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In this Issue...*Ameliorating Anemia in Lower Risk Myelodysplastic Syndromes*

Progress in the identification, prognostic stratification, and treatment for patients with myelodysplastic syndrome (MDS) has brought us to a new era in the management of a disease which is rising in prevalence with the aging of the American population. Clinicians have for years relied largely upon supportive measures, such as the judicious use of blood product transfusions, iron chelation, and hematopoietic growth factors. Management considerations have now evolved into strategies of active intervention that offer the prospect of potentially modifying the natural history of disease. Although promising, several questions remain as to the benefits of such new treatment approaches.

In this month's issue, we focus on recent publications characterizing the impact of transfusion dependency in patients with lower risk MDS, the effect of response to erythropoietic agents on the natural history of disease, the development of novel and perhaps more active agents, and the continually evolving role of allogeneic stem cell transplantation.

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Guest Faculty Disclosures

+ **Alan List, M.D.**

Dr. List has indicated he serves a consultant and investigator with the Celgene Corporation, receives grant/research support from Scios and indicated a financial relationship with Pharmion.

+ **Unlabelled/Unapproved Uses**

Dr. List will refer to unlabeled or unapproved uses of drugs or products in his presentation when he cites the use of CC-5013 or Revlimid ; recombinant erythropoietin, darbepoetin alpha, and thalidomide.

Commentary

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It has been 23 years since the French-American-British (FAB) group established the first morphologic classification for the diagnosis and characterization of the pre-leukemic disorders, which they termed the myelodysplastic syndromes (MDS). Since its introduction, the subsequent two decades have yielded continuous improvement in the characterization of these disorders, their prognostic stratification, and our therapeutic options. Recombinant hematopoietic growth factors were introduced in the late 1980's, with recombinant erythropoietin assuming a role of primary therapy for the management of anemia in patients with lower risk MDS. We quickly learned that fewer than 20% of unselected patients benefit from erythropoietin treatment; however, those individuals with low transfusion burden (<2 units per month) and low endogenous erythropoietin production (serum erythropoietin <500 mU/ml) have the highest probability of benefit. With the recognition that the addition of recombinant human granulocyte-colony stimulating factor (G-CSF) improves response to erythropoietin, up to a third of patients can expect to benefit with a reduction in transfusions and possible rise in hemoglobin. The National Comprehensive Cancer Center Network (NCCN) recognizes this strategy in their management recommendations (www.nccn.org), advising that patients with a favorable erythropoietin response profile should initiate treatment with recombinant erythropoietin, to be followed by the addition of G-CSF in the absence of adequate hematologic improvement.

Management alternatives for the anemic patient with MDS have evolved in parallel with refinements in the characterization of both the prognosis and the pathobiology of the disease. The International Prognostic Scoring System (IPSS), introduced in 1997, has emerged as the principal staging system for MDS and is applied routinely to discern management goals¹. An international working group of MDS investigators recommended that for patients with Low- or Intermediate-1 risk MDS (in which survival is measured in years), the goal of treatment should be restoration of effective hematopoiesis; whereas for those with higher risk disease (in which survival is short), extension of survival and suppression of leukemia are paramount². With the introduction of the World Health Organization (WHO) morphologic classification, we now have an even better opportunity to discriminate prognosis and perhaps improve the selection of therapy³.

While there is no doubt that these changes have refined the decision tree, the clinical impact of these established practice patterns and the potential role of new therapies remain unanswered. When attempting to optimize management decisions for a given individual with MDS, clinicians must consider a wide range of questions:

- Does the reliance upon red blood cell transfusions adversely impact the natural history of the disease in patients with lower risk MDS?
- What advantages can be expected for those patients that respond to erythropoietic promoting agents?
- Given the risks of allogeneic stem cell transplantation, at what point (if any) should this procedure be considered for patients with lower risk MDS?
- As new erythropoietic promoters arrive, what should their role be in the management of anemia in lower risk patients, and what selection criteria should be considered?

As the above questions indicate, therapeutic decisions for patients with lower risk MDS remain a challenge, and — given the heterogeneity of the disease — must be individualized. The publications reviewed herein provide further insight as to the impact of transfusion therapy and erythropoietic agents on the natural history of the disease in lower risk patients, strategies to optimize the timing of allogeneic stem cell transplantation, and criteria to assist us in the selection of appropriate treatment.

References

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3. Vardiman JW, Harris NL, Brunning RD: [The World Health Organization \(WHO\) classification of the myeloid neoplasms](#). Blood 2002;100:2292-22302.

Impact of Red Blood Cell Transfusion-Dependence and the World Health Organization (WHO) Classification on Overall Survival

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Malcobati et al performed a retrospective analysis of 467 patients diagnosed with MDS at the University of Pavia (Italy) in the decade between 1992 and 2002. Patients were reclassified according to WHO morphologic subgroup as well as IPSS score, and patient mortality was further compared to standardized mortality ratios for an age-matched Italian population. Additional demographic factors such as red blood transfusion dependence and iron loading were included in the analysis to delineate the effect (if any) on clinical outcome. The primary objective of the study was to evaluate the prognostic value of the WHO classification relative to both the elements of the IPSS and demographic features as a basis for clinical decision making.

Although retrospective in nature, this study represents the first attempt to discern prognosis relative to age-matched controls. Importantly, reclassification of the morphologic diagnosis according to WHO criteria showed high concordance among the reviewing pathologists, exceeding 95%. Their analysis confirmed the prognostic value of classification according to WHO — but perhaps of greater importance, they found that those patients with isolated erythroid dysplasia (rather than bi- or tri-lineage cytologic dysplasia) had a more prolonged survival which did not differ from that of the general population. Analysis of the value of IPSS prognostic variables within WHO morphologic subgroups showed that the number of peripheral blood cytopenias was not predictive for outcome among either low or higher risk WHO disease subsets. In fact, the only IPSS variable that added further prognostic discrimination was cytogenetic pattern, and its influence was limited to those WHO categories without an elevation in blast percentage.

Although these findings may appear intuitive, the data confirm the notion that the WHO and IPSS are complementary. Moreover, the authors identified a demographic variable not captured by either classification that had an independent adverse connotations for both overall and leukemia free survival: red blood cell transfusion dependence. When analyzed by multivariate analysis, both red blood cell transfusion dependence and cytogenetic pattern emerged as significant variables impacting outcome within WHO subgroups. Furthermore, when total transfusion burden was quantitated according to the number of monthly transfusions, transfusion burden incrementally affected overall and leukemia-free survival after adjusting for cytogenetic pattern. These findings are remarkable and indicate that persistence of transfusion dependence may translate into more aggressive disease biology. The clinical impact of iron overload was discernable in patients without excess blasts who are expected to have more prolonged survival. Congestive heart failure in particular was more common among transfusion-dependent patients (P=0.01). Indeed the adverse effect of secondary iron overload increased with every 500 ng/ml rise in serum ferritin above a 1000 ng/ml threshold.

This report is the first to show that transfusion-dependence impacts not only quality of life for individuals with lower risk disease, but adversely affects overall survival, independent of its relation to secondary organ damage. Although these findings require confirmation, they have important implications for decisions concerning disease altering therapy. Perhaps patients with lower risk disease that are transfusion-dependent should be considered for treatment with DNA methyl-transferase inhibitors to extend leukemia-free survival or be considered as earlier candidates for allografting before the onset of iron overload. Of equal importance, these observations raise the question as to whether new therapies that ameliorate red cell transfusion-dependence can effectively modify the disease's relentless natural history for such patients. The latter can be addressed only through appropriately designed prospective randomized trials.

Howe et al from the Nordic MDS Group performed an analysis of their experience treating lower risk MDS with recombinant erythropoietin and G-CSF to determine the correlation, if any, of WHO category on hematologic response. Like the Malcobati study, this analysis was retrospective, involving 103 patients with MDS treated in three clinical trials. Classification by WHO subgroup reliably predicted therapeutic response to the cytokine combination, with a lower frequency of response in patients with refractory anemia with ringed sideroblast (RARS) with multi-lineage dysplasia (RCMD-RS) compared to those with RARS and isolated erythroid dysplasia (9% vs. 75% ; P=0.03). These observations complement the findings from the Italian study and demonstrate that those patients with multi-lineage dysplastic RARS are less responsive to cytokine therapy, and should therefore be considered for alternate treatments to restore erythropoiesis. In addition to transfusion burden and serum erythropoietin concentration, these findings show that WHO subgroup provides an added discriminatory element to discern the potential merit of erythropoietin treatment, thereby permitting selection of those individuals with reasonable probability of benefit.

1. Malcobati L, Porta MG, Pasutto C, Invernizzi R, Boni M et al. "Prognostic factors in life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making." J Clin Oncol 2005;23:7594-7603.

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2. Howe RB, et al, The WHO classification of MDS does make a difference. Blood 2004; 103:3265-3270.

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Effect of Anemia Treatment with Recombinant Cytokines on AML Progression and Survival in MDS

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While the identification of response variables permits selection of patients who are most likely to benefit from cytokine treatment, the long term safety and potential risk of potentiating progression to acute leukemia have not been defined. Jadersten and colleagues performed a retrospective analysis of 129 patients treated by the Nordic MDS Group between 1990 and 1995 with recombinant erythropoietin and G-CSF. The lead follow-up time was sufficiently prolonged, i.e., 45 months from the closure of enrollment on the Nordic studies. Overall, 32% of the patients responded to the cytokine combination and continued on maintenance therapy for a median duration of treatment of 23 months (range, 3-116 months). Erythroid responses, characterized by either a ≥ 1.5 g/dl rise in hemoglobin or transfusion independence, were longer in patients who experienced a rise in hemoglobin to ≥ 11.5 g/dl, compared to less robust partial responders (29 versus 12 months, $P=0.006$). Low or Intermediate-1 risk IPSS category was associated with a longer response duration compared to those with intermediate-2 or high risk disease (25 vs. 7 months, $P=0.002$).

The authors found that the interval to AML progression was more prolonged in good and intermediate response profile groups compared to those with a poor response profile (52 vs. 13 months, $P=0.008$). To gain insight into the effect, if any, of the cytokine treatment on disease natural history, the authors compared the treated patients to 334 patients matched for age and prognostic variables from the IPSS data base. Multivariate Cox regression analysis showed no difference in survival or risk of AML evolution between the two patient populations.

Although retrospective, these findings provide reassurance that the cytokine combination can yield durable responses without an adverse effect on the natural history of the disease. Moreover, erythropoietin treatment for patients with higher risk disease offers low probability of benefit, and when effective, is of short duration.

1. Jadersten M, Montgomery SM, Dybedal I, et al. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood*. 2005; 106(3): 803-811.



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Novel Therapeutics for the Management of Anemia in MDS

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While recombinant erythropoietin is the cornerstone of anemia management for patients with MDS in the United States, active treatment schedules mandate frequent dosing intervals ranging from three times per week to weekly administration. The Food and Drug Administration (FDA) recently approved an erythropoietic stimulating protein with more prolonged duration of action, i.e., darbepoetin alpha (Aranesp®), for the treatment of anemia associated with non-myeloid malignancies. The half-life of darbepoetin alpha is extended more than 2-fold compared to erythropoietin alpha or beta as a result of hyper-sialylation of carbohydrate moieties, allowing more extended treatment schedules.

In the first published experience in MDS reported by Musto and colleagues, treatment with subcutaneous darbepoetin alpha at a dosage of 150 μ g weekly yielded erythroid responses in 15 of 37 patients (40%) with a predominance of major responses ($n=13$) as defined by the International Working Group criteria. Major responses were relatively durable and maintained after 7 to 22 months. Although darbepoetin alpha treatment in patients with solid tumors is associated with a small but measurable increase in the risk of thrombo-embolic complications, no similar events were reported in this study.

A second trial performed by Bernard et al with the Group Francais des MDS evaluated weekly treatment with 300 mg of darbepoetin alpha during a 12 week induction in lower risk patients with a favorable erythropoietin response profile (i.e., serum erythropoietin <500 mU/ml). Although presented only in abstract form, the authors note that 34 of 55 (62%) patients responded, including 26 major erythroid responses.

Multivariate analyses performed in both the Bernard and Musto studies identified the response variables of low transfusion burden and low endogenous serum erythropoietin concentration to have independent predictive power for darbepoetin response, analogous to the profile for recombinant erythropoietin. Nonetheless, in each of these studies, treatment interval could be extended to every two weeks or longer to maintain response. Moreover, the promising response rates in these preliminary studies suggest that darbepoetin alpha, by virtue of its extended half life, may have sufficient activity to obviate the need for addition G-CSF, thereby providing a considerable cost savings. Prospective randomized trials are needed to further define this agent's magnitude of benefit and safety profile.

While the application of cytokine response variables allows us to refine the selection of candidates for treatment with recombinant erythropoietin, it raises the question of what we should consider for the majority of patients who will not benefit from cytokine therapy. Novel therapeutics with unique mechanisms of action are therefore needed to fill the void in management options for such patients. One such agent is lenalidomide (CC-5013, Revlimid®; Celgene Corporation), which is a structural analogue of thalidomide with a more favorable safety profile and promising activity in patients not responsive to erythropoietic cytokines. Lenalidomide has 100- to 1,000-fold greater potency than thalidomide, with pharmacologic effects that include the potentiation of erythropoietin receptor signaling.

In a study by List et al. involving 43 patients that had either failed treatment with recombinant erythropoietin or had poor cytokine response profile, three dosing schedules were investigated: continuous treatment with 25mg or 10 mg daily, and 10 mg daily for 21 days every four weeks. After 16 weeks of therapy, 24 patients responded (56%) with 21 major responses characterized by sustained transfusion independence or a >2 g/dl rise in hemoglobin. Erythroid response rate was karyotype-dependent and was highest among those patients with a chromosome 5q31 interstitial deletion (81% = deletion 5q, 57% = normal karyotype, and 12% = other abnormalities). Responses were clinically meaningful and durable. The median sustained hemoglobin in major responders was 13.4 g/dl and the median duration of transfusion-independence had not been reached after a median 81 week follow-up.

Unlike cytokine treatment, cytogenetic responses were reported in 65% of informative patients. Patients harboring a chromosome 5q31 deletion were the most responsive, with complete cytogenetic responses in 10 of 12 patients (83%) compared to 1 of 8 patients with other cytogenetic abnormalities. The most common and dose-dependent adverse effects were neutropenia and thrombocytopenia, which were manageable with treatment interruption and dose reduction. This initial study suggests that lenalidomide is highly active in patients that would otherwise not benefit from cytokine therapy. Moreover, the high frequency of erythroid and cytogenetic response among patients with chromosome 5q31 deletion suggests that in this particular disease subset, lenalidomide may hold promise as disease altering therapy.

Furthering this line of research, List et al. recently completed a multicenter Phase II confirmatory trial which was presented in abstract form at the 2005 meeting of the American Society of Clinical Oncology. The primary objective of the study was to evaluate the frequency of transfusion-independence in response to treatment with lenalidomide in transfusion-dependent, Low or Intermediate-1 risk MDS patients with chromosome 5q31 deletion, either alone or accompanied with other chromosomal abnormalities. 148 patients were treated in the study. Using an intent-to-treat analysis, 67% of patients achieved transfusion-independence after 24 weeks of therapy with an overall major and minor erythroid response rate of 75%. Cytogenetic responses were reported in 74% of patients, with 44% achieving a complete cytogenetic remission. As in the initial study, responses were durable with 70% of the major responders remaining transfusion free after a median follow-up of 58 weeks. Central review of bone marrow morphology showed a remarkably high frequency of complete histological response. Cytologic dysplasia resolved in 36% of evaluable patients, and both bone marrow myeloblast and ringed sideroblast percentages were reduced to the normal range in 75% of patients with either excess blasts or RARS at study entry. This highly active agent was recently reviewed by the Oncology Drug Advisory Committee (ODAC) of the FDA, which recommended full approval for lower risk MDS patients with chromosome 5q31 deletion. Although, the data are encouraging, the optimal dose and schedule of lenalidomide continues to be evaluated in a randomized phase III trial that is underway in Europe.

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☰ Timing of Allogeneic Stem Cell Transplantation in Lower Risk MDS

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Allogeneic stem cell transplantation is recognized as the only potentially curative treatment for patients with MDS. However, considering the advanced age of the MDS population and the high occurrence of procedure-related morbidity and mortality, the role for this approach in patients with lower risk disease remains in question. Cutler et al performed a decision analysis study to determine the optimal timing of bone marrow transplantation for MDS patients with an HLA- identical sibling donor. A Markov Decision Model was applied to analyze transplant outcome according to three transplantation strategies: (1) transplantation at the time of diagnosis; (2) transplantation at the time of AML progression; (3) delayed transplantation before leukemia transformation.

The authors identified 260 transplant patients from the International Bone Marrow Transplant Registry and the Fred Hutchinson Cancer Research Center. Transplant outcome for these patients was compared to 184 patients matched for age and IPSS score from the IPSS data base. For patients with Low or Intermediate-1 risk MDS, the delayed transplantation strategy was associated with the greatest number of life years gained compared to transplantation at the time of leukemia progression; conversely, immediate allogeneic transplantation adversely effected projected survival. The benefit of delayed transplantation was even greater among younger individuals (less than 40 years of age). In contrast, transplantation at the time of diagnosis maximized survival for patients with Intermediate-2 and High risk IPSS categories.

This study for the first time demonstrates that early allogeneic stem cell transplantation is not justified in lower risk patients, and therefore should be reserved for those individuals in whom the disease has progressed.

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the value of the WHO classification as a clinical decision-making tool in the treatment of MDS.
- Evaluate current and evolving treatment options for the management of anemia in MDS.
- Discuss the impact of new research on the timing of allogeneic stem cell transplantation.

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