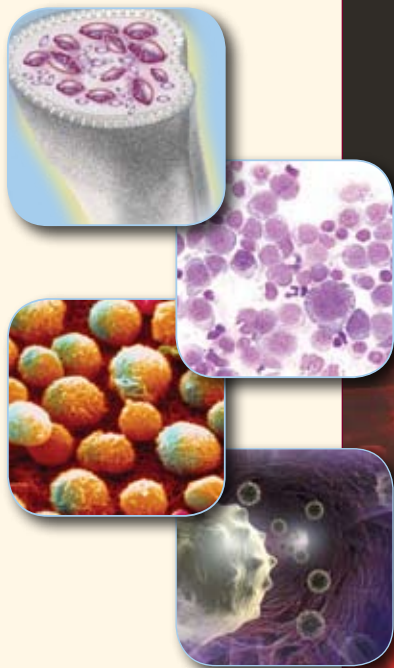


Common Hematologic Malignancies in the Elderly:
Removing Age as a Barrier to Effective Treatment

*Myelodysplastic Syndromes: Clinical
Updates With Consideration of the
Unique Needs of the Older Patient*



*An e-newsletter
that reviews
recent advances
in the diagnosis,
prognostication,
risk-adapted
treatment selection,
and management
of adverse events in
patients with MDS,
with consideration of
the unique needs of
the older patient*

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Common Hematologic Malignancies in the Elderly: Removing Age as a Barrier to Effective Treatment

Myelodysplastic Syndromes: Clinical Updates With Consideration of the Unique Needs of the Older Patient

Intended Audience

This continuing education activity is designed for oncology nurses and nurse practitioners, as well as other health care professionals interested in the care of elderly patients with myelodysplastic syndromes (MDS)

Learning Objectives

At the completion of this activity, participants should be better able to

- Explain the use of risk-adapted treatment selection for MDS
- Summarize recent clinical trials and their significance in the care of the patient with MDS
- Discuss treatment of the older adult with MDS
- Describe management strategies for MDS patients experiencing myelosuppression


Rationale and Purpose

This activity—designed as a series of 4 e-newsletters—presents the latest developments in the care of older adults with hematologic malignancies to facilitate state-of-the-art medical and nursing care. Promoting evidenced-based practice guidelines will improve integration of new therapies into clinical practice, thereby affecting patient outcomes and enhancing quality of life. This fourth e-newsletter focuses on symptom management and treatment updates for MDS and discusses the management of myelosuppressive complications of treatment for these patients.

Continuing Education

To access the learning assessment and evaluation form online, visit HemNLSer.cme360.net

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Activity Overview

This activity—designed as a series of 4 e-newsletters—presents the latest developments in the care of older adults with hematologic malignancies to facilitate state-of-the-art medical and nursing care.

Promoting evidence-based practice guidelines will improve integration of new therapies into clinical practice, thereby affecting patient outcomes and enhancing quality of life. The activity's faculty—Sandra Kurtin, RN, MS, AOCN, ANP-C, Beth Faiman, MSN, APRN, BC, AOCN, and Barbara Rogers, CRNP, MN, AOCN, ANP-BC—present data and concepts specific to the unique needs of older adults as applied to patients with myelodysplastic syndromes (MDS), non-Hodgkin lymphomas (NHL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).

This fourth and final e-newsletter focuses on symptom management and treatment updates for MDS and discusses the management of myelosuppressive complications and treatment for these patients.

Three e-newsletters are already published and available:

- E-newsletter 1: summarizes the satellite symposium Removing Age as a Barrier to Treatment in Elderly Patients With Hematologic Malignancies (ONS Congress in San Diego, California, on May 14, 2010), and covers unique needs and clinical trial findings related to older adults with hematologic malignancies
- E-newsletter 2: focuses on symptom management including updates for MM and CLL, covering management of neuropathy, thromboembolic events, and renal complications of treatment
- E-newsletter 3: focuses on symptom management and treatment updates for NHL and HL and discusses fatigue, infectious complications, and hypersensitivity in these patients

The importance of these e-newsletters is supported by data collected from a survey of the 245 oncology professionals who attended the satellite symposium.

- Participants were both experienced oncology professionals with more than 15 years of experience (42%) and many new to the field (25%) (an opportunity to mentor new staff)

- The majority worked in inpatient units (40%) or outpatient clinics (32%), emphasizing the need for strategies to facilitate seamless transition across practice settings
- 51% to 75% of patients in the practices represented at the meeting, and more than 55% of patients in practices surveyed in an e-mail pre-session questionnaire, were over age 65, suggesting a need to learn more about specific requirements of older adults with cancer
- A majority of participants (75%) felt that patients over age 70 might require different therapeutic approaches based on age alone
- Participants' greatest challenges in the nursing management of older adults with hematologic malignancies included myelosuppression (38%) and fatigue (21%).

Through this series of e-newsletters, participants gain knowledge of the unique needs of elderly patients with hematologic malignancies. They learn about clinical trials studying the most effective therapies, factors important in choosing the most effective treatment, and nursing management of common disease- or treatment-related adverse events specific to this population.

INTRODUCTION

The myelodysplastic syndromes (MDS) represent a group of clonal myeloid malignancies with variable clinical presentation, disease trajectory, prognosis, and indications for treatment. The disease is characterized by ineffective hematopoiesis and a variable risk of leukemic transformation. The typical patient with MDS is 70 to 75 years old, presenting with cytopenia-related symptoms including fatigue, exertional dyspnea, unusual bruising or bleeding, and recurrent infections—symptoms that may be attributed to age or underlying comorbidities, which are common in this age group. Yet many patients are asymptomatic at the time of diagnosis, with cytopenias noted on routine physical exam. The older adult population represents a heterogeneous group with variability in overall health (comorbidities and medications used to treat them) and in psychosocial, financial, and health belief systems. Given the heterogeneity of this population, along with that of MDS, strategies that allow for individualized risk-adapted treatment for both MDS and common comorbidities in older adults will provide the best opportunity for optimal outcomes.

The majority of clinical management of the MDS patient is provided in the outpatient setting and requires active participation of the patient and caregivers for monitoring of adverse events and adherence to treatment

protocols. Several key scientific updates were presented at the American Society of Hematology (ASH) meeting (December 2010), the 11th International Symposium on Myelodysplastic Syndromes (May 2011), and the American Society of Clinical Oncology (ASCO) meeting (June 2011). This newsletter reviews recent advances in the diagnosis, prognostication, risk-adapted treatment selection, and management of adverse events in patients with MDS, with consideration of the unique needs of the older patient.

THE CHANGING EPIDEMIOLOGY OF MDS: RISING INCIDENCE OR GROWING FAMILIARITY?

The French-American-British (FAB) Classification system for MDS was introduced in 1976, with revision in 1982. A similar system was created by the World Health Organization (WHO) in 1997 and revised in 2001 (Figure 1). These classification systems have undergone further revision with a growing familiarity with the morphologic and molecular attributes of MDS and refinement of diagnostic hematopathology. As the diagnosis and classification of MDS have been refined, epidemiologic data relative to MDS have also undergone changes.

Retrospective Analysis: Underreporting of MDS

The first epidemiologic data specific to MDS in the United States were collected between 2001 and 2003, with an estimated age-adjusted US MDS incidence of 3.4 per 100,000, or approximately 10,000 new cases per year.¹ On the basis of these same data, an estimated 60,000 US individuals are living with MDS. More recent data have reported much higher estimates of both incidence and prevalence. Cogle and colleagues² evaluated the incidence of MDS by using

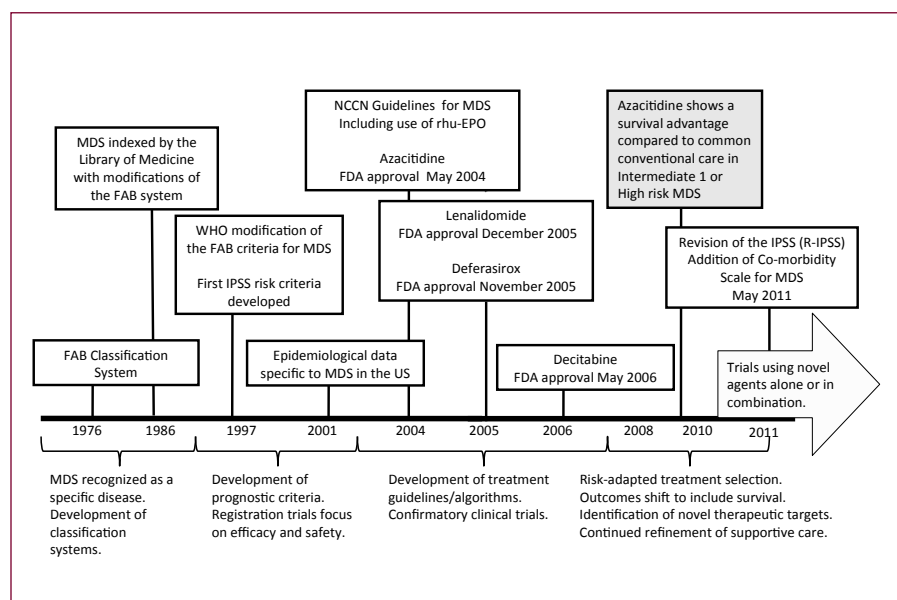


Figure 1. Scientific developments in the management of MDS. (Adapted with permission from Kurtin. 2008. [https://www.meniscus.com/mds-cll-mm.](https://www.meniscus.com/mds-cll-mm))

a claims-based algorithm to evaluate the Surveillance, Epidemiology, and End Results (SEER)–Medicare database with ICD-9 codes, confirmatory blood counts, and bone marrow analysis. The estimated incidence of MDS in 2005 for persons 65 years of age or older was 75 per 100,000, considerably higher than the SEER estimates of 20 per 100,000 for that same year. This study had a number of potential limitations including a retrospective analysis and reliance on the coding of diagnoses, which historically has been subject to the billing definition of clinical diagnoses most often selected by coders, not clinicians. The true incidence of MDS is likely somewhere between 3.4 and 75 per 100,000. Yet several additional findings support an underreporting of MDS, including limited outpatient reporting of new cases to the SEER registry (which is based on an inpatient model), exclusion of patients who have transformed to acute myelogenous leukemia (AML) from antecedent MDS common in higher-risk MDS, and the lack of adequate diagnostic evaluation to confirm the MDS diagnosis.²

Effects of Increased Diagnosis and Active Therapy Availability

Importantly, all these data precede the availability of active therapies, which likely increase the prevalence rates for MDS and the diagnostic evaluation of older patients presenting with cytopenias.^{3,4} Additional factors thought to contribute to the anticipated rise in incidence and prevalence include increased inclusion of MDS in the differential diagnosis of cytopenias in elderly patients, improved diagnostic capabilities of hematopathologists, and the expected rise in secondary or treatment-related MDS (tMDS).

Accurate estimates of incidence and prevalence are critical to estimating the disease burden, effect on patients and health care services, and development of effective management and support strategies.

Two Recent Online Surveys: Patients' Lack of Clarity About MDS Diagnosis

Most current epidemiologic data estimate the median age of the MDS patient to be greater than 70 years. Two recent online surveys with a collective 557 patients indicate a younger median age with a range of 62 to 66 years.^{3,5} Although online surveys likely capture a younger, more computer-savvy population, it is important to consider the implications for medical coverage, ability to work, and possible treatment implications in this preretirement age group.

Sekeres et al³ conducted an online survey of 3131 patients with MDS registered with the Aplastic Anemia and Myelodysplastic Syndromes Association. A total of 358 patients completed the survey. The median age in this survey was 65 years, with 51% female and with an average of 3 years since MDS diagnosis. Interestingly, the median time from the first detected abnormal hematologic findings for participants was 6 years, perhaps indicating a delay in diagnosis with potential implications for the expected disease trajectory in these patients. Despite the median of 3 years from initial diagnosis, only 45% of the patients could identify their International Prognostic Scoring System (IPSS) risk category (67% low risk, 33% higher risk), only 42% of patients knew their blast percentage, and only 7% recalled having MDS described to them as a type of cancer. Patients

in this survey indicated some frustration with the lack of clarity in labeling MDS as a nonmalignant disease, which interfered with the ability to utilize insurance policies specific to a cancer diagnosis.⁶

A second online survey was conducted by the MDS Foundation, including 199 patients with MDS who had a median age of 63 years and a median time since diagnosis of 3 years, similar to the other survey respondents. Of these patients, 28% did not know their FAB subtype, and 47% did not know their IPSS score. Of the patients knowing their IPSS score (n = 105), most indicated intermediate-1 risk (23%, n = 46) followed by low risk (19%, n = 37). Most survey participants were retired (48%), but one-third of the patients continued to work either full time or part time; of those working, 19% were no longer able to work at the time of the survey and 7% of patients had to reduce their work schedule, with potential implications for insurance coverage, financial concerns, and family dynamics.⁵

CAUSE OF DEATH IN PATIENTS WITH MDS: IMPLICATIONS FOR TREATMENT

A number of recent studies have indicated that the leading cause of death in patients with MDS—in more than 75% of cases—is related to the disease itself. The variability in life expectancy based on risk category is well characterized and provides the basis for the IPSS. Life expectancy of intermediate-2–risk or high-risk MDS is generally measured in months, and leukemic transformation is common and often the cause of death in untreated patients.⁷ In contrast, patients with lower-risk

MDS (low–intermediate-1) have a variable prognosis, with leukemic transformation in untreated patients being much less common and the cause of death less clear.⁸

Retrospective Review of Patients on Supportive Care Only

Garcia-Manero and colleagues⁹ conducted a retrospective review of 273 patients with low-risk MDS (29% low risk, 79% intermediate-1 risk) referred to the M.D. Anderson Cancer Center between 1980 and 2004 to determine the cause of death. Importantly, these patients received supportive care only (no disease-modifying treatment), which eliminated treatment-related adverse events as a cause of death. The median age at presentation was 66 years with a median overall survival of 59 weeks.

Disease-related factors were listed as the cause of death in 84% of the patients (n = 230) and included infections (38%), AML transformation (15%), and hemorrhage (13%). The most common infections included pneumonia (40%) and sepsis (38%). Fungal (58%) and bacterial (25%) pneumonias were most common, indicating the importance of baseline evaluation including chest x-ray with ongoing surveillance for atypical pneumonias in this elderly population. Fungal infections are most often seen in patients with prolonged neutropenia, raising the question of neutrophilic functional abnormalities in these patients as a result of their disease. The underlying cause of death for patients experiencing hemorrhage included central nervous system bleeding in 26% of those cases and gastrointestinal and pulmonary hemorrhage in 24% of cases, again indicating the need for close

monitoring, safety evaluations, fall prevention, and discussion of bleeding precautions.

The published data do not describe the characteristics of cytopenias at the time of death, making analysis of bleeding tendencies more difficult, and many patients with moderate cytopenias remain asymptomatic with no episodes of active bleeding. Existing cytopenias resulting from underlying disease are not likely to improve without treatment. Supportive care measures may provide temporary improvement in some cases; however, these measures do not affect the underlying disease. Initiating treatment earlier in the course of disease on the basis of established triggers for treatment may improve hematopoiesis, limiting these disease-related causes of mortality.

RISK-ADAPTED TREATMENT SELECTION: TREATING THE OLDER PATIENT WITH MDS

Given the increasing incidence and prevalence of MDS with the median age of 70 to 76, together with the knowledge that the leading cause of death in this population is due to disease-related factors, development of strategies feasible for older adults is critical. Risk-adapted, individualized treatment strategies that incorporate prognostic features of the disease and the individual patient provide the best tools for this approach.

IPSS for Risk Stratification

The IPSS, developed in 1997 prior to the availability of active therapies, has long been the best-known risk stratification tool for this purpose. The IPSS assigns a risk category based on the number of cytopenias,

cytogenetic abnormalities, and percentage of blasts in the bone marrow sample. The score correlates with 1 of 4 risk groups (low, intermediate-1, intermediate-2, and high), each with projected median survival and risk of leukemic transformation (Table 1).

Although the IPSS has provided a critical model for risk stratification, it is limited by being applicable 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) has been proposed, with additional risk factors including transfusion burden, depth of cytopenias (in particular, thrombocytopenia), revised cytogenetic risk groups, bone marrow fibrosis, and lactate dehydrogenase (LDH). It will also add a fifth risk category (Table 1).¹⁰ 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.

Survey Addressing Unique Needs of Older Patients With MDS

More recently, discussion of the unique needs of the older adult with MDS, including comorbidities and refinement of supportive care strategies, has been introduced. However, MDS remains a rare disease that is 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.¹¹ Yet chronologic age alone should not determine treatment.

Table 1. IPSS Risk Categories (1997) Prior to Active Therapies

Score	0	0.5	1.0	1.5	2.0
Bone marrow myeloblasts	< 5%		5%-10%	11%-20%	21%-30% (considered AML)
Karyotype	Normal, del(5q), del(Y), del(20q) as sole abnormalities	Other abnormalities	del(7), 7+, or ≥ 3 abnormalities		
Number of cytopenias	0, 1	2, 3	Anemia (hemoglobin < 10 g/dL), neutropenia (absolute neutrophil count < 1800/μL) and/or thrombocytopenia (platelets < 100,000/μL)		

Current IPSS and Proposed Revised IPSS With Survival and Risk of Leukemic Transformation

Current IPSS n = 816				Proposed Revisions to IPSS: IPSS-R* n = 4417		
Category	Score	Median Survival, y	Evolution to AML, y (25%)	Risk Category Proposed Changes	Median Survival, y	Evolution to AML, y (25%)
Low	0	5.7	9.4	Very low	6.8	NR
Intermediate-1	0.5-1.0	3.5	3.3	Low	4.3	10.1
Intermediate-2	1.5-2.0	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

*IPSS-R is still being modified by the International Working Group for Prognosis in Myelodysplastic Syndromes (IWG-PM), including assignment of scores and the final attributes of each category.

Results of an online survey were presented at the 2010 Oncology Nursing Society symposium titled *Common Hematologic Malignancies in the Elderly: Removing Age as a Barrier to Effective Treatment*. Fifty-one to seventy-five percent of the patients in the practices represented by conference participants and more than 50% of patients in practices of participants surveyed in the pre-session questionnaire were over age 65, indicating the importance of learning more about the specific needs of the older adult with cancer. When asked to indicate the age at which their perception of the treatment for an older patient would be influenced, the majority of participants (27%) felt that being over age 75 might entail age-

based differences in therapeutic approach. The greatest challenge in treatment of older adults with hematologic malignancies included myelosuppression and fatigue.

Life Expectancy Considerations

Based on the 2010 US census data, life expectancy for an individual with independent function at age 65 is 19.8 years. If the life expectancy without treatment of their hematologic malignancy is 2 years, then we have a lot to gain by offering these patients therapy based on careful analysis of performance status, comorbidities, and risk analysis of disease attributes. Several recent clinical updates have provided evidence that older patients with MDS may benefit from disease-modifying therapies.

UPDATES IN THE TREATMENT OF MDS

There are currently 3 Food and Drug Administration (FDA)-approved agents for the active treatment of MDS: azacitidine, decitabine, and lenalidomide (Table 2). Each agent was approved on the basis of key trials validating safety and efficacy (Table 2). Treatment selection is based on several factors: (1) the characteristics of the individual patient, including comorbidities, performance status, lifestyle, finances, and quality of life; (2) characteristics of the disease, including IPSS risk category and individual disease characteristics; and (3) currently available treatment options.⁴

Table 2. FDA-Approved Agents for Treatment of MDS

	Azacitidine	Decitabine	Lenalidomide
Indication	All 5 FAB subtypes (RA, RARS, RAEB, CMML, RAEB-T)	Int-1/Int-2 /high risk per IPSS, as well as tMDS	Transfusion-dependent MDS, low-Int-1 MDS with del(5q) with or without additional chromosomal abnormalities
Therapeutic Target and Sensitivity	DNA methyltransferase inhibitor RNA and DNA Proteins and microenvironment No data on use after decitabine failure	DNA methyltransferase inhibitor DNA specific Direct cytotoxic effect May be effective in patients previously treated with azacitidine	Immunomodulatory drug (IMiD) Del(5q)— possible direct cytotoxic effect on clone Without del(5q)—drug may target disease microenvironment Most effective in patients with del(5q) Activity has been demonstrated in non-del(5q) patients
Mode of Use	SC or IV × 7 days every 28 days Outpatient regimen Treat until unacceptable toxicity or disease progression	IV daily for 5 days over 1 hour every 28 days Outpatient regimen Treat until unacceptable toxicity or disease progression	10 mg orally days 1-21 every 28 days Outpatient regimen
Primary End Points Met (IWG)	Improved overall survival (7-day dosing) Hematologic improvement (trilineage) Transfusion independence Cytogenetic response Safety and efficacy	Hematologic improvement Transfusion independence Cytogenetic response Safety and efficacy	Hematologic improvement Transfusion independence Cytogenetic response Efficacy and safety
Median Time to Response	Median time to first response: 2-3 cycles Median time to best response in AZA-001: 92% by 12 cycles Median time from first response to best response: 3-5 cycles	Median time to first response: 2 months Median time to best response: 2 months	Median time to first response: 4-6 weeks (MDS-003) Mean time to first dose modification: 80% of patients—21 days Median duration of drug holiday: 22 days Time between first and second dose modification: (mean) 51 days (34%)
Common Adverse Events and Treatment Considerations	Myelosuppression (most common) Injection-site reactions Nausea and vomiting Constipation Contraindicated in patients with hepatic tumors Use with caution in renal impairment May cause fetal harm	Myelosuppression (most common) Nausea and vomiting Constipation Hyperbilirubinemia Use with caution in renal impairment May cause fetal harm	Myelosuppression (most common) Rash Diarrhea Requires renal dose adjustment Nonteratogenic in animal studies Analog of thalidomide Must be prescribed through Revassist for safety

Data from Kurtin,¹¹ Kurtin and Demakos,¹² Scott and Deeg,¹³ and Blum.¹⁴

Patients with low-intermediate-1-risk disease have a more favorable prognosis and may not require immediate interventions. Indications for treatment in these patients

include progressive or symptomatic cytopenias, transfusion dependence, or other indications of disease progression, such as a rising blast count. Given the poor prognosis at

the time of diagnosis, patients with intermediate-2-risk or high-risk disease are evaluated immediately for active treatment. The evaluation includes estimation of performance

status, assessment of comorbidities, transplant eligibility, caregiver support, and the patient's wishes.¹²

Several updates have been provided with suggested refinement of current administration protocols, recommendations for duration of therapy, strategies to effectively treat older patients, and possible selection of therapies based on molecular attributes of the disease. A number of clinical trials are in progress, exploring novel agents for the treatment of MDS (Table 3).

UPDATES ON HYPOMETHYLATING AGENTS

Two hypomethylating agents are currently FDA approved: azacitidine (Vidaza) and decitabine (Dacogen). Current data suggest that these agents work in ways not yet fully characterized and that hypomethylation is not the only mechanism of activity.^{16,17} However, hypermethylation is common in MDS, is a constant process, and is thought to play an important role in leukemogenesis, supporting the continuation of hypomethylating agent administration for the treatment of MDS until there is evidence of disease progression or unacceptable toxicity.¹²

Azacitidine Study: Survival Advantage Over Conventional Care

Silverman and colleagues¹⁸ performed a subset analysis of the international phase III AZA-001 trial comparing azacitidine, 75 mg/m² subcutaneously on days 1 to 7 using a 28-day cycle, to conventional care in patients with IPSS intermediate-2-risk or high-risk MDS and 20% to 30% blasts. The median age of these patients was 69 years, with a range of 43 to 83 years. Survival for this risk group is generally poor (0.4-1.2 years).

The results of the AZA-001 trial have been previously reported with evidence of improved overall survival (median > 9 months) and a delay in time to AML progression of > 6 months compared with conventional care.¹⁹ Furthermore, the survival advantage was seen irrespective of age, including patients over age 75 years. Of the 179 patients who received azacitidine, 91 achieved a response (complete response [CR] or partial response [PR]) using IWG criteria. Importantly, although a median of 4 cycles were received prior to first response, 91% of the patients achieved their first response within 6 cycles, and the remaining 9% of the responders achieved their first response by 12 months.

For slightly more than half of the patients (52%), the first response was the best response achieved. The remaining 48% of the patients, however, continued to have improved response with continued treatment at a median of 3 cycles after the first response. Of the responding patients, 92% had achieved the best response by cycle 12.

Given the documented improvement in overall survival, this analysis supports the need to allow a minimum of 6 cycles of azacitidine treatment before determining response and continuing treatment beyond the time of best response. It also provides evidence that patients over the age of 75 who are fit for treatment can benefit from disease-modifying treatment.

Decitabine Studies: Clinical Benefit and Improved Quality of Life

Although survival data have not been documented in patients receiving decitabine, several studies have shown clinical benefit and improvement in quality of life.^{15,20} A recent European study compared low-dose decitabine (15 mg/m² IV over 4 hours 3 times a day for 3 days every 6 weeks) to best supportive care. The majority of patients

Table 3. Current Clinical Trials Exploring Novel Agents for MDS Treatment

Agent	Mechanism of Action	Phase	Indication
Alemtuzumab	Anti-CD52 immune modulation	II	Lower risk, hypoplastic
Oral azacitidine	Hypomethylating agent	II	Lower risk
Arry-614	P38MAPK inhibitor	I	Lower risk
Deferasirox	Iron chelation	III	Lower risk
Clofarabine	Nucleoside analog	II	Int and higher risk
Sapacitabine	Nucleoside analog	II/III	Int and higher risk
ON190	Unknown	III	Hypomethylating failure

Garcia-Manero.¹⁵

(92%) had high-risk disease (IPSS intermediate-2 or high), including 57% with poor cytogenetics. The median age of the population was 70 years (29% > 75 years) with an ECOG performance status of 1-2 in 80% of the patients. Progression-free survival (PFS) was improved (6.6 vs 3.3 months; $P = .004$) in the group receiving decitabine, and patients receiving decitabine reported improvement in fatigue and physical functioning, with borderline improvement in most other quality of life scales.

Given the high-risk characteristic of this older adult population with improvement in PFS and quality of life, further investigation of decitabine regimens, which allow outpatient administration and alternative dosing, is recommended.

TET-2 Mutation as an Indicator of Sensitivity to Hypomethylating Agents

Although azacitidine and decitabine have provided effective treatment options for patients with high-risk MDS, many patients have limited benefit or no response. Recent efforts to isolate biomarkers that contribute to the pathogenesis of MDS or that allow selection of therapies based on a molecular profile have identified the ten-eleven translocation-2 (TET-2). TET-2 is the most common gene mutation in MDS (16%-26%) and is thought to be involved in the regulation of gene expression.^{21,22} Although there are conflicting reports of the prognostic significance of TET-2, the presence of a TET-2 mutation has been correlated with improved response to azacitidine.²¹⁻²³ To date, no specific molecular target has been identified to allow targeted therapy for MDS. The isolation of the TET-2

mutation as an indicator of improved sensitivity to hypomethylating agents may allow a method for preferential treatment selection based on improved sensitivity, much like the KRAS mutation has been explored in trials studying the use of epidermal growth factor receptor antagonists in colorectal cancer.

Investigating an Oral Formulation

MDS remains a rare disease that is 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.¹¹ The frequency of office visits associated with injectable or intravenous therapies often presents a challenge for these patients. Garcia-Manero and colleagues conducted a phase I study of an oral formulation of azacitidine in 49 patients with MDS ($n = 29$), chronic myelomonocytic leukemia (CMML, $n = 4$), or acute myeloid leukemia ($n = 8$) to explore the bioavailability and clinical activity of oral azacitidine. In this small phase I trial, oral azacitidine was found to have clinical and biological activity at a daily dose of 480 mg for 7 consecutive days, every 28 days.²⁴ The dose-limiting toxicity for the oral formulation was grade 3/4 diarrhea.²⁴

Early Initiation of Active Treatment

In addition to the well-described rising blast count, the chromosome 7 abnormalities or complex karyotype, atypical localization of immature precursors (ALIP), and, more recently, isolation of the Tp53 gene are associated with early leukemic transformation and indicate the need for early initiation of active

treatment.^{21,25} Elderly patients with AML thought to be due to antecedent MDS also require immediate evaluation and are often best treated with therapies commonly used to treat MDS.

UPDATES ON IMMUNOMODULATORY AGENTS

Lenalidomide, a second-generation immunomodulatory agent, is approved in the United States for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality, with or without additional cytogenetic abnormalities. The del(5q) is the most common cytogenetic abnormality in MDS.²¹ The efficacy and safety of lenalidomide was demonstrated in 3 clinical trials (MDS-001, MDS-002, and MDS-003; Table 3). On the basis of these trials, lenalidomide is the treatment of choice in patients with del(5q) MDS.²⁶

More recently, the MDS-004 trial conducted in Europe compared the efficacy and safety of lenalidomide 5 mg versus 10 mg administered daily for 21 consecutive days using a 28-day cycle versus placebo in transfusion-dependent MDS patients with del(5q). Patients receiving lenalidomide, either 5 or 10 mg, showed improved response (48% for 5 mg, 61% for 10 mg, 8% for placebo; $P < .001$) compared with placebo with similar rates of transfusion independence, cytogenetic responses, and toxicity profiles in the lenalidomide arms.²⁷ Based on the results of this trial and the previous data from the MDS-001 and MDS-003 trials, the recommended dose for lenalidomide is 10 mg daily for 21 days every 4 weeks.²⁸

MANAGEMENT OF ADVERSE EVENTS, SUPPORTIVE CARE, AND THE PRESERVATION OF QUALITY OF LIFE

Treatment response in most cases requires a minimum of 4 to 6 months of active therapy, and the best response may not be evident for up to 9 months.¹² To improve the potential benefit, it is critical to prepare the patient and family for this time frame and reinforce a commitment to at least 4 to 6 months of therapy before response can be adequately evaluated. Aggressive supportive care should be instituted for all patients, and each drug has specific recommendations for dose modifications or drug holidays in the presence of more severe or symptomatic cytopenias.¹² With a limited potential for cure, preservation of quality of life and independent function should remain a priority. 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, with complex comorbidities, or not wishing to pursue active therapies, supportive care alone is an appropriate standard of care.

Setting Expectations Regarding Toxicities

The most common toxicity associated with all active therapies for MDS is myelosuppression, which most often consists of moderate but asymptomatic cytopenias that may be present for extended periods without the need for any intervention.²⁹ Cytopenias often get worse before they get better, and patients may require more

frequent transfusions before achieving hematologic improvement or transfusion independence. The typical median time to response of several weeks to months may be disconcerting for patients and providers with a potential to view these expected cytopenias as unacceptable toxicity or treatment failure.

Setting expectations for anticipated toxicities, establishing a protocol for reporting, and developing standards for interventions will provide reassurance to the patient and limit unnecessary discontinuation of therapy. Monitoring the CBC, differential, and platelet count is recommended weekly for the first 8 weeks of treatment, and then as clinically indicated. Each drug has specific recommendations for frequency of laboratory monitoring, dose modifications, or drug holidays in the presence of more severe or symptomatic cytopenias. Stable moderate asymptomatic cytopenias require continued monitoring but may not require discontinuation of therapy, may not require intervention, and may not have a negative effect on patients' quality of life.²⁹

SUMMARY

The science related to understanding the pathobiology of MDS, opportunities for treatment, and effective management of patients is evolving. Although significant progress has been made in the last decade, many questions remain unanswered. The majority of patients with MDS are older, requiring a working knowledge of the unique needs of the older adult for effective management. Optimal patient outcomes will require us to build on the effective management of primary MDS, which can succeed

only with effective management of comorbidities and proactive management of common adverse events, such as myelosuppression. This will require a change in perspective with regard to age as a limiting factor for active treatment.

REFERENCES

1. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. *Cancer*. 2007;109:1536-1542.
2. Cogle R, Craig BM, Rollison DE, List AF. Incidence of the myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. *Blood*. April 29, 2011;[Epub ahead of print]. doi:10.1182/blood-2011-02-337964.
3. Sekeres M. Epidemiology, natural history, and practice patterns of patients with myelodysplastic syndromes in 2010. *J Natl Compr Canc Netw*. 2011;9:57-63.
4. Kurtin S. Leukemia and myelodysplastic syndromes. In: Yarbro et al, eds. *Cancer Nursing: Principles and Practice*. 7th ed. Sudbury, MA: Jones & Bartlett LLC. 2011:1369-1398.
5. Kurtin S, Demakos E. Disease burden associated with quality of life in myelodysplastic syndromes: findings from a Web-based survey. *Leuk Res*. 2011;S142 [poster].
6. Sekeres MA, Maciejewski JP, List AF, et al. Perceptions of disease state, treatment expectations, and prognosis among patients with myelodysplastic syndromes: results from an internet based survey. *Oncologist*. 2011. doi:10.1634/theoncologist.2010-0199.
7. Greenberg PL, Attar E, Bennett JM, et al. Myelodysplastic syndromes: clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2011;9:30-56.
8. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89:2079-2088.
9. Garica-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower-risk myelodysplastic syndrome. *Leukemia*. 2008;22:538-543.
10. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R), developed by the International Prognostic Working Group for Prognosis in MDS (IWG-PM). *Leuk Res*. 2011;35:S6. Abstract 14.

11. Kurtin S. Risk analysis in the treatment of hematological malignancies in the elderly. *J Adv Pract Oncol*. 2010;1:119-129.
12. Kurtin S, Demakos E. An update in the treatment of myelodysplastic syndromes. *Clin J Oncol Nurs*. 2010;14:E29-E44. doi:10.1188/10.CJON.E24-E39.
13. Scott B, Deeg J. Myelodysplastic syndromes. *Annu Rev Med*. 2010;61:345-358.
14. Blum W. How much? How frequent? How long? A clinical guide to new therapies for myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Prog*. 2010;2010:314-321.
15. Garcia-Manero G. Myelodysplastic syndromes: 2011 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2011;86:491-498.
16. Steensma DP, Stone RM. Practical recommendations for hypomethylating agent therapy of patients with myelodysplastic syndromes. *Hematol Oncol Clin North Am*. 2011;24:389-406. doi:10.1016/j.hoc.2010.02.012.
17. Garcia-Manero G, Fenaux P. Hypomethylating agents and other novel strategies in myelodysplastic syndromes. *J Clin Oncol*. 2011;29:516-523. doi: 10.1200/JCO.2010.31.0854.
18. Silverman LR, Fenaux P, Mufti GJ, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. *Cancer*. 2011;117:2697-2702.
19. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. *Lancet Oncol*. 2009;10:223-232.
20. Lubbert M, Sucui S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndromes (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Leukemia Group of the German MDS Study Group. *J Clin Oncol*. April 11, 2011;[Epub ahead of print]. doi:10.1200/JCO.2010.30.9245.
21. Bejar R, Levine R, Ebert B. Unraveling the molecular pathophysiology of myelodysplastic syndromes. *J Clin Oncol*. 2011;29:504-515.
22. Tiu RV, Visconte V, Traina F, et al. Updates in cytogenetics and molecular markers in MDS. *Curr Hematol Malig Rep*. 2011;6:126-135.
23. Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET-2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leuk Res*. April 15, 2011;[Epub ahead of print].
24. Garcia-Manero G, Gore S, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol*. 2011;[Epub ahead of print]. doi:10.1200/JCO.2010.34.4226.
25. Jadersten M, Saft L, Smith A, et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. *J Clin Oncol*. April 25, 2011;[Epub ahead of print]. doi:10.1200/JCO.2010.31.8576.
26. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes—v2.2011. www.nccn.org.
27. Fenaux P, Giagounidis A, Selleslag DL, et al. Safety of lenalidomide (LEN) from a randomized phase III trial (MDS-004) in low-/int-1-risk myelodysplastic syndromes (MDS) with a del(5q) abnormality. *J Clin Oncol*. 2010;28(suppl):15s. Abstract 6598.
28. Komrokji RS, Sekeres MA, List AF. Management of lower-risk myelodysplastic syndromes: the art and evidence. *Curr Hematol Malig Rep*. 2011;6:145-153.
29. Kurtin S, List AF. Durable long-term responses in patients with myelodysplastic syndromes treated with lenalidomide. *Clin Lymphoma Myeloma*. 2009;9:E10-E13. doi:10.3816/CLM.2009.n.053.

ADDITIONAL READINGS

- List A, Dewald G, Bennett J, et al for the Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355:1456-1465.
- List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med*. 2005;352:549-557.
- Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood*. 2008;111:86-93.
- Schanz J, Tuchler H, Sole F, et al. Proposal of a new comprehensive cytogenetic scoring system for primary MDS. Presented at the 15th Congress of the European Hematology Association, Barcelona, Spain, June 10-13, 2010. Abstract 3446.
- Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. *J Clin Oncol*. 2002;20:2429-2440.

Common Hematologic Malignancies in the Elderly

Removing Age as a Barrier to Effective Treatment

Myelodysplastic Syndromes: Clinical Updates With Consideration of the Unique Needs of the Older Patient

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1. The first epidemiologic data specific to MDS in the United States were collected between 2001 and 2003. More recent data have reported much higher estimates of both incidence and prevalence. One factor thought to contribute to this rise is
 - a. Inclusion of MDS in the differential diagnosis in elderly patients
 - b. Decrease in the secondary or treatment-related MDS
 - c. Exclusion of patients who have transformed to acute myelogenous leukemia
 - d. Exclusion of elderly patients being evaluated for cytopenias
2. The leading cause of death in patients with MDS is
 - a. Cardiomyopathy
 - b. Disease-related factors
 - c. Myelosuppression
 - d. Renal failure
3. Risk-adapted, individualized evaluation strategies that incorporate prognostic features of the disease and the individual patient provide the best tools for this approach. The International Prognostic Scoring System (IPSS), developed in 1997, uses number of cytopenias and cytogenetic abnormalities, and percentage of blasts in the bone marrow sample. With the availability of more active therapies, a revised IPSS (IPSS-R) has been proposed. Additional factors that correlate with prognosis and are suggested for inclusion in the IPSS-R include
 - a. Elevated LDH and albumin levels
 - b. Thrombocytopenia after first treatment and elevated LDH levels
 - c. Thrombocytopenia at time of diagnosis and decreased albumin levels
 - d. Thrombocytopenia at time of diagnosis and transfusion burden
4. In addition to the key principles related to characteristics of the patient and disease, the clinician must consider the most recent clinical trials data to guide treatment. An example of recent information is
 - a. Lenalidomide 10 mg daily for 21 days every 4 weeks is recommended as the initial dose for treatment
 - b. Azacitidine does not show any survival benefit compared with conventional therapy
 - c. Decitabine requires inpatient administration due to toxicities
 - d. All 3 of these agents should show a response in 3 weeks, or they are not considered effective
5. Recent efforts to isolate biomarkers that contribute to the pathogenesis of MDS or that allow selection of therapies based on a molecular profile have identified the TET-2 mutation. Although more research is needed, this shows promise as an indicator of
 - a. Improved sensitivity to immunomodulatory agents
 - b. Improved sensitivity to hypomethylating agents
 - c. Decreased sensitivity to immunomodulatory agents
 - d. Decreased sensitivity to hypomethylating agents
6. Treatment response in most cases requires active therapy for a minimum of
 - a. 1 to 2 months
 - b. 3 to 4 months
 - c. 4 to 6 months
 - d. 7 to 8 months

(Continues on next page)

Common Hematologic Malignancies in the Elderly Removing Age as a Barrier to Effective Treatment

*Myelodysplastic Syndromes: Clinical Updates With Consideration
of the Unique Needs of the Older Patient*

Learning Assessment and Evaluation Form

(continued from previous page)

7. The most common toxicity with all active therapies for MDS is myelosuppression. When monitoring patients, it is important to note that cytopenias
- Should improve a week after the first treatment
 - Should improve 2 weeks after the first treatment
 - Often get worse before they get better
 - Dramatically improve after the first treatment, then get worse
8. In caring for patients with MDS, it is important to establish a protocol for reporting and monitoring blood counts. The recommended protocol is to monitor the CBC, differential, and platelet counts
- Weekly for the entire time the patient receives treatment
 - Weekly for the first 8 weeks, then as clinically indicated
 - Weekly for the first 4 weeks, then as clinically indicated
 - Weekly for the first 2 weeks, then as clinically indicated
9. Prior to participating in this activity, how confident were you in recognizing and managing patients at risk for myelosuppression?
- Not confident 1 2 3 4 5 6 7 Very confident
10. After participating in this activity, how confident are you in recognizing and managing patients at risk for myelosuppression?
- Not confident 1 2 3 4 5 6 7 Very confident
11. Prior to participating in this activity, how confident were you in caring for elderly patients with MDS?
- Not confident 1 2 3 4 5 6 7 Very confident
12. After participating in this activity, how confident are you in caring for elderly patients with MDS?
- Not confident 1 2 3 4 5 6 7 Very confident