

ADVANCES IN LLM

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Section Editor: Susan O'Brien, MD

Treating Myelodysplastic Syndrome When Hypomethylating Agents Stop Working



Elias Jabbour, MD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

H&O For a long time, myelodysplastic syndrome (MDS) was considered a preleukemic condition, meaning that everyone diagnosed with the disease would eventually develop leukemia. Does this belief still hold?

EJ MDS is a common disorder, and if we lived for hundreds of years, eventually we would all develop MDS. This condition is a stem cell disease in which the maturation of cells is blocked. The blood stem cells fail to mature into blood cells and the immature blast cells either die in the bone marrow or move into the bloodstream, occupying space that should be available to healthy blood cells.

It is true that for many years, we believed that everyone with MDS would eventually develop leukemia. It turns out that this concept is not true. In fact, only about 30% of patients with advanced-stage MDS progress to leukemia; the remaining patients usually die of MDS. Low-risk MDS has a lower rate of transformation to leukemia than high-risk MDS.

H&O Broadly, what are the current treatment options for MDS?

EJ MDS is very difficult to treat. The only curative approach is allogeneic bone marrow transplant, but the population affected by MDS tends to be older, which can rule out this rigorous procedure as an option.

Several years ago, laboratory research uncovered that hypermethylation within certain genes associated with MDS was important in the pathogenesis of the disease. Hypomethylating agents were developed as a way to

block that mechanism of action within cells. Two such drugs, azacitidine and decitabine, were approved by the US Food and Drug Administration (FDA) in 2004 and 2006, respectively, after clinical trials showed prolonged survival time among MDS patients treated with them. Several trials showed response rates ranging from 15% to 40%, depending on the criteria used to define response. Patients treated with azacitidine had improved survival in a trial led by Pierre Fenaux, with a median survival of 24 months compared with 14 months for patients receiving best conventional care.

It is important to understand that the way we use hypomethylating agents has evolved dramatically since their initial approval. Before we consider how to treat patients with MDS for whom hypomethylating agents have stopped working, we first need to be sure that we are using these drugs correctly. The experience during the past several years has shown us a great deal that we did not understand previously. Adjusting the way we use these drugs could go a long way toward both ensuring the best outcome and prolonging response time.

H&O What do clinicians now understand about the best use of hypomethylating agents that was not known at the time of their initial approval?

EJ First, we used to believe that only patients who had a complete response to the treatment would have improved survival. But we now know that any response, even stable disease, correlates with a better long-term outcome.

The second lesson is regarding the number of treatment courses. After giving 1 course of chemotherapy, we

used to give another course if the patient responded and no further chemotherapy if the patient did not respond. After years of experience, we now know that patients may require several courses of chemotherapy before the disease responds. Many times, patients are referred to me after 1 or 2 courses of chemotherapy with their disease considered to have failed hypomethylating agents. In reality it may take 6 courses of chemotherapy to elicit a response, which is a new concept for most of us who treat MDS.

Also, it appears that courses of chemotherapy need to be given one after the other, without a break in between. Initially we would administer the treatment and, if the patient's blood counts were low after 4 weeks, we would pause until the patient recovered. But experience has shown us that waiting between treatment rounds allows the disease to progress. With hypomethylating agents for MDS, it is best to provide treatment courses back to back.

Finally, we now understand that as long as the patient is responding, the treatment should not be stopped. Years ago, clinicians would treat MDS with hypomethylating agents for 1 or 2 years and then stop. But MDS is similar to chronic myeloid leukemia, in which the disease will relapse if you halt treatment with tyrosine kinase inhibitors. MDS is the same: maintenance therapy should be given for extended periods. As long as the patient is benefiting, the treatment should be continued.

H&O What are the differences between low-risk and high-risk MDS?

EJ The categories of low- and high-risk MDS are mainly defined by the percentage of blast cells present and the karyotype. With regard to karyotype, cytogenetic features have been identified that are associated with poorer or better prognosis. A 2007 study published in *Blood* identified 684 cytogenetic categories, where median survival was 53.4 months among patients with normal karyotypes and 8.7 months among patients with complex cytogenetic anomalies. In addition, a low percentage of blast cells is associated with a better prognosis than a high percentage of blast cells. In 2012, an updated version of the International Prognostic Scoring System (IPSS) was published in *Blood*. Based on data from international institutions, the IPSS includes 5 cytogenetic prognostic subgroups and provides a comprehensive categorization for patients with MDS across the spectrum of prognosis.

H&O What is the difference between high- and low-risk MDS in terms of response to hypomethylating agents?

EJ High-risk MDS is an aggressive disorder. The use of hypomethylating agents has induced responses in about

15% to 40% of the patients, leading to a median survival of 2 years. The median survival time for high-risk MDS is less than 1 year if untreated.

With low-risk MDS, it is important to understand that the disease may progress rapidly despite treatment. There may be genomic instability that results in transformation to a more aggressive form of the disease. In the past, clinicians have followed a watch-and-wait approach with low-risk MDS, but now we are finding that this approach may not be ideal because the disease can transform into a more aggressive form very quickly.

H&O How are patients with high-risk MDS treated when hypomethylating agents stop working?

EJ There are not any standard treatment options for this scenario. Transplantation may be recommended, but it is not always helpful in this setting. Clinical trials are sorely needed to advance the treatment of high-risk MDS.

Experimental drugs are under investigation for MDS. A recent randomized trial of rigosertib, a phosphoinositide 3-kinase (PI3K) inhibitor, after hypomethylating agent failure did not meet its primary endpoint of improved survival among patients with high-risk MDS. However, subset analyses are underway and may reveal a benefit for some patients.

H&O How is low-risk MDS treated if hypomethylating agents stop working?

EJ Low-risk MDS falls into 2 categories: low-risk disease that becomes high-risk, and low-risk disease that remains low-risk. With low-risk MDS in general, the average median survival is 17 months, an outcome that is better than with high-risk MDS but still poor. Looking more closely, low-risk MDS that becomes high-risk is associated with a survival time of about 12 months, whereas for disease that remains low-risk, the survival time is approximately 3 years.

So it is clear that outcomes for all MDS patients are not ideal, and improved treatments are needed. Patients who stop responding to hypomethylating drugs should be referred to a clinical trial or be considered for allogeneic stem cell transplantation, if they are candidates.

H&O Could you describe some of the ongoing clinical trials for MDS?

EJ First, we need clinical trials to investigate how we can improve outcomes with hypomethylating drugs. One ongoing study is looking at watch-and-wait vs intervention for low-risk MDS, to clearly establish whether immediate treatment improves outcomes for this subgroup of

patients. For high-risk MDS, there is a trial investigating combination therapy with a hypomethylating agent plus a histone deacetylase inhibitor, one of several trials exploring optional treatment regimens.

In addition to rigosertib, other drugs currently in clinical trials include clofarabine, a chemotherapy drug approved for pediatric acute lymphoblastic leukemia, and also an immunotherapy agent that inhibits the programmed death-1 protein. Anti-inflammatory drugs are also being investigated in early-stage clinical trials.

H&O In light of these considerations, could you describe your treatment recommendations for a patient with MDS that has stopped responding to hypomethylating agents?

EJ At the time of treatment failure, I first assess whether the patient has low-risk or high-risk disease. If the patient has high-risk MDS, I will recommend transplantation, and will also consider any clinical trials available. Currently there is no standard of care. Allogeneic stem cell transplantation may be indicated for high-risk patients, but not for low-risk patients. For high-risk disease, if a patient is eligible and has a donor, then I would likely recommend transplantation first, and use the clinical trial option as a bridge to transplantation.

H&O Do immunotherapy drugs seem particularly promising for MDS?

EJ It is too soon to say. The mechanism of action of these agents for MDS is not yet known. There are some in vitro data suggesting that immunotherapy could be effective for MDS, but the phase 1 trial is still in its early stages.

H&O With regard to other experimental agents, are there any indicators that they may be effective for MDS?

EJ Again, it is too soon to say. The rationale is solid for exploring drugs that inhibit p53 and PI3K. Research has revealed numerous pathways involved in the development and progress of MDS, and there are several inhibitors available that target those pathways. But none of these agents has made it far enough in clinical trials to clearly determine efficacy. Right now, the way to optimize the treatment of MDS is to use the hypomethylating agents in the best way possible, and when these agents stop working, to consider a clinical trial or, for high-risk patients, a transplant.

Suggested Reading

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