Current State of the Art: Management of Higher Risk Myelodysplastic Syndromes

Rami S. Komrokji

Abstract

The higher risk myelodysplastic syndrome (MDS) patients, defined by the International Prognostic Scoring System (IPSS) as intermediate-2 or high-risk groups, compromise a third of MDS patients who have an expected survival of less than 1.5 years. Our ability to better define higher risk MDS improved with the proposal of new clinical risk models such as the revised IPSS and by integration of molecular data, including somatic gene mutations. Allogeneic hematopoietic stem-cell transplantation (AHSCT) remains the only curative option. In higher risk MDS patients, proceeding early with AHSCT is associated with maximum survival gain. The decision to pursue AHSCT is individualized according to disease risk, comorbidities, and functional status. The role of therapy before AHSCT remains controversial, and the role of post-AHSCT maintenance is evolving. Hypomethylating agents are the only medications that alter the natural history of the disease. Azacitidine is the only drug reported to improve overall survival in higher risk MDS patients. Appropriate use and assessment of response is key for assuring patients benefit of such limited options. Treatment after failure of hypomethylating agents is an unmet need. The role of detectable somatic gene mutations in prognosis and tailoring therapy continue to emerge.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. S1, S39-43
Keywords: Allogeneic stem cell transplant, High risk, Hypomethylating agents, Management, MDS

Introduction

Myelodysplastic syndromes (MDS) are a group of malignant stem-cell neoplasms. MDS are characterized clinically by bone marrow failure with resultant cytopenias and its related complications. Pathologically, morphologic dysplasia is the hallmark of the disease. MDS may evolve into acute myeloid leukemia (AML) in 30% to 40% of cases.[1] However, the majority of patients die of disease-related complications.

In the last few years, we have learned much more about the biology of the disease. We explored the role of somatic gene mutations in disease pathogenesis and evolution.[2,3] We now recognize the impact of somatic gene mutation on prognosis.[3] The role of inflammation, immune deregulation, and the microenvironment is an area of research, which, it is hoped, will open the door for future new therapeutic opportunities.[4-6]

I focus here on higher risk MDS and how it is defined, the current status of its management (Figure 1), and potential future directions.

Malignant Hematology Department, H. Lee Moffitt Cancer Center, Tampa, FL

Submitted: Feb 9, 2016; Accepted: Feb 9, 2016

Address for correspondence: Rami S. Komrokji, MD, Malignant Hematology Department, H. Lee Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33612
E-mail contact: Rami.komrokji@moffitt.org

Who Is Considered a Higher Risk MDS Patient?

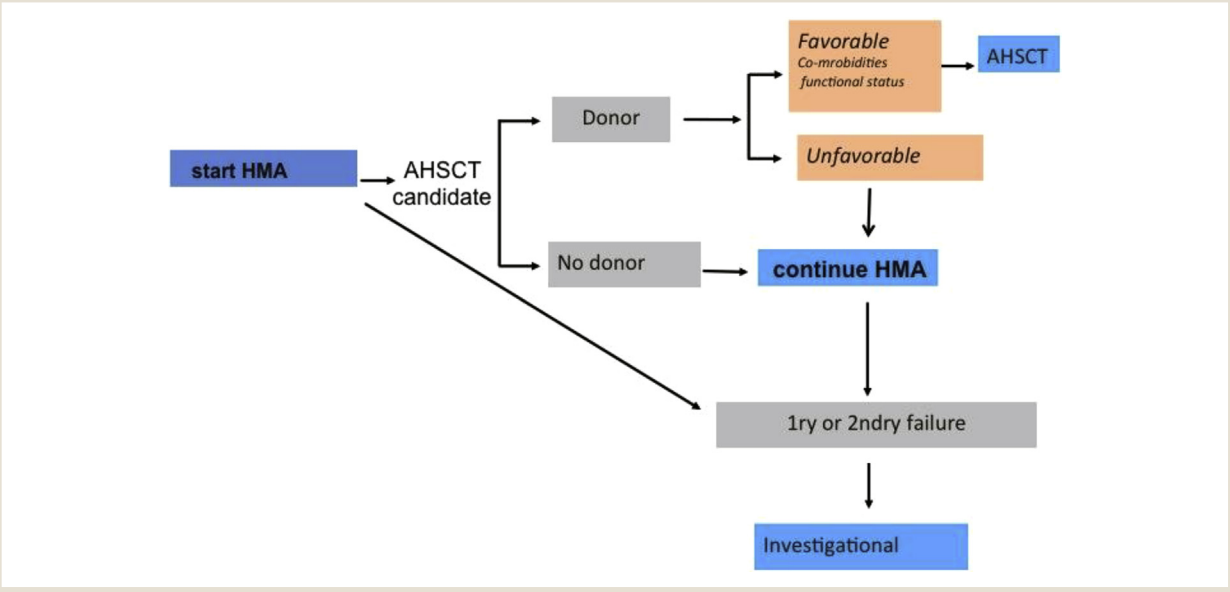
Naturally, higher risk MDS would be defined as the MDS subtypes associated with the higher chance of AML transformation and worse overall survival (OS). Historically, the International Prognostic Scoring System (IPSS) was the most commonly used tool to define higher risk MDS.[7] Patients are classified on the basis of cytopenias, myeloblast percentage, and cytogenetics. One third of MDS patients are classified as intermediate-2 or high risk by IPSS with an expected OS of < 1.5 years.

New clinical risk models refine the prognostic value of IPSS. The revised IPSS (R-IPSS) and global and low-risk MD Anderson models upstage the disease of approximately 25% of patients classified as lower risk.[8-10] In a recent study of 291 patients (26%) who survived ≤ 24 months from diagnosis, only 37% and 45% were classified as MD Anderson Lower-Risk Prognostic Scoring System category 3 and R-IPSS categories of intermediate or higher, respectively ($P = .06$).[11]

There are emerging data on the prognostic role of somatic gene mutations. Bejar et al demonstrated that the presence of 1 of 5 somatic gene mutations *P53*, *RUNX1*, *ASXL-1*, *EZH-2,* and *ETV-6* was associated with an inferior outcome independent of IPSS and upstaged patient risk in the low, intermediate-1, and intermediate-2 risk categories one stage higher, respectively.[3] The prognostic role of somatic mutations was also examined in the context of R-IPSS.[12,13] The number of somatic mutations also affects outcome. *SF3B1,* a

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.02.019

Figure 1 Current Algorithm for Management of Higher Risk MDS



Abbreviations: AHSCT = allogeneic hematopoietic stem-cell transplantation; HMA = hypomethylating agent; MDS = myelodysplastic syndromes.

spliceosome mutation, is the only somatic mutation associated with favorable outcome in MDS patients.[13]

In our practice, to estimate patient disease risk, we use IPSS, complemented by one of the new risk models (R-IPSS or the global MD Anderson model), and we assess the presence of somatic gene mutations.

Allogeneic Hematopoietic Stem-Cell Transplantation (AHSCT)

AHSCT remains the only curative option for MDS patients. The decision to pursue AHSCT depends on weighing the potential benefit (cure) versus risk (transplant-related mortality and quality of life). The decision should always be individualized on the basis of patient disease risk, goals of treatment, comorbidities, and the patient's functional status.

Markovian decision analysis models suggest that for patients with higher risk MDS, the maximum gain in survival is proceeding directly to AHSCT, while in lower risk MDS, it is better to wait until disease progression. The same results apply for reduced-intensity AHSCT in older patients.[14,15]

The most important predictor of outcome after AHSCT is disease status. A retrospective multicenter analysis was performed of 1333 MDS patients aged 50 years or older who received a transplant within the European Bone Marrow Transplant network since 1998. The median recipient age was 56 years. There were 811 human leukocyte antigen–matched siblings (61%) and 522 (39%) unrelated donor transplants. Five hundred patients (38%) received standard myeloablative conditioning, and 833 (62%) received reduced-intensity conditioning. The 4-year estimate for OS of the whole cohort was 31%. On multivariate analysis, use of reduced-intensity conditioning and advanced disease stage at transplantation (myeloblasts > 5% and poor-risk cytogenetics) were associated with an increased relapse rate. In contrast, advanced disease stage at transplantation, use of an unrelated donor, and reduced-intensity conditioning were independent variables associated with nonrelapse mortality.[16] Recent studies suggest that the detection of somatic mutations, particularly including *p53* mutation, at the time of AHSCT is associated with poor outcome.[17]

The role of induction chemotherapy before AHSCT is controversial. Retrospective studies have suggested no difference in outcome. However, most patients who received intensive chemotherapy had higher myeloblast percentages. Among patients who received intensive chemotherapy, those who experienced complete response had a better outcome.[18] A prospective observational study suggested that the outcome was similar if patients were treated with hypomethylating agents (HMA) before transplantation compared to intensive chemotherapy.[19]

The questions that remain open in 2015 include: what is the role of myeloblasts reduction before AHSCT? What is the benefit of complete cytogenetic response before AHSCT? At the molecular level, is there benefit of allele reduction before AHSCT? And finally, what is the role of maintenance after AHSCT, and who benefits from such a strategy?

HMA in Higher Risk MDS

HMA remain the standard of care for the majority of higher risk MDS patients. Azacitidine was the only drug that demonstrated an OS in the context of a randomized clinical study in MDS. In the pivotal AZA-001 trial, azacitidine was shown to significantly