Myelodysplastic Syndromes:
The Challenge of Developing Clinical Guidelines and Supportive Care Strategies for a Rare Disease

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Myelodysplastic syndromes (MDS) represent a group of clonal myeloid malignancies with variability in clinical presentation and disease trajectory, as well as prognosis and treatment recommendations (Kurtin & Demakos, 2010). MDS is considered to be a rare disease that is most common in adults older than age 70. The disease is 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, 2011). This supplement is intended to provide the oncology clinician with an overview of MDS and provide tools for the clinical management and support of patients with MDS.

Background

Although scientific discovery has been robust, MDS remains a disease most common in a heterogeneous population (the older adult) with evolving principles of pathobiology, treatment options, and prognosis. Despite the accumulation of scientific data detailing the malignant attributes of the MDS clone and the fact that most patients die as a result of their disease, many clinicians continue to describe MDS to patients as a blood disorder, bone marrow failure state, or form of anemia (Bejar, Levine, & Ebert, 2011; Dayyani et al., 2010; Sekeres, 2011). Collectively, these findings indicate the need for clarity in the definition of MDS as well as education of healthcare providers about the scientific advances in the field of pathobiology of MDS and its treatment.

The first epidemiologic data specific to MDS in the United States was collected from 2001–2003 with an estimated age-adjusted incidence of 3.4 per 100,000 people, or about 10,000 new cases per year (Ma, Does, Raza, & Mayne, 2007). An estimated 60,000 individuals are currently living with MDS in the United States; however, more recent data have estimated much higher incidence and prevalence rates. Cogle, Craig, Rollison, and List (2011) assessed the incidence of MDS in the United States using a claims-based algorithm to evaluate the Surveillance, Epidemiology and End Results (SEER) Medicare database using International Classification of Diseases, 9th edition, Clinical Modification codes; confirmatory blood counts; and bone marrow analysis. With this model, the estimated incidence of MDS in 2005 for adults 65 years of age and older was 75 per 100,000, considerably higher than the SEER estimates of 20 per 100,000 for that same year. However, Cogle et al. (2011) has a number of potential limitations, including retrospective analysis and reliance on the coding of diagnoses, which historically has been subject to billing definitions of clinical diagnoses most often selected by coders, not clinicians. The true incidence of MDS is likely somewhere between the two estimates. The underreporting of MDS is also suggested by more recent analyses, based on several limitations in the current data sets: limited outpatient reporting of new cases to the SEER registry (based on an inpatient model), exclusion of patients whose disease transformed to acute myeloid leukemia from antecedent MDS (common in higher-risk MDS), and lack of adequate diagnostic evaluations to confirm the diagnosis of MDS.

Because of the advent of active therapies that are capable of modifying the natural history of MDS and extending survival outcomes for many patients, older adults presenting with cytopenias are more often being evaluated for MDS. As a result, the prevalence rates for MDS are expected to increase in coming

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Digital Object Identifier:10.1188/12.CJON.S1.5-7

years as the familiarity of healthcare providers increases (Kurtin, 2011; Sekeres, 2011). The expected increase in treatment-related MDS will also contribute to a rising incidence of MDS. Based on these trends, MDS is expected to become the most common myeloid malignancy; however, it remains poorly understood (Sekeres, 2011). To estimate disease burden and the effect on healthcare services and to develop effective treatment and support strategies, accurate estimates of incidence and prevalence of MDS are critical.

Assessment and Treatment

In more than 80% of MDS cases, the leading cause of death is related to the disease itself (Dayyani et al., 2010). Although a wide variability exists in life expectancy based on the disease attributes and individual patient characteristics, studies of large cohorts have identified risk stratification criteria that can aid prognostic estimates. The International Prognostic Scoring System (IPSS), developed in 1997 before the availability of active therapies, is the most commonly used risk stratification tool for this purpose (Greenberg et al., 1997). The IPSS assigns one of four risk categories (low, intermediate-1, intermediate-2, and high) based on the number of cytopenias, cytogenetic abnormalities, and percentage of blasts in the bone marrow sample. Although each risk category has a projected median survival and associated risk of leukemic transformation, its use is limited to the time of original diagnosis, and the system fails to incorporate disease characteristics that have been found to correlate with prognosis since its original development. Using prognostically important risk factors (e.g., depth of cytopenias [anemia, thrombocytopenia, and neutropenia], bone marrow blasts, refined cytogenetic subgroups), a revised IPSS (IPSS-R) has been proposed that will add a fifth risk category (very low, low, intermediate, high, and very high) (Greenberg, Tuechler, et al., 2011). The International Working Group for Prognosis in Myelodysplastic Syndromes continues to refine the specific criteria for the IPSS-R, including assignment of scores and the final attributes of each risk category. Additional details specific to disease classification and risk stratification will be reviewed within this supplement.

> Some patients are not offered active therapies because of their age, and others discontinue treatment prematurely because of a perceived lack of benefit or concern about persistent cytopenias.

Three agents are currently approved by the U.S. Food and Drug Administration for the active treatment of MDS: azacitidine, decitabine, and lenalidomide (Kurtin, 2011). Patient characteristics (e.g., comorbidities, performance status, lifestyle, quality of life), disease characteristics (e.g., risk status, cytogenetics), and available treatment options all influence treatment selection. In the first article, Ridgeway, Fechter, Murray, and Borràs (2012) provide a summary of the treatment options available to date for both low-risk and high-risk MDS, including international variances in availability. A summary of current clinical trials provides insight into evolving treatment options. The article also emphasizes the limited approved treatment options, the importance of maximizing each option, and the need for continued patient enrollment in clinical trials to facilitate the development of new therapies.

Given the limited number of approved therapies for MDS, effective management of each treatment option is critical to provide each patient the best opportunity for successful treatment. Most patients with MDS are managed in an outpatient setting, and most are older than age 65 years. A multidisciplinary team approach that focuses on the application of clinical tools and strategies for patient and family support, clear definitions of the disease and treatment goals, anticipation of common adverse events, and integration of proactive management strategies will provide the best opportunity for optimal treatment outcomes (Kurtin, 2011). Familiarity with the key concepts of treatment triggers, individualized risk-adapted therapy, expectations for early cytopenias and the time required for first and best response, comfort with sustained moderate asymptomatic cytopenias, and continuation of treatment until disease progression or unacceptable toxicity will allow individualized support of the patient with MDS and improve the opportunity for favorable outcomes. In the second article, Kurtin, Demakos, Hayden, and Boglione (2012) provide practical tools for managing the patient with MDS, including development of a partnership with the patient and family.

Support Strategies

MDS remains an incurable disease. However, a small number of patients achieve a prolonged response to allogeneic bone marrow transplantation. But given the advanced age of patients, common comorbidities, and the lack of a suitable sibling donor, allogeneic transplantation is not an option for the majority of patients with MDS. Active therapies and supportive care for MDS require an understanding of potential issues impacting quality of life and appropriate interventions. All patients with MDS should receive supportive care, including transfusion support, administration of growth factors when appropriate, management of comorbidities, iron chelation therapy when appropriate, and treatment of any acute diagnoses (including infections). For patients with limited performance status or complex comorbidities, or those not wishing to pursue active therapies, supportive care alone is an appropriate standard of care. The final three articles in this supplement provide important strategies for support of the patient with MDS. In the third article, Shah, Kurtin, Arnold, Lindroos-Kolqvist, and Tinsley (2012) provide an update on iron chelation therapy for treatment of transfusion-associated iron overload. Red blood cell transfusion dependence is inevitable for most patients with MDS because of ineffective erythropoiesis and is known to be associated with iron overload (Steensma, 2011). The IPSS-R, the World Health Organization's Prognostic Scoring System, and the MD Anderson prognostic model for MDS include hemoglobin levels or transfusion burden or a history of transfusion as an unfavorable prognostic indicator in patients with MDS (Garcia-Manero, 2011; Greenberg, Attar, et al., 2011; Greenberg, Tuechler, et al., 2011; Komrokji, Sekeres, & List, 2011). Iron chelation therapy has been correlated with improved clinical outcomes (Greenberg, Tuechler, et al., 2011); however, a lack of consensus exists about who will benefit most from iron chelation therapy, and available treatment options may be associated

with adverse events. Shah et al. (2012) also provide a review of the physiology of transfusion-related iron overload, strategies for identifying and monitoring at-risk patients, and guidelines for the safe administration of iron chelation therapies.

With a limited potential for cure, preservation of quality of life and independent function should remain a priority. Data specific to quality of life in patients with MDS are relatively recent. In the fourth article, Thomas, Crisp, and Campbell (2012) provide an update on the key considerations for quality of life in patients with MDS with discussion of supportive care strategies, the impact of uncertainty in this rare disease, and insight into the patient and family perspective. Providing support to the patient and family is critical. In the fifth and final article, Kurtin, Paterson, et al. (2012) summarize the currently available international resources for patients with MDS and their caregivers, including discussion of the most commonly asked questions and how a nurse might provide information to address these inquiries.

Conclusion

MDS, primarily a disease afflicting older adults, is increasing in incidence and prevalence. Development of therapeutic MDS strategies feasible in the older adult population will be necessary given that the leading cause of death in that population is from disease-related factors. 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 risk stratification criteria, and understanding of how to effectively support patients on treatment. However, 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, and others discontinue treatment prematurely because of a perceived lack of benefit or concern about persistent cytopenias. Some patients choose not to pursue active therapies and opt for supportive care alone. Other patients simply do not respond to the 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, expected disease trajectory, options for treatment, risks and benefits of the treatment, what might happen if they do not pursue treatment, and what is required if they do pursue treatment.

This supplement has been developed by members of the MDS Foundation International Nurse Leadership Board and staff of the MDS Foundation who specialize in patient advocacy to provide information to providers for the enhancement of care for patients with MDS.

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