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Advances in HR-MDS: Updates in Diagnosis, Risk Assessment, and Current Standard of Care Challenges

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Here's Dr. Rami Komrokji.

Chapter 1: Epidemiology, Pathogenesis, & Diagnosis

Dr. Komrokji:
Hi, I'm Dr. Rami Komrokji, and I'm the Vice chair of the Malignant Hematology Department at Moffitt Cancer Center. Today, we are going to discuss myelodysplastic syndrome and the major recent updates in the field that may help us provide better care for patients with this complex disease.

Let's begin by taking a closer look at MDS, also known as myelodysplastic syndromes. MDS is a term that are a spectrum of clonal myeloid stem cell neoplasms, characterized by bone marrow failure with peripheral cytopenias and a tendency to progress to acute myeloid leukemia, or AML for short.[1,2] In fact, about 30 percent of patients will transform to AML, and the majority of patients will unfortunately die from complications of the disease.[3,4]

MDS is a disorder that mainly affects older adults, with a median age at diagnosis over 70 years, a male to female ratio of 1.67, and an increased rate that increases with age. Initially described by the French-American-British classification, or FAB method in the 1970s. The classification of MDS has since been expanded by the World Health Organization, or WHO, classification system. This classification system has been revised three times since 2001, most recently in 2022. Also in 2022, a new group, the International Consortium Classification or ICC for short, established a new classification system from WHO with some key differences. We will talk more about these latest updates to MDS classification in the next chapter.[3,4]

It also wasn't until 2001, the same year that the original WHO classification came out, that MDS became a reportable condition to cancer registries, as before this was considered precancerous rather than neoplastic. As a result of these classification and diagnostic changes, and this lack of standard data collection until fairly recently, estimating incidence and prevalence of MDS has been challenging. Current estimates show that in the U.S.A, about 13,400 cases are diagnosed per year, but even this could be an underestimate.[3]

Most patients with MDS will experience a chronic disease; however, one in three will progress to AML.[5] The patients who have higher-risk MDS not only transform to AML sooner, but do so with poorer survival outcomes. In fact, the median overall survival rate for patients with Higher risk-MDS is about one and a half years.[6,7] With that background in mind, let's dive a bit into the etiology and some of the driving pathways of MDS.

Most cases of MDS are of unknown cause. However, secondary MDS is a subset that is due to industrial or agricultural toxin exposure such as benzene. And therapy-related MDS can result from prior radiotherapy, alkylating agents, or antimetabolites causing DNA

damage.[3] And while the underlying cause of MDS isn't yet fully understood, advances in cytogenetic and molecular testing have helped to discover some of its driving pathways.

In fact, about 50 percent of patients with MDS will have a recurrent chromosomal abnormality on cytogenetic testing, and at least 90 percent of patients with MDS will have some somatic gene mutations detected when next-generation sequencing is performed.[1,2,4]

Now MDS is an interplay of clonal hematopoiesis, inflammatory milieu of the bone marrow, and immune rearrangements. So we can look at the somatic gene mutations and the abnormal clonal stem cells to determine some underlying pathways involved, which point to defects in normal cell proliferation, differentiation, maturation, and accelerated apoptosis, including disruption in RNA splicing, signal transduction, transcription factors, chromatin modification, and DNA methylation.[1,4,8,9]

Now let's talk about diagnosing MDS. The diagnosis of MDS is based on a combination of clinical, morphological, and genetic criteria. The minimal diagnostic criteria for MDS requires persistent cytopenia with the exclusion of other primary causes for dysplasia or cytopenia. Additionally, at least one of following criteria must be met:[10,11]

1. Dysplasia of at least ten percent in one or more of the three major bone marrow cell lines
2. A blast count between five to 19 percent and/or
3. An MDS-defining genetic abnormality.

In our patients, we typically see evidence of this hematopoietic disruption incidentally on lab work as a cytopenia in one or more cell line —anemia, thrombocytopenia, or neutropenia.[9] But the disease may be more severe at presentation in Higher Risk-MDS, so the patients may have symptoms such as fatigue or shortness of breath, abnormal bruising or bleeding, or infection.[12] A persistent, unexplained cytopenia is an essential element for an MDS diagnosis. Once a routine workup has ruled out common causes, we'd obtain a bone marrow aspirate biopsy. And here is where we really depend on our hematopathologist, as we want to determine not only the percentage of blasts in the aspirate and the peripheral blood, but also the morphology of the cells and the structure of the bone marrow environment – be it hypercellular or fibrotic.

All of this information can help us not only determine the diagnosis of MDS, but identify the subtype to help with classification, which we'll talk more about in the next chapter.[1,9,13] Next, we also perform cytogenetic and molecular testing to determine if our patient has any of those recurrent genetic abnormalities, especially those associated with a poorer prognosis. This information will be important for developing a prognostic score, as that's going to help tailor our treatment.[14]

Announcer: Chapter 2: Updates in Classification, Prognosis, & Response Criteria

Now that we've caught up a bit on the background and diagnosis of MDS, let's turn to some of the recent updates and major revisions to classification tools that we use in practice. The WHO classification system for MDS has been definitive in helping to categorize and diagnose MDS for over two decades and across multiple revisions, the last being in 2016.[15] Since then, we've had significant advances in the molecular and genetic understanding of the disease. And so in 2022, the WHO released a new revision with the fifth version of the classification system, including a few notable changes:[16] For one, although "MDS" keeps its name, it will now stand for myelodysplastic neoplasms in order to be more accurate being a malignant condition.[16]

Next, the grouping of MDS entities will be based on defining genetic abnormalities and morphological characteristics, rather than the previous classification-based on grouping subtypes, mainly by morphology only.[16] The WHO recognizes molecularly defined MDS subtypes. A new genetic subtype of MDS has been introduced for patients with the TP53 mutation, MDS with biallelic TP53 inactivation. And then there are the SF3B1 and division 5q molecular defined entities.[16]

And finally, WHO eliminated blast cutoffs for most AML types with defining genetic alterations, while retaining the 20 percent blast cutoff to delineate MDS from AML. The WHO recognizes MDS with increased blasts—previously called excess blasts—with type 1 (5 to 9 percent myeloblasts) and type 2 (10 to 19 percent myeloblasts), as MDS-IB2. WHO also points out that MDS-IB2 may be recognized as similar to AML for therapy considerations as well as clinical trial design.[16]

As I mentioned earlier, a different group of experts who were previously affiliated with the WHO system working group formed the ICC, to proceed with a separate new classification system for the MDS that was also inclusive of prognostic genetic mutations. The ICC released their first edition classification system in 2022, and there are important ideas to note here, as well:[2] Like the WHO fifth version, the ICC has defined AML with a blast percent of 20 or more. And both groups have defined new genetic subtypes for patients with TP53 mutation; in ICC's classification scheme these are MDS with biallelic mutated TP53 and MDS/AML with mutated TP53.[2]

However, unlike the WHO, the ICC has designated a new category called MDS/AML for adult patients who have 10 to 19 percent blasts in the peripheral blood or bone marrow. In doing so, the ICC suggests that these patients may be eligible for both MDS and AML clinical trials to optimize the management of these patients with aggressive disease.[2]

Now that we've reviewed these recent updates in classifying MDS, let's highlight some advances in the prognostication of MDS. Because MDS presents in a variety of subtypes, each with various factors affecting the rates of AML transformation and survival, accurate prognostication for individual patients can be challenging. But as treatment goals for Higher risk-MDS differ greatly than for lower-risk MDS, estimating risk is an important step in guiding treatment plans for each patient. And so, standardized risk assessment tools are used to stratify treatment based on prognostic scoring.[3]

The most widely used prognostic tool is the Revised International Prognostic Scoring System, or the IPSS-R.[6,13] This system stratifies MDS patients into five categories of risk in terms of AML transformation and overall survival. The categories span from very low, low, intermediate, high, to very high-risk.[6,13] High Risk MDS is the umbrella containing the intermediate, high, and very high-risk groups with a score greater than 3.5, whereas lower risk MDS includes the intermediate, low, and very low-risk groups with a score of 3.5 or below.[6,13]

The IPSS-R is calculated with three measures: the presence and severity of cytopenias, the percentage of blasts, and the presence of cytogenetic abnormalities.[13] Before the revision, the original scoring system only considered the number of cytopenias but not their severity, placed much less weight on cytogenetics, and was less precise predicting for lower risk MDS.[9]

The IPSS-R individualized risk score can not only provide AML transformation and overall survival prognostic information for untreated patients with MDS, but also help clinicians guide management and treatment decisions. The IPSS-R is not a dynamic tool and can only be used at time of diagnosis.[13] However, the last IPSS-R version is from 2012 preceding a lot of what we know about specific somatic mutations associated with MDS confirming additional risk.[13] So, the International Working Group for Prognosis in MDS, or IWG-PM, developed and validated the new Molecular International Prognostic Scoring System for Myelodysplastic Syndromes, or known as the IPSS-M.[14]

This new risk assessment system develops a prognostic score using data from marrow blast percentages, cytopenias, 16 main effect genes, and 15 residual genes.[14] The new score is personalized, and it is on a continuous scale and can also be categorized into six risk levels.[14]

As a result of these inclusions, IPSS-M has been shown to have superior prognostic accuracy to the IPSS-R, as during development, the IPSS-M improved prognostic discrimination across all clinical endpoints and re-stratified 46 percent of patients in comparison to IPSS-R.[14]

Lastly, the IWG also created response criteria for MDS in 2000 and have since revised these twice—in 2006 and 2018—to define and harmonize the clinical assessment of response to treatment for clinical trials, regulatory reviews, and clinical practice. The prior update in 2018 focused only on Lower risk MDS, and the group has just released a proposal for revision in 2023 to address higher risk MDS patient-centered clinically relevant outcomes. Also, the group reviewed and revised the criteria due to concerns that the prior version may not fully capture the clinical benefits of investigational drugs; they may not adequately serve as valid surrogate measures for meaningful clinical end points; or the variability in interpretation may lead to interobserver inconsistency.[17]

The 2023 IWG MDS response criteria includes some of the following key differences from the 2006 version: [17] The hemoglobin threshold for complete remission, or CR, was decreased from greater than 11 grams per deciliter to greater than 10 grams per deciliter, as maintaining a hemoglobin level at the former level hasn't been shown to be associated with improved survival, whereas the new cutoff is aligned with AML response criteria as well.[17]

Two new categories of near complete response or near CR were introduced as provisional response criteria to recognize the significance of hematologic improvement along with morphologic marrow blast response. The first, CR with limited count recovery, or CRL, would replace the previous category of marrow CR, which is now eliminated.[17]

The second provisional response category is CR with partial hematologic recovery, or CRh, which may have relevance if there's been a bone marrow blast reduction with a partial, yet clinically relevant, improvement in neutrophil and platelet counts.[17]

For those just tuning in, you're listening to *Project Oncology on* ReachMD. I'm Dr. Rami Komrokji, and today I'm talking about MDS and the recent major changes to classification and prognostic tools.

Announcer: Chapter 3: Treatment Goals & Current Standard of Care

I just reviewed some of the major changes to how we classify and prognosticate MDS. So now let's turn our attention towards treatment. For Lower risk MDS, the treatment goals for this usually chronic disease are reducing symptoms, decreasing or eliminating transfusions, and minimizing morbidity associated with chronic cytopenias.[8]

But as we discussed, Higher risk MDS has a devastating prognosis, and so treatment should be initiated promptly with the goals of prolonging overall survival and improving or maintaining quality of life. And this may include improving cytopenias, achieving remission, and also preventing or delaying transformation to AML.[6,8]

Patients with Higher Risk-MDS typically receive supportive care to manage cytopenias and infectious complications of the disease, such as transfusions for anemia and thrombocytopenia. And while the transfusions can symptomatically improve the quality of life for a patient, studies have shown that transfusion dependency is independent risk factor that predicts worse outcomes.[18]

The only potential curative treatment for Higher Risk-MDS is an allogeneic stem cell transplant. Unfortunately, not all higher risk MDS patients can undergo transplant due to advanced age, comorbidities, poor performance status, or lack of a suitable donor.[6,19]

And so the standard of care treatment for patients with Higher risk MDS who are not eligible for transplant, which are the vast majority, are hypomethylating agents as they have been shown to reduce risk of AML transformation. Even so, only azacytidine has been shown to offer a survival benefit in this high-risk mortality population based on a single randomized controlled clinical trial called the phase III AZA-001 study, which compared azacytidine to conventional care regimens. In that study, the median, overall survival in the azacytidine group was significantly improved at 24.5 months compared to 15 months in the conventional care group.[6,19] Several real-life data and registry studies have shown lower median overall survival benefits with azacytidine, at 13 to 16 months, than what was reported by the AZA-001 trial.[20]

In order to get a more realistic estimate of the overall survival benefit with azacitidine using various study types, Zeidan et al pooled overall survival data, including the AZA-001 trial. Additionally, with four trials that met the inclusion criteria, and with comparable baseline characteristics of patients, the median overall survival of patients in the azacytidine arm was 19.2 months.[20]

These results were further supported by another systematic review and meta-analysis by Hasegawa et al, which analyzed 34 publications that included 16 unique studies which reported first-line azacytidine monotherapy safety and efficacy outcomes in patients with higher risk MDS. They found pooled complete remission to be 16 percent across the studies, and pooled median overall survival in the azacytidine group to be 16.4 months.[6]

Now, in 2017 a large population-based analysis using SEER- Medicare database evaluated survival outcomes of 1,187 MDS patients who received hypomethylating agent therapy, and the median overall survival for these patients was 14 months.[7]

And so if we put it all together, we see that the only curative treatment for Higher risk MDS is transplant, but unfortunately, few patients are eligible. And for the majority of patients who can not undergo transplant, we now have evidence from several studies that the overall survival on the current standard of care treatment may be lower in the real-world settings, with the median potential benefit being somewhere between 14 to 19 months.[6,20]

With all that being said, it's clear that there remain significant unmet needs for safe and effective treatment for patients who already have a very poor prognosis with Higher Risk-MDS and limited treatment options to improve survival and quality of life.[3]

Our knowledge and understanding of MDS is evolving, as seen in the recent updates in classification, prognostication, and response criteria we reviewed earlier. And continued advances will be critical for managing patients in the clinic and developing newer therapies that can help patients live longer and live better. Thank you very much for listening.

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