



Michele Sassi. *Blue Boat*. Photograph. Taconic Lake, New York.

Current approaches and novel therapeutics on the horizon for myelodysplastic syndromes are discussed.

Treatment Options for Myelodysplastic Syndromes

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Myelodysplastic syndromes are a heterogeneous collection of bone marrow stem cell diseases. As a result, one should recognize that an appropriate treatment option for one patient may differ significantly from that for another. The spectrum of care for myelodysplastic syndrome (MDS) ranges from simple supportive management to highly aggressive therapies such as chemotherapy and/or bone marrow transplantation. In between these two disparate options are “intermediate” therapies, which include the newly approved azacitidine (Vidaza[®], Pharmion Corp; Boulder, Colo) and a host of other agents that are currently in development. These newer modalities have been promulgated based on their ability to impact one or more of the pathophysiological features believed to characterize at least a subset of patients with MDS.

Supportive Care

The cornerstone of therapy for years has been “best supportive care,” given to virtually every patient with MDS,

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but this approach is unlikely to change the natural history of the disorder. Despite the recent approval of azacitidine, supportive care alone will remain an important treatment option for many patients with MDS. Supportive care consists of transfusions for symptomatic anemia or symptomatic thrombocytopenia, treatment of infections with antibiotics, and growth factors designed to improve one or more cytopenias.¹ These approaches are summarized in Table 1.

Recombinant erythropoietin alfa (EPO; Procrit[®], Ortho-Biotech; Bridgewater, NJ) is frequently used to support the anemia in patients with MDS.¹ It is important to ensure that the patient is iron replete prior to starting erythropoietin therapy. This assessment is based on an iron stain performed on the bone marrow aspirate. If iron stores are absent, a source of bleeding should be suspected and repletion is indicated.

If the endogenous EPO level is >500 mIU/mL, it is unlikely that the patient will respond. If the level is <100 mIU/mL, the chance of response is approximately 30%. A trial of recombinant EPO or darbepoetin alfa (Aranesp[®], Amgen Inc; Thousand Oaks, Calif) should last for at least 6 weeks. One or two attempts at dose increases may be appropriate in the event of initial failure. However, some data indicate that the addition of granulocyte colony-stimulating factor (G-CSF; Neupogen[®], Amgen Inc; Thousand Oaks, Calif) at low doses (0.3–3 µg/kg per day) may potentiate the response derived from erythropoietin alone.^{2,5}

Table 1. — Best Supportive Care Synopsis

Transfusions	Majority
Anemia	Majority, EPO response in 20%–30% Ensure adequate baseline iron stores Baseline EPO level correlated with response G-CSF helpful in poor EPO responders
Neutropenia/infections	30%–35% have ANC <1000–1500/ μ L, yet only 10% have infection No indication for routine antibacterial prophylaxis CSF support improves ANC (75% of patients) but has no impact on overall survival
Thrombocytopenia	25%–50% of patients Thrombopoietic agents (thrombopoietin, MGDF, interleukin-11) have no significant impact on transfusion needs

ANC = absolute neutrophil count
EPO = erythropoietin
G-CSF = granulocyte colony-stimulating factor
MGDF = megakaryocyte growth and development factor

Myeloid growth factors can reliably improve the white blood cell count in patients with MDS. However, to date, they have not been associated with a reduction in infections or an improvement in survival.¹ Hellstrom-Lindberg et al^{6,7} developed a prognostic model to predict which patients would benefit from the combination of EPO and G-CSF, suggesting that those without large transfusion requirements and/or low serum EPO levels are more likely to respond.

Thrombocytopenia is often a concern. However, there are no thrombopoietic agents indicated in MDS. For example, interleukin-11 (IL-11, oprelvekin; Neumega®, Wyeth Labs; Collegeville, Pa) has thrombopoietic activity, for which the drug was approved for use after intensive chemotherapy, but IL-11 has undergone only limited testing in patients with MDS.⁸

The role of iron chelation is controversial, even in heavily transfused MDS patients. The clinical impact of iron overload in MDS is not well defined. Deferoxamine (Desferal®, Novartis; East Hanover, NJ), the only approved iron-lowering agent in the United States, must be given subcutaneously and is poorly tolerated.

Chemotherapy: What Value and Where?

Chemotherapy was considered a poor option for patients with MDS because of the intrinsic deficit in proximal bone marrow stem cells. A lesion at the primitive stem cell level would suggest the need to ablate the entire marrow compartment, so chemotherapy would have to ablate the most infantile cell for efficacy. However, Estey et al⁹ suggested that responses in patients with MDS with excess blasts are as likely as in those with acute myeloid leukemia (AML) if patient age and cytogenetic status are controlled.

Although there may be a role for AML-type induction chemotherapy for select patients—particularly those in

whom pre-marrow transplant cytoreduction is deemed desirable—long-term survival extension with chemotherapy alone in MDS is rare (Fig 1). Less-intense chemotherapy, such as low-dose cytosine arabinoside (Ara-C), may have a limited role in MDS. Despite the feasibility of intense chemotherapy in MDS, the widespread use of chemotherapeutic regimens in the 1990s failed to substantially change the outcome (Fig 2).⁹

Transplantation: The Only Known Curative Option

Bone marrow transplantation (BMT), the only known curative modality in MDS, is an option for few patients because of older age, comorbidities, or lack of a donor. In the future, nonmyeloablative allogeneic BMT and molecular typing of unrelated donors may make this option more widely available.

Which patients with MDS should be considered for a potentially curative BMT, albeit with high treatment-related mortality? Those with low-risk disease (based on the Inter-

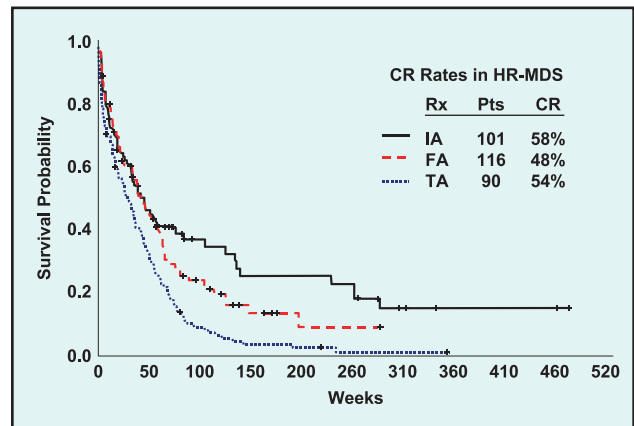


Fig 1. — Complete remission and survival rates with various chemotherapy regimens. From Estey EH, Thall PF, Cortes JE, et al. Comparison of idarubicin + ara-C (IA), fludarabine + ara-C (FA), and topotecan + ara-C-based (TA) regimens in the treatment of newly diagnosed acute myeloid leukemia, refractory anemia with excess blasts in transformation, or refractory anemia with excess blasts. *Blood*. 2001;98:3575-3583. Reprinted with permission of the American Society of Hematology.

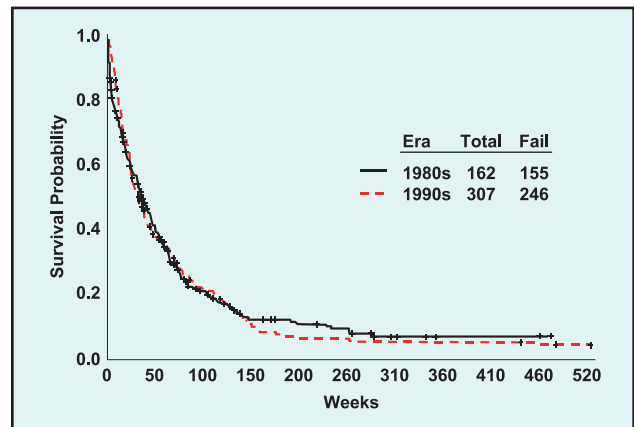


Fig 2. — Survival rates before (1980s) and after (1990s) the use of chemotherapy. Reprinted with permission of E. H. Estey, MD.

national Prognostic Scoring System) seem to be the best transplant candidates, but they have the longest survival with medical therapy. Cutler et al¹⁰ developed a model to identify those patients who should have early transplant, those who should have transplant delayed for several years, and those who would be candidates only following disease progression. Derived answers suggest an inverse relationship between patient prognosis and the need for transplant (eg, a poor prognosis suggests a greater benefit from transplant). Additionally, the younger the patient, the more appropriate the patient is for BMT.¹¹ Whether induction chemotherapy is needed to reduce the blast burden prior to transplant is unclear. Patients who respond to such intensive therapy fare better after transplant, but this outcome could reflect the biological features of the disease rather than the benefit of chemotherapy.

Newer Options

Given the possible aplastic anemia-like immune-mediated suppression of hematopoiesis, one option for some patients with MDS is immunosuppressive therapy with antithymocyte globulin and/or cyclosporine A.¹² Younger thrombocytopenic patients and those with certain HLA subtypes appear to be more amenable to response with immunosuppression.

Thalidomide is another available drug with modest activity in indolent histological subtypes of MDS.¹³⁻¹⁶ Based on the antiangiogenic properties of thalidomide, testing by Raza et al¹³ showed that approximately 20% of patients with MDS without excess blasts experience a decrease in transfusion requirement. However, many patients cannot tolerate prolonged exposure to thalidomide.

Azacitidine, the only FDA-approved drug for MDS, is a DNA methyltransferase inhibitor that is discussed later in this supplement by Lewis Silverman, MD. Other available agents such as amifostine and arsenic trioxide have been used with minimal success in patients with MDS and are not routinely appropriate.^{17,18}

On the Horizon

Several agents are being developed for the treatment of MDS. CC5013 (Revimid®, Celgene Corp; Warren, NJ) is a thalidomide analog with a reduced toxicity profile. Reduction in red blood cell transfusion in patients with MDS, particularly 5q- syndrome, has been reported.¹⁹ Due to the possibility that angiogenesis or proangiogenic molecules may be playing a pathophysiological role in MDS, vascular endothelial growth factor receptor inhibitors (eg, PTK-747) are also in development.

Drugs that enhance transcription of differentiation-associated genes by allowing acetyl groups known as histone deacetylase inhibitors (eg, suberoylanilide hydroxamic acid [SAHA]) to attach to the histone DNA protein coat are also in clinical development.

Moreover, signal transduction inhibitors are a class of agents that disrupt the signals which promote proliferation

in leukemic or myelodysplastic cells. For those few patients with MDS whose disease is based on an activation of tyrosine kinase, such drugs may have a therapeutic role.²⁰

Approximately 10% to 30% of patients with MDS have an activating mutation in one of the Ras family proteins. Farnesyltransferase inhibitors disrupt Ras activity by stopping the addition of a farnesyl group to Ras, thereby preventing membrane attachment and activation. One such agent is associated with a 20% complete response rate in untreated patients with AML.²¹ However, the activity of farnesyltransferase inhibitors in MDS has been modest.²²

Given the myriad of available options, the most appropriate treatment strategy is determined by the patient's age, chromosome status, IPPS score, and philosophy about life. Azacitidine is now available for routine use in patients with MDS, and research will evaluate whether combining this active drug with other agents that are either currently available or in development will provide further benefit.

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