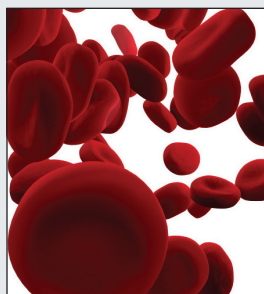


■ Article

# Treatment of Myelodysplastic Syndromes: Practical Tools for Effective Management

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Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies with variability in clinical presentation, disease trajectory, treatment goals, and expected outcomes. The treatment of patients with MDS, therefore, often differs from patient to patient. Tools are needed to aid effective communication with patients, their caregivers, and their dedicated team of healthcare professionals. The use of methods often employed in clinical trials can help healthcare providers diagnose and classify risk status, track trends within patient responses, manage adverse events, set treatment expectations, and provide ongoing supportive care. This article discusses several tools and strategies available for the management of patients with MDS throughout the continuum of their disease.

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**T**he variability in clinical presentation, disease trajectory, prognosis, and treatment recommendations make myelodysplastic syndromes (MDS) a complicated diagnosis for healthcare professionals and patients alike (Kurtin & Demakos, 2010). MDS are characterized by ineffective hematopoiesis, progressive bone marrow failure, and a variable risk of leukemic transformation thought to result from complex interactions between the malignant clone and the bone marrow microenvironment (Kurtin, 2011b).

Clarity in the information provided to the patient and caregivers is critical to optimal treatment outcomes. In particular, early identification of adverse events with prompt intervention may reduce their severity, potentially improving clinical outcomes and patient quality of life (QOL). Consistent descriptions should be given of what the diagnosis of MDS implies (myeloid malignancy), what treatments are available, when to start treatment (treatment triggers), the goals of therapy including the expected duration of therapy, anticipated side effects and how they will be managed, and how the patient and caregiver can

take active roles in tracking the patient's progress. Practical tools and strategies for clinical management of patients newly diagnosed with MDS are described, including patient and family education throughout the disease continuum.

The peak incidence for MDS is in the seventh and eighth decades of life, with a median age of 76 years at diagnosis (Kurtin & Demakos, 2010; Sekeres et al., 2011). Older adults represent a heterogeneous group that has a wide variability in a number of attributes (e.g., physiologic function, cultural, sociologic, economic) that may affect treatment decisions (Kurtin, 2010). Comorbidities are common in older adults and may affect treatment tolerance and prognosis (Naqvi et al., 2011). Given the heterogeneity of the disease and the heterogeneity of the older adult population, strategies that allow for individualized, risk-adapted treatment selection will provide the best outcomes (Kurtin, 2010). With a limited potential for cure, preservation of QOL and independent function should remain a priority. Careful consideration of the patient and disease-related factors, including the expectations and

wishes of the patient, are necessary to empower the patient to become an active participant in their care.

## Diagnostic Evaluation and Disease Classification

A typical patient with MDS will be an older adult presenting with symptoms related to underlying cytopenias, such as fatigue, exertional dyspnea, recurrent infections, unexplained bruising, or bleeding (Catenacci & Schiller, 2005; Kurtin & Demakos, 2010). Many patients are asymptomatic and are found to have abnormal blood counts on routine evaluation. Other explanations for presenting cytopenias, particularly anemia, must be excluded during the differential diagnosis (Kurtin, 2011a). This process may require several weeks to months depending on the vigilance of the provider in investigating potential

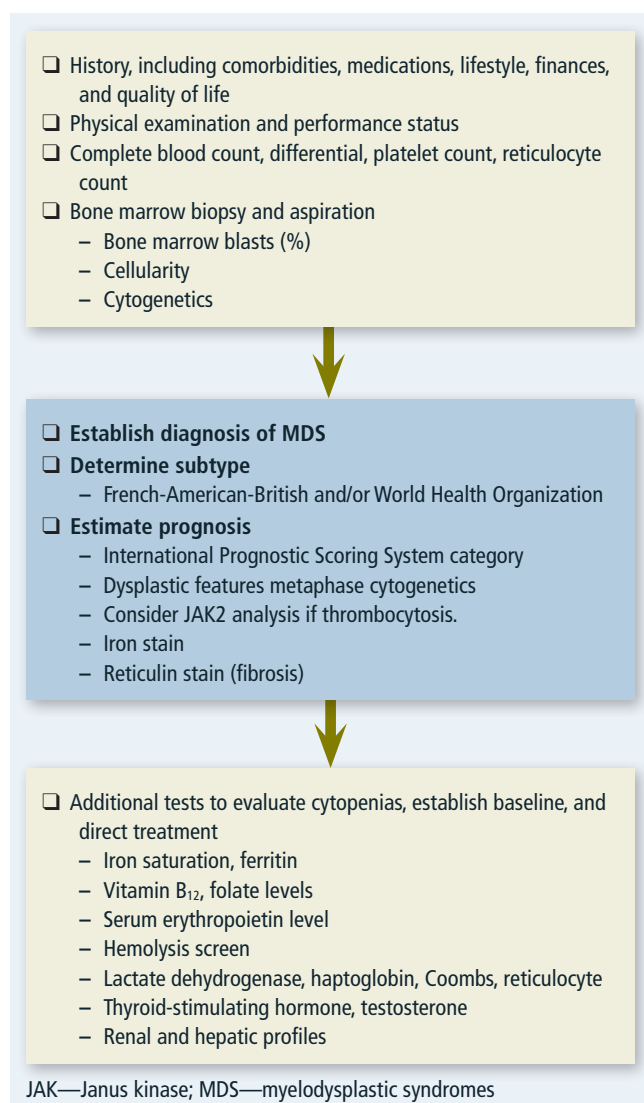
causes of cytopenias and the presence or absence of their associated symptoms. Given the older age of most patients, the presence of anemia is often attributed to more benign etiology (Price, Mehra, Holmes, & Schrier, 2011).

A bone marrow biopsy and aspirate are required to obtain the tissue diagnosis and estimate prognosis with the hallmark findings of dysplasia, one or more cytopenias, blasts (variable percentage), and the presence or absence of cytogenetic abnormalities (Kurtin, 2011). Epidemiologic trends project a rise in the prevalence of MDS—thought to be a result of the aging general population, increased diagnostic evaluation of older patients presenting with cytopenias, inclusion of MDS in the differential diagnosis of cytopenias in older adult patients, the availability of treatment, increasing familiarity with the morphologic characteristics of MDS by hematopathologists, and secondary or treatment-related MDS (Kurtin, 2010, 2011a). The results of the diagnostic evaluation are necessary to establish an MDS diagnosis, classify the disease, and assign a risk category (see Figure 1).

The French-American-British classification system was originally used for acute myeloid leukemia (AML) and was later expanded to provide the first categorization of MDS (Komrokji, Zhang, & Bennett, 2010). The International Prognostic Staging System (IPSS) was later developed to address expected overall survival and risk of leukemic transformation. In 1999, elements of the IPSS and French-American-British classification systems as well as developments in diagnostic morphology were used to develop the World Health Organization classification system. The IPSS was developed before the availability of active therapies and assigns a risk category based on the number of cytopenias and cytogenetic abnormalities and the percentage of bone marrow blasts (Greenberg et al., 1997). The score correlates with one of four risk groups (low, intermediate-1, intermediate-2, and high), each with projected median survival and risk of leukemic transformation (see Table 1).

Although the IPSS has provided a critical model for risk stratification, applicability is limited to only at the time of the original diagnosis and does not incorporate more recent disease characteristics found to correlate with prognosis. A revised IPSS (IPSS-R) is being developed and will include additional risk factors, including hemoglobin level, depth of cytopenias (thrombocytopenia in particular), revised cytogenetic risk groups, and lactate dehydrogenase. It also will add a fifth risk category (Greenberg et al., 2011). The International Working Group for Prognosis in Myelodysplastic Syndromes (IWG-PM) continues to refine the specific criteria for the IPSS-R, including assignment of scores and the final attributes of each risk category.

Discussions have taken place on the unique needs of older adults with MDS, including comorbidities and refinement of supportive care strategies. However, MDS remains a rare disease most common in older patients who often have one or more comorbid conditions, may have limited caregiver support, and often face financial limitations relative to health-care services (Kurtin, 2010). Age alone, however, should not determine treatment eligibility. Treatment selection should be based on the individual disease and patient characteristics (in addition to age), the goals of therapy based on this analysis, and the common adverse events documented in clinical trials, with consideration of how these may affect the individual patient.



**FIGURE 1. Checklist of Diagnostic Evaluations for MDS**

*Note.* From "Current Approaches to the Diagnosis and Management of Myelodysplastic Syndromes," by S. Kurtin, 2011, *Journal of the Advanced Practitioner in Oncology*, 2(Suppl. 2), p. 11. Copyright 2011 by Harborside Press. Reprinted with permission.

Patient assessment remains as much an art as a science. Various assessment strategies and methods are conducted across the continuum of care for patients with MDS by members of the multidisciplinary team (e.g., physicians, nurses, specialized geriatric teams, case managers, social workers). The types of assessment will range from unaided judgment to formal assessment protocols and tools, with data sources that include interviewing the patient or family, reviewing the

patient hospital record, or eliciting information from other care providers.

## Treatment Selection, Triggers, and Goals

Three active agents are available for the treatment of MDS, with variable availability depending on the specific global region. Azacitidine, in May 2004, became the first U.S. Food and

**TABLE 1. Risk Stratification of Myelodysplastic Syndromes: IPSS and Proposed Revisions With Survival and Risk of AML Transformation**

| IPSS Risk Categories <sup>a</sup>                                                                                                                                                                                                                                     |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------|--------------------------|--------------------------------|
| Item                                                                                                                                                                                                                                                                  | Score                                                                                                                                                         |                                                                                  |                                                                                                          |                             |                          |                                |
|                                                                                                                                                                                                                                                                       | 0                                                                                                                                                             | 0.5                                                                              | 1                                                                                                        | 1.5                         | 2                        |                                |
| Bone marrow myeloblasts                                                                                                                                                                                                                                               | < 5%                                                                                                                                                          | 5%–10%                                                                           | 5%–10%                                                                                                   | 11%–20%                     | 21%–30% (considered AML) |                                |
| Karyotype                                                                                                                                                                                                                                                             | Normal, del(5q), del(Y), del(20q) as sole abnormality                                                                                                         | Other abnormality                                                                | 7+, del(7), or three or more abnormalities                                                               | –                           | –                        |                                |
| Number of cytopenias                                                                                                                                                                                                                                                  | 0, 1                                                                                                                                                          | 2, 3                                                                             | Anemia (Hgb < 10 g/dl), neutropenia (ANC < 1,800 mcl), and/or thrombocytopenia (platelets < 100,000 mcl) |                             |                          |                                |
| IPSS and Proposed IPSS-R <sup>b</sup> Risk Categories                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| IPSS (N = 816)                                                                                                                                                                                                                                                        |                                                                                                                                                               |                                                                                  |                                                                                                          | Proposed IPSS-R (N = 4,417) |                          |                                |
| Risk Category                                                                                                                                                                                                                                                         | Score                                                                                                                                                         | Median OS (Years)                                                                | Evolution to AML (25%) (Years)                                                                           | Risk Category               | Median OS                | Evolution to AML (25%) (Years) |
| Low                                                                                                                                                                                                                                                                   | 0                                                                                                                                                             | 5.7                                                                              | 9.4                                                                                                      | Very low                    | 6.8                      | N/R                            |
| Intermediate-1                                                                                                                                                                                                                                                        | 0.5–1                                                                                                                                                         | 3.5                                                                              | 3.3                                                                                                      | Low                         | 4.3                      | 10.1                           |
| Intermediate-2                                                                                                                                                                                                                                                        | 1.5–2                                                                                                                                                         | 1.2                                                                              | 1.1                                                                                                      | Intermediate                | 2.3                      | 2.8                            |
| High                                                                                                                                                                                                                                                                  | ≥ 2.5                                                                                                                                                         | 0.4                                                                              | 0.2                                                                                                      | High                        | 1.5                      | 1.2                            |
|                                                                                                                                                                                                                                                                       |                                                                                                                                                               |                                                                                  |                                                                                                          | Very high                   | 0.9                      | 0.7                            |
| Summary of Proposed Revisions for IPSS-R Scoring <sup>b,c</sup>                                                                                                                                                                                                       |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| Attributes                                                                                                                                                                                                                                                            |                                                                                                                                                               | Diagnostic Findings                                                              |                                                                                                          |                             |                          |                                |
| <b>Karyotype</b>                                                                                                                                                                                                                                                      |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| Very good                                                                                                                                                                                                                                                             | Del(11q), –Y                                                                                                                                                  |                                                                                  |                                                                                                          |                             |                          |                                |
| Good                                                                                                                                                                                                                                                                  | Normal, del(5q), del(12p), del(20q), double including del(5q)                                                                                                 |                                                                                  |                                                                                                          |                             |                          |                                |
| Intermediate                                                                                                                                                                                                                                                          | +8, i(17q), +19, +21, any other single, any other double, independent clones der(3)(q21)/der(3)(q26), double including, –7/7q–, complex (three abnormalities) |                                                                                  |                                                                                                          |                             |                          |                                |
| Poor                                                                                                                                                                                                                                                                  |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| Very poor                                                                                                                                                                                                                                                             | Complex (more than three abnormalities)                                                                                                                       |                                                                                  |                                                                                                          |                             |                          |                                |
| Cytopenias associated with adverse risk                                                                                                                                                                                                                               |                                                                                                                                                               | Thrombocytopenia at presentation, anemia with high transfusion burden            |                                                                                                          |                             |                          |                                |
| Other factors considered in OS                                                                                                                                                                                                                                        |                                                                                                                                                               | Elevated lactate dehydrogenase level, elevated ferritin level, comorbidity score |                                                                                                          |                             |                          |                                |
| <sup>a</sup> Use before active therapies to determine prognostic outcome. Based on information from Greenberg et al., 1997.                                                                                                                                           |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| <sup>b</sup> The IPSS-R is still being modified by the International Working Group for Prognosis in Myelodysplastic Syndromes, including assignment of scores and final attributes of each risk category.                                                             |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| <sup>c</sup> The IPSS-R is designed to be used at any point during the course of the disease. Based on information from Greenberg et al., 2011.                                                                                                                       |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| AML—acute myeloid leukemia; ANC—absolute neutrophil count; der—derivative; Hgb—hemoglobin; i—inversion; IPSS—International Prognostic Scoring System; IPSS-R—International Prognostic Scoring System—Revised; N/R—not reached; OS—overall survival                    |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |
| <i>Note.</i> From “Current Approaches to the Diagnosis and Management of Myelodysplastic Syndromes,” by S. Kurtin, 2011, <i>Journal of the Advanced Practitioner in Oncology</i> , 2(Suppl. 2), p. 12. Copyright 2011 by Harborside Press. Reprinted with permission. |                                                                                                                                                               |                                                                                  |                                                                                                          |                             |                          |                                |

Drug Administration (FDA)-approved therapy for MDS (Celgene Corporation, 2011). Azacitidine was shown to provide a survival advantage when compared with three commonly used approaches for treatment of high-risk MDS, including standard leukemia induction chemotherapy, low-dose cytarabine, or best supportive care (Fenaux, Mufti, et al., 2009). Azacitidine has now been approved in a number of other countries based on the safety and efficacy data. Two additional compounds, lenalidomide (approved by the FDA in December 2005) and decitabine (approved by the FDA in May 2006), have shown benefit in disease response, including hematologic improvements and transfusion independence, but no survival benefit has been noted to date in reported trials for either drug (Celgene Corporation, 2009; Fenaux, Giagounidis, et al., 2009; Kantarjian et al., 2006; List et al., 2006; Lubbert et al., 2011; SuperGen, Inc., 2010). Use of lenalidomide and decitabine outside of the United States is restricted to clinical trials or specialty access programs. Each of these treatments has distinct characteristics, including therapeutic targets, mode of administration, and associated adverse events (see Table 2).

Treatment selection is based on several factors: the characteristics of the individual patient, including comorbidities, performance status, lifestyle, finances, and QOL; characteristics of the disease, including IPSS risk category and individual disease characteristics; and currently available treatment options (Kurtin, 2011a). Patients with low- or intermediate-1-risk disease have a more favorable prognosis and may not require immediate intervention. Indications for treatment in those patients include progressive or symptomatic cytopenias, transfusion dependence, or other indications of disease progression, such as a rising blast count.

Transfusion dependence is inevitable for most patients with MDS (because of ineffective erythropoiesis), and is known to be associated with iron overload (Hershko, 2005; Kurtin, 2007). The World Health Organization's Prognostic Scoring System and the MD Anderson Cancer Center Scoring System for MDS include transfusion burden or a history of transfusion as an unfavorable prognostic indicator in patients with MDS (Garcia-Manero, 2010; Greenberg et al., 2011; Komrokji, Sekeres, & List, 2011). Tracking of serial serum ferritin levels in

**TABLE 2. Currently Available Active Therapies for MDS**

| Variable                            | Azacitidine                                                                                                                                                                                          | Decitabine                                                                                                                                                | Lenalidomide                                                                                                                                                                                             |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Indication                          | All French-American-British classification system subtypes                                                                                                                                           | IPSS-defined int-1 and -2, high risk, and tMDS                                                                                                            | Transfusion dependent MDS, including low, int-1 with del(5q) with or without additional chromosomal abnormalities                                                                                        |
| Therapeutic target and sensitivity  | DNA methyltransferase inhibitor that alters RNA and DNA methylation as well as affects proteins and microenvironment<br>No data on use following decitabine failures                                 | DNA-specific DNA methyltransferase inhibitor with direct cytotoxic effect<br>May be effective in patients previously treated with azacitidine             | IMiD® immunomodulatory agent<br>Del(5q): direct cytotoxic effect on clone; most effective in these patients (MDS-003)<br>Non-del(5q): alters tumor microenvironment; activity demonstrated (MDS-002)     |
| Mode of use and duration of therapy | Subcutaneous or IV × seven days per 28-day cycle<br>Outpatient regimen<br>Treat until unacceptable toxicity or progressive disease                                                                   | IV × five days for one hour per 28-day cycle<br>Outpatient regimen<br>Treat until unacceptable toxicity or progressive disease                            | Oral, 10 mg, days 1–21 per 28-day cycle<br>Outpatient regimen<br>Treat until unacceptable toxicity or progressive disease                                                                                |
| Common adverse events               | Myelosuppression, injection site reactions, nausea and vomiting, and constipation<br>Contraindicated in patients with hepatic tumors<br>Use with caution in renal impairment<br>May cause fetal harm | Myelosuppression, nausea and vomiting, constipation, and hyperbilirubinemia<br>Use with caution in patients with renal impairment<br>May cause fetal harm | Myelosuppression, rash, and diarrhea<br>Dose adjustment for patients with renal impairment<br>Must be prescribed through RevAssist® program because it is an analog of thalidomide, which is a teratogen |
| Key clinical trial outcomes         | AZA-001 (Silverman et al., 2011)                                                                                                                                                                     | ADOPT (Steensma et al., 2009)                                                                                                                             | MDS-003 (List et al., 2006)                                                                                                                                                                              |
| Primary endpoints met               | Improved overall survival (seven-day dosing), hematologic improvement (trilineage), transfusion independence, cytogenetic response, and safety and efficacy                                          | Hematologic improvement, transfusion independence, cytogenetic response, safety and efficacy                                                              | Hematologic improvement, transfusion independence, cytogenetic response, safety and efficacy                                                                                                             |
| Median time to response             | First: two cycles<br>Best: 92% by 12 cycles<br>From first to best: three cycles                                                                                                                      | First: 1.7 months<br>Best: 54% within first two cycles                                                                                                    | MDS-003 (del[5q])<br>First: 4.7 weeks<br>Time to transfusion independence: 4.6 weeks                                                                                                                     |

ADOPT—Alternative Dosing for Outpatient Treatment; int—intermediate; IPSS—International Prognostic Scoring System; MDS—myelodysplastic syndromes; tMDS—treatment-related MDS

Note. From "Current Approaches to the Diagnosis and Management of Myelodysplastic Syndromes," by S. Kurtin, 2011, *Journal of the Advanced Practitioner in Oncology*, 2(Suppl. 2), p. 13. Copyright 2011 by Harborside Press. Reprinted with permission.

Name: \_\_\_\_\_ Gender: M / F Patient Identification Number: \_\_\_\_\_

Date of Birth: \_\_\_\_\_ Blast (%): \_\_\_\_\_ Cytogenetics: \_\_\_\_\_

Initial Diagnosis: \_\_\_\_\_ IPSS Score: low / intermediate-1 / intermediate-2 / high

Date of First Transfusion/Number of Lifetime Transfusions: \_\_\_\_\_

| Date of<br>transfusion | Days or weeks since<br>last transfusion | Number of units<br>transfused | Total number<br>of transfusions | Transfusion<br>complications | Serum ferritin<br>(mcg/L) | Hemoglobin<br>(g/dl) | WBC and ANC<br>(cells/mcl) | Platelets/mcl |
|------------------------|-----------------------------------------|-------------------------------|---------------------------------|------------------------------|---------------------------|----------------------|----------------------------|---------------|
|                        |                                         |                               |                                 |                              |                           |                      |                            |               |
|                        |                                         |                               |                                 |                              |                           |                      |                            |               |
|                        |                                         |                               |                                 |                              |                           |                      |                            |               |
|                        |                                         |                               |                                 |                              |                           |                      |                            |               |

| Date | Other Therapies | Notes |
|------|-----------------|-------|
|      |                 |       |

| Date | Other Therapies | Notes |
|------|-----------------|-------|
|      |                 |       |

| Date | Other Therapies | Notes |
|------|-----------------|-------|
|      |                 |       |

ANC—absolute neutrophil count; IPSS—International Prognostic Staging System; WBC—white blood cell

FIGURE 2. Myelodysplastic Syndromes Transfusion Tracker

Note. Courtesy of MDS Foundation and Celgene Corporation. Reprinted with permission. Available at <http://cjon.sup.mds-foundation.org>.

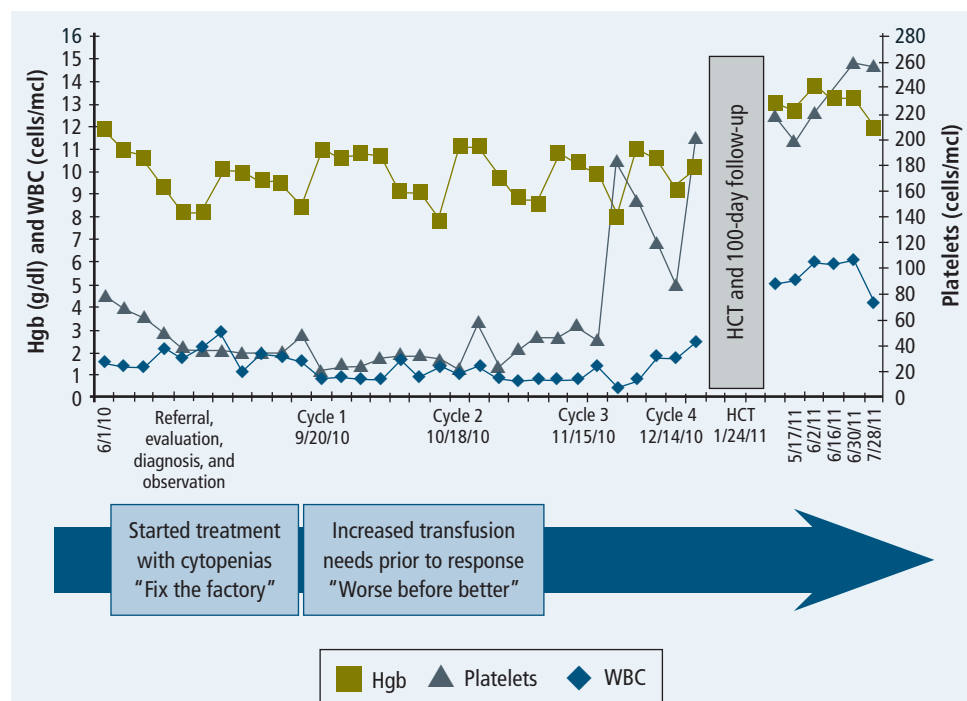
transfusion-dependent patients is the most common strategy for monitoring iron overload, which has been suggested as a poor prognostic indicator in some prognostic models (Greenberg et al., 2011; Kurtin & Demakos, 2010; Malcovati et al., 2005). Some debate remains on the etiology of inferior survival in transfusion-dependent patients or patients with elevated serum ferritin levels; however, transfusion dependence is recognized as an

indication to initiate treatment (Greenberg et al., 2011; Harvey, 2010; National Comprehensive Cancer Network [NCCN], 2011b; Pullarkat, 2009). Transfusion dependence also is associated with lower health-related QOL (Jansen et al., 2003; Oliva et al., 2001; Spiriti et al., 2005).

Achievement of transfusion independence is a common clinical trial endpoint and is included in the IWG criteria for

complete hematologic response (Cheson et al., 2006). A reduction in the number of transfusions in an eight-week period (hematologic improvement as defined by the IWG criteria) may be the first indication of response to treatment. Therefore, implementation of a system for tracking transfusions in individual patients will provide a practical tool for identifying treatment triggers and response to therapy. Patients may have laboratory evaluations, clinical visits, and blood transfusions performed in three or more different settings. Providing patients and their caregivers with tracking tools that can be updated and taken to any clinical setting or provider will empower patients to take an active role in their care and will assist each provider in review of recent trends (see Figure 2).

Additional treatment triggers include progressive or symptomatic cytopenias thought to indicate ineffective hematopoiesis. Patients with a hemoglobin of less than 10 g/dl and platelet counts less than 50,000 mcl have been shown to have inferior survival and lower health-related QOL (Garcia-Manero, 2010; Kurtin & Demakos, 2011). Transfusion remains the primary strategy for the treatment of anemia and thrombocytopenia; although the criteria for transfusions vary by region and country, these patients generally require more frequent monitoring. Many patients function very well with moderate but asymptomatic cytopenias; therefore, evaluating not only the laboratory indicators but also patient symptoms is critical. Consideration of comorbidities is also required because many patients with underlying heart disease or those who require anticoagulation therapy will require



**Case Study:** A 39-year-old woman with refractory cytopenia with multilineage dysplasia, International Prognostic Scoring System intermediate-1–risk MDS, normal female karyotype, and presenting with thrombocytopenia (32,000 platelets/mcl), neutropenia (absolute neutrophil count 850), and hemoglobin 11.2 g/dl. Subsequent rapid decline in platelet count occurred in a one-month period. Treatment was initiated with azacitidine 75 mg/m<sup>2</sup> per day on days 1–5 and days 8–9 despite the presence of cytopenias. Blood count monitoring

occurred two to three times per week with transfusion support for both platelets and packed red blood cells allowed during outpatient management; evidence of trilineage hematopoietic response was observed after the fourth cycle of treatment. Following allogeneic stem cell transplantation, using her sister as a donor, the patient had a complete response and 100% donor chimerisms during evaluation at post-transplantation day 100. She was discharged for outpatient management on day 30 following transplantation.

**Discussion Points:** Although the patient is younger than the average patient with MDS, this case illustrates optimal response to therapy in a young transplantation-eligible patient with a suitable sibling donor and highlights several key clinical management strategies.

- Patients presenting with cytopenias as a result of underlying MDS are not likely to have improvement in their blood cell counts without active therapies, with the exception of patients presenting with anemia in the presence of a low serum

erythropoietin level who may benefit from erythropoietin administration.

- Blood counts are likely to get worse before they get better, and patients may require more frequent transfusions in the early phase of treatment.
- Treatment response may not be evident for four to six cycles.
- All patients eligible for HCT should be evaluated at the time of diagnosis to allow integration of HCT into the overall treatment plan.

HCT—hematopoietic stem cell transplantation; Hgb—hemoglobin; MDS—myelodysplastic syndromes; WBC—white blood cell

**FIGURE 3. Case Study 1: Initiating Treatment in a Patient With Existing Cytopenias With Trilineage Response Following Four Cycles of Azacitidine**

different parameters for monitoring and treatment. Patients with existing cytopenias thought to be related to underlying disease will require initiation of treatment in the presence of low cell counts and, although challenging, can be effectively managed with vigilant monitoring, frequent laboratory analysis, and active participation of the patient as illustrated by the case study in Figure 3.

Given the poor prognosis at the time of diagnosis, patients with intermediate-2- or high-risk disease are evaluated immediately for active treatment. The evaluation takes into account estimation of performance status, assessment of comorbidities, transplantation eligibility, caregiver support, and the patient's wishes (Kurtin & Demakos, 2010). Early initiation of disease-modifying treatment is indicated for attributes thought to be associated with leukemic transformation, including a rising blast count, chromosome 7 abnormalities or complex karyotype, atypical localization of immature precursors, and, more recently, isolation of the *TP53* gene (Bejar, Levine, & Ebert, 2011; Jadersten et al., 2011; Verburgh et al., 2003). Older adult patients with AML thought to be associated with antecedent

MDS also require immediate evaluation; optimal outcomes may be achieved with therapies commonly used to treat MDS (Steensma & Stone, 2010).

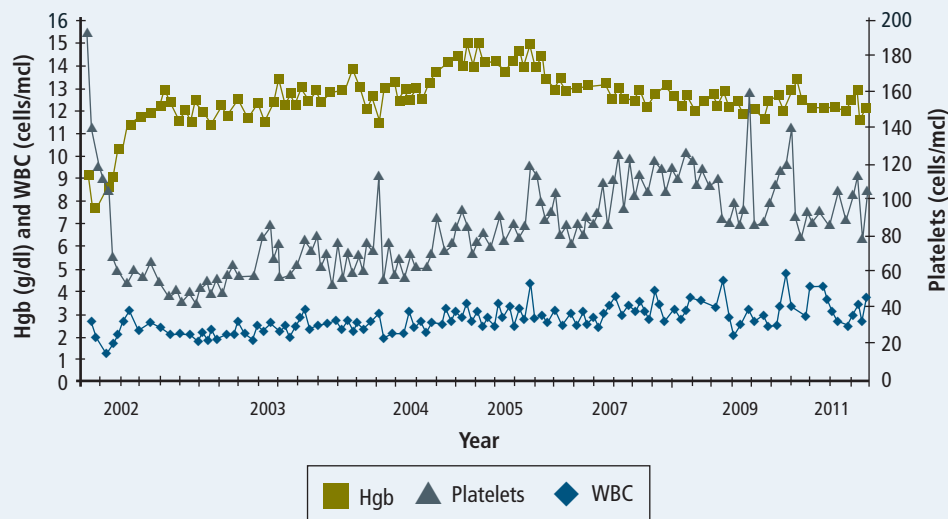
The goals of therapy for a patient with low- or intermediate-1-risk MDS are to improve hematopoiesis and maintain or improve QOL (Komrokji et al., 2011). A patient with intermediate-2- or high-risk disease may die very quickly of the disease or as a result of leukemic transformation, often making treatment at the time of diagnosis necessary, with the primary goal being survival. Importantly, the IPSS-R may further define the indications for treatment when formalized as it applies to a broader range of patients. For example, a patient who presents with a platelet count of less than 50,000 mcl, an absolute neutrophil count of less than 800 mcl, normal cytogenetics, and low bone marrow blasts is considered low risk in the current IPSS system, but may be considered to be in a higher risk group in the IPSS-R, potentially changing the goals of therapy and triggers for treatment as illustrated in the case study described in Figure 3.

The majority of therapies for MDS are provided in an outpatient setting, placing the bulk of responsibility for monitoring

**TABLE 3. Nursing Management of Common Adverse Events of Myelodysplastic Syndromes Treatments**

| Adverse Event               | Signs and Symptoms                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anemia                      | Fatigue, dyspnea, dizziness, tachycardia, and palpitations  | <p>Management of packed red blood cell transfusions</p> <p>Patients with underlying cardiac disease are at increased risk for congestive heart failure exacerbation and may require diuresis with transfusions.</p> <p>Benefits are temporary and rarely restore hematocrit to normal.</p> <p>Transfusions should be based on symptoms, not general hematocrit parameters.</p> <p>Monitoring for iron overload in transfusion-dependent patients and need for iron chelation therapy</p> <p>Administration of erythropoietin agents for patients with a serum erythropoietin level less than 500 mU/ml</p> <p>Initiate active therapies for transfusion-dependent patients with serum erythropoietin levels greater than 500 mU/ml.</p> <p>Assist the patient in maintaining a flow sheet for laboratory results and transfusion dates, blood type, and any antibodies.</p> |
| Gastrointestinal toxicities | Nausea, vomiting, and diarrhea                              | <p>Nausea and vomiting are more common with hypomethylating agents.</p> <p>Administration of antiemetics is recommended before drug administration.</p> <p>5HT<sub>3</sub> antagonists are commonly used but may increase the incidence of constipation; discussion of a prophylactic bowel regimen is important, particularly in patients with thrombocytopenia.</p> <p>Diarrhea is more common with lenalidomide.</p> <p>Patient education for use of over-the-counter antidiarrhea agents, hydration, and diet</p>                                                                                                                                                                                                                                                                                                                                                       |
| Neutropenia                 | Fever, cough, dysuria, abdominal pain, and diarrhea         | <p><b>Monitoring</b></p> <p>Blood counts weekly for the first eight weeks of treatment and then a minimum of monthly or as clinically indicated</p> <p><b>Management</b></p> <p>Administration of recombinant granulocyte colony-stimulating factor</p> <p>Same-day administration with azacitidine or decitabine not recommended</p> <p>No contraindication to same-day administration with thalidomide and lenalidomide</p> <p>Patients receiving active therapies may require drug holiday and dose adjustment.</p> <p>Early recognition of infections</p> <p>Antimicrobial therapy for active infections—prophylactic antibiotics are not generally recommended to avoid resistance</p> <p>Patient education for infection precautions and reportable signs and symptoms</p>                                                                                            |
| Thrombocytopenia            | Petechiae, ecchymosis, epistaxis, hemoptysis, and hematuria | <p>Platelet transfusions based on risk of bleeding</p> <p>Careful monitoring of concomitant medications with antiplatelet effect</p> <p>Patient education for bleeding precautions, emergency management, and reportable signs and symptoms</p> <p>Thrombopoiesis-stimulating proteins currently in clinical trials</p> <p>Patients receiving active therapies may require a drug holiday and dose adjustment.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

*Note.* From "Myelodysplastic Syndromes: Diagnosis, Treatment Planning, and Clinical Management," by S.E. Kurtin, 2007, *Oncology (Williston Park)*, 21(11, Suppl. Nurse Ed.), p. 45. Copyright 2007 by UBM Medica. Adapted with permission.



**Case Study:** A 68-year-old man with refractory anemia, del(5q) MDS, started lenalidomide as part of the MDS-001 trial. The graph above shows a sustained response to lenalidomide during more than nine years. The rapid onset of cytopenias required the first drug holiday on day 18. The drug holiday was a full 21 days with subsequent dose reduction.

The patient has required two additional dose reductions and is now taking 5 mg daily on a 21/28 day schedule. He has sustained but asymptomatic cytopenias, which have not required hospitalization, and has had no further dose modifications since 2004. The patient continues to work full time and has an excellent quality of life.

#### Discussion Points:

- Careful monitoring of blood counts in the first eight weeks of treatment is necessary to institute recommended dose modifications and supportive care strategies.
- Drug holidays and dose modifications based on drug-specific guidelines provide useful strategies for the management of treatment-related cytopenias.
- Sustained moderate but asymptomatic cytopenias (neutropenia and thrombocytopenia) may be

common in patients receiving lenalidomide and other active therapies for MDS (the new normal).

- In the absence of acute symptoms (e.g., fevers, chills, active infection, bleeding, elective surgeries), cytopenias do not require intervention, dose reduction, or discontinuation of therapy.
- Continuation of therapy until unacceptable toxicity occurs or disease progression is noted, based on International Working Group criteria, is recommended.

Hgb—hemoglobin; MDS—myelodysplastic syndromes; WBC—white blood cell

**FIGURE 4. Case Study 2: Sustained Response to Lenalidomide for Nine Years With Moderate But Asymptomatic Cytopenias**

adverse events on the patient and caregivers. An effective plan for communication and clear guidelines for the patient and caregiver are necessary to achieve optimal outcomes. Setting expectations for the patient and family requires informed consent. Much like the stringent requirements of a clinical trial, providing the patient and family with a definition of the disease, the proposed therapy with rationale, a description of the potential risks and benefits of treatment and any alternative treatment options, and how response will be measured is necessary for informed consent. In addition, requirements for the frequency of office visits, laboratory testing, diagnostic procedures such as a bone marrow biopsy and aspirate, and the possible need for transfusions or other supportive care should be discussed. The process may require more than one visit and should optimally include members of the multidisciplinary team. In the clinical trial setting, these elements often are included in a study schema and fast-facts sheet for the providers and a consent form, patient

calendar, and often a diary for the patients. Although emulation of a clinical trial model is not feasible in most general practice settings because of limitations in time and staffing, taking the key elements of this process and creating a blueprint for the currently approved therapies for both providers and patients will help to set expectations, engage the patient in the treatment process, and build a foundation for consistent communication.

The oncology nurse is critical in coordinating visits, providing the patient and family with information about the treatment, assisting the patient with tracking their progress, and reinforcing key concepts to allow safe and effective outpatient treatment. The key concepts include how the treatment will be administered, the frequency of dosing, any restrictions on diet or activity, common adverse events, a clear set of guidelines for signs or symptoms that need immediate attention, and who to contact and how (see Appendix A). First response to treatment, in most cases, requires a minimum of four to six months of active therapy, and the majority of patients achieve best responses within 12 months (Kurtin & Demakos, 2010; Silverman et al., 2011). To improve the potential for benefit, preparing the patient and family for this time frame and reinforcing a commitment to at least four

to six months of therapy is critical. The intensity of visits and supportive care needs will typically diminish with continued treatment in responding patients.

## Supportive Care and Aggressive Management of Adverse Events

All patients with MDS should receive supportive care including transfusion support, administration of growth factors when appropriate, and management of comorbidities and any acute diagnoses, including infections. For patients with limited performance status or complex comorbidities or those patients not wishing to pursue active therapies, supportive care alone is an appropriate standard of care (Kurtin, 2011b).

Given the limited number of active treatment options available, proactive and aggressive management of adverse events

is critical to allow continuation of each treatment long enough to obtain optimal response (see Table 3). Early identification and prompt intervention for common adverse events will limit severity and reduce the probability of discontinuing treatment. Again, the majority of care is provided in the outpatient setting, with the patient and family bearing the bulk of the responsibility for early identification of adverse events. Patient and family education with consistent information, frequent reinforcement of key concepts, and active participation of the patient and family is critical to optimize outcomes.

Myelosuppression is the most common toxicity for all active therapies in MDS (Celgene Corporation, 2009, 2011; SuperGen Inc., 2010). Cytopenias often get worse before they get better, and patients may require continued transfusions before achieving hematologic improvement or transfusion independence. Given the median time to response in most patients of several weeks to months (Kurtin & Demakos, 2010; Silverman et al., 2011), these cytopenias may be disconcerting for the patient and the providers, who could view this as a sign of unacceptable toxicity or treatment failure. Setting expectations for

TABLE 4. MDS: Disease Snapshot

| Feature                                                                       | Key Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epidemiology                                                                  | 15,000–20,000 new cases each year, with 35,000–50,000 existing cases. The average age at diagnosis is 72 years.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Etiology                                                                      | Genetic instability, chemical exposure, tobacco use, mutagens, autoimmune disease, or simply unknown in the majority of cases (about 80%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Stem cell defect<br>Myeloid progenitor cell                                   | Intrinsic factors (e.g., malignant clone, cytogenetic abnormalities) and epigenetic DNA modification (hypermethylation)<br>Extrinsic factors (e.g., bone marrow microenvironment, stromal dysregulation, cytokine abnormalities) and imbalance of apoptosis and proliferation                                                                                                                                                                                                                                                                                                                                                                                      |
| Chromosomal findings<br>Cytogenetic abnormality present in about 40% of cases | <b>Favorable:</b> -Y, del(5q), -20q<br><b>Intermediate risk:</b> +8 and other<br><b>Poor risk:</b> complex (more than three abnormalities); chromosome 7 abnormalities: 7q, -7, del(7p); inv16, t(8:12) indicative of acute myeloid leukemia                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Additional prognostic factors indicating high-risk disease                    | Increased transfusion burden (more than two units in four weeks); increased blast cells (greater than 20% implies leukemic transformation); severe thrombocytopenia or neutropenia at diagnosis; atypical localization of immature precursors; bone marrow fibrosis, elevated ferritin, elevated lactate dehydrogenase—considered unfavorable; and ongoing analysis of more sensitive testing for chromosomal and molecular attributes                                                                                                                                                                                                                             |
| Staging                                                                       | FAB/WHO (morphology) and IPSS/WPSS (risk stratification)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Response criteria                                                             | International Working Group criteria 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Disease characteristics (all are incurable)                                   | <b>IPSS low and intermediate-1 risk:</b> indolent course; low probability of leukemic transformation<br><b>IPSS intermediate-2 and high risk:</b> rapidly progressive course with early transformation to acute leukemia                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Clinical presentation                                                         | Cytopenias (anemia most common), fatigue, infection, and bleeding                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Treatment triggers                                                            | Transfusion dependence, progressive or symptomatic cytopenias, increased blasts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Key concepts for effective treatment                                          | Supportive care alone does not prevent disease progression (no effect on the underlying disease).<br>Disease-modifying therapies for MDS generally require a minimum of four to six months to achieve response; premature discontinuation may limit potential for an optimal response.<br>Treatment should continue until disease progression or unacceptable toxicity.<br>Aggressive concurrent management of cytopenias is essential to effective therapy.<br>Treatment goals include reduced transfusion burden, delayed time to leukemic transformation, improved quality of life, and prolonged survival.<br>Chromosomal abnormalities have prognostic value. |
| FDA-approved therapies                                                        | Azacitidine, decitabine, and lenalidomide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| In clinical trials or used based on other approved indications                | TLK199, src family kinase inhibitors, clofarabine, arsenic trioxide, valproic acid, and thalidomide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Key supportive care concerns                                                  | Iron overload, cytopenias, injection site reactions, gastrointestinal toxicities, fatigue, and rash (with lenalidomide)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

FAB—French-American-British classification system; FDA—U.S. Food and Drug Administration; inv—inversion; IPSS—International Prognostic Scoring System; MDS—myelodysplastic syndromes; WHO—World Health Organization; WPSS—WHO Prognostic Staging System

Note. From "Leukemia and Myelodysplastic Syndromes," by S. Kurtin (p. 1392). In C.H. Yarbro, D. Wujcik, and B.H. Gobel (Eds.), *Cancer Nursing: Principles and Practice* (7th ed.), 2011, Sudbury, MA: Jones and Bartlett. Copyright 2011 by Jones and Bartlett. Adapted with permission.

toxicities, establishing a protocol for reporting, and developing standards for interventions will provide reassurance to the patient and limit unnecessary discontinuation of therapy. Each drug has specific recommendations for dose modifications or drug holidays in the presence of more severe or symptomatic cytopenias (Celgene Corporation, 2009, 2011; SuperGen Inc., 2010).

Importantly, sustained moderate but asymptomatic cytopenias may persist for months or years in patients who achieve transfusion independence and should be viewed as the “new normal” (see Figure 4). Unlike chronic myelogenous leukemia in which complete hematologic improvement and absence of cytogenetic abnormalities is required for a complete response and improved survival, patients with MDS who achieve transfusion independence may never achieve complete hematologic normalization and may continue to have an abnormal karyotype (Kurtin & List, 2009). Although stable moderate asymptomatic cytopenias require continued monitoring, they do not require discontinuation of therapy, may not require intervention, and may not have a negative effect on the patient’s QOL. The patient presented in Figure 4 illustrates sustained moderate cytopenias with no interruption in treatment, no episodes of hospitalization, and sustained transfusion independence. In some cases, such as the treatment of patients with del(5q) receiving lenalidomide, the development of thrombocytopenia after initiating treatment may be an indication of favorable response (Sekeres et al., 2008). Unlike AML, in which an expectation of a hypocellular bone marrow by day 14 following induction therapy with hematologic normalization and the absence of an abnormal clone at day 28 exists, treatment response in MDS may not be evident for several weeks or months, with persistent cytogenetic abnormalities detectable despite achievement of transfusion independence with improvement in QOL (NCCN, 2011a; Sekeres et al., 2008). Because responses to some active therapies may occur late following treatment initiation, clinical benefit can be maximized by continuing therapy until disease progression or unacceptable toxicity (Silverman et al., 2011).

Clear communication of these principles to the patient and family as well as any collaborating providers will reduce the anxiety associated with expected cytopenias and delayed time to response along with the feeling that treatment has failed or is too toxic (Kurtin & Demakos, 2010). Perhaps the greatest tool for illustrating overall improvement and the concept of the new normal is a graphing or tracking tool that will provide visual evidence of trends. Gradual improvement in transfusion requirements may be the first indication of response. Stable disease with transfusion independence is considered a good outcome in the patient with MDS and may translate into improved overall survival.

## Summary

Many promising scientific developments have occurred in the understanding of MDS, its underlying pathobiology, opportunities for novel targets that may offer new treatment options, refinement of the risk stratification criteria, and effective support of patients on treatment. However, the current treatment options are limited, and many patients still die as a result of their disease. Some of these patients are not offered active therapies because of their age, whereas others discontinue treatment

## Implications for Practice

- ▶ Outcomes for patients with myelodysplastic syndromes (MDS) can be enhanced through the use of individualized, risk-adapted strategies for treatment that take into account treatment goals based on a patient’s risk status.
- ▶ Tools to track trends in diagnostic measurements, transfusion requirements, and responses to therapy can help to guide therapeutic recommendations through recognition of triggers for treatment, supportive care use, and disease progression.
- ▶ Treatment blueprints can enable healthcare providers, including oncology nurses, to provide clear communication and guidance to patients and their families about what to expect with regard to specific therapies and which symptoms require immediate intervention.

prematurely because of a perceived lack of benefit or concern about persistent cytopenias. In addition, some patients choose not to pursue active therapies and pursue supportive care alone. Other patients do not respond to current therapies, reinforcing the need for continued clinical trials. All patients require the support of the oncology team, relying on them to explain their disease, the expected disease trajectory, options for treatment, risks and benefits of the treatment, what is required if they do pursue treatment, and what might happen if they do not pursue treatment or if it does not work (see Table 4).

The oncology nurse is in a unique position to provide patients and their families with practical tools that will give clear definitions, set expectations, and empower patients and their families to take an active role in patient care. Familiarity with the key concepts of individualized risk-adapted therapy, setting expectations for early cytopenias, the time required for first and best response, comfort with sustained moderate asymptomatic cytopenias and the new normal, and continuation of treatment until disease progression or unacceptable toxicity will allow individualized support of patients with MDS.

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### For Exploration on the Go



The MDS Foundation offers a wide range of information for healthcare providers treating patients with myelodysplastic syndromes. Access the information by opening a barcode scanner on your smartphone. Point your phone at the code and take a photo. Your phone will link to the content automatically.

Access this content at [www.mds-foundation.org/for-healthcare-professionals](http://www.mds-foundation.org/for-healthcare-professionals).

Name: \_\_\_\_\_ DOB: \_\_\_\_\_ MR#: \_\_\_\_\_ Visit#: \_\_\_\_\_

|                                                                                                                                                             |              |                                                  |        |        |                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------|--------|--------|---------------------|
| <b>Diagnosis:</b> MDS                                                                                                                                       | ICD 9:238.74 | <b>Regimen:</b> Lenalidomide                     | HT: cm | WT: kg | BSA: m <sup>2</sup> |
| <b>Approved Indications<sup>a</sup>:</b>                                                                                                                    |              |                                                  |        |        |                     |
| <b>Allergies (Drug, Food, Environmental):</b> _____                                                                                                         |              |                                                  |        |        |                     |
| <input type="checkbox"/> No known drug allergies <input type="checkbox"/> No known food allergies <input type="checkbox"/> No known environmental allergies |              |                                                  |        |        |                     |
| <b>Course #:</b> _____ of _____                                                                                                                             |              | <b>Start Date for Cycle #1 of Therapy:</b> _____ |        |        |                     |

| MEDICATION AND DOSE |                          | PATIENT'S DOSE                                                  | ROUTE    | ADMINISTRATION TIME AND FREQUENCY                                                                                                                                                   |
|---------------------|--------------------------|-----------------------------------------------------------------|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                   | Lenalidomide (Revlimid®) | <input type="checkbox"/> 10 mg<br><input type="checkbox"/> 5 mg | By mouth | One tablet daily with or without food at the same time:<br><input type="checkbox"/> Days 1–21 every 28 days <input type="checkbox"/> Daily<br><input type="checkbox"/> Other: _____ |

#### Begin Therapy (Day 1):

|                                                                                                         |                        |                   |             |
|---------------------------------------------------------------------------------------------------------|------------------------|-------------------|-------------|
| <b>Treatment Parameters:</b> Do not initiate treatment if: (Will use clinic standards if not indicated) | WBC <<br>ANC <         | PLT <<br>CR >     | Bilirubin > |
| <b>Protocol Modification (reason):</b>                                                                  | <b>Effective Date:</b> |                   |             |
| <b>Other Provider Signature:</b>                                                                        | <b>ID #</b>            | <b>Date/Time:</b> |             |
| <b>Attending Provider Signature:</b>                                                                    | <b>ID #</b>            | <b>Date/Time:</b> |             |

#### PRETREATMENT EVALUATION

|   |                                                            |                                                                                                                                                                                                                                                                                                                                                        |
|---|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Informed consent                                           | <input type="checkbox"/> Consent form signed: Date: _____ (included in EHR)                                                                                                                                                                                                                                                                            |
| 2 | Registration with RevAssist®<br>www.revassist.com          | Must be prescribed through RevAssist program for safety.<br>Celgene Customer Care Center: toll-free at 1-888-423-5436                                                                                                                                                                                                                                  |
| 3 | Pretreatment laboratory                                    | <input type="checkbox"/> CBC, differential, platelet count<br><input type="checkbox"/> Complete metabolic panel<br><input type="checkbox"/> Serum erythropoietin level<br><input type="checkbox"/> TSH <input type="checkbox"/> Serum testosterone (men only)                                                                                          |
| 4 | Pretreatment patient education                             | <input type="checkbox"/> Consultation with clinical coordinator/patient navigator<br><input type="checkbox"/> Chemotherapy education course (date): _____<br><input type="checkbox"/> Treatment and transfusion tracking tool<br><input type="checkbox"/> Lenalidomide (Revlimid®) patient information packet                                          |
| 5 | <input type="checkbox"/> Referral to financial coordinator |                                                                                                                                                                                                                                                                                                                                                        |
| 6 | Common adverse events                                      | <ul style="list-style-type: none"> <li>• Myelosuppression (most common)</li> <li>• Rash (generally transient); pruritus is common in early phase of treatment</li> <li>• Diarrhea</li> <li>• Use with caution in renal impairment (refer to Micromedex)</li> <li>• Analog of thalidomide (Lenalidomide is nonteratogenic in animal studies)</li> </ul> |

#### FOLLOW-UP PROTOCOL

|   |                                                                                          |                                                                                                                                                                                                                                                                                                                     |
|---|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Weekly laboratory analysis for first eight weeks                                         | <input type="checkbox"/> CBC, differential, platelet count<br><input type="checkbox"/> Complete metabolic panel                                                                                                                                                                                                     |
| 2 | Provider/nursing visit for toxicity check, reinforcement of teaching (first eight weeks) | <input type="checkbox"/> Provider visit (99214) <input type="checkbox"/> weekly <input type="checkbox"/> every other week <input type="checkbox"/> other<br><input type="checkbox"/> Nursing visit (99211) <input type="checkbox"/> weekly <input type="checkbox"/> every other week <input type="checkbox"/> other |

<sup>a</sup> From List et al., 2005, 2006; Raza et al., 2008.

ANC—absolute neutrophil count; BSA—body surface area; CBC—complete blood count; CR—creatinine; DOB—date of birth; EHR—electronic health record; HT—height; MDS—myelodysplastic syndromes; MR—medical record; PLT—platelets; TSH—thyroid-stimulating hormone; WBC—white blood cell; WT—weight

### APPENDIX A. Blueprint for Patients With MDS Treated With Lenalidomide

**Note.** Courtesy of the University of Arizona Cancer Center. Used with permission. This blueprint may be reprinted for noncommercial use and is available at <http://cjon.sup.mds-foundation.org>.