Update on Myelodysplastic Syndromes: New Approaches to Classification and Therapy

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Myelodysplastic syndromes have long provided hematologists with difficult therapeutic challenges, and until recently treatment options beyond supportive care were limited. Recent advances in our understanding of hematopoiesis, immunology, and genetics have led to a better understanding of the natural history of these disorders and have facilitated development of more rational and targeted treatment approaches. A number of promising agents are in various phases of study, including arsenic trioxide, CC5013, the farnesyltransferase inhibitors, and DNA methyltransferase inhibitors. In addition, less intensive strategies for allogeneic stem cell transplantation now permit us to offer potentially curative therapy to a larger proportion of patients. Optimal management of an individual patient requires consideration of the disease and its expected course, available treatment options, the patient's age and condition, and an ongoing assessment of the goals of therapy.

CLASSIFICATION AND PROGNOSTIC GRADING

The French-American-British (FAB) Morphology Group classification system was last modified in 1982, and categorized MDS on the basis of blood and bone marrow morphology. This scheme has recently been replaced by the World Health Organization descriptive classification, which incorporates cytogenetic and immunophenotypic information and reorganizes disease categories. The most significant change in the new system is lowering of the threshold for defining acute myelogenous leukemia from 30% to 20% blasts in the bone marrow or blood, eliminating the typically transient category of refractory anemia with excess blasts in transformation (RAEB-t). High-grade MDS is now subdivided into RAEB-1 (5% to 9% blasts in the marrow) and RAEB-2 (10% to 19% blasts in the marrow and/or 5% to 19% blasts in the blood). Low-grade MDS (less than 5% blasts in marrow/blood) has been parsed to create several new categories. This includes designation of MDS with isolated del(5q) as a distinct clinicopathologic entity, which is typically characterized by a relatively hypoplastic marrow, hypolobulated megakaryocytes, macrocytic anemia with relative sparing of neutrophil and platelet counts, and a low risk of progression to acute leukemia. Finally, chronic myelomonozytic leukemia has been placed in a new classification scheme termed “myelodysplasia/myeloproliferative disorders” (along with juvenile chronic myelogenous...
leukemia and atypical chronic myelogenous leukemia), in recognition of the difficulty in assigning these disorders to either category on the basis of clinical features and natural history. Table 1 compares the two classification systems.

The most widely used grading system for assessing prognosis in MDS is the International Prognostic Scoring System (IPSS). The IPSS was the product of an international workshop that compiled and analyzed clinical, cytogenetic, pathologic, and outcome data on 816 patients with primary MDS who were part of seven previously reported studies. Patients who had received intensive chemotherapy or transplantation were excluded. Multivariate analysis identified cytogenetic abnormalities, percentage of bone marrow blasts, and number of cytopenias as the most significant predictors of survival and progression to acute leukemia. A weighted model was developed that separates patients into four distinct risk groups with respect to median survival: low, 5.7 years; INT-1, 3.5 years; INT-2, 1.2 years; and high, 0.4 years. Details of the IPSS are presented in Tables 2 and 3.

**TREATMENT OPTIONS FOR MYELODYSPLASTIC SYNDROME**

Despite the many therapeutic trials conducted over the years, most treatment options for MDS have limited efficacy. Major modalities of therapy include supportive care, hematopoietic growth factors, biologically targeted therapies, immune manipulations, chemotherapy, and allogeneic marrow or stem cell transplantation. The goals of therapy depend on the age and condition of the patient, and the immediate and potential problems posed by the patient’s hematologic disorder. The range of therapeutic aims includes palliation of the symptoms associated with cytopenias, treatment of impending or overt leukemia, and alteration of the natural history of the disorder. The only potentially curative approach is allogeneic transplantation. Unfortunately, transplantation is a realistic option for the minority of patients with MDS, given that most are over the age of 65 at the time of diagnosis.10,11

| Table 1. Comparison of French-American-British and World Health Organization classifications of Myelodysplastic Syndrome |
|---|---|
| **FAB** | **WHO** |
| Refractory anemia (RA) | Refractory anemia (RA) |
| Refractory anemia with ringed sideroblasts (RARS) | Refractory anemia with ringed sideroblasts (RARS) |
| Refractory anemia with excess blasts (RAEB) | Refractory anemia with excess blasts-1 (RAEB-1) |
| Refractory anemia with excess blasts in transformation (RAEB-t) | Refractory anemia with excess blasts-2 (RAEB-2) |
| Chronic myelomonocytic leukemia (CMML) | Chronic myelomonocytic leukemia (CMML) |


| Table 2. International Prognostic Scoring System for Risk Assessment in Primary Myelodysplastic Syndrome |
|---|---|---|---|---|
| Prognostic Variable | Score |
|---|---|---|---|---|
| Bone marrow blast (%) | 0 | 0.5 | 1 | 1.5 | 2 |
| Karyotype* | Good | Intermediate | Poor |
| Cytopenias | 0-1 | 0-1 |

*Karyotype: Good, normal, −5, del(5q); poor, complex (>3 abnormalities or chrom 7 abnormalities; intermediate, others.

Data from Greenberg et al.9
One difficulty in assessing the utility of new therapies has been the lack of truly objective criteria for evaluating response to treatment. In an effort to resolve this issue, an International Working Group convened by the National Cancer Institute has proposed a set of standardized response criteria to aid in evaluating MDS clinical trials. These criteria have been a topic of considerable discussion, particularly with regard to what constitutes a clinically meaningful hematologic improvement. Nevertheless, the International Working Group criteria remain the most widely used tool for assessing response to therapy in clinical trials.

Hematopoietic Growth Factors

Hematopoietic growth factors, including erythropoietin (Epo), granulocyte-macrophage colony-stimulating factor, granulocyte-colony stimulating factor (G-CSF), and interleukin (IL)-11, have shown modest utility in improving the cytopenias associated with MDS. About 20% of patients with symptomatic anemia will have a significant response to Epo administration, and response is strongly correlated with low endogenous Epo levels (<500 mU/mL). The longer-acting darbepoietin alpha also appears to have activity in this setting. It is not widely appreciated that addition of low doses of G-CSF (~1 mcg/kg/day) is synergistic with Epo in stimulating erythropoiesis, with an approximate doubling of the response rate in anemic patients.

Infections related to neutropenia and/or functional neutrophil deficits are the most important causes of death in patients with MDS. Administration of G-CSF or granulocyte-macrophage colony-stimulating factor to neutropenic patients results in a predictable increase in the neutrophil count in most patients; however, the clinical benefit of prophylactic use has been difficult to document. In a phase III multicenter randomized trial comparing chronic administration of G-CSF with observation, there was no survival benefit associated with G-CSF. In fact, for the subgroup with advanced MDS, survival was shorter in the G-CSF arm, and there was a suggestion that progression to leukemia might be accelerated by growth factor administration. Based on these data, routine prophylactic use of the granulocyte colony stimulating factors is not recommended; however, these agents may be useful for short-term use in neutropenic patients with active infection.

The utility of IL-11 as a stimulator of thrombopoiesis is currently being explored. In a small pilot study in thrombocytopenic patients, low-dose IL-11 produced significant platelet count improvements in five of the 11 patients.

“Biologically Targeted” Therapies

Pathophysiologic studies in MDS show both increased proliferation and increased apoptosis of hematopoietic precursors, abnormalities mitochondrial function, increased angiogenesis, and disruption of normal hematopoietic-stromal interactions. Many of these changes are mediated by inflammatory cytokines such as tumor necrosis factor-α and IL-6, which have been targeted in numerous therapeutic strategies. Pathophysiology notwithstanding, strategies aimed at blocking inflammatory cytokines and/or angiogenesis such as amifostine, pentoxiphylline-cipro-dexamethasone, thalidomide, and soluble tumor necrosis factor-α receptor (enbrel) have thus far produced limited success in the treatment of MDS. It remains to be seen whether these agents will be more useful in combination approaches.

One of the most promising investigational agents for therapy of MDS is CC5013 (Revimid; Celgene Corp, Warren, NJ) a member of a new class of immunomodulatory drugs that have antiangiogenic activity and are potent stimulators of natural killer- and T-cell-mediated antitumor activity. Updated results of a multicenter phase II study of treatment of MDS with CC5013 show erythroid responses in 21 of 33 evaluable patients (64%). The erythroid response rates were highest in patients with early stage MDS, with 71% of patients with a low/
Int-1 IPSS score responding versus 25% of Int-2/high score patients. Interestingly, 10 of 11 patients (91%) with 5q-syndrome achieved red cell transfusion independence, and responders had restoration of a normal karyotype. Larger multicenter trials are ongoing to better define the utility and mechanisms of action of this novel agent.

Arsenic trioxide (ATO) is also under study for the treatment of myeloid malignancies including MDS. In vitro studies suggest that ATO has pleiotropic effects including induction of terminal differentiation and apoptosis, modulation of cytokine release, and inhibition of angiogenesis. Preliminary data from two single-arm studies of ATO in MDS suggest response rates of 20% to 25%. Responses have been seen in both low- and high-risk patients, including occasional major reductions in blasts. In a small study of the combination of ATO and thalidomide, responses were seen in four of eight evaluable patients. Multicenter single-agent trials are ongoing, and the potential for ATO as part of combination therapy is also being further explored. Other investigational treatment approaches include farnesyltransferase inhibitors (FTIs) and receptor tyrosine kinase inhibitors. Phase I data with the farnesyltransferase inhibitor R115777 appear promising, with objective responses in six of 20 MDS patients treated. DNA Methyltransferase Inhibitors

Transcriptional repression of critical growth control genes through DNA methylation of upstream regulatory regions has been identified in many malignant and premalignant states. In MDS, methylation of the cyclin-dependent kinase p15(INK4b) is seen in a substantial fraction of MDS cases, and sequential sampling studies suggest it is a late event in disease progression. These observations provided a rationale for clinical investigation of DNA methyltransferase inhibitors.

The nucleoside analogues 5-azacytidine (5-Aza C) and decitabine have activity both as DNA methyltransferase inhibitors and cytotoxic agents, and single-arm studies have shown activity of both agents in MDS cases, and sequential sampling studies suggest it is a late event in disease progression. These observations provided a rationale for clinical investigation of DNA methyltransferase inhibitors.

The Cancer and Leukemia Group B conducted a randomized study of intermittent subcutaneous 5-Aza C versus supportive care in 191 patients with symptomatic MDS. Of note, 77% of patients in the study were beyond refractory anemia/refractory anemia with ringed sideroblasts at entry. A 60% response rate was seen in the 5-Aza C arm (7% complete response, 53% partial response or improved) versus 5% receiving supportive care (all improved). Significant differences between the two groups were seen in median time to leukemic progression (21 months vs 13 months) and median overall survival (18 months vs 11 months). In addition, various measures of quality of life were improved in the 5-Aza C arm. It remains to be determined whether the effects of 5-Aza C in this setting are primarily because of cytotoxic or demethylating activities. Examination of the survival curves indicates that 5-Aza C does not change the ultimate outcome of MDS. Nevertheless, this is the only randomized study to show a survival benefit over supportive care for patients with MDS, and will serve as a frame of reference for further studies.

Immunosuppressive Therapy

Evidence of immune dysregulation is also present in some MDS patients, including increased numbers of cytotoxic T cells and skewing of the T-cell repertoire. The mechanism of immune-mediated suppression of hematopoiesis is not yet clear, but may be indirect, through suppression of normal hematopoietic precursors in the marrow. Molldrem et al reported a trial of equine antithymocyte globulin therapy (40 mg/kg/day for 4 days) in 61 patients with transfusion-dependent MDS (37 refractory anemia, 10 refractory anemia with ringed sideroblasts, 14 RAEB). Red cell transfusion independence was achieved in 34% of patients. In addition, platelet and neutrophil responses were observed in 47% and 55% of affected patients, respectively. Response to therapy was associated with improved survival, although infectious deaths occurred in nine patients (15%), all nonresponders. Multivariate analysis showed that younger age, shorter duration of red cell transfusion dependence, and the HLA-DRB1 15 haplotype were associated with response to ATG. Of interest, although the presence of a skewed T-cell repertoire does not predict for response to ATG, response is associated with outgrowth of a more normal distribution of T cells. Further studies are needed to better define which patients will respond to immunosuppressive therapy, particu-
larly given the significant infectious risks associated with ATG and other agents.

**Intensive Chemotherapy**

Intensive chemotherapy is an option for patients with secondary acute myelogenous leukemia (AML) or impending leukemic progression. Standard AML induction regimens using cytarabine and an anthracycline typically produce complete remissions in only 30% to 50% of MDS and secondary AML patients, and remissions are typically brief unless consolidated by additional chemotherapy or stem cell transplantation. The topoisomerase I inhibitor topotecan showed promising activity in early studies, both alone and in combination with other agents.49-51 Guilhot et al52 recently reported the results of a multicenter randomized trial of TAG (topotecan, cytarabine, and G-CSF) versus a standard regimen of IDAG (idarubicin, cytarabine, and G-CSF) in 238 patients with advanced MDS and secondary AML. Complete remission rates were similar in the two groups (40.3% for TAG, 46.2% for IDAG; P = NS), as were serious adverse events and median survival (44 weeks for both groups). In practice, topotecan is proving an effective agent for treatment of myeloid malignancies, particularly in patients who cannot receive anthracycline therapy. Nevertheless, response rates of MDS patients to standard induction chemotherapy remain poor.

Combining chemotherapy with other types of agents is an area of active investigation. We are currently conducting a phase I study of cytarabine and topotecan followed by escalating doses of the anti-CD33 calicheamicin conjugate gemtuzumab ozogamicin (Mylotarg; Wyeth Pharmaceuticals, Collegeville, PA) for patients with advanced MDS and secondary AML. To date, 15 patients have been treated and the maximum tolerated dose has not been reached. Based on intent to treat, eight of 15 patients (53%) have achieved complete morphologic and cytogenetic complete remission following a single cycle of chemotherapy, and most responders have been able to go on to additional therapy or allogeneic transplantation.

**Allogeneic Transplantation**

Allogeneic marrow or stem cell transplantation is the only therapy with curative potential for patients with MDS. Applicability is limited by the older age of most MDS patients, toxicities related to the transplant maneuver, and the availability of suitable donors. Sierra et al53 reported on a series of 452 patients with primary MDS who received marrow or blood stem cell transplants from HLA-matched siblings between 1989 and 1997, identified through the International Bone Marrow Transplant Registry.53 Disease-free survival at 3 years was 40% in this series, but transplant-related mortality and relapse rates were 37% and 23%, respectively. Risk of transplant-related mortality was associated with increasing age, and relapse risk was associated with IPSS score, percentage blasts in the marrow, and receipt of a T-cell depleted graft. Transplantation using unrelated donors has historically carried an even higher risk of transplant-related mortality (about 50%), largely as a consequence of an increased risk of graft-versus-host disease (GVHD) and attendant complications.54,55 These data fit well with smaller series, and illustrate the challenges of allogeneic transplantation in this patient population.

Advances in supportive care including improved antimicrobials, the use of blood (as opposed to marrow) stem cell grafts,56 and targeted busulfan dosing57 have reduced the risks associated with conventional (myeloablative) allogeneic transplantation enough that patients up to the age of 65 are now considered at most transplant centers. The Seattle group reported on a series of 50 patients between 55 and 66 years of age who received allogeneic transplants for MDS following various (myeloablative) conditioning regimens.58 Relapse-free survival at 3 years was 42%; non-relapse mortality was 39% at 2 years. Survival correlated with IPSS risk group and FAB category, reflecting an increased risk of relapse associated with more advanced disease. For each FAB category, survival was higher for patients conditioned with targeted busulfan and cyclophosphamide than for those receiving other regimens. These data illustrate the feasibility of allogeneic transplantation in healthy older patients who would previously have been excluded from consideration solely on the basis of age.

Another transplant approach under investigation is the use of reduced intensity or nonmyeloablative conditioning regimens.59-63 Aims of this strategy are to reduce early toxicities, shorten the period of pancytopenia, and reduce the risks of GVHD, facilitating safer transplantation of older patients and those with comorbid conditions. Nu-
numerous studies in patients with hematologic malignancies confirm that it is possible to achieve durable engraftment of matched related or unrelated donor stem cells following a variety of reduced intensity preparative regimens.64-67 Early morbidity and mortality are reduced relative to conventional approaches; however, GVHD, opportunistic infections, and relapse remain significant problems.

Only a few studies have specifically addressed the utility of reduced-intensity transplantation for MDS, and confirm the feasibility of the approach in this disease setting.68-70 In general, relapse rates were high and survival was poor in patients transplanted with >5% marrow blasts; however, this is also the case after myeloablative transplantation. Chronic GVHD appears protective for relapse, also the case after myeloablative transplantation. The optimal strategy for management of an individual patient with MDS depends on the expected natural history of the hematologic disorder, patient age and comorbidities, the availability of suitable allogeneic donors, and patient preference when presented with the potential risks and benefits of various treatment options. Older patients (>60 to 65 years of age) with relatively low-risk disease (IPSS low or INT-1 risk categories) may be appropriately managed with transfusion support, Epo ± G-CSF, and established low toxicity treatment such as 5-Aza C, or low-risk investigational therapies. For patients with 5q- MDS, CC5013 may prove to be the treatment of choice. Initial management of younger patients with low-risk disease is similar to that of their older counterparts, but those in otherwise good condition should be evaluated early on at a transplant center. Immunosuppressive therapy (ATG ± other agents) may be considered for some low-risk patients, but until further data are available, should probably be restricted to infection-free patients carrying HLA-DRB1 15 with evidence of a PNH clone and/or a relatively hypocellular marrow. In older patients with higher-risk disease, treatment considerations include nonmyeloablative allogeneic transplantation, 5-Aza C, and investigational treatment approaches. All younger patients with INT-2 or high-risk disease should be considered as candidates for immediate allogeneic transplantation. For those without a transplant option, aggressive investigational approaches such as combinations of chemotherapy and targeted agents are appropriate.

**INDIVIDUALIZING THE THERAPEUTIC APPROACH**

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**SUMMARY**

Advances in our understanding of the genetics and pathophysiology of MDS are improving the pathologic and clinical classification of the multiple entities that comprise this diverse disease group. A prognostic score generated from readily available information at diagnosis translates into estimated survival for an individual patient and serves as a guide for therapy. Allogeneic stem cell transplantation may be curative, but is still not an option for most MDS patients. Other treatment options are largely supportive, and include transfusions, hematopoietic growth factors, 5-Aza C, and investigational targeted therapies (immunomodulatory drugs, ATO, farnesyltransferase inhibitors, immunosuppressive agents, and various combination approaches). Application of newer molecular technologies to the problem of MDS offers the possibility of identifying novel therapeutic targets, and for predicting which patients are most likely to respond to a given treatment strategy. Patient participation in well designed clinical trials will allow this opportunity to be translated most rapidly into improved patient care.

**REFERENCES**

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