An Update on the Treatment of Myelodysplastic Syndromes

Sandra E. Kurtin, RN, MS, AOCN®, ANP-C, and Erin P. Demakos, RN, CCRC

Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal disorders of myeloid hematopoietic stem cells affecting about 300,000 people worldwide. Ineffective hematopoiesis and clonal proliferation result in significant cytopenias in affected individuals. Patients are categorized into risk groups (i.e., low, intermediate [1 and 2], and high) based on severity of cytopenias, cytogenetic abnormalities, and the presence of bone marrow blasts. The only potentially curative treatment for MDS is hematopoietic stem cell transplantation, which often is not an option because of advanced age at diagnosis (median age = 76 years). Several alternative treatments to hematopoietic stem cell transplantation show great promise. For low- and intermediate-1-risk MDS, the novel antitumor immunomodulatory agent lenalidomide is approved for patients with del(5q), and two different hypomethylating agents, azacitidine and decitabine, are approved for intermediate-2- and high-risk MDS. Trial results have increased the understanding of these treatments, alone or in combination with other therapies. Effective treatment often requires at least three to six months to achieve a clinical response. In the meantime, or in addition to active therapy, supportive care has a positive effect on quality of life. Greater understanding of the factors affecting MDS treatment options will assist oncology nurses in facilitating the optimal combination of treatment, supportive care, and management of adverse events.

New clinical data on myelodysplastic syndromes (MDS) were presented at the 50th and 51st annual meetings of the American Society of Hematology (ASH) in December 2008 and 2009, and the 44th annual meeting of the American Society of Clinical Oncology in May 2008. Integration of the most current scientific data into clinical practice will promote optimal care for patients with MDS. This article reviews the epidemiology, natural history, diagnosis and staging, and treatment goals for patients with MDS, and provides an update on clinical advances in MDS management from the meetings.

Epidemiology

MDS are a group of stem cell disorders characterized by abnormal and ineffective hematopoiesis in one or more blood cell lineages, with an underlying dysplastic bone marrow (Nimer, 2008). The incidence of newly diagnosed MDS exceeds 10,000 cases in the United States annually (Ma, Does, Raza, & Mayne, 2007; Surveillance, Epidemiology and End Results, 2007). MDS are most common in older adult patients, and age is the greatest risk factor for developing MDS. At the time of diagnosis, 86% of patients are 60 years or older. The incidence of MDS rises from 3.4 cases per 100,000 in the general population to more than 25 cases per 100,000 in people older than 75 years (Ma et al., 2007). Among patients diagnosed with MDS, 14% have been treated for other primary tumors prior to diagnosis (Ma et al., 2007).

At a Glance

✦ The goals of treatment for myelodysplastic syndromes (MDS) are to prolong overall survival, reduce transfusion burden, and improve quality of life.
✦ Newer treatment options for MDS include antitumor immunomodulatory and hypomethylating agents.
✦ Effective treatment often requires a minimum of three to six months of therapy to achieve a clinical response.

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Natural History

The natural history of MDS ranges from cytopenia of a single cell line, such as refractory anemia, to the development of acute myeloid leukemia (AML) in 20% of untreated patients (Greenberg et al., 1997). A higher bone marrow blast count and unfavorable cytogenetics are factors associated with the evolution of MDS to AML. Signs and symptoms of MDS are related primarily to the cytopenias associated with the disease. Clinical symptoms include fatigue, recurrent infections, and, less commonly, bleeding and bruising (Hoffmann & Koeffler, 2005). As many as 80% of newly diagnosed patients with MDS are anemic, and 85% have thrombocytopenia. In addition, 20%–40% die of neutropenia-related infections (Hellström-Lindberg, 2008). In a review of Medicare data, Goldberg, Mody-Patel, and Chen (2008) showed that 74% of patients with MDS suffered cardiac disease—significantly more than observed in the entire Medicare cohort (42%; p < 0.001). During the three-year study period, 45% of patients developed infectious complications, 79% required hospitalization, 59% had one or more emergency room visits, and 39% died. The median Medicare payment for patients with MDS in the United States was $17,556, compared with $1,459 for all other Medicare claims. These findings underscore the burden of MDS in the United States and the importance of adequate treatment and supportive care.

Diagnosis and Staging

As the clinical and pathobiologic features of MDS become more familiar to clinicians, MDS becomes a part of the differential diagnosis and is detected more often in patients presenting with cytopenias, particularly anemia in the older adult population (Kurtin & List, 2009). These patients often present first to their primary care providers. Diagnosis of MDS requires evaluation of a complete blood count with differential cell count, peripheral blood smear, bone marrow aspiration, biopsy, and cytogenetic analysis (National Comprehensive Cancer Network [NCCN], 2010). Historically, classification systems for MDS have been based on cell morphology and bone marrow blast counts. The most common classification systems used are the French-American-British (FAB) (Bennett et al., 1982) and the World Health Organization (WHO) versions (Arber et al., 2008; Vardiman, Harris, & Brunning, 2002). Specific disease attributes associated with variable risk are characterized to estimate prognosis and are included in the International Prognostic Scoring System (IPSS) and the WHO-based Prognostic Scoring System (WPSS) (Brunning et al., 2008; Greenberg et al., 1997; Haase et al., 2007; Vardiman et al., 2002) (see Tables 1 and 2). The percentage of bone marrow blasts, presence of cytogenetic abnormalities, and number of cytopenias are used to assign a prognostic group ranging from low- to high-risk disease.

The IPSS was the first system to stratify patients according to their risk of death or evolution to AML (Greenberg et al., 1997). The newer WPSS has five prognostic groups (compared with four in IPSS) with distinct survival times and probabilities of progression to AML (Malcovati et al., 2007). Although the IPSS is limited to newly diagnosed patients with MDS, the WPSS can be applied at any time during the disease course (Malcovati et al., 2007). It has been shown that the WPSS improves survival prediction and identifies patients with very low-risk disease who may achieve long-term survival (Park, Kim, et al., 2008). Kantarjian, O’Brien, et al. (2008) also developed a new MDS risk model that is applicable to all patients with MDS regardless of prior treatment or duration of disease. This model, which accounts for thrombocytopenia, transfusion burden, and serum

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**Table 1. Classification Systems Used to Define Staging in Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>FAB SUBTYPE</th>
<th>WHO MODIFICATION</th>
<th>MORPHOLOGIC AND CYTOGENETIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA; less than 5% blasts</td>
<td>RA</td>
<td>Unilineage dysplasia; less than 5% blasts; less than 15% ringed sideroblasts</td>
</tr>
<tr>
<td></td>
<td>RCMD</td>
<td>Dysplasia in 10% or more of two or more myeloid lineages; no Auer rods; ± 15% ringed sideroblasts</td>
</tr>
<tr>
<td>MDS-unclassified</td>
<td>Dysplasia in less than 10% of one or more myeloid lineages; less than 5% blasts; evidence of cytogenetic abnormalities common in MDS</td>
<td></td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>Normal or increased megakaryocytes; isolated del(5q) abnormality; no Auer rods; less than 5% blasts</td>
<td></td>
</tr>
<tr>
<td>MDS with isolated del(5q) Sqq syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RARS (with 15% or more ringed sideroblasts)</td>
<td>RARS</td>
<td>15% or more ringed sideroblasts; erythroid dysplasia only; less than 5% blasts</td>
</tr>
<tr>
<td></td>
<td>RCMD and ringed sideroblasts</td>
<td>Dysplasia in 10% or more of two or more myeloid lineages; no Auer rods; more than 15% ring sideroblasts</td>
</tr>
<tr>
<td>RAEB; 5%–20% blasts</td>
<td>RAEB-I (5%–10% blasts)</td>
<td>Unilineage or multilineage dysplasia; 5%–9% blasts; no Auer rods</td>
</tr>
<tr>
<td></td>
<td>RAEB-II (11%–20% blasts)</td>
<td>Unilineage or multilineage dysplasia; 10%–19% blasts; Auer rods may be present</td>
</tr>
<tr>
<td>RAEB-t; 21%–30% blasts</td>
<td>AML</td>
<td>More than 20% blasts</td>
</tr>
</tbody>
</table>

AML—acute myeloid leukemia; FAB—French-American-British; MDS—myelodysplastic syndromes; RA—refractory anemia; RAEB—refractory anemia with excess blasts; RAEB-t—refractory anemia with excess blasts in transformation; RARS—refractory anemia with ringed sideroblasts; RCMD—refractory cytopenias with multilineage dysplasia; WHO—World Health Organization

lactate dehydrogenase level, may have more prognostic value than the IPSS.

Patient outcomes vary depending on disease presentation. Indeed, among untreated patients with MDS, median survival varies from 5.7 years in low-risk patients to 0.4 years in patients with high-risk disease (Greenberg et al., 1997). For patients with del(5q) as the sole chromosomal aberration, median survival is 73 months compared to 19.3 months for patients with more than one aberration. Transfusion need at diagnosis is the most independent parameter for survival, with transfusion-dependent patients having a median survival of 39 months versus 97 months for transfusion-independent patients (p = 0.00005) (Germing et al., 2009).

### Treatment Goals and Options

The goals of treatment for patients with MDS are to prolong overall survival, reduce transfusion burden, and improve quality of life (QOL). These goals can be achieved by altering the natural history of the disease, improving peripheral blood counts, and alleviating disease-related complications. Goals can be objectively measured with parameters of survival, disease remission, progression, evolution to AML, cytogenetic response, QOL, and hematologic improvement (Cheson et al., 2000).

Treatment options for individual patients with MDS depend on the disease classification, prognostic stage, and the age and health status of the patient (NCCN, 2010) (see Figure 1). For patients with lower-risk disease (IPSS-classified low- or intermediate-1-risk) and symptomatic anemia, options include the immunomodulatory agent lenalidomide for patients with del(5q) (List et al., 2006); erythropoietin-stimulating agents (ESAs) such as epoetin alfa or darbepoetin alfa for patients with low serum erythropoietin levels (500 mU/ml or less) and low hematopoietic response; alternatively, lenalidomide, azacitidine, or decitabine may be considered (NCCN, 2010).

For patients with intermediate-2- or high-risk MDS, intensive therapy with allogeneic stem cell transplantation (ASCT) remains the only potentially curative treatment option. However, few patients with MDS are young and healthy enough to tolerate this treatment approach (Cutler et al., 2008). For the majority of patients who are not candidates for ASCT, treatment options include azacitidine or decitabine, clinical trials, or supportive care. In addition, all patients receiving active therapy should receive continuous supportive care.

Oncology nurses should have a thorough understanding of treatment doses and administration. They also should monitor any anticipated adverse events and be involved in the management of adverse events (Demakos & Linebaugh, 2005). Nurses should have a comprehensive overview of the advantages and disadvantages of the available therapies and be involved in patient and caregiver education to help patients make informed choices about future treatment options (Kurtin, 2006; Thomas, 2007).

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**Table 2. Risk-Based Stratification of Myelodysplastic Syndromes—International Prognostic Scoring System and Proposed Modifications**

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Proposed Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow myeloblasts</td>
<td>Less than 5%</td>
<td>5%–10%</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Normal, or del(5q), del(Y), and del(20q) as sole abnormalities</td>
<td>Other abnormalities</td>
</tr>
<tr>
<td>Chromosome 7 abnormalities or complex (three or more) abnormalities</td>
<td>–</td>
<td>Favorable: del(12p), del(9q), t(15q), del(15q), 21+, X–, t(7q), 21– Intermediate-1: del(11q), 8+ Intermediate-2: t(11q23), any del(3q) abnormalities</td>
</tr>
<tr>
<td>Number of cytopenias</td>
<td>0, 1</td>
<td>2, 3 Anemia (hemoglobin &lt; 10 g/dl), neutropenia (ANC &lt; 1,800/mcl), and/or thrombocytopenia (platelets &lt; 100,000/mcl) Adverse risk: Thrombcytopenia at presentation; high transfusion burden</td>
</tr>
</tbody>
</table>

**Note:** Low risk has a numeric score of 0, intermediate-1 of 0.5–1, intermediate-2 of 1.5–2, and high of greater than 2.


**AML**—acute myeloid leukemia; **ANC**—absolute neutrophil count
Current Treatment Options

Table 3 summarizes the published data on lenalidomide and the hypomethylating agents azacitidine and decitabine (Adés et al., 2009; Fenaux, Giagounidis, et al., 2009; Fenaux, Mufti, et al., 2009; Goldberg & Steensma, 2009; Grövdal et al., 2008; Lyons, Cosgriff, et al., 2009; Sekeres, Maciejewski, et al., 2008; Wijermans et al., 2008).

**Lenalidomide:** Lenalidomide is approved in the United States for the treatment of patients with transfusion-dependent anemia from low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality, with or without additional cytogenetic abnormalities. Lenalidomide also is an option in patients with serum erythropoietin levels of 500 mU/ml or less and no response to epoetin alfa or darbepoetin alfa, with or without granulocyte colony-stimulating factor (G-CSF), or in patients with serum erythropoietin levels greater than 500 mU/ml and poor probability for response to immunosuppressive therapy (NCCN, 2010). The recommended starting dose of lenalidomide for patients with MDS is 10 mg per day.

List et al. (2005, 2006) demonstrated high efficacy with lenalidomide in patients with low- and intermediate-1-risk MDS and del(5q). Seventy-six percent of patients (n = 148) had a reduced transfusion requirement, 67% achieved complete transfusion independence, and cytogenetic improvement was observed in 73% of patients. Almost all (90%) of the patients achieved transfusion independence within three months of treatment, with a median time to response of 4.6 weeks (range 1–49 weeks) (List et al., 2006). A follow-up evaluation of six patients participating in the MDS-001 trial indicated that the response to lenalidomide was durable, with sustained transfusion independence up to 6.5 years, and showed evidence of sustained cytogenetic remissions in some patients (Kurtin & List, 2009).

Fenaux, Giagounidis, et al. (2009) reported the results of the subsequent randomized, double-blind, phase III study which compared the efficacy of two doses of lenalidomide (5 mg and 10 mg) in lenalidomide-naive patients with red blood cell transfusion-dependent low- and intermediate-1-risk del(5q) MDS. Transfusion independence for 26 consecutive weeks or longer was achieved by 56%, 41%, and 6% of patients treated with 10 mg lenalidomide, 5 mg lenalidomide, and placebo, respectively (p < 0.001 versus placebo for both lenalidomide doses). Complete cytogenetic response was achieved by 24% of patients in the 10 mg arm and 11% in the lenalidomide 5 mg arm (versus 0% for placebo). Among patients treated with lenalidomide 5 mg and 10 mg, grade 3–4 neutropenia occurred in 74% and 75%, respectively (versus 15% for placebo), and grade 3–4 thrombocytopenia in 33% and 41%, respectively (versus 2% for placebo). These data support the use of lenalidomide 10 mg as a starting dose.

Lenalidomide also has been shown to be beneficial in patients with low- and intermediate-1-risk MDS with karyotypes other than del(5q), producing hematologic improvement in as many as 43% of the 214 patients (Raza et al., 2008). The median interval to the

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**Figure 1. Recommendations for the Treatment of Myelodysplastic Syndromes**

*Note.* Based on information from Kurtin, 2006; National Comprehensive Cancer Network, 2010.
### Table 3. Clinical Trial Data on the Use of Lenalidomide, Azacitidine, and Decitabine in Patients With Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>TREATMENT PLAN</th>
<th>OUTCOME</th>
<th>MAJOR TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine (Fenaux, Mufti, et al., 2009)</td>
<td>75 mg/m² per day SC for seven days of every 28-day cycle</td>
<td>Azacitidine significantly improved OS compared with CCR (24.5 months versus 15 months; p = 0.001) in intermediate-2- and high-risk MDS.</td>
<td>Peripheral cytopenias</td>
</tr>
<tr>
<td>Azacitidine (Grövdal et al., 2008)</td>
<td>Postchemotherapy maintenance: 60 mg/m² or 75 mg/m² SC for five days of a 28-day cycle</td>
<td>Median complete response duration was 13.5 months; median OS was 20 months.</td>
<td>Injection site reaction and hematologic events</td>
</tr>
<tr>
<td>Azacitidine (Lyons, Cosgriff, et al., 2009)</td>
<td>Three treatment regimens were assessed: (a) 75 mg/m² per day SC for five days on, then two days off, then two days on treatment; (b) 50 mg/m² per day SC for five days, followed by two days no treatment, then five days on treatment; and (c) 75 mg/m² per day SC for five days; each of 28-day cycle</td>
<td>Similar beneficial effects on TI and HI with all three regimens, with the five-day 75 mg/m² per day regimen as the most convenient</td>
<td>Hematologic events, fatigue, nausea, and injection-site erythema</td>
</tr>
<tr>
<td>Decitabine (Goldberg &amp; Steensma, 2009)</td>
<td>20 mg/m² IV for five days of a 28-day cycle</td>
<td>Cytogenetic response correlated with hematologic response, TI, and improved survival.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Decitabine (Wijermans et al., 2008)</td>
<td>15 mg/m² over four hours IV, every eight hours on days 1–3 of a six-week cycle, maximum of eight cycles versus best supportive care</td>
<td>No significant difference in OS or acute myeloid leukemia-free survival; overall response was significantly improved (34% versus 2%).</td>
<td>Hematologic and gastrointestinal events</td>
</tr>
<tr>
<td>Lenalidomide (Adés et al., 2009)</td>
<td>10 mg per day orally for 21 days of a 28-day cycle</td>
<td>Hematologic response was 27% and TI was 25% in intermediate-2- and high-risk del(5q) MDS.</td>
<td>Hematologic events</td>
</tr>
<tr>
<td>Lenalidomide (Fenaux, Giagounidis, et al., 2009)</td>
<td>5 mg on days 1–28 or 10 mg on days 1–21, both of a 28-day cycle, or placebo</td>
<td>TI for 26 or more consecutive weeks was achieved by 56%, 41%, and 6% of patients treated with 10 mg lenalidomide, 5 mg lenalidomide, or placebo.</td>
<td>Hematologic events</td>
</tr>
<tr>
<td>Lenalidomide (Sekeres, List, et al., 2008)</td>
<td>10 mg per day orally for 21 days of a 28-day cycle</td>
<td>Development of cytopenias linked to achieving TI in patients with del(5q) MDS</td>
<td>Hematologic events</td>
</tr>
</tbody>
</table>

CCR—conventional care regimen; HI—hematologic improvement; MDS—myelodysplastic syndromes; OS—overall survival; SC—subcutaneously; TI—transfusion independence

Beginning of the red blood cell transfusion-independence period was 4.8 weeks (range = 1–39 weeks) (Raza et al., 2008).

Sekeres, Maciejewski, et al. (2008) reported an important analysis of data from two phase II clinical studies, MDS-002 (karyotypes other than del(5q)) and MDS-003 (del(5q)), evaluating lenalidomide in low- and intermediate-1-risk patients. In patients with the del(5q) karyotype, the development of treatment-related cytopenias correlated with clinical response to lenalidomide. Patients who saw their platelet count decreased by 50% or more during treatment were more likely to achieve transfusion independence than patients who did not (70% versus 42%, respectively; p = 0.01). Similarly, among patients with normal baseline absolute neutrophil count (ANC), those with an ANC decrease of 75% or greater were more likely to achieve transfusion independence than those with an ANC decrease of less than 75% or stable ANC (82% versus 51%, respectively; p = 0.02). This correlation was not observed in non-del(5q) patients, suggesting that a direct cytotoxic effect of lenalidomide on the del(5q) clone results in a positive erythroid response, and that lenalidomide is likely to exert its effects by a different mechanism in non-del(5q) patients.

Le Bras et al. (2009) described the use of lenalidomide in a compassionate use program in France. A total of 95 patients with low- or intermediate-1-risk del(5q) MDS were treated with lenalidomide for 48 weeks. Erythroid response was achieved by 65% of patients, with transfusion independence in 63%. Median time to transfusion independence was 16 weeks and, among patients with del(5q), del(5q) with one abnormality, and del(5q) with more than one abnormality, transfusion independence was achieved by 65%, 54%, and 67%, respectively. The overall survival rate at 16 months was 86%. During the first eight weeks of therapy, grade 3–4 neutropenia and thrombocytopenia occurred in 62% and 25% of patients, respectively, leading to dose reduction in 55% of patients.

Oliva et al. (2009) reported the effects of lenalidomide on QOL in patients with low- or intermediate-1-risk del(5q) MDS. At 12 and 24 weeks, 85% of patients had an erythroid response associated with transfusion independence and significant improvements in hemoglobin level, with 38% of patients achieving a cytogenetic response at 24 weeks. Progressive increases in physical and social QOL also were observed throughout the 24 weeks in responding patients.

Adés et al. (2009) reported data from a phase II study of lenalidomide treatment in 47 patients with intermediate-2- and high-risk del(5q) MDS from transfusion-dependent anemia. Hematologic response was observed in 13 patients (27%), and
12 patients achieved transfusion independence for a median duration of 6.5 months. Most patients who achieved a complete response had isolated del(5q), and none of the patients with more than one additional cytogenetic abnormality responded. These results support a potential role for lenalidomide in the treatment of higher-risk MDS, although it may be ineffective as a single agent in patients with complex cytogenetics.

In a phase II study, Möllgård et al. (2009) investigated the efficacy of lenalidomide monotherapy in 25 patients with high-risk MDS or AML with del(5q) or monosomy 5 who were ineligible for induction therapy or had relapsed or refractory disease. Lenalidomide was administered for 16 weeks at increasing doses from 10 mg to 30 mg, with eight weeks at the highest dose. Overall, seven patients completed 16 weeks of therapy, of which six (86%) had a treatment response. Of the 20 patients who began lenalidomide treatment, 30% had a cytogenetic or bone marrow response. The data demonstrate the efficacy of lenalidomide in patients with MDS and AML with advanced disease and complex karyotypes. Responses may be improved by combining lenalidomide with additional agents.

**Hypomethylating agents:** Azacitidine and decitabine are hypomethylating agents and are considered low-intensity therapies because of their relatively low toxicities. Both are indicated for patients with all five FAB subtypes of MDS: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia, or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia (Celgene Corp., 2008; Eisai, Inc., 2008).

In patients with low- and intermediate-1-risk MDS, azacitidine and decitabine are recommended for patients with serum erythropoietin levels of 500 mU/ml or less and no response to epoetin alfa or darbepoetin alfa, with or without G-CSF; in patients with serum erythropoietin levels of greater than 500 mU/ml and poor probability for response to immunosuppressive therapy; and in patients with thrombocytopenia or neutropenia (NCCN, 2010).

In patients with higher-risk MDS who are unsuitable for high-intensity treatment or ASCT, azacitidine (Silverman et al., 2002, 2006) and decitabine (Kantarjian et al., 2006) have been shown to provide clinical benefits compared with best supportive care. Azacitidine has been shown to prolong survival compared with conventional care in the AZA-001 study (Fenaux, Mufti, et al., 2009), and decitabine is associated with improved time to AML transformation and death, but a survival advantage has not been demonstrated (Kantarjian et al., 2006; Wijermans et al., 2008). Based on the findings from the AZA-001 study, the NCCN guidelines were updated to recommend azacitidine as the preferred agent (category 1) in patients with intermediate-2- or high-risk MDS (NCCN, 2010).

**Azacitidine:** Final results from the AZA-001 trial, a large phase III study comparing azacitidine with conventional care regimens in 358 patients with intermediate-2- or high-risk MDS, were reported by Fenaux, Mufti, et al. (2009). The treating physicians preselected one of three different conventional care interventions (best supportive care, low-dose cytarabine, or intensive chemotherapy) best suited to each patient and then randomized patients to receive azacitidine (n = 179) or conventional care regimens (n = 179). The primary end point was overall survival, which was significantly longer in those treated with azacitidine (24.5 months versus 15 months; p = 0.0001). This marked the first survival benefit reported in higher-risk patients with MDS. Importantly, at two years, 51% of patients treated with azacitidine were alive compared with only 26% in the conventional care group (p < 0.0001). Significantly more patients treated with azacitidine experienced hematologic improvement than patients receiving conventional care (49% versus 29%; p < 0.0001), and a significantly higher proportion of patients in the azacitidine group who were transfusion dependent at baseline achieved transfusion independence (45% versus 11%; p < 0.0001). Peripheral cytopenias were the most common grade 3–4 adverse events, and the most common treatment-related nonhematologic adverse events included injection-site reactions with azacitidine, and nausea, vomiting, fatigue, and diarrhea with azacitidine, low-dose cytarabine, and intensive chemotherapy (Fenaux, Mufti, et al., 2009).

Several subgroup analyses also were presented (Fenaux, Gattermann, et al., 2010; Hellström-Lindberg et al., 2008; List, Fenaux, et al., 2008; Mufti et al., 2008; Santini, Fenaux, Mufti, Hellström-Lindberg, List, et al., 2008; Seymour et al., 2008; Silverman et al., 2008) (see Table 4). These analyses showed that azacitidine improved survival even when patients who achieved complete response were excluded from the analysis, suggesting that complete eradication of the malignant clone is not necessary for prolonged survival and raising the question of whether complete response is a valuable study end point (List, Fenaux, et al., 2008). The analyses also showed that 81% of patients achieved a first response by six cycles, and that the quality of response improved with extended azacitidine therapy, suggesting that continuing azacitidine in the absence of unacceptable toxicity or disease progression may maximize patient benefit (Silverman et al., 2008). The data support the understanding of the role of hypermethylation in patients with MDS and suggest that continued administration of hypomethylating agents, such as azacitidine, likely allows the expression of genes necessary for differentiation and normal hematopoiesis. Fenaux, Gattermann, et al. (2010) conducted an additional analysis of AZA-001, which further compared the outcomes with azacitidine versus low-dose cytarabine, the most widely used low-dose chemotherapy in higher-risk patients who are ineligible for intensive therapy. Of the 94 patients preselected to receive cytarabine, 45 were subsequently randomized to treatment with azacitidine and 49 to low-dose cytarabine. After two years, 54% and 27% of patients treated with azacitidine and cytarabine, respectively, remained alive. The median duration of any hematologic response (complete response, partial response, or hematologic improvement) was significantly longer with azacitidine compared with cytarabine (21 months versus 7 months). Other analyses indicated that azacitidine improved QOL measurements, delayed time to AML evolution, and was effective and well tolerated in specific subpopulations with poor prognosis, such as older adults, who are not good candidates for high-dose therapy (Fenaux, Mufti, et al., 2010; Santini et al., 2009; Seymour et al., 2008) and those with the −7/del(7q) abnormality (Mufti et al., 2008).

A separate study by Itzykson et al. (2009) found that the administration of azacitidine in 45 “fit” older adult patients (older than 80 years) was well tolerated with response rates and toxicity profiles similar to those in younger patients, emphasizing that age alone should not exclude treatment with azacitidine. Miller,
Table 4. Subanalyses From a Phase III Trial Comparing Azacitidine With Conventional Care Regimens in Patients With Higher-Risk Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>MAIN FINDINGS</th>
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<tbody>
<tr>
<td>Fenaux, Gattermann, et al., 2010</td>
<td>The two-year survival rate for azacitidine was 54% versus 27% for low-dose cytarabine. The rate of hematologic response or improvement for azacitidine was 84% versus 37% for low-dose cytarabine. Median duration of any hematologic response or improvement was 21 months for azacitidine versus 7 months for low-dose cytarabine.</td>
</tr>
<tr>
<td>Hellström-Lindberg et al., 2008</td>
<td>The percentage of patients who progressed to AML was similar in both treatment arms (33% with azacitidine versus 31% with CCR), but median time to AML transformation was delayed with azacitidine (26.1 months versus 12.4 months).</td>
</tr>
<tr>
<td>List, Fenaux, et al., 2008</td>
<td>Azacitidine improved survival compared with CCR, even when patients who achieved CR were excluded (hazard ratio for overall survival 0.65; 95% CI 0.48–0.88). The one-year survival rate for patients with CR, partial response, HI, or stable disease was similarly high (97%, 86%, 96%, and 73%, respectively), compared with those who experienced disease progression during azacitidine treatment (29%).</td>
</tr>
<tr>
<td>Mufti et al., 2008</td>
<td>Azacitidine survival benefit was evident in patients with −7/del(7q) (median survival 13.1 months with azacitidine versus 4.6 months with CCR; p = 0.003).</td>
</tr>
<tr>
<td>Santini, Fenaux, Mufti, Hellström-Lindberg, List, et al., 2008</td>
<td>Compared with patients who received CCR, those treated with azacitidine were more likely to achieve transfusion independence (11% versus 45%, respectively) and HI (29% versus 49%) and were less likely to develop an infection requiring IV antimicrobial treatment (relative risk 0.67; 95% CI 0.35–1.2; p = 0.133). The average duration of hospitalization was about seven days per patient-year less in the azacitidine group.</td>
</tr>
<tr>
<td>Seymour et al., 2008</td>
<td>Older adult patients benefited from azacitidine therapy; in patients older than 75 years, the two-year survival rate was 55% with azacitidine versus 15% with CCR (p = 0.0003).</td>
</tr>
<tr>
<td>Silverman et al., 2008</td>
<td>The median number of azacitidine treatment cycles to first response was 3 (range = 1–22). Overall, 81% of patients achieved first response within six cycles, and 90% achieved first response within nine cycles. The first response was the best response in 57% of patients, whereas the remaining 43% had improvement in response after receiving a median of four additional cycles.</td>
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</table>

AML—acute myeloid leukemia; CCR—conventional care regimen; CI—confidence interval; CR—complete response; HI—hematologic improvement

Fenaux, Beach, Gidwani, and Khan (2009) reported that, when compared with decitabine, azacitidine is more cost-effective as a result of its lower cost and greater clinical benefits.

Grövdal et al. (2008) evaluated azacitidine as postchemotherapy maintenance therapy in patients who achieved a complete response following induction chemotherapy. Among the 23 patients treated with azacitidine, the median complete response duration was 13.5 months, and four patients had a complete response duration longer than 24 months (the median overall survival was 20 months). Nine of 10 patients without methylation prior to treatment maintained this status throughout the period of complete remission. Maintenance therapy with azacitidine was well tolerated; side effects included mild rash at the injection site and myelosuppression (grades 1–3) in five patients.

Musto et al. (2010) reported the results of a retrospective analysis of 74 patients with low- or intermediate-1-risk MDS treated with azacitidine. Patients received subcutaneous azacitidine at a dose of 75 mg/m² per day, or at a fixed dose of 100 mg per day for a median of seven courses (range = 1–30). The overall response rate (complete response plus partial response plus hematologic improvement) was 46% (52% in patients who completed at least four cycles of treatment). The most relevant toxicities observed were grade 3–4 myelosuppression (22%) and infections (7%).

At ASH 2008, data were presented on patients from the AVIDA registry with either secondary MDS (Grinblatt et al., 2009a) or high-risk MDS (Grinblatt et al., 2009b). Both studies concluded that the response rates achieved with azacitidine in community-based settings are comparable to those from the AZA-001 trial.

The use of alternative dosing schedules of azacitidine was reported by Lyons, Cosgriff, et al. (2009), who are conducting an ongoing, multicenter, community-based, open-label study. To date, 151 patients with MDS (mostly FAB lower-risk disease) have been randomized to one of the following regimens: (a) azacitidine 75 mg/m² for five days, followed by a two-day break, then 75 mg/m² for two days (the 5-2-2 group); (b) azacitidine 50 mg/m² for five days, followed by a two-day break, then 50 mg/m² for five days (the 5-2-5 group); or (c) azacitidine 75 mg/m² for five days (the 5 group). All regimens produced hematologic improvement (44%, 45%, and 56% of patients, respectively), which was on average similar to the hematologic improvement of 49% achieved with the U.S. Food and Drug Administration (FDA)-approved dosing of azacitidine (75 mg/m² for seven days [of every 28-day cycle]) used in the AZA-001 study (Fenaux, Mufti, et al., 2009). In the Lyons, Larson, et al. (2009) study, the rate of red blood cell transfusion independence was 50%, 55%, and 64% for the three azacitidine doses (all higher than the 45% achieved with FDA-approved dosing [Fenaux, Mufti, et al., 2009]), and the incidence of grade 3–4 adverse events was 84%, 77%, and 58%, respectively. A retrospective analysis of data from a registry of Spanish patients with MDS (N = 144, including about 50% of patients with intermediate-2 or high-risk disease) by García et al. (2009) reported overall response rates (complete response plus marrow complete response plus partial response plus hematologic improvement), which favored the administration of azacitidine 75 mg/m² for seven days (74%) versus the 5-2-2 schedule (65%) or the five-day regimen (58%).
Garcia-Manero et al. (2009) reported a phase I, open-label, dose-escalation study to evaluate oral azacitidine. Forty-five patients with AML or MDS received 75 mg/m² azacitidine subcutaneously for seven days in cycle 1, followed by 120 mg per day orally for seven days in cycle 2. Doses were then increased sequentially with a 3 + 3 design. Dose-limiting toxicity was grade 3–4 diarrhea at 600 mg. Other grade 3–4 adverse events included febrile neutropenia, infection, nausea, vomiting, fatigue, and thrombocytopenia. Responses following six cycles of azacitidine were assessed in 14 patients, with complete response in 29% of patients, stable disease in 43%, disease progression in 21%, and response not assessed in 7%. The data indicate that oral azacitidine is active and well tolerated, with a manageable side-effect profile, in patients with MDS and AML. Evaluation of prolonged and twice-daily treatment is planned.

**Decitabine:** Results of a phase III European study comparing decitabine with best supportive care in patients with higher-risk MDS were presented at ASH 2008 (Wijermans et al., 2008). Decitabine was given as a four-hour IV infusion at a dose of 15 mg/m² every eight hours for the first three days of a six-week cycle, for a maximum of eight cycles. Compared with best supportive care alone, decitabine improved response rates (34% versus 2%) but did not delay death or AML transformation significantly. The main adverse events associated with decitabine therapy are hematologic and gastrointestinal issues.

A multicenter phase II trial was conducted to examine the efficacy and safety of an alternative decitabine dosing regimen in patients with MDS across all FAB classifications. Decitabine administered at a dose of 20 mg/m² IV over one hour once daily for five days every four weeks compared favorably to the three-day regimen. Responses were defined according to the International Working Group 2006 criteria (Cheson et al., 2006). The five-day schedule resulted in overall improvement rates of 51% in patients with de novo MDS, 45% in patients with secondary MDS, and 44% in those who had received prior disease-modifying agents (Steensma, Baer, et al., 2008). Meaningful cytogenetic response was achieved in 52% of patients with any FAB subtype, an IPSS score of 0.5 or greater, abnormal cytogenetics at baseline, and at least one adequate post-baseline cytogenetic result. Of particular note, 53% of the responders had poor-risk cytogenetics at baseline (Godley et al., 2008). The most common grade 3–4 toxicities were cytopenias, with febrile neutropenia (26%) more common in the decitabine arm than among patients receiving supportive care (7%). The five-day dosing schedule also demonstrated efficacy and manageable toxicity in 55 older adult patients (median age = 74 years), in whom the response rate was 26% (24% complete response) (Cashen et al., 2008), and in 13 patients with either high-risk MDS or relapsed AML presenting as MDS, in whom 46% achieved a complete response plus major cytogenetic response (Parovichnikova et al., 2008). A review of four decitabine trials comparing the three-day versus the five-day dosing schedules found comparable overall improvement across all trials, with a trend toward improved outcomes for higher numbers of treatment cycles (Steensma, Kantarjian, & Wijermans, 2009).

An additional multicenter phase II study investigated the efficacy of the decitabine five-day dosing schedule through 24 months in 116 patients with MDS of any IPSS risk category. Iastrebner et al. (2009) reported an overall improvement rate of 35% among the 99 evaluable patients. This included a complete response in 19%, partial response in 4%, hematologic improvement in 8%, and stable disease or better in 50% of patients. Median time to first response and best response was 2.2 and 3.9 months, respectively, and 2% of patients responded after cycle 4.

Geils (2009) reported the results of a subgroup analysis based on data from two decitabine studies (Kantarjian et al., 2006; Steensma et al., 2009) that included older adult patients (aged 65–75 years and older than 75 years) with MDS. The overall response rate (complete response plus marrow complete response plus partial response) was 38% in patients aged 65–75 years and 23% in those older than 75 years. The incidence of grade 3–4 anemia, leukopenia, neutropenia, and thrombocytopenia was lower in patients aged 65–75 versus those older than 75.

Goldberg and Steensma (2009) presented data at ASH 2009 from an analysis of 33 patients with MDS who were treated with decitabine on an outpatient basis in the ADOPT study. A cytogenetic response occurred in 53% of these patients. A hematologic response was noted in 76% of cytogenetic responders compared with 18% of cytogenetic nonresponders (p = 0.003). A cytogenetic response also was associated with a longer duration of hematologic response, increased rates of transfusion independence, and improved survival.

**Azacitidine versus decitabine:** The efficacy of hypomethylating agents in patients with MDS was assessed in a meta-analysis (Kumar, List, Hozo, & Djulbegovic, 2009) of data from four randomized, controlled trials. The analysis revealed that hypomethylating agents improve overall survival, event-free survival, and response rates compared with supportive care alone. In addition, azacitidine was found to provide significantly longer overall survival and higher response rates than decitabine; however, a randomized, controlled trial comparing azacitidine and decitabine is needed to confirm these results. As the process of hypermethylation in MDS is continuous, a need exists to continue therapy until evidence appears of disease progression or unacceptable toxicity (Fenaux, Mufti, et al., 2009).

**Novel Combination Strategies**

The presence of multiple cellular and genetic abnormalities in MDS is common and suggests that combination therapy targeting different mechanisms of action may be beneficial. Several studies have evaluated novel combination treatment strategies (Borthakur et al., 2008; Faderl et al., 2008, 2009; Garcia-Manero et al., 2009; Issa et al., 2008; Kantarjian, Giles, et al., 2008; Lyons, Larson, et al., 2009; Michaelis et al., 2009; Sekeres, List, et al., 2008; Silverman et al., 2009; Voso et al., 2008) (see Table 5).

Sekeres, List, et al. (2008) conducted a phase I trial evaluating lenalidomide plus azacitidine in patients with higher-risk MDS. No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. Various dosing regimens of azacitidine (75 mg/m² on days 1–5 or 50 mg/m² on days 1–5 and 8–12) and lenalidomide (5 mg or 10 mg per day on days 1–14 or 1–21) were investigated. The combination was effective; 12 of 17 (71%) evaluable patients responded, including seven (41%) complete responses, and responses were seen at all dose levels. The investigators recommended a regimen of subcutaneous azacitidine 75 mg/m² on days 1–5 and oral lenalidomide 10 mg...
**Table 5. Novel Treatment Approaches for Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>TREATMENT PLAN</th>
<th>OUTCOME</th>
<th>MAJOR TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA plus gemtuzumab ozogamicin</td>
<td>AZA 75 mg/m² per day for seven days; gemtuzumab ozogamicin 3 mg/m² day 8</td>
<td>OR was 27%</td>
<td>Infections and infusion reactions</td>
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<tr>
<td>(Michaelis et al., 2009)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AZA plus LEN (Sekeres, List, et al., 2008)</td>
<td>Escalating doses of AZA and LEN in 28-day cycles, maximum seven cycles</td>
<td>OR was 71%</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>AZA plus romiplostim (Kantarjian, Giles, et al., 2008)</td>
<td>AZA 75 mg/m² per day SC on days 1–7 of a 28-day cycle; romiplostim 500 mcg or 750 mcg per week SC</td>
<td>Romiplostim improved platelet nadir and reduced thrombocytopenic events and platelet transfusion needs.</td>
<td>Arthralgia, rash, and hypersensitivity reactions</td>
</tr>
<tr>
<td>AZA plus vorinostat (Silverman et al., 2009)</td>
<td>Escalating doses of AZA and vorinostat</td>
<td>OR was 86%</td>
<td>Fatigue and anorexia</td>
</tr>
<tr>
<td>AZA plus VPA plus ATRA (Voso et al., 2008)</td>
<td>AZA 75 mg/m² days 1–7; VPA 600–1,500 mg per day; ATRA 30 mg/m² days 8–27</td>
<td>OR was 30%</td>
<td>Neurologic events</td>
</tr>
<tr>
<td>Oral AZA (Garcia-Manero et al., 2009)</td>
<td>AZA 75 mg/m² SC for seven days in cycle one, AZA 120 mg per day orally for seven days in the second cycle</td>
<td>Complete response in 29% and 43% of patients</td>
<td>Hematologic events, gastrointestinal events, and infection</td>
</tr>
<tr>
<td>Clofarabine (Faderl et al., 2008)</td>
<td>15 mg/m² or 30 mg/m² per day over one hour IV or 40 mg/m² per day orally for five days four to six weeks</td>
<td>OR was 47%</td>
<td>Myelosuppression, neutropenic fever, and acute renal failure</td>
</tr>
<tr>
<td>Clofarabine (Faderl et al., 2009)</td>
<td>40 mg/m² per day orally for five days every four to six weeks</td>
<td>OR was 46%</td>
<td>Myelosuppression, acute renal failure, and infection</td>
</tr>
<tr>
<td>DEC plus gemtuzumab ozogamicin</td>
<td>DEC 20 mg/m² days 1–5; gemtuzumab ozogamicin 3 mg/m² day 5 (also day 15 of first cycle)</td>
<td>OR was 22%</td>
<td>Hematologic events, infections, and infusion reactions</td>
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<tr>
<td>(Borthakur et al., 2008)</td>
<td></td>
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<tr>
<td>DEC with or without VPA (Issa et al., 2008)</td>
<td>DEC 20 mg/m² IV days 1–5 every four weeks with or without VPA 50 mg/kg orally days 1–7</td>
<td>No significant difference in OR (43% versus 52%) or OS</td>
<td>Neurologic events</td>
</tr>
<tr>
<td>LEN plus romiplostim (Lyons, Larson, et al., 2009)</td>
<td>LEN 10 mg daily 28-day cycle; romiplostim 500 mcg or 750 mcg per week SC</td>
<td>Romiplostim improved platelet nadir and reduced thrombocytopenic events and platelet transfusion needs.</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**ATRA—all-trans retinoic acid; AZA—azacitidine; DEC—decitabine; HI—hematologic improvement; LEN—lenalidomide; OR—overall response; OS—overall survival; SC—subcutaneously; SD—stable disease; VPA—valproic acid**

per day on days 1–21 for future study. The most common grade 3–4 adverse event was febrile neutropenia (two patients). No dose reductions occurred from adverse events. Additional studies evaluating sequential administration of azacitidine and lenalidomide are planned (Sekeres, List, et al., 2008).

A phase II study conducted by Lyons, Larson, et al. (2009) assessed a combination of lenalidomide and romiplostim, a thrombopoiesis-stimulating peptibody, in 39 patients with lower-risk MDS. Patients were randomized to four cycles of treatment with placebo, romiplostim 500 mcg, or romiplostim 750 mcg administered once weekly in combination with lenalidomide 10 mg. The incidence of clinically significant thrombocytopenia was lower with romiplostim plus lenalidomide compared with placebo. Platelet counts remained above $50 \times 10^9/L$ for the study duration among patients receiving romiplostim, but not among those in the placebo arm. MDS treatment response was achieved by 8%, 36%, and 15% of patients treated with placebo, romiplostim 500 mcg, and romiplostim 750 mcg, respectively, and was higher among romiplostim-treated patients irrespective of baseline del(5q) status. The incidence of adverse events was similar between treatment groups, although fewer lenalidomide dose reductions and treatment delays from thrombocytopenia occurred in the romiplostim arms.

Kantarjian, Giles, et al. (2008) presented preliminary data on the combination of azacitidine and romiplostim in patients with severely thrombocytopenic lower-risk MDS. This three-arm, randomized, phase II trial evaluated azacitidine alone or in combination with 500 mcg or 750 mcg of weekly romiplostim. The addition of romiplostim to azacitidine reduced the incidence of clinically significant thrombocytopenic events and the need for platelet transfusions, and increased platelet counts. Treatment-related adverse events were reported in two patients in the romiplostim groups and included arthralgia (one patient) and rash and hypersensitivity (one patient each).
Vorinostat (suberoylanilide hydroxamic acid) is an oral histone deacetylase inhibitor that has demonstrated single-agent activity in patients with MDS and AML (Garcia-Manero et al., 2008). Silverman et al. (2009) presented promising results of vorinostat in combination with azacitidine. Various dosing schedules were investigated, including azacitidine given at either 55 mg/m² or 75 mg/m² on days 1–7 plus vorinostat given at 200 mg or 300 mg per day (two or three times daily) for 3, 7, or 14 days. Overall, 18 of 21 (86%) evaluable patients responded, including 53% with complete response, or complete response with incomplete blood count recovery. The median time to response was two treatment cycles. The severity of fatigue was associated with the duration of vorinostat exposure; cumulative fatigue of grade 3 severity occurred after cycle 2. The combination of azacitidine and vorinostat was safe, tolerated in repetitive cycles, and active in patients with lower- and higher-risk MDS and AML. The preliminary data appear promising compared to those achieved with azacitidine or vorinostat alone (Fenaux, Mufti, et al., 2009; Garcia-Manero et al., 2008; Silverman et al., 2002, 2006). A phase II study using an optimized design is planned.

Michaelis et al. (2009) retrospectively analyzed the use of azacitidine plus gemtuzumab ozogamicin in 56 patients with AML or high-risk MDS, either in relapsed or refractory disease or as first-line therapy. Complete response was achieved by 27% of patients, including five patients with poor-risk cytogenetics, with a median overall survival of 40 weeks (range = 9–118 weeks). Grade 3–4 nonhematologic toxicities, primarily infection or infusion reactions, occurred in 50% of patients. The combination of azacitidine and gemtuzumab ozogamicin in these patients is currently under investigation in a prospective trial.

Voso et al. (2008) showed that the combination of azacitidine, valproic acid, and all-trans retinoic acid was well tolerated and active in patients with higher-risk MDS. Of the 27 patients who completed eight cycles of therapy, 8 (30%) had a complete response or partial response, 3 (11%) had major hematologic improvement, and 10 (37%) had stable disease. Neurologic toxicity occurred in six patients.

Decitabine with or without valproic acid was assessed in a randomized, phase II study in patients with AML or MDS (43 of 76 patients had intermediate-1-, intermediate-2-, or high-risk MDS) (Issa et al., 2008). In a preliminary analysis, response and survival rates were similar in both treatment arms. The addition of valproic acid was associated with neurologic toxicity, including somnolence and confusion.

Borthakur et al. (2008) conducted a phase II trial evaluating the combination of decitabine and the anti-CD33 antibody gemtuzumab ozogamicin in patients with higher-risk MDS or AML. Significant grade 3–4 cytopenias, infections, and infusion-related reactions were reported. This combination showed promising activity, particularly in less-heavily pretreated patients with higher-risk MDS.

**Clofarabine:** Clofarabine is an adenosine nucleoside analog that inhibits DNA synthesis and repair and induces apoptosis and other anticancer mechanisms. Responses have been observed after treatment with clofarabine in heavily pretreated, relapsed, or refractory patients with acute lymphoblastic leukemia, AML, and high-risk MDS (Korycka, Lech-Marada, & Robak, 2008). Faderl et al. (2008) reported phase II data in patients with higher-risk MDS. Of the 61 patients receiving varying doses of IV or oral clofarabine, 42 (69%) had intermediate-2- or high-risk MDS and 39 (64%) had failed prior therapy with a hypomethylating agent. The overall response rate was 47%, including a complete response rate of 30%. Myelosuppression and neutropenic fever requiring hospitalization were common in patients treated with clofarabine, but prolonged myelosuppression lasting beyond 42 days was rare. Common nonhematologic adverse events were nausea, vomiting, skin rash, hyperbilirubinemia, and transaminase elevations, but these were rare at grade 3 or higher. Acute renal failure occurred in seven patients.

A second phase II study by Faderl et al. (2009) reported the efficacy of oral clofarabine in 31 patients with intermediate-2- or high-risk MDS. The starting dose of oral clofarabine was 40 mg/m² per day for five days every four to six weeks (n = 6), but was first reduced to 30 mg/m² per day orally for five days (n = 19) and then to 20 mg/m² per day for five days (n = 7) because of toxicities. Patients who had previously failed therapy with hypomethylating agents had lower response rates to clofarabine treatment. Optimal doses and schedules to balance the activity and toxicity of clofarabine need to be determined.

**Supportive Care**

Many patients with IPSS low-risk disease do not succumb to AML transformation but, rather, suffer from complications of cytopenias, iron overload, or treatment-related toxicities (Gardin & Fenaux, 2004). These effects contribute to the overall burden of MDS, even in patients with a good prognosis. Therefore, supportive care in patients with MDS is increasingly important. Supportive care includes clinical monitoring, psychosocial support, QOL assessment, transfusions, antibiotics, bleeding prophylaxis, iron chelation therapy, and growth factor support for cytopenias (NCCN, 2010). Treatment for anemia may require chronic blood transfusions, which increase the risk of developing iron overload (Cazzola & Malcovati, 2005). Intensive therapy may lead to additional complications, including additional myelosuppression and neurologic effects (Nimer, 2008).

In a national survey of 290 newly diagnosed patients with MDS, 58% received supportive care, including ESAs (43%), antibiotics (16%), growth factors (12%), and iron chelation therapy (1%) (Van Bennekom, Abel, Anderson, Stone, & Kaufman, 2008). In an analysis of Medicare data, 46% of patients with MDS received transfusions, 45% received growth factor support, and 2% received iron chelation therapy during the three-year study period (Goldberg et al., 2008).

**Anemia and iron overload:** Anemia may be successfully managed with ESAs in some patients with MDS, but most patients will become transfusion dependent because of ineffective erythropoiesis. Chronic red blood cell transfusions can lead to iron accumulation in the heart, liver, and other tissues. Symptoms often go unnoticed and may not be evident until the patient has developed serious organ damage and secondary symptoms of heart failure, hepatic failure, endocrinopathies, and bone marrow suppression. Transfusion dependency and the development of iron overload are strong independent predictors for decreased survival and increased AML transformation (Sanz et al., 2008). Therefore, iron chelation therapy is an important component of supportive care for patients with transfusion-dependent MDS. The availability of an oral iron chelator, such as
deferasirox, is a major advance in this setting. At ASH 2008, List, Baer, et al. (2008) presented 12-month data from a phase II trial of heavily iron-overloaded patients with low- and intermediate-1-risk MDS that confirmed that deferasirox effectively reduces iron overload and is well tolerated. Rose et al. (2010) reported that, over 2.5 years, iron chelation therapy leads to significantly improved overall survival in regularly transfused patients with low- or intermediate-1-risk MDS (median overall survival = 124 months versus 53 months without iron chelation therapy; p < 0.0003). Despite the proven benefits of iron chelation therapy, less than 60% of patients with MDS with indications for iron chelation therapy receive it (Raptis et al., 2008). This highlights the importance of providing adequate supportive care for patients with MDS. Monitoring serum ferritin levels and the total number of transfusions are essential variables to consider when implementing iron chelation therapy. In addition, the use of deferasirox requires close monitoring of certain kidney and liver laboratory parameters, as it could lead to renal or hepatic impairment or failure and could cause gastrointestinal hemorrhage, which could be fatal in certain patients, such as older adults and those with high-risk MDS with underlying renal or hepatic impairment or low platelet counts (Novartis Pharmaceuticals, 2010). The incidence of iron overload is most common after transfusion of 20 units of packed red blood cells.

**Nonhematologic comorbidities:** MDS is most common in older adults with a higher incidence of nonhematologic comorbidities. A study of 1,344 patients with MDS by Della Porta et al. (2008) found the incidence of nonhematologic comorbidities to be 54%, with cardiac disease being the most common (25%) and the leading cause of nonleukemic death. The onset of a comorbidity significantly affected the risk of nonleukemic death (hazard ratio [HR] = 4.31; p < 0.001) and cardiac disease (HR = 4.16) and death (HR = 4.88; p < 0.001 for both). Serum ferritin levels in this group were significantly related to the risk of cardiac disease and death (p = 0.001). Onset of cardiac, liver, and renal complications; pulmonary disease; and solid tumor were found to independently affect the risk of nonleukemic death. Complete evaluation of comorbidities, initiation of active therapies for MDS to minimize transfusion burden, and intervention for iron overload may reduce the incidence of nonleukemic death.

**Fatigue:** The impact of fatigue in patients with MDS was highlighted by Steensma, Heptinstall, et al. (2008) through the development of an Internet-based QOL survey for patients with MDS. Patients reported excessive fatigue and had poor scores on the Functional Assessment of Cancer Therapy–Anemia and the Brief Fatigue Inventory. Fatigue correlated poorly with hemoglobin levels but was associated with impairment in health-related QOL and inability to work or participate in activities. Comprehensive evaluation of each patient with MDS, including anemia, pain, sleep disturbances, and emotional distress or depression, may identify factors contributing to fatigue.

**Treatment-Related Adverse Effects**

The side effects of lenalidomide have been well characterized and include myelosuppression (neutropenia and thrombocytopenia), rash, diarrhea, fatigue, and venous thromboembolism (Kurtin & Sokol, 2006). Practical recommendations regarding the use of lenalidomide, specifically in patients with MDS, were reported in Giagounidis et al. (2008). In most cases, neutropenia and thrombocytopenia may be managed with lenalidomide dose reductions or delays (Giagounidis et al., 2008). Thromboembolism is much less common in patients with MDS (Brandenburg et al., 2008) than in those with multiple myeloma, for which lenalidomide is administered concurrently with dexamethasone. Therefore, if no antecedents of venous thromboembolism exist, thromboprophylaxis in patients with MDS is not recommended (Giagounidis et al., 2008).

The most common adverse events associated with hypomethylating agents are injection-site reactions, gastrointestinal events, and hematologic events (Demakos & Linebaugh, 2005). In a phase III trial evaluating azacitidine, most adverse events were transient (median duration = 13 days), were not serious, and resolved during the study (Santini, Fenaux, Mufti, Hellström-Lindberg, Silverman, et al., 2008). Less than 1% of adverse events required discontinuation of azacitidine therapy and were managed with treatment delays, medication, transfusions, or other measures. Injection-site reactions persisted for a median of 12 days, and less than 15% of patients required medical treatment (e.g., corticosteroids and/or antihistamines). Diarrhea, nausea, and vomiting lasted for a median of 1–4 days, and constipation lasted about one week. These events were effectively managed with antiemetics and laxatives. Grade 3–4 hematologic events typically occurred during the first one or two cycles, and less than 10% of patients required hospitalization. Hematologic events were managed primarily with treatment delays or transfusions for anemia or thrombocytopenia. The proactive management of potential adverse events is important to prevent early discontinuation or dose reductions of azacitidine and to ensure optimal treatment benefit.

The use of 5-HT₃ antagonists is recommended for the management of nausea and vomiting (NCCN, 2009). A preventive bowel regimen including a stool softener and a mild laxative will reduce constipation. Aggressive management is particularly important in patients with thrombocytopenia to reduce the risk of rectal bleeding. Subcutaneous injection-site reactions can vary greatly from patient to patient. The authors of this article strongly recommend rotating the injection site for each subcutaneous injection to the lateral and posterior aspects of the upper arm or thigh, or the abdomen (fatty tissue). If multiple injection sites are used daily, separate the injection sites by at least one inch. General local erythema can be diminished by applying corticosteroids and antihistamines topically for pruritus. Administration of growth factors for neutropenia effectively reduces the incidence of neutropenic fever (NCCN, 2010). The authors of this article recommend that growth factors be administered 24 hours after the administration of demethylating agents because of their cytotoxic effect.

Optimal response may require several months of treatment with novel agents. Myelosuppression is an expected effect of all active therapies for MDS. Therefore, the aggressive management of cytopenias, particularly during the initial cycles of treatment, is essential to continue treatment long enough to achieve the best outcome (Kurtin & List, 2009). Careful monitoring of blood counts, particularly in the first 8–12 weeks of therapy, allows for early intervention, prevents more serious adverse events, and reduces the need for premature discontinuation. A system for monitoring blood counts, including documentation and a
dedicated discussion among the healthcare provider, nurse, and the patient to review the findings and any recommendations for interventions, is the best strategy. Reviewing signs and symptoms with the patient and his or her support network will allow prompt intervention and reduce the risk of hospitalization or treatment discontinuation.

Patient and family education, including a clear discussion of the expected disease trajectory, the role of supportive care, options for active therapies based on risk stratification, and anticipated toxicities, will enable the patient to make informed treatment decisions.

An online survey of 300 patients with MDS reported by Sekeres et al. (2009) found that the majority of patients had abnormal blood counts for many years prior to the MDS diagnosis. Terminology used to describe the diagnosis varied widely, with “bone marrow disorder” being a common description (80%). The term “cancer” was used in only 7% of the cases. Few patients were aware of their IPSS risk category. MDS is a difficult disease to understand, so use of patient education materials provided by organizations such as the MDS Foundation, which use patient-friendly language and illustrations to describe the bone marrow, peripheral blood cells, and their function, and the abnormalities associated with the disease and its treatment, can facilitate discussion. Several patient information Web sites are available through reputable groups such as the MDS Foundation (www.mds-foundation.org) and the Leukemia and Lymphoma Society (www.leukemia.org). Patient-specific information on individual agents or supportive care can be found on Web sites dedicated to individual products.

Conclusions

Scientific and medical advances in active therapies and supportive care for MDS provide hope for patients and their caregivers. Key advances include oral iron chelation therapy, lenalidomide for del(5q) low- or intermediate-1-risk disease, and azacitidine and decitabine for patients with higher-risk disease. Data on the use of these agents in different populations, different schedules, and novel combinations also are promising. New data on the use of iron chelation therapy and ESAs underscore the importance of providing adequate supportive care to patients with MDS. Vigilant clinical assessment by the oncology nursing professional is crucial to preventing unnecessary dose reductions, dose delays, early discontinuation of therapy, or increases in morbidity and mortality. The “right recipe” for patient care includes proactive and precise nursing assessment skills, multidisciplinary collaboration, and a strong commitment to enhancing the lives of patients and their families. Specific consideration for older adult patients is essential. Combining evolving scientific breakthroughs with complementary nursing management strategies offers the best opportunity for favorable patient outcomes.

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