Update on Treatments for Patients With Myelodysplastic Syndrome

Guillermo Garcia-Manero, MD
Associate Professor of Medicine
Chief, Section of Myelodysplastic Syndromes
Department of Leukemia
University of Texas
M.D. Anderson Cancer Center
Houston, Texas

What is the current standard of care for myelodysplastic syndrome (MDS)?

The standard of care for MDS depends on the risk of the patient. To assess risk, most physicians use one of the known staging models—the classic one being the International Prognostic Scoring System (IPSS), which divides patients into lower risk (which includes low and intermediate-1 risk) and higher risk (which includes intermediate-2 and high risk)—2 very different groups of patients. For the last few years, several other models have been developed to better estimate the risk among these patients. For example, there is the World Health Organization Classification-Based Prognostic Scoring System (WPSS), which is used in Europe. At M.D. Anderson Cancer Center, we have developed 2 models: one is for low-risk disease, and the other is more of a global MDS model. The low-risk model is very important because it applies to patients with low/intermediate-1 risk MDS, and what we have found is that prognosis in these patients can range from a survival of 9 months to never dying from the disease, which means that there is much heterogeneity in this patient population.

With this in mind, strategy for patients with lower-risk disease will highly depend on factors such as the transfusion needs, cytogenetic profile, and percentage of blasts in the patient. Therefore, care for these patients will vary from observation, and supportive care (eg, iron chelation) for those who are not transfusion dependent, with low percentage of blasts and diploid cytogenetics; to the use of growth factor support (mainly erythropoietic-stimulating agents) for anemic patients with or without adding a myeloid growth factor such as granulocyte colony-stimulating factor (G-CSF); to the use of lenalidomide (Revlimid, Celgene) for patients with a chromosome 5 alteration with anemia. The use of hypomethylating agents is less understood but is commonly done in patients with low/intermediate-1 disease who are transfusion dependent, perhaps with increased percentage of blasts.

For patients with higher-risk MDS, the standard is a little better defined. For patients who have intermediate-2 to high-risk disease, the standard of care will now be the use of a hypomethylating agent—5-azacitidine (Vidaza, Celgene) or decitabine (Dacogen, Eisai). The question is what to do with younger patients with high-risk MDS, and older patients who have MDS that resembles acute myeloid leukemia (AML; eg, those with blasts 20–30). There are a number of studies that are looking at hypomethylating agents in the very old (ie, ages over 70 and even 80), and it appears that 5-azacitidine and decitabine are safe in this age group and also very active in terms of modifying the natural history of the disease. Dr. Fenaux published an article in the Journal of Clinical Oncology looking at older patients with MDS who have 20–30% blasts.1

This question is more complex in younger patients. Most physicians will treat MDS patients younger than 60 with some type of induction chemotherapy (eg, an AML program). In our group, we still offer that type of therapy to our younger patients. For example, in my own practice, if the patient is very young and diploid, I would be more enthusiastic about using high-dose chemotherapy. However, if a patient is young and has abnormal cytogenetics, particularly a chromosome 5 or 7 alteration or other complex karyotypes, I would be more inclined to use a hypomethylating-based therapy, because the data suggest that patients with abnormal cytogenetics do poorer; induction chemotherapy response rates are low, and toxicity becomes relatively high.

The ultimate goal for these patients is allogeneic bone marrow transplantation; there are now ample data
indicating that bridging patients to transplantation with a hypomethylating agent is equal or superior to proceeding with more intense and toxic types of programs. In terms of transplantation, I think the jury is still out. There is no formal study comparing transplantation versus more modern forms of therapy for MDS like hypomethylating agents; it is difficult to know which is better. There are models that may predict subsets of patients with lower-risk disease who do better if transplantation is delayed (Cutler, personal communication). For patients with high-risk disease, the data indicate that transplanting sooner rather than later is better. However, again, there is no formal study comparing transplantation and hypomethylating agents.

I see these interventions as being sequential; in my practice, I delay transplant as much as I can because there is no formal study comparing transplantation versus more bocytopenic purpura. Therefore, it is also a little too early for us to decide on its role in MDS. It is important that we wait for results from large randomized trials.

**H&O What do we know of new agents for patients with lower-risk MDS?**

**GGM** There were not much data presented at the 2009 American Society of Hematology (ASH) meeting regarding new agents for lower-risk MDS. Within the low-risk studies, in my opinion, the most important study was the initial report of a study called MDS004.\(^2\) MDS004 is a trial performed mainly in Europe; patients were randomized between 2 dose schedules of lenalidomide (5 mg or 10 mg) versus placebo. According to an oral presentation by Dr. Fenaux, patients on 10 mg did better than those on 5 mg in terms of responses. By and large, compared to placebo, the data very nicely confirmed the phase II trials that Dr. List had done in the United States with single-arm trials of lenalidomide, which made these data very positive.\(^3\) There was the question of whether lenalidomide can increase the risk of AML transformation in patients with low-risk disease, and this analysis showed that the risk of transformation was approximately 1–6%, which is no different from the natural history that you would expect in patients with MDS and a chromosome 5 alteration.

In terms of growth factors, romiplostim (Nplate, Amgen) was the only agent that was noticeably presented, but I think that it is still a little too early to see if this drug has a role in MDS. Currently, there is a very big randomized trial led by Amgen investigating this drug in MDS, but in my opinion, the data of romiplostim in combination with decitabine, 5-azacitidine, and lenalidomide, have been relatively modest. Additionally, there are some safety issues remaining with romiplostim in patients with MDS, particularly the risk of AML transformation and induction of myelofibrosis. I believe we have to wait a little bit to hear more.

Another agent called eltrombopag (Promacta, GlaxoSmithKline) also attracted attention, but this agent is not approved for MDS; it is approved for idiopathic thrombocytopenic purpura. Therefore, it is also a little too early for us to decide on its role in MDS. It is important that we wait for results from large randomized trials.

**H&O What studies interested you regarding low-risk MDS patient care?**

**GGM** From a clinical perspective, there were 3 presentations of low-risk MDS that I think were of interest at ASH. The first was a poster presented by the group at the National Institutes of Health (NIH) that described the role of alemtuzumab (Campath, Genzyme) in patients with MDS. This group pioneered the use of immunotherapy in patients with MDS and developed an algorithm that allows prediction of response to antithymocyte globulin (ATG)-based therapy. They hypothesized that alemtuzumab would have a role analogous in MDS to that reported with ATG. They presented data in approximately 20 patients—to treat those 20 patients they had to screen more than 100 patients who fit the criteria for response. Those patients who fit the criteria for response had very impressive outcomes with alemtuzumab. They had a response rate that was close to 90% in patients with intermediate-1 disease and approximately 40% in patients with intermediate-2 disease; they also reported that 5 of the 7 patients with abnormal cytogenetics also had a response. These are really nice data because the schedule that this study group used was 10 mg intravenously for 10 days and for only 1 cycle, which was very safe. If these data were to be validated, I think alemtuzumab would surely replace ATG, a therapy that is significantly more complicated to use and has suboptimal results. Although this study is a pilot study and still needs to be validated, I believe it provides very important data for patients with low-risk MDS.\(^4\)

Another study that was of interest was my trial of oral azacitidine, which could also be applied to patients with higher-risk disease. I am very enthusiastic about this study because what we have done is develop an oral formulation of azacitidine. The study was mainly a phase I trial, and we found that if we gave this drug for 7 days, the toxicity profile was very good. Interestingly, even if the pharmacokinetic and pharmacodynamic profiles were significantly lower than what we saw with parenteral azacitidine, the responses were very encouraging. We reported a response rate of approximately 30% in MDS, which compares very nicely with what we see with regular parenteral azacitidine. Moreover, I actually think that we underrepresented the
data because the study called for responses at 7 months; if someone had a response at month 2 and lost it at month 6, the patient was not counted as a responder—and we saw some such cases. Therefore, when pertaining to respondents from M.D. Anderson Cancer Center, the response rate (ie, complete response) is probably in excess of 50% with oral azacitidine. This study is very preliminary but also very exciting because it has shown azacitidine to be safe and easy to administer. Currently, the study is looking at a treatment regimen of 14 days or 21 days, giving the drug twice or 3 times a day. We are currently working on the first manuscript for this study.5

Another report of interest was a study by my colleagues and I that looked at 2 regimens of very low doses of decitabine: 20 mg given subcutaneously daily for 3 days versus 20 mg subcutaneously once a week for 3 weeks. We found that the regimen of daily administration for 3 days was superior to weekly administration for 3 weeks. However, more importantly was that the response was stable in approximately 70% of the patients (trilineage). Most of the patients in the 3-day schedule are still alive and doing very well. We need a little more follow-up on this study.6

We had always suspected that these hypomethylating agents at lower doses may be as effective as the higher doses, despite the fact that blood levels and pharmacokinetic and pharmacodynamic effects are lower. Now with the aforementioned clinical trials, we are confirming this concept. Another reason why these studies are important is that responses seem to be durable. We currently have patients on oral azacitidine going on 3 years of therapy, and I think that is very exciting.

**H&O What are the advances in upfront therapy in high-risk patients?**

**GGM** Although there were not much new data on upfront therapy for high-risk patients presented at ASH 2009, there was a very interesting study on lenalidomide in high-risk patients receiving a daily high dose of 50 mg. The study was mainly geared towards treatment of patients with AML, but it showed good responses (eg, 30%), which indicates that higher doses of lenalidomide can be used in patients with AML or high-risk MDS.7

In my opinion, there were 3 reports of 3 trials pertaining to treatment for those who had previously failed hypomethylating therapy that were interesting. The first is a study by Dr. Elaine Sloand that looked at a drug called ON1910 (Onconova). This new agent is being developed for patients who had failed hypomethylating therapy. The investigators found that the drug is very safe and has potential activity. The study included a small group of patients, but they reported approximately 40% overall response, and in patients who had failed azacitidine it was 2 of 4. The study showed a nice toxicity profile, and therefore this agent is going to be tested in an approval study for high-risk patients who had failed prior hypomethylating agents.8

The second study is on sapacitabine (Cyclacel). Our group has presented at ASH and American Society of Clinical Oncology a number of times with this compound. It is a very interesting oral nucleoside analog that has a specific mechanism of action that induces only single-strand DNA breaks. The bottom line is that the drug is very well tolerated. We reported a response rate of approximately 30% in patients who had failed prior hypomethylating-based therapy. This drug is also being studied in older AML patients as well as in MDS patients.7

Lastly, clofarabine (Clolar, Genzyme) is probably the most powerful of the compounds found potentially effective in patients who had previously failed hypomethylating agent therapy. Oral clofarabine has the most mature data in the patient population, with a response rate of approximately 30%.8

**References**