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Nontransplantation Options for Patients with Myelodysplastic Syndromes

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The myelodysplastic syndromes (MDS) are a complex, heterogeneous group of myeloid malignancies. The last decade has brought a revolution both in our ability to classify these disorders and in the number of nontransplantation therapeutic alternatives available for patients with MDS. In general, patients with MDS are classified using the International Prognostic Scoring System (IPSS) into lower-risk and higher-risk categories. Approximately two-thirds of MDS patients are in the lower-risk category at initial presentation. There is a tendency to observe these patients until they become transfusion-dependent.

We recently developed a prognostic model that allows the identification of patients with lower-risk disease but poor prognosis [1]. This model is based on a score that considers patient age, cytogenetics, percentage of marrow blasts, hemoglobin level, and platelet count. Depending on the score value, the median survival of the patients with lower-risk disease can range from less than 12 months to not achieved. Of note, a large majority of the patients referred to M.D. Anderson Cancer Center are in the poor-prognosis lower-risk category. Validation and prospective use of this model could facilitate allow the development of early interventions, including allogeneic stem cell transplantation.

Current therapeutic alternatives for patients with lower-risk disease [2] include supportive care (eg, transfusions, growth factors, antibiotics) and directed therapies, such as lenalidomide in patients with alterations of chromosome 5 and anemia [3]. The role of hypomethylating agents is less well established in these patients; these agents are commonly used in patients who have not benefited from growth factor-or lenalidomide-based therapy. Several ongoing studies are currently investigating the use of lower doses of either decitabine or 5-azacitidine (including an oral formulation) in these patients [4-6]. These interventions have not been clearly shown to modify the natural history of patients with lower-risk disease, however.

The treatment approach for patients with higher-risk disease has evolved significantly over the last 5 years. Previously, most of these patients either were not treated or were exposed to an acute myelogenous leukemia (AML)-like induction program. This type of strategy is associated with higher mortality and short duration of response. The introduction of hypomethylating agents has led to significant changes in the treatment of these patients. Both decitabine and 5-azacitidine have clinical activity in higher-risk MDS, and a recent randomized phase III trial found that decitabine therapy improved survival in patients with higher-risk disease [7,8]. But despite their activity and excellent toxicity profile, these agents are associated with relatively low complete response rates and a prolonged time to response (up to several months), and, consequently, patients may be treated chronically with no clear benefit in terms of transfusion needs. Outcomes are poor in patients who experience relapse or progress after hypomethylation-based therapy [9]. The use of these agents is currently being incorporated in the treatment of elderly persons with AML. The use of more intensive therapies in younger patients is a matter of debate.

Despite these advances, however, the prognosis in patients with MDS remains poor. This is due in part to the current lack of molecular targets that can be used for therapeutic development. Active areas of clinical research include the development of new nontoxic agents for patients with lower-risk disease, combination epigenetic therapies for higher-risk disease, and treatments for patients who do not benefit from hypomethylating agents. Various agents aimed at lower-risk MDS are currently in development, including histone deacetylase inhibitors, glutathione S-transferase pi inhibitors, and p38MAPK inhibitors. As mentioned earlier, several ongoing studies are investigating very-low-dose decitabine and azacitidine therapy; preliminary reports indicate minimal myelosuppressive effects and induction

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of transfusion-independence in close to 70% of patients [4]. The oral formulation of 5-azacitidine is of interest as well. Data reported at the 2009 American Society of Hematology meeting (to be updated at the 2010 meeting) indicate that despite the significantly lower pharmacokinetic and pharmacodynamic characteristics of oral 5-azacitidine compared with its parenteral form, therapy with the oral form is associated with significant clinical activity and safety in patients with MDS. Chronic low-dose use also could have a significant impact in patients with lower-risk MDS. Several large-scale randomized studies in patients with lower-risk MDS are currently underway, including studies of lenalidomide in patients non-del5q MDS, thrombomimetic agents in patients with thrombocytopenia, and iron chelation therapy.

Current investigations in higher-risk MDS are focusing either on attempts to improve current results with the use of hypomethylating agents upfront or on the development of new treatment strategies for patients who no longer benefit from these agents. Combination epigenetic therapies with histone deacetylase inhibitors [10] and lenalidomide [11] could potentially improve outcomes in these patients. Finally, a number of drugs, including clofarabine and sapacitabine, are currently under study in the post–hypomethylating agent setting. Although these drugs have demonstrated evidence of clinical activity, most likely they will not be considered definitive treatments for these patients [12,13]. Although genetic alterations are rare in patients with MDS, a small fraction of patients may harbor alterations of *Flt-3*, *JAK2*, and *Ras*. Specific inhibitors for these agents, such as MEK inhibitors in the case of *Ras*, in development for the treatment of other leukemias are being investigated in MDS as well.

In summary, a number of investigational and standard approaches are currently available for patients with MDS. These approaches, as well as the role of transplantation, should be carefully discussed with the patient, family, and physicians involved in the case and should be based on realistic expectations of tolerability, natural progression of disease without therapy, and specific prognostic and molecular characteristics of the patient.

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