Myelodysplastic Syndromes: Updates and Nuances

Kim-Hien T. Dao, DO, PhD

KEYWORDS

- Myelodysplastic syndrome • Anemia • Azacitidine
- Therapy-related myelodysplastic syndrome • Blood and marrow transplant

KEY POINTS

- Myelodysplastic syndrome (MDS) is characterized by low blood cell counts, abnormal blood cell development, clonal genetic markers, and increased propensity toward AML.
- The recent genetic characterization of MDS has advanced various aspects of clinical management.
- Novel therapies are emerging to address common drivers of MDS development and disease progression.
- Patients with MDS should always be considered for clinical trial participation whenever possible to support scientific discoveries toward improving outcomes.

INTRODUCTION

In this review article, I discuss anemia caused by underlying MDS, a hematologic malignancy associated with widely varying clinical presentations, mutation patterns, and patient outcomes. *Myelo* means marrow and *dysplasia* means abnormal development. MDS is characterized by low blood cell counts, abnormal blood cell development, clonal genetic markers, and increased propensity toward acute myeloid leukemia (AML). The general incidence in the US population is approximately 4.8 per 100,000 per year but is as high as 30 to 60 per 100,000 per year in people over 70 years old (Surveillance, Epidemiology, and End Results Cancer Statistics Review, 1975–2010. National Cancer Institute; 2013). There is a slight male-to-female predominance (1.26–1). Risk-adapted monitoring and therapy are essential cornerstones of MDS clinical management. Over the past 5 years, advances in massive parallel sequencing technology have enabled genetic characterization of MDS to a point where the focus has now shifted toward translating these findings to improve patient outcomes. This will require, for example, integration of genetic data and disease behavior to help

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Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, Mail Code: UHN73C, 3181 South West Sam Jackson Park Road, Portland, OR 97239, USA
E-mail address: daok@ohsu.edu

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choose/design better therapies, exploitation of synthetic lethality based on mutational exclusivity, and defining the genetic and biologic determinants of the good responders versus poor responders to various existing therapies. The use of genetic markers to predict and monitor risk for disease relapse may improve the selection of conditioning regimens and maintenance therapies in the setting of allogeneic blood and marrow transplant (BMT). The availability of molecular genetic testing has also helped with the diagnosis of MDS and other prediagnostic conditions, especially when dysplasia is not overtly present or World Health Organization (WHO) criteria are not met based on absolute cutoffs (eg, >10% dysplasia in a cell lineage). I present these discussions points using clinical vignettes that broadly represent common situations. I will not provide in-depth coverage of the genetics of MDS, prognostic systems, treatment options, allogeneic BMT, and drugs in the pipeline. The discussion points focus on integrating genetic data into diagnostic and prognostic considerations, managing patients who fail DNA methyltransferase (DNMT) inhibitors, and evaluating patients for allogeneic BMT. I discuss potential future directions in clinical management and translational research in MDS.

CLINICAL VIGNETTE 1: DIAGNOSTIC CONSIDERATIONS IN MYELODYSPLASTIC SYNDROME

A previously healthy 37-year-old man presented with progressive fatigue and dyspnea on exertion over the course of a few weeks. He was found to have a hypoproliferative anemia with hemoglobin level of 6.3 g/dL and reticulocyte of 0.15%. His platelet count, white blood cell count (WBC), and WBC differential were unremarkable. His blood smear was otherwise unremarkable. There was no laboratory evidence of hemolysis. He also reported intermittent fevers and diffuse body aches. His bone marrow biopsy showed hypercellular marrow (100% cellularity), marked myeloid hyperplasia, mild dysplasia in granulocytes (dyspoeisis in <10%), mild reticulin fibrosis, 3% blasts enumerated by morphology, slightly increased megakaryocytes with occasional clusters and small forms, scant erythropoiesis, and focally increased plasma cells (overall 2%). He had a normal male karyotype, and *BCR-ABL* and *JAK2*-V617F were not detected. He required frequent red blood cell transfusions to maintain hemoglobin above 7.0 g/dL. He was referred for discussion of treatment recommendations for newly diagnosed MDS.

ASSESSMENT OF CLINICAL VIGNETTE 1

The patient is relatively young with rapid onset of symptoms mainly due to symptomatic anemia. The median age of MDS diagnosis is 76 years old[1] and the typical clinical presentation tends to be indolent and progressive over months not weeks. However, approximately 6% of cases of MDS are diagnosed in people under 50 years old.[1] The patient does not have the standard risk factors for MDS, including, for example, advanced age, hereditary marrow failure syndromes, industrial benzene or other solvent exposure, and prior chemotherapy and radiation.[2] In addition to cytopenias, the complete blood cell count and a blood smear in an MDS patient may also reveal bilobed (pseudo–Pelger-Huët), hypersegmented, or hypogranulated neutrophils, unexplained macrocytosis (>100 fL) and oval-shaped red blood cells (macro-ovalocytes), elevated red blood cell distribution width, and giant or hypogranulated platelets. The patient did not have any of these findings. Thus, even before looking closer at his outside bone marrow biopsy slides and ordering molecular testing on his blood, I had already considered other possible diagnoses of anemia.