, and improved quality of life.

**Summary**

In recent years, the number of documented cases of MDSs has increased in the United States, indicating that the disease is much more common than previously thought. The incidence
of MDSs worldwide ranges from 1.0–12.6 per 100,000 per year, depending on the population (Hamblin, 2002; McNally, Rowland, Roman, & Cartwright, 1997). However, the incidence is consistently greater for individuals older than 70 years. The rising number of cases of MDSs may be explained partly by the increased number of bone marrow studies performed on older adults with mild cytopenias, accompanied by improvements in diagnostic capabilities and overall understanding of the disease (Aul et al., 1998). Clinicians are becoming more astute at recognizing symptoms and achieving a precise diagnosis (which may confirm MDS) so that early interventions can be implemented. As more patients are diagnosed with MDSs and ongoing trials evaluate novel therapies, oncology nurses must become familiar with the unique clinical diversity of the disease and new treatment options.

The goals of therapy are to minimize toxicities, improve quality of life, improve blood counts, and prolong survival. Currently, the only curative treatment for MDSs is bone marrow transplant. Unfortunately, few patients are within the age and risk category to be considered for the aggressive and expensive procedure. The lack of effective curative therapy for most patients with MDSs emphasizes the need for continued research in this area. With several ongoing clinical trials, the NCCN guidelines may be used to guide decisions for optimal patient management by emphasizing individualization of treatment and taking into account the natural history of the disease, biologic features, and patient preferences. Therapeutic goals must be weighed against the limitations imposed by individual prognostic factors: a patient’s age, performance status, coexisting medical conditions, concurrent medications, related toxicities, and financial considerations.

Patients with stable low- to intermediate-risk MDS may be managed successfully with supportive care in the absence of disease progression.

Several new options exist for the management of patients with low- to intermediate-risk MDS. Azacitidine and lenalidomide are the first FDA-approved active therapies and have shown some effect on the underlying disease with promise for controlling disease progression and affecting survival. Ongoing clinical trials will further increase the number of therapeutic options for patients with MDSs with good performance status who require active therapy to control their disease. Awareness of the advantages and disadvantages of each therapy will assist oncology nurses in supporting patients as they make treatment decisions with respect to the novel therapeutic options. Newer therapies require time, often three to four months, for a measurable response. Patients often develop progressive cytopenias prior to experiencing improvement in their disease. Familiarity with each treatment option, the unique needs of the older adult population, management of transfusions and iron chelation therapies, and the risk associated with myelosuppression in the MDS population provide a unique challenge to oncology nurses.

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