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Hypomethylating Agents in Myelodysplastic Syndromes

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H&O What are myelodysplastic syndromes (MDS)?

WB The term describes a heterogeneous group of diseases that have a great deal of variability in terms of presentation, prognosis, and treatment. There are approximately 10,000 new cases diagnosed each year in the United States. Most of the patients who present with MDS are elderly; the median age is approximately 72 years. This advancing age has important implications for the selection of the best available treatment. Treating a 72-year-old patient is not the same as treating a 32-year-old patient, no matter what the disease is. The fact that most MDS patients are elderly means that they generally have other comorbidities, and they are less hardy in terms of their ability to safely receive intensive therapy.

H&O What is the current treatment approach?

WB The treatment approach depends on each case, and it runs the gamut from intensive treatment to supportive care. Each patient must be considered individually. For example, a younger patient with very aggressive disease would be treated quite intensively, with the aim to engender disease response and then get the patient to an allogeneic donor cell transplant procedure, which offers the potential of a cure. In an older patient with indolent disease, who cannot tolerate that type of intensive therapy, the best option may be supportive care.

The first and most important step in deciding what treatment to use in a patient with an MDS is to perform a thorough risk assessment. There are a number of different risk assessment prognostic models; the most common is probably the International Prognostic Scoring System (IPSS). The IPSS divides patients into categories ranging from low, low-intermediate, high-intermediate, and high risk for disease, progression, and disease-related complications, including death. A patient with low-risk disease will be managed very differently from a patient with high-risk disease. We are learning more about how best to use these models and how to improve them. At the 2010 American Society of Hematology (ASH) meeting, data from a study by Corrales-Yepez and colleagues were presented, which validated a prognostic model system initially proposed by researchers at M.D. Anderson Cancer Center. This new model system uses clinical factors to categorize patients more precisely than the IPSS. Studies suggest that it refines the IPSS in distinguishing patients who have more aggressive disease from patients who have more indolent disease, which is very important because it helps to determine how aggressive treatment should be.

H&O What are hypomethylating agents, and how are they used?

WB There are 2 hypomethylating agents approved by the US Food and Drug Administration: azacitidine (Vidaza, Celgene) and decitabine (Dacogen, Eisai). These compounds are closely related, chemically speaking, and they have a unique mechanism of action. In solid tumor oncology with cytotoxic chemotherapy, historically, the usual approach to treatment is to use chemotherapy in regimens

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that are as intense as is tolerable. The dosing of the drug is maximized, with the hope that the disease course can be altered while keeping side effects just below an intolerable level. In contrast, the hypomethylating agents are not dosed at a maximal drug level; they are dosed essentially at one tenth of the tolerable dose. This approach is based on data from the past decades, which suggest that these drugs work in a different way at lower doses than they do at higher doses. At high doses, these drugs are cytotoxic chemotherapy agents, much like any other chemotherapy agent. But at lower doses, they seem to have a different property, that is, they work as hypomethylating agents. What that means is that at lower doses, these drugs do not initiate an event that kills the cell, but instead they alter the signaling in the cell by re-expressing genes that are aberrantly silenced. Many genes are regulated, at least in part, by promoter methylation. In cancer cells, some genes can essentially be turned off by promoter hypermethylation, such as genes that control growth differentiation of the cell or regulation of other genes. A turned-off tumor-suppressor gene contributes to the process of cancer. Azacitidine and decitabine can reverse that abnormal process and re-express the gene, so that the cell will essentially behave the right way again. Time will tell if this novel proposed mechanism of these agents accurately reflects reality.

In hypomethylating therapy, the disease cell must be continuously re-exposed to treatment over time. I view it as chipping away at the disease because only a small percentage of the cells are hit each time. One very important concept in the use of hypomethylating agents is that they must be given in repetitive cycles for a long duration.

H&O What are the clinical trials supporting the use of hypomethylating agents in patients with MDS?

WB The first clinical trial that started the move toward approval of these agents was done by the Cancer and Leukemia Group B (CALGB). It showed that MDS patients treated with azacitidine had a reasonable—albeit relatively low—response rate. The patients also showed improvement in transfusion needs and quality of life; essentially, patients who received the drug felt better than they had before.

That study started a cascade of trials, leading ultimately to a randomized trial by Fenaux and coworkers in which azacitidine was compared to what has been called conventional care regimens (eg, from a selection of alternative treatment approaches chosen by the treating physician). There were 3 conventional care regimens: intensive therapy, low-dose cytosine arabinoside (ARA-C), and supportive care. The treating physician selected the best conventional care regimen for a particular patient, and then that patient was randomized to receive either the conventional care therapy or azacitidine. The trial demonstrated that azacitidine did not just improve blood counts or help patients feel better, but that it altered the natural history of the disease. Patients receiving azacitidine had a significant survival benefit compared with the patients receiving any of the conventional care regimens. This outcome was really encouraging and wonderful because it showed that we are finally at a point at which MDS therapies can be effective, at least in subsets of patients. Azacitidine is commonly given now, at least to patients with higher-risk disease. Clearly, however, outcomes need to be improved further for MDS patients.

Decitabine is a structural cousin to azacitidine. Its approval pathway was relatively similar. Patients receiving decitabine were shown to have improved quality of life and decreased transfusion requirements as compared with patients who received supportive care. A 2008 randomized trial from the European Organisation for Research and Treatment of Cancer Leukemia and German MDS Study Groups did not show a survival benefit with decitabine treatment. There may be a number of reasons for that lack of benefit, including the dosing schedule used. It is possible that with today's knowledge of how hypomethylating agents can be given optimally—that is, at low doses, repetitively, for multiple cycles over time—that decitabine might have been as successful as azacitidine has been.

H&O Are hypomethylating agents associated with notable adverse events?

WB The most important adverse events associated with these drugs are myelosuppression and increased risk of infection. The problem, of course, is that low blood counts and risk of infection are already concerns for MDS patients. However, data for both drugs show that the very patients who might be affected most severely by the drugs' side effects are the same patients who could achieve the most benefit from their use. More specifically, in an older patient with low blood counts, there is a concern that these drugs could knock the blood counts down further and put the patient at a greater risk of infection. Fortunately, this concern has not been substantiated by data from subset analyses. Patients who are older and who have disease-related cytopenias at trial entry are not at increased risk for infection or bleeding as compared with patients who receive supportive care or other conventional therapies. In the azacitidine survival trial, patients over age 75 still had a substantial survival benefit with azacitidine over conventional care. That is a very important finding.

H&O Are there certain MDS patients who are more or less likely to benefit from treatment with hypomethylating agents?

WB The azacitidine survival trial included MDS patients who were essentially high-intermediate risk or high risk, meaning that they had a high likelihood of experiencing complications including transformation to acute myeloid leukemia or death, in the next 1 or 2 years. In these types of patients, it is important to have a treatment that can potentially alter the natural history of the disease. The goal is essentially to try and push through some of the complications to achieve a survival benefit. The lesson from the azacitidine trial is the importance of maintaining a long-term commitment to continue on with the drug; the median number of cycles was 9. It is important, in my opinion, for patients to stay on these drugs at the doses that have been shown to be effective. There is much discussion about the best dose and the best schedule. It is difficult to evaluate results when regimens deviate from those used in published trials.

In a lower-risk patient who does not have neutropenia or platelet-transfusion dependence, there may be fewer concerns about disease-related toxicities, and the goal of treatment may be different. The goal may not be to achieve a survival benefit, but rather to reduce the patient's transfusion needs and improve quality of life. It is important to clarify management goals at the beginning of treatment. For a high-risk patient, there is little benefit to using the drug at all unless it is administered in multiple cycles over time. In a lower-risk patient who may have red cell transfusion dependence but no other evidence of disease—at least in the peripheral blood—treatment might be less aggressive. The prognostic models can be very helpful in making decisions about when to start therapy and how aggressive to be.

The fruits of laboratory research are beginning to refine our understanding of who should receive these agents, of who might benefit. A number of investigators, including our own group, are trying to identify ways to predict which patients might respond better to hypomethylating agents. Our group recently showed that *microRNA-29b* (*miR-29b*) may be predictive of response for AML patients treated with decitabine. At ASH, the French MDS group presented early data suggesting that *TET2* mutations may be associated with increased response to azacitidine. This study by Itzykson and coworkers demonstrated that presence of a *TET2* mutation predicted a higher response rate to azacitidine. It did not predict a higher survival rate, but I think that this finding marks the beginning of a molecular diagnostic approach. Without question, this approach is going to be the secret to moving the care of MDS patients further faster.

H&O What are the treatment schedules of azacitidine and decitabine in MDS?

WB For azacitidine, the typical treatment schedule is 75 mg/m^2 given subcutaneously or intravenously for days 1–7 of a 28-day cycle. There is much discussion about whether treatment can be given on days 1–5 instead of on days 1–7. Another option may be to give treatment on days 1–5, have the weekend off, and then give treatment on the next Monday and Tuesday, a regimen known as the "5-2-2" schedule. One practical reason behind the 5-2-2 schedule is that most community oncology centers are not open on the weekend. However, in the trial showing a survival benefit, azacitidine was given on days 1–7 every 28 days, and I think that fidelity to that regimen is probably important for the drug's activity when possible.

It is possible that we may find better schedules. There was a recent abstract from the Eastern Cooperative Oncology Group looking at azacitidine in combination with an investigational agent, entinostat (Syndax), with a novel dosing schedule. The addition of entinostat did not seem to confer any benefit. However, the novel dosing schedule of azacitidine, in which the drug was given at a slightly lower dose for 10 days, had promising implications in terms of response. This schedule should be tested further.

With decitabine, the most commonly used approach in the United States is 20 mg/m^2 intravenously over 1 hour for 5 days every 28 days. Again, the idea is to administer the drug in repetitive cycles over time. There are European data looking at a different schedule of administration, in which the drug is given 3 times a day for 9 doses. This approach lacks practicality, at least for patients in the United States. In the vast majority of cases, decitabine is given once a day for 5 days every 28 days.

H&O What are the future directions of therapy for MDS?

WB The most important aspect is that therapy will be based on a better understanding of the disease. There is an appreciation that the disease is even more heterogeneous than previously thought. At the 2010 ASH meeting, several abstracts presented data from genomic studies looking for mutations. These studies show huge variability and heterogeneity in the disease.

The next leap forward in the care of patients with MDS will be built on the backbone of understanding the pathophysiology of the disease. In the next few years, we should have a much better foundation upon which to understand the disease itself, and thereby to design and implement therapies properly.

Suggested Readings

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