How Do We Treat... ...Patients with Myelodysplastic Syndromes?

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Myelodysplastic syndromes (MDS) are a group of clonal diseases characterized by ineffective hematopoiesis resulting in peripheral blood cytopenias and increased risk of progression to acute myeloid leukemia (AML). As a result of its association with hematopoietic stem-cell aging, MDS is predominantly a disease of the elderly. Although multiple advances have been made in the last decade in terms of understanding the pathophysiology and biology of this disease, appropriate diagnosis and classification still remains one of the challenges in the community and, in fact, still leads to an underdiagnosis of MDS. Incorporation of cytogenetic, molecular, and flow assays has improved our potential to diagnose patients with MDS.

Defining the Risk: The First Step in Patient Treatment

Once an adequate diagnosis of MDS is made, the main objective for the treating physician is to optimize therapy by adequately defining the patient’s risk and prognosis. To this end, multiple prognostic scoring systems have been developed and should be applied in order to tailor treatment and calculate prognosis.

The International Prognostic Scoring System (IPSS) has been established as the backbone of these prognostic systems and, for two decades since its development in 1997, has allowed stratification of patients into lower- (Low/Int-1 IPSS) or higher-risk (Int-2/High IPSS) disease.

The recently revised version, IPSS-R, improves our ability to further define disease risk by increasing the prognostic weight of cytogenetic alterations, possibly the most important disease-related prognostic variable.

Although IPSS-R should be considered the standard scoring tool, most available therapeutic data generated within clinical trials or clinical practice was developed in the era of IPSS and, therefore, extrapolation of IPSS-R risk groups to IPSS groups when selecting therapy has yet to be prospectively confirmed. Due to this, in our daily practice, we still use IPSS in order to define risk when considering treatment options.

Despite the potential of both IPSS and IPSS-R to define risk, a subset of patients have outcomes inferior to those expected from IPSS or IPSS-R calculations. Although most patients with lower-risk MDS have a significantly improved survival and lower risk of transformation when compared with higher-risk MDS, some of these “lower”-risk patients perform poorly and behave in a fashion more similar to that of higher-risk disease.

Our group developed the MD Anderson Cancer Center lower-risk scoring system in an intent to identify such patients. By using this model, lower-risk patients can be divided into three categories with patients in category 2 and especially in category 3 having outcomes similar to those with higher-risk disease. Hence, we encourage the use of this model when tailoring therapy in patients with lower-risk disease in order to try to identify these higher-risk lower-risk patients to be able to optimize their outcomes.

How to Treat Lower-Risk Disease

For patients with lower-risk MDS, treatment objectives should be focused on the control of cytopenias and transfusion dependency, the main prognostic factor in these patients. Initiation of therapy should be considered for all patients with symptomatic cytopenias.

For patients with anemia, a course of erythropoietic stimulating agents (ESAs) should be considered. Although no randomized prospective clinical trials have been developed to specifically analyze the efficacy of these agents, available studies report response rates ranging from 23 to 79 percent, with a median response of approximately 43 percent.

Learning Objectives for This Month’s CME Activity: After participating in this CME activity, readers should be better able to identify treatment strategies to optimize therapy for patients with myelodysplastic syndromes (MDS).
be considered higher-risk lower-risk MDS, treatment with low-dose hypomethylating agents including both decitabine or azacitidine could be considered at a reduced dose schedule. Several studies have explored this approach and showed significant responses including complete remission and acquisition of transfusion independence with minimal hematopoietic toxicity.

Defining the need for allogeneic stem-cell transplant in patients with low-risk MDS will undoubtedly be an issue any hematologist will have to discuss with his patients. Although transplant remains the only curative treatment option in MDS, transplant-related mortality and morbidity mainly in the form of graft-versus-host disease (GVHD) remains a significant limiting factor.

Due to the expected outcome of patients with lower-risk disease and the risks associated with the procedure, transplant should not be considered for lower-risk patients upfront, with the exception of those with hypoplastic MDS, and should be restricted to young patients who fail multiple lines of therapy. However, due to the time required for identification of potential donors we believe all potential candidate patients should be referred to transplant evaluation at diagnosis.

How to Treat Higher-Risk Disease

For patients with higher-risk disease, treatment objectives vary significantly and should be focused in the reduction and delay of transformation and prolongation of survival.

To this end, hypomethylating agents have become the standard of care, inducing responses in up to 40 percent of patients, significantly improving survival compared with best supportive care or chemotherapy and, more importantly, being able to induce responses irrespective of cytogenetic alterations.

When treating patients with both azacitidine or decitabine, oncologists will commonly have to deal with significant cytopenias, transient increases in transfusion dependency, and episodes of neutropenic fever. Worsening of cytopenias during the first four to six cycles of therapy (the mean number of cycles required to define definite response to therapy) should not discourage the clinician and the patient and should be considered an expected side effect of therapy prior to observing its effectiveness. Reevaluation of the disease should be considered after two or three cycles and periodically after that.

Additionally, whenever there is suspicion of progression or loss of response due to progressive cytopenias after an initial response, bone marrow evaluation with cytogenetic analysis should be performed.

It is important to adequately identify patients who derive clinical benefit from therapy but who experience increased hematological toxicity in the form of prolonged cytopenias. For such patients we usually increase cycle periodicity to every five or six weeks as needed and, in fact, many such patients subsequently recover counts appropriately. Additional dose reductions can also be reasonable to optimize treatment for responding patients with drug-induced cytopenias.

Irrespective of these available therapies, treatment outcomes are still suboptimal, and we therefore believe enrollment in a clinical trial after diagnosis of high-risk MDS should be considered whenever possible.

As in lower-risk disease, approaching the issue of stem cell transplantation with the patient is paramount. However, unlike in lower-risk MDS, there is evidence to support considering allogeneic stem-cell transplant upfront in patients with high-risk disease. Available data indicate that transplant is the only curative therapy and can in fact confer a benefit in terms of survival. Nevertheless, the issue of transplant timing remains controversial and several important factors should be considered prior to advising the patient to undergo such a high-risk procedure.

Appropriate disease control prior to transplant is essential, and we recommend initial therapy within a clinical trial or with hypomethylating agents to try to decrease disease burden and achieve some form of cytogenetic response before transplantation.

The use of AML-like chemotherapy in this setting should be restricted to fit patients with >10% blasts and diploid cytogenetics. Of note, recent studies show poor outcomes after transplant in patients with very high-risk features such as monosomal karyotype (mainly monosomy 7) or presence of DNMT3A or TP53 mutations. For such patients, especially in the presence of multiple high-risk features, transplant should be discouraged as frontline therapy, and participation in clinical trials should be considered.

Finally, when considering patients for transplant we should always consider the type of donor available. Although haploidentical donor and cord blood transplantation outcomes have significantly improved in the last decade we believe such transplant modalities should be considered only within a clinical trial and should not yet be considered as standard practice.

How to Manage Failure to Hypomethylating Agents

Although up to 40 percent of patients will respond to azacitidine and decitabine, responses, in a significant proportion of patients, will be short-lived with eventual loss of response, resulting in poor outcome with median survival of only a few months.

For such patients, enrollment in clinical trials should be considered the standard of care, with subsequent allogeneic stem-cell transplantation for eligible patients when possible.

Examples of clinical trials include a Phase III trial of the multikinase inhibitor rigosertib and the incorporation of PD1/PDL1 inhibitors to the hypomethylating agents. Patients with good-risk cytogenetic features may respond to low-dose clofarabine-based therapy, and a fraction of patients may have mutations in IDH1 genes or FLT3 and RAS that could make them candidates for specific targeted therapy approaches.