Advances in Personalized Therapeutic Approaches in Myelodysplastic Syndromes

Presented by Rafael Bejar, MD, PhD

ABSTRACT

Often unrecognized and underdiagnosed, myelodysplastic syndromes (MDS) are a rare group of cancers in which the bone marrow fails to produce sufficient healthy blood cells. Although patients with lower-risk MDS can live for >5 years, those with high-risk disease that evolves into acute myeloid leukemia is associated with significantly lower overall survival. At the NCCN 2019 Annual Congress: Hematologic Malignancies, Dr. Rafael Bejar summarized current standard treatment options for patients with MDS and discussed the importance of genetic testing to identify mutations that may impact treatment. Finally, Dr. Bejar described emerging personalized treatment strategies for the management of this disease.

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Optimizing Therapy for Individual Patients

Myelodysplastic syndromes (MDS) are a group of bone marrow failure disorders characterized by ineffective hematopoiesis. For many patients with lower-risk MDS, life expectancy can exceed 5 years. However, for those with higher-risk MDS that evolves into acute myeloid leukemia (AML), overall survival (OS) is significantly reduced. At the NCCN 2019 Annual Congress: Hematologic Malignancies, Rafael Bejar, MD, PhD, Associate Professor, UC San Diego Moores Cancer Center, discussed current standard-of-care treatment in the NCCN Guidelines for MDS, which is split into 2 separate algorithms addressing lower-risk and higher-risk MDS. He also described emerging personalized treatment strategies for the management of MDS, including the increased role of genetic testing to identify high-impact mutations.

As Dr. Bejar explained, researchers have identified dozens of different somatic genetic mutations that can lead to MDS. Most patients will have >1 mutation and a unique pattern of mutation, as genetic profiles in MDS demonstrate a great deal of heterogeneity. “No two patients with MDS are truly alike,” said Dr. Bejar. “Unfortunately, somatic mutation is not a static process but evolves over time. Additional mutations will accumulate, often leading to a more profound phenotype of worsening cytopenias, and approximately 30% of patients will eventually experience progression to secondary AML.”

Personalized Risk Assessment

Using a case study involving a 65-year-old healthy man who presented with fatigue and shortness of breath, Dr. Bejar illustrated how genetic testing is used to generate a personalized risk assessment that will inform

treatment. After a bone marrow biopsy revealed a hypercellular bone marrow with clear dysplasia, 1% blasts in the bone marrow aspirate, dysplasia in all 3 cell types, and a karyotype with isolated del(5q)—elements that are characteristic of MDS—Dr. Bejar used the Revised International Prognostic Scoring System (IPSS-R) to assess the patient's risk.¹ According to the IPSS-R, the patient was in the low-risk group. Patients with an IPSS-R score ≤ 3.5 are classified as having lower-risk disease, whereas those with a score > 3.5 are considered to have higher-risk disease (Figure 1).

“The different groups in the IPSS-R stratify quite nicely, with big differences in OS between patients in the highest-risk group and those in the lowest-risk group,” said Dr. Bejar, who noted that median OS in the low-risk group is approximately 5 years. “Accordingly, the NCCN Guidelines for MDS are divided into 2 almost completely separate algorithms, with one treatment approach for lower-risk patients and another for those with higher-risk MDS.”

As Dr. Bejar explained, for patients with isolated del(5q) and lower-risk MDS, the treatment of choice is lenalidomide (Figure 2). Patients in this population frequently respond to treatment (overall response rate, 50%–80%), and responses are typically deep and durable. On average, patients experience responses lasting >1.5 years, with many responses exceeding >2 years.

For patients without del(5q) deletion, however, alternative options, such as erythropoiesis-stimulating agents (ESAs), are usually considered first. According to Dr. Bejar, patients with very low hemoglobin levels and who are heavily transfusion-dependent are unlikely to respond to ESAs. For those with endogenous erythropoietin levels <200 U/L and who are mildly transfusion-dependent, an

Figure 1. Revised IPSS-R.

Abbreviations: ANC, absolute neutrophil count; AML, acute myeloid leukemia; IPSS-R, Revised International Prognostic Scoring System.

Adapted from Schanz J, Tüchler H, Solé F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *J Clin Oncol* 2012;30:820–829; and Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood* 2012;120:2454–2465.

ESA will likely increase hemoglobin levels to the point of transfusion independence.

A new approach targeting transforming growth factor (TGF)- β signaling is on the horizon. A phase II study of luspatercept, a novel fusion protein that blocks TGF- β superfamily inhibitors of erythropoiesis, showed a significant reduction in transfusion requirements among patients with anemia due to lower-risk MDS with ring sideroblasts.² Furthermore, time-to-response was fairly rapid and the response was sustained for the 24-week analysis period. Although not yet FDA-approved, luspatercept could be approved in 2020, said Dr. Bejar.

High-Impact Genetic Mutations

Although the IPSS-R is the gold standard for defining clinical risk in patients with MDS, it does consider somatic mutations, said Dr. Bejar, who noted that certain mutations can portend a worse prognosis. An analysis of >400 patients stratified by IPSS-R risk group showed that such adverse mutations were present in approximately 20% of patients with very-low-risk MDS (Figure 3).³ These patients had a median OS that was nearly one-third shorter than that of low-risk patients without these

mutations. For patients with low and intermediate IPSS-R risk, median OS was approximately 50% shorter compared with those without mutations. A separate analysis of nearly 2,000 patients with MDS sequenced at centers around the world noted that patients with a greater number of somatic mutations had inferior OS.⁴ “I’m not advocating that we necessarily count mutations to determine a patient’s prognosis, given that the presence of certain mutations is worse than others,” said Dr. Bejar. “Some mutations may simply be neutral with regard to prognosis.”

This collaborative analysis with the International Working Group for Prognosis in MDS found that 42% of patients with MDS have a mutation that is associated with worse prognosis than predicted by the IPSS-R.⁴ These adverse, somatically mutated genes included *ASXL1*, *RUNX1*, *EZH2*, *CBL*, and *NRAS*, among others. “It seems like we’re underestimating risk in a substantial number of patients,” Dr. Bejar observed. “If a patient is on the intermediate-risk border with one of these adverse-risk mutations, I would argue that their clinical behavior is going to be similar to that of traditional, higher-risk individuals.”

Figure 2. Treatment for myelodysplastic syndromes is risk-stratified in the NCCN Guidelines for Myelodysplastic Syndromes, Version 2.209. To view the most recent version, visit NCCN.org.

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; ESAs, erythropoiesis-stimulating agents.

TP53 Mutations

One genetic lesion that has recently come under greater scrutiny is mutation in *TP53*, a common resistance marker for patients whose disease progresses on lenalidomide. As Dr. Bejar discussed, data suggest that mutations of *TP53* are particularly adverse in almost all settings, including patients who are undergoing transplantation. In a study of >1,500 patients, *TP53* mutations were shown to be associated with approximately 50% shorter long-term survival when compared with those without the mutation.⁵ Additionally, even younger patients with this mutation had notably poor outcomes.

“At our center, we don’t perform traditional transplants for patients with *TP53* mutations anymore,” said Dr. Bejar. “We try to perform a transplant that includes something else that we think could increase the chances

of long-term survival.” One potentially promising option for patients with *TP53*-mutated disease is intensive therapy with decitabine. Welch et al⁶ identified a very-high-response rate for patients who received high-dose decitabine and had *TP53* mutations in the setting of MDS or AML. “Strikingly, by the fourth cycle of treatment, investigators actually observed cytoreduction of the *TP53*-mutant clone,” said Dr. Bejar. “This suggests that if the transplant is timed appropriately after treatment, patients might have less residual disease and may have a longer time to relapse, allowing their graft to take hold. This approach is now being tested in clinical studies.”

Another option for patients who are unable to undergo a traditional transplant is the experimental drug APR-246, which is believed to stabilize mutant forms

Figure 3. Impact of mutations by IPSS-R group.

Abbreviations: G, good; Inter, intermediate; mut, mutation; VG, very good.

Adapted from Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood* 2014;124:2793–2803.

of *TP53*, thereby allowing the mutated gene to carry out its normal endogenous function. Data from phase I and II studies have demonstrated both a high rate of response and durable responses through the follow-up period.⁷ Nevertheless, said Dr. Bejar, APR-246 will probably not keep patients in long-term remission on its own, but will be combined with other agents in future studies.

Lastly, Dr. Bejar discussed the possibility of a personalized approach involving use of immunotherapeutic agents in MDS. Studies at MD Anderson Cancer Center are currently combining PD-1 and PD-L1 inhibitors with hypomethylating agents. At UC San Diego, studies are

currently evaluating a neoantigen-targeted approach using patients' own T cells selected for their ability to recognize tumor-associated mutated peptides. "Our hope is that these approaches could produce long-lasting immunologic responses in these patients," said Dr. Bejar.

Disclosures: Dr. Bejar has disclosed that he is a scientific advisor for Celgene, NeoGenomics, AbbVie, Astex, and Daiichi-Sankyo; has received grant/research support from Takeda and Celgene; and is on the advisory board for Celgene/Acceleron.

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