



Stephen W. Joy. *Sunset*. Photograph. Northwood Lake, New Hampshire.

*An updated algorithm for management of myelodysplastic syndromes incorporates newer effective treatment options.*

## Methyltransferase Inhibitors: Changing the Treatment Algorithm for Myelodysplastic Syndromes

*Alan List, MD*

The development of new, more effective treatment strategies for the myelodysplastic syndromes (MDS) has for the first time jettisoned the management approach away from the reliance on supportive measures alone toward one of active intervention. Coincident with the adoption of the International Prognostic Scoring System (IPSS) to gauge expectation for survival, the physician is presented with an unprecedented opportunity to marry treatment with the specific medical needs of the patient, which will permanently change the treatment algorithm for MDS.

The evolution of MDS therapy is the product of incremental advancements in our understanding of disease biology and prognosis. The National Comprehensive Cancer Network (NCCN) guidelines provide a platform for management recommendations according to stratification by the IPSS.<sup>1</sup> Existing recommendations preceded the approval by the Food and Drug Administration (FDA) of

the first therapeutic for MDS and therefore remain firmly entrenched in the use of recombinant cytokines, supportive care, and unproven chemotherapy regimens, with an emphasis on the need for clinical trial participation. With the FDA approval of azacitidine (Vidaza<sup>®</sup>, Pharmion Corp; Boulder, Colo) and convincing results from the Cancer and Leukemia Group B (CALGB) phase III trial,<sup>2</sup> the treatment algorithm for MDS must be redefined. This report outlines a new treatment paradigm for MDS that incorporates the first approved agent in the class of DNA methyltransferase inhibitors (MTIs). These recommendations reflect consensus guidelines proposed by the supplement editor and contributors who built on existing NCCN recommendations to incorporate prognostic stratification, patient age, and the evolving treatment armamentarium.

### Treatment of Low-Risk Patients

Management decisions for patients with MDS must consider both the natural history of disease and patient preference. Implicit in the International Working Group recommendations and the NCCN guidelines is the premise that patients with low or intermediate-1 risk (Int-1) IPSS categories experience longer survival, therefore ameliorating hematologic deficits and quality of life should represent the principal therapeutic goals. The NCCN recommends that this begin with recombinant hematopoietic

---

*From the Hematologic Malignancies Program at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida.*

*Address correspondence to Alan List, MD, Program Leader, Hematologic Malignancies, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612. E-mail: listaf@moffitt.usf.edu*

*No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.*

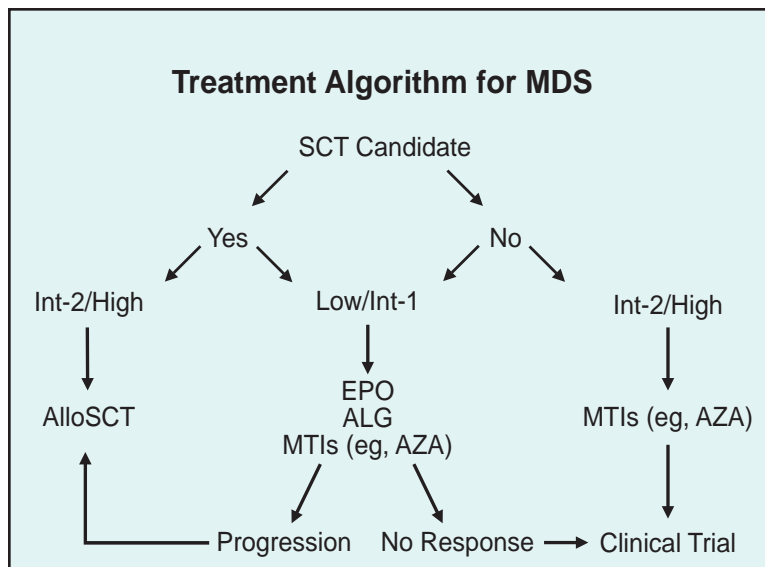


Fig 1. — MDS treatment algorithm (SCT = stem cell transplantation, AlloSCT = allogeneic stem cell transplantation, EPO = epoetin, ALG = antilymphocyte globulin, MTIs = methyltransferase inhibitors, AZA = azacitidine). Source: MDS Core Curriculum Editorial Board, March 2004.

cytokines as a supplement to supportive measures. Platelet and red blood cell transfusions for symptomatic cytopenias, as well as growth factors such as recombinant erythropoietin (EPO; Procrit®, Ortho-Biotech; Bridgewater, NJ) for anemia and myeloid growth factors such as granulocyte colony-stimulating factor (G-CSF; Neupogen®, Amgen Inc; Thousand Oaks, Calif) for infection complicating neutropenia, remain the initial approach for such individuals. Proper candidate selection is essential to optimize benefit. Patients with the highest probability of erythroid response are those with low red blood cell transfusion requirements (<2 units/month), low endogenous EPO response (<100 mU/mL), and morphologic subtypes of refractory anemia (RA) and RA with ringed sideroblasts (RARS) with minimal non-erythroid dysplasia. For others, alternate strategies should be considered.<sup>1</sup>

Left unabated, iron stores will become saturated. However, reliable noninvasive measures on which to base decisions concerning chelation therapy are lacking. Cumulative red blood cell transfusions exceeding 25 units generally exceed 7 g of iron and thus should raise consideration for iron chelation in EPO failures with 3 or more years expected survival (Fig 1).<sup>1</sup> Recognition that the pathological findings referred to as the “MDS phenotype” can be driven by varied biologic mechanisms has placed greater emphasis on screening to identify those treatments with the greatest probability of benefit for a given individual. Although not as yet captured in NCCN guidelines, immunosuppressive therapy with antilymphocyte globulin (ALG) or cyclosporine offers the potential for sustained improvement in erythropoiesis for lower-risk patients of younger age, DR-15 class II histocompatibility antigen phenotypes, and transfusion-dependent anemia of relatively short duration.<sup>3,4</sup> Table 1 shows the stratification of patients by risk category and therapeutic options using

the aforementioned screening measures. For lower-risk patients in whom such treatments are ineffective or of low potential benefit, azacitidine should be considered.

Azacitidine, the first DNA MTI to be approved by the FDA, produces multilineage hematopoietic effects while favorably altering the propensity for leukemia progression. Randomized multicenter trials have provided convincing evidence that MTIs are superior to supportive care.<sup>2</sup> Although the CALGB trial preceded development of the IPSS, stratification by the French-American-British (FAB) morphologic category indicates that the potential to extend survival may not be limited to patients with high-risk disease.<sup>2</sup>

Although stem cell transplantation (SCT) remains the only curative option for MDS, comparative registry analysis indicates that life expectancy for lower-risk patients may be unnecessarily curtailed by early allografting, whereas deferring SCT until disease progression allows the greatest opportunity for life extension.<sup>5</sup> For this reason, SCT should no longer be considered in lower-risk patients until evidence of disease progression, thereby emphasizing the use of treatments with limited and acceptable safety profiles. Azacitidine fills a long-standing therapeutic void for patients who are poor candidates for cytokine or immunosuppressive therapy (Fig 1).

### Treatment of Higher-Risk Patients

Despite its risk, SCT should be considered as early as possible for patients with higher-risk MDS. However, SCT realistically is applicable to only a small fraction of patients, in

Table 1. — Treatment Selection for MDS According to Risk and Patient Age

Age	Lower Risk (Int-1, Low)	Higher Risk (Int-2, High)
Young (potential candidate for SCT)	Clinical trial	Stem cell transplantation
	Growth factors	Clinical trial
	Antilymphocyte globulin	MTIs (eg, azacitidine)
	Thalidomide	Chemotherapy
	MTIs (eg, azacitidine)	
	CC5013	
Older	Clinical trial	Clinical trial
	Growth factors	MTIs (eg, azacitidine)
	Antithymocyte globulin	
	Thalidomide	
	MTIs (eg, azacitidine)	
	CC5013	
MTIs = methyltransferase inhibitors		
Source: E. Estey, MD, R. Stone, MD, A. List, MD, S. Gore, MD.		

particular younger patients with histocompatible donors. Therefore, for the majority of higher-risk patients, azacitidine has emerged as the treatment of choice (Fig 1).

Perhaps the most important finding from the CALGB trial is the beneficial effect of azacitidine on progression-free survival. For this reason, azacitidine has emerged as the treatment of choice for those individuals who are not immediate transplant candidates. Even among transplant candidates, treatment with azacitidine should be considered in those individuals for whom a volunteer donor must be identified, thereby possibly abating leukemia progression until SCT can proceed. Given the excess mortality that accompanies induction chemotherapy and its unproven impact on survival compared with less aggressive treatments such as azacitidine, the former approach should be reserved for clinical trials.

The availability of newer MDS therapies such as azacitidine, together with our enhanced biologic understanding, has affected treatment of all patients with MDS and has necessitated evaluation of a new algorithm that incorporates these newer treatment options.

## Contributor Perspectives

### ***RICHARD STONE, MD:***

---

Potential candidacy for SCT should include the initial consideration in young patients with MDS designated as "high risk" because of its curative properties. Elderly patients, patients considered low risk, and older patients who in tandem have been deemed "high-risk" should initially either receive azacitidine or participate in a clinical trial. Referral to an appropriate clinical trial should include a determination as to whether the trial is feasible or medically indicated for a specific patient.

Select subsets of patients will also continue to meet criteria for treatment with chemotherapy. These include younger patients with low platelet counts as well as patients with proper HLA type who have a hypoplastic marrow and are deficient in excess blasts. For all others, azacitidine therapy or clinical trial enrollment should be the initial consideration beyond determination of transplantation status. Azacitidine therefore is now the principal therapy for "average" patients with MDS in whom transplantation is not anticipated. Its new role for this devastating disease stems from its established safety and efficacy profiles, coupled with its broad range of indication.

### ***STEVEN GORE, MD:***

---

The availability of MTIs has substantially changed the entire approach to care for patients with myelodysplastic syndrome. This drug class is the first associated with a hematologic response rate in the range of 50% to 60%. In contrast, even in the most responsive growth factor risk group, a positive reaction to combination growth factor therapy would be limited to 30% to 40%. Therefore, therapies now exist for MDS that can ameliorate cytopenias in

50% to 60% of patients. More important, there are now data from the CALGB phase III trial of azacitidine as well as from preliminary decitabine data, currently published on the Internet by SuperGen Inc, suggesting that, compared to observation, patients treated with these agents have a prolonged duration of stable disease or lack of progression to acute myeloid leukemia.

Although prolongation of overall survival for these agents has not yet been shown, it can be said that the lack of progression to acute myeloid leukemia, within the context of MDS, is associated with overall patient improvement, enhanced survival potential, and superior quality of life. Additionally, due to the inclusive nature of the CALGB trial, these data pertain not only to those patients considered high risk, but also to those of "low-risk" status, IPSS low risk, or at least Int-1 risk MDS. With the exclusion of patients who are considered most stable, ie, those in the lowest-risk IPSS groups, the true RARS with a low-risk IPSS, the RAs with a low-risk IPSS, and possibly the 5q- patients, all others will be confronted with the decision of whether to take a drug that will slow down the progression of the disease and potentially help their cytopenias. When confronted with this choice, it does not seem logical that one would opt not to receive an MTI as their first or certainly second aligned therapy. In summary, MTIs may now have radically altered the prior treatment paradigm.

### ***LEWIS SILVERMAN, MD:***

---

Currently, MDS is a disease with no specific treatments unless the patient is young and has a suitable donor as well as "low-risk" disease or has high-risk disease that can be converted to low-risk disease. For patients who do not conform to one of these two factions, the options beyond supportive care have been sparse. Azacitidine has now received approval for treatment of MDS patients in all five subgroups. As such, it is a first-line treatment for a large segment of the MDS population.

For patients with low-risk disease who are predominantly anemic, azacitidine is a reasonable alternative when other therapies have failed. Patients with only modest transfusion requirements in whom EPO was unsuccessful can be maintained with supportive care, but for those with substantial transfusion requirements, azacitidine is a reasonable alternative. Additionally, for patients with severe cytopenias, even in the Int-1 or low-risk setting, azacitidine following EPO failure is an appropriate alternative treatment. For younger patients, it may be an alternative for those who are not good candidates for allogeneic stem cell transplants.

For patients with Int-2 or high-risk disease, azacitidine becomes first-line therapy and possibly the treatment of choice demonstrated by its activity in the phase III trial. A reasonable guide to its use would be the entry criteria that were utilized for that trial. For patients meeting those criteria, azacitidine is a first-line therapy.

## Conclusion

The recent FDA approval of azacitidine has changed the therapeutic landscape for all patients with MDS. This perspective is a common point of agreement shared by our contributors. The new treatment paradigm for MDS should reflect this addition as well as the means by which the MTI class fits with respect to age, transplantation status, and IPSS score. It is hoped that this supplement will stimulate a discussion within the hematology community so that future guidelines appropriately reflect the role of this important class of drugs and allow for incorporation of other novel therapies to be available in the future.

## References

1. *National Comprehensive Cancer Network Practice Guidelines in Oncology V1.2004*. Myelodysplastic syndromes. 10/31/2003 National Comprehensive Cancer Network. Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/mds.pdf](http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf). Accessed September 7, 2004.
2. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. *J Clin Oncol*. 2002;20:2429-2440.
3. Molldrem JJ, Leifer E, Baheci E, et al. Antithymocyte globulin for treatment of bone marrow failure associated with myelodysplastic syndrome. *Ann Intern Med*. 2002;137:156-163.
4. Saunthararajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. *Blood*. 2002;100:1570-1574.
5. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for myelodysplastic syndromes: delayed transplantation for low risk myelodysplasia is associated with improved outcome. *Blood*. 2004;104:579-585.