The Myelodysplastic Syndromes

Series Editor:
Eric D. Jacobsen, MD
Instructor in Medicine, Harvard Medical School, Department of Medical Oncology, Brigham & Women’s Hospital and Dana-Farber Cancer Institute, Boston, MA

Contributor:
Gregory A. Abel, MD, MPH
Fellow in Oncology and Hematology, Dana-Farber Cancer Institute, Boston, MA

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INTRODUCTION

The myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis and a tendency to transform to acute myelogenous leukemia (AML). These disorders range in clinical severity from incidentally found disease manifesting as mild anemia, to highly symptomatic MDS characterized by severe anemia, neutropenia, and/or thrombocytopenia and their sequelae (hemorrhage and infection). In general, the syndromes are distinguishable from de novo AML by the relative stability of the constituent blood counts over time,\(^1\) which provides a sizable window for treatment. However, MDS can be extremely difficult to manage given its predilection for elderly patients who often harbor symptomatic comorbid conditions and have difficulty tolerating chemotherapy.

Despite these challenges, there have been recent improvements in the way that MDS is diagnosed, classified, and treated. Although supportive care (eg, treatment of infections, red blood cell [RBC] and platelet transfusions, hematopoietic growth factors) has long been the standard for management of MDS,\(^2\) there are now 3 medications specifically approved for its treatment, several others that are routinely used as part of its comprehensive management, and many others currently under investigation. For younger patients with high-risk disease, hematopoietic stem cell transplantation is also an option. This manual will review the clinical evaluation, diagnosis, and treatment options for patients with MDS.

EPIDEMIOLOGY AND PATHOGENESIS

Although rare, MDS is thought to be underreported due to its indolent nature and predilection for elderly patients who may die of other causes before the syndrome is diagnosed. Incidence rates for MDS first became reportable to the National Cancer Institute’s Surveillance Epidemiology and End Results Program (SEER) in 2001; in 2003, there were an estimated 10,300 cases per 100,000 persons per year.\(^3\) The incidence of MDS increases with age: age-specific incidence rates are thought to be about 5 per 100,000 for persons aged 50 to 59 years as compared to 49 per 100,000 for persons aged 70 to 79 years.\(^4\)

- Are there any known predisposing factors that cause MDS?

Most cases of MDS are thought to be idiopathic, although some predisposing risk factors have been indentified. These include age, male gender, excessive alcohol use, exposure to radiation, exposure to immunosuppressive therapy, certain genetic syndromes (eg, Down syndrome, Fanconi anemia), and occupational chemical exposures (eg, lead, benzene).\(^2\) When a clear association is found, the syndrome is called secondary MDS (s-MDS). Radiotherapy and medications used to treat malignancy (eg, alkylating agents) have also been implicated in the etiology of a subset of s-MDS called therapy-related MDS (t-MDS).\(^5,6\) t-MDS is even more difficult to treat than spontaneously occurring MDS and has a higher likelihood of transformation to AML.\(^6,7\)

A multistep genetic progression model has been proposed for MDS, given that older age and certain types of radiation/chemotherapy are associated with the development of clinically significant disease, and that MDS has a tendency to progress to AML. In this model, inherited or acquired genetic defects conspire with additional environmentally caused genetic events to cause gains and/or losses of specific chromosome regions or functionality in hematopoietic stem cells.\(^8\) As with other types of malignancy, defective clones predominate through competitive survival advantage and excessive proliferation.\(^9\) Thus, disease-altering treatments for MDS are focused on either replacing the defective clone with a healthy one (eg, stem cell transplantation) or regulating genetic and epigenetic events that contribute to the maintenance of that clone (eg, DNA methyltransferase inhibitors, histone deacetylase inhibitors).

In MDS, malignant clones have a survival advantage but are defective in completing normal hematopoiesis. The syndrome is unique among hematologic malignancies in that it possesses a seemingly contradictory state of a normocellular or hypercellular bone marrow that coexists with progressive peripheral cytopenias.\(^10\)