Myelodysplastic Syndromes: Diagnosis and Treatment

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CME Activity

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Abstract

In the past few years, new biological insights into the myelodysplastic syndromes (MDS) resulting from molecular genetic analysis have improved pathologic understanding, but treatment advances have not kept pace. More than 40 genes are now known to be recurrently mutated in MDS. However, because most of these genes encode spliceosome components, chromatic remodeling factors, epigenetic pattern modulators, or transcription factors rather than more easily inhibited activated tyrosine kinases, there are as of yet few narrowly targeted therapies available for MDS. Three drugs—azacitidine, decitabine, and lenalidomide—were approved by the US Food and Drug Administration for MDS indications a decade ago, and these agents can improve hematopoiesis, delay disease progression, and improve survival and quality of life for a subset of patients. However, only a few patients with MDS respond to these agents, and their benefit is temporary. The only potentially curative therapy for MDS is allogeneic hematopoietic stem cell transplant, but owing to the advanced age of many patients with MDS and the frequency of serious comorbid conditions, less than 10% of patients currently undergo stem cell transplant. This narrative review summarizes the current understanding of MDS and treatment options for these challenging disorders.

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The myelodysplastic syndromes (MDS) are the most commonly diagnosed acquired bone marrow failure syndromes in adults.[1] The umbrella term *MDS* is used to describe a heterogeneous group of chronic myeloid neoplasms characterized by ineffective clonal hematopoiesis and abnormal "dysplastic" cell morphology, resulting in peripheral blood cytopenias and functional blood cell abnormalities.[2,3] The MDS are inherently unstable and

may progress over time, including evolution to acute myeloid leukemia (AML). Acute myeloid leukemia is currently defined by the World Health Organization (WHO) as at least 20% blasts in the marrow or blood or the presence of either myeloid sarcomas or certain AML-defining karyotypes, such as t(15;17) and t(8;21). Therefore, all patients with MDS have less than 20% marrow blasts, by definition.[4]

EPIDEMIOLOGIC PROFILE

Owing to the use of ambiguous diagnostic terminology, the exclusion of MDS cases from most cancer registries, and the incomplete evaluation of many older patients with cytopenias, the incidence and prevalence of MDS have been difficult to estimate accurately.[5] Data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results Program (which has captured MDS cases since 2001) suggest that 10,000 to 12,000 new cases are diagnosed in the United States each year (ie, ~3-4 cases per 100,000 persons per year).[6] However, analysis of Medicare claims in conjunction with Surveillance, Epidemiology, and End Results data indicates that the actual incidence of MDS in the United States may be closer to 30,000 to 40,000 new cases per year—several times higher than the incidence of AML.[7]

Aging is the most important risk factor for the development of MDS. Owing to errors in DNA replication and spontaneous mutations from normal metabolic by-products (eg, conversion of cytosine to thymidine by oxidative deamination from reactive oxygen species), coding mutations accumulate in hematopoietic stem cells at a mean ± SD rate of 0.13±0.02 exonic mutations per year of life.[8] When an acquired DNA mutation or combination of mutations promotes growth or generates a survival advantage to a hematopoietic stem or progenitor cell, clonal hematopoiesis emerges. Approximately 10% of individuals older than 70 years have clonal mutations in genes associated with myeloid neoplasia, such as *DNMT3A, TET2*, and *SF3B1*, and these persons have a 0.5% to 1% chance per year of acquiring additional mutations that lead to progression to MDS or another hematologic neoplasm, similar in magnitude to the risk of monoclonal gammopathy of undetermined significance progressing to myeloma.[9,10]

In the United States and Western Europe, the median age at diagnosis of MDS is approximately 70 years, and the incidence increases steadily with age. In Eastern Europe and parts of Asia, the median age at diagnosis is younger than in the West, for unclear reasons. Although MDS have a modest male predominance, a specific MDS subtype—MDS associated with isolated deletion of the long arm of chromosome 5, hypolobated megakaryocytes, and erythroid hypoplasia (so-called 5q− syndrome)—is more common in women.[11]

Approximately 85% to 90% of MDS cases are idiopathic and result from aging-related hematopoietic stem cell injury. Secondary or therapy-related MDS (t-MDS) represents 10% to 15% of cases.[12] Myelodysplastic syndrome can be induced by exogenous DNA-damaging agents, including DNA alkylating drugs (eg, cyclophosphamide and melphalan), inhibitors of topoisomerase II (eg, etoposide), ionizing radiation, and volatile hydrocarbons (eg, benzene). Although it can be difficult to prove a direct link between an exposure and subsequent MDS development, features supporting t-MDS rather than de novo MDS include complex karyotype (defined as ≥3 acquired chromosome abnormalities), abnormalities of chromosomes 5 and 7, and *TP53* mutation.

Pediatric MDS, which are rare, are frequently associated with inborn disorders such as Fanconi anemia, Down syndrome, and congenital neutropenia.[13] Germline mutations in *RUNX1* and *GATA2* transcription factors also predispose to MDS. Germline *RUNX1* mutations are associated with a prodrome of thrombocytopenia that is often mistaken for immune thrombocytopenia, and *GATA2* mutations may be associated with monocytopenia, mycobacterial infections, and lymphedema (MonoMAC syndrome).[14,15]

CLASSIFICATION

The fourth edition of the *WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues*, published in 2008, is currently the most widely used MDS classification (Table 1).[4] The 2008 WHO MDS classification is similar to the earliest formal MDS classification, the 1982 MDS classification of the French-American-British Cooperative Group. In 2016, a revision of the WHO classification will be published that will simplify classification and formally address the role of molecular genetic testing in myeloid neoplasia diagnosis. The current WHO classification has limited prognostic

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