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Active treatment strategies for MDS modify the disease's natural history, reduce the leukemia potential, and can prolong survival.

Treatment Strategies to Optimize Clinical Benefit in the Patient With Myelodysplastic Syndromes

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In recent years we have witnessed a transformation in care for patients with myelodysplastic syndromes (MDS) following approval by the US Food and Drug Administration of the first agents for treatment of the disease. Emerging evidence indicates that active treatment strategies modify the natural history of the underlying disease and hence lower the potential for leukemic transformation while prolonging survival. The methyltransferase inhibitor (MTI) azacitidine, in particular, has shown the capacity to extend survival in higher-risk disease in a post-approval phase III trial while demonstrating an improved risk/benefit profile in a new dosing schedule. By utilizing an MTI as a bridge to transplantation, allogeneic stem cell transplantation can now be postponed for appropriate candidates until a suitable donor is identified. Results of iron chelation studies indicate that the improved compliance of an oral iron chelator yields greater iron storage reduction with sustained suppression of the labile plasma form. The current active treatment paradigm for MDS incorporates the most recent strategies yielding improved disease outcomes and patient survival.

Introduction

The myelodysplastic syndromes (MDS) are clinically challenging hematopoietic stem cell malignancies whose prevalence is rising with the aging of the American population. These disorders are characterized by ineffective hematopoiesis with progressive cytopenias

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Abbreviations used in this paper: MDS = myelodysplastic syndrome, RBC = red blood cell, MTI = methyltransferase inhibitor; HSCT = hematopoietic stem cell transplantation, ESA = erythropoiesis-stimulating agent, IPSS = International Prognostic Scoring System, IST = immunosuppressive therapy, NCCN = National Comprehensive Cancer Network, AML = acute myelogenous leukemia.

and a propensity for transformation to acute leukemia. According to recommendations of an International Working Group,¹ the major goal of therapy for patients with lower-risk disease, ie, low-risk and intermediate-1 categories as defined by the International Prognostic Scoring System (IPSS), is hematologic improvement. For higher-risk patients, ie, intermediate-2 and high-risk categories, the focus turns to modifying the natural history of disease and extending survival.² These prognostically distinct therapeutic goals have only recently begun to merge as new data indicate that certain therapies for lower-risk disease may similarly modify the disease course and, as a consequence, improve survival.

Supportive care has been the historic standard for management of patients with MDS. This includes red blood cell (RBC) transfusions to alleviate symptoms of

anemia, platelet transfusions to decrease thrombocytopenic hemorrhagic risk, iron chelation therapy to reduce transfusional hemosiderosis, and hematopoietic growth factors as appropriate. Historically, active therapeutic strategies have been classified by inherent toxicity, ie, low-intensity or high-intensity. Although now outdated, this perspective includes biologic response modifiers or immunosuppressants as low-intensity treatments and lower-intensity chemotherapy. The methyltransferase inhibitors (MTIs) are the newest members of the class of lower-intensity therapeutics that have been shown to decrease leukemia potential and improve survival.³⁻⁷ Lenalidomide, a thalidomide analog that possesses immunomodulatory activity, has high remitting activity in transfusion-dependent patients with lower-risk disease and chromosome 5q deletion [del(5q)]. High-intensity therapy, which includes intensive leukemia-type induction chemotherapy and hematopoietic stem cell transplantation (HSCT), is traditionally reserved for patients with higher-risk disease in whom the risks of the treatment could be justified.

In this overview, we examine the current treatment recommendations for MDS and propose modifications to the treatment algorithm. Appropriate utilization of erythropoiesis-stimulating agents (ESAs) is discussed, along with recommendations for lower-risk patients who have a poor ESA response profile or fail ESA therapy. The impact of results of recent clinical trials and the evolving role of the MTIs are reviewed along with the new place for this class of therapeutics in the treatment paradigm. In addition, we summarize emerging data examining the effects of treatments for lower-risk patients on the natural history of MDS and the timing of HSCT. Lastly, the role of supportive care, including iron chelation therapy, is examined.

Primary Therapy for Lower-Risk MDS

Initiation of treatment in lower-risk patients must take into account the symptomatic cytopenia and cytogenetic disease markers. The National Comprehensive Cancer Network (NCCN) Practice Guidelines recommend that selection of therapy should consid-

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Fig 1A. — Treatment algorithm for MDS for low-risk, intermediate-1 disease with significant cytopenias. Reproduced with permission from the NCCN (2.2008) Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology. © National Comprehensive Cancer Network, 2008. To view the most recent and complete version of the guideline, go online to www.nccn.org.

er three important clinical features: age, comorbidities, and IPSS-defined risk category.⁸ The MDS panel members have proposed an initial treatment algorithm by stratifying lower-risk patients with clinically significant cytopenias into several treatment groups (Fig 1A-B). Selection of primary therapy for anemia is based on four key response determinants: age, RBC transfusion burden (in particular, frequency of transfusions and duration of transfusion dependence), endogenous serum erythropoietin level, and disease karyotype. RBC transfusion dependence is an independent prognostic factor affecting overall survival and risk of acute myeloid leukemia (AML) progression in patients without excess blasts (Fig 2).^{9,10} The incremental negative effect of transfusion dependence may be interpreted as a surrogate clinical measure of the severity and magnitude of maturation impairment in MDS, thereby implying that leukemia potential and natural history of disease can be modified only if effective erythropoiesis and clonal maturation potential are restored.

Erythropoiesis-Stimulating Agents

Recombinant human erythropoietins (rhu-EPO; Procrit®, Ortho Biotech Products LP, Raritan, New Jersey; Epogen®, and Aranesp®, Amgen Inc, Thousand Oaks, California) remain the standard of care for initial management of anemia in patients with lower-risk disease.

The Nordic MDS Study Group was one of the first to model ESA response variables, identifying RBC transfusion needs of less than 2 units per month and serum EPO level less than 500 mU/mL as covariates for ESA response. In unselected patients, approximately 22% achieved a major erythroid response, whereas for those with the most favorable profile, erythroid response rate was 74%.^{11,12}

The World Health Organization (WHO)-defined number of dysplastic lineages was found by Howe et al¹³ to also have predictive power for ESA response. In a review of the Nordic Group experience, they reported that patients with refractory cytopenias with multilineage dysplasia and ringed sideroblasts (RCMD-RS) responded poorly to ESA compared to patients with

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Fig 1B. — Treatment algorithm for MDS for intermediate-2, high-risk disease. Reproduced with permission from the NCCN (2.2008) Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology. © National Comprehensive Cancer Network, 2008. To view the most recent and complete version of the guideline, go online to www.nccn.org.

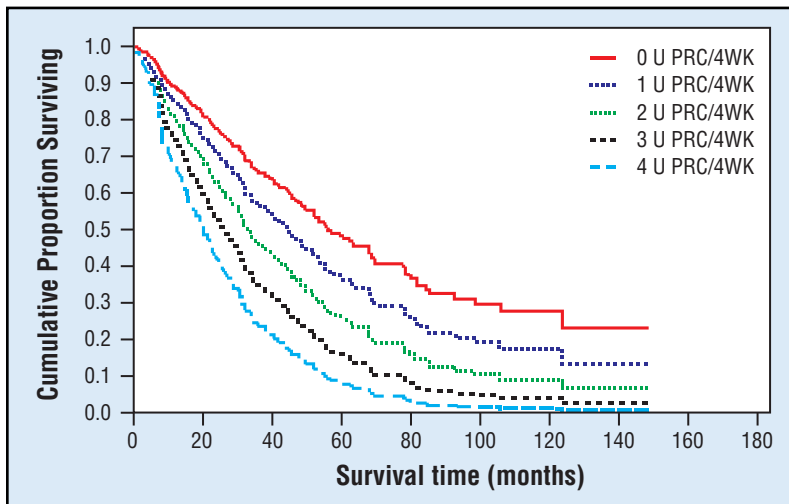


Fig 2. — Survival of MDS patients according to transfusion intensity. From Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica*. 2006;91(12):1588-1590. © 2006 Ferrata Storti Foundation. Reprinted with permission.

refractory anemia with ringed sideroblasts (RARS) (9% vs 75%, $P = .003$). In addition, in WHO categories with less than 5% bone marrow blasts, 51% of patients with single lineage dysplasia were alive at 67 months compared with a median survival of 28.5 months in those with multilineage dysplasia ($P = .03$) (Fig 3). Similarly, patients with a poor ESA response profile had a shorter duration of response and a corresponding higher frequency of AML transformation with an overall survival of less than 21 months.¹⁴ The Groupe Francophone des Myélodysplasies (GFM), however, did not confirm a difference in response rates for patients with RARS based on the presence or absence of multilineage dysplasia. Retrospective analysis of their ESA experience suggested that presence of del(5q) did not have a strong modifying effect in erythroid response rate but did significantly shorten response duration from an average of 24 to 12 months ($P = .019$).¹⁵ Treatment with darbepoetin alfa (Aranesp), a highly glycosylated ESA with a longer half-life than epoetin alpha (Procrit®, Epogen®), has produced comparable response rates at dosing intervals ranging from every 1 to 3 weeks.

Treatment with ESAs may improve quality of life in patients as well as reduce the need for transfusion support. Moreover, recent data suggest a survival benefit with ESA treatment that is greatest in ESA responders. In one case-matching study in Pavia, Italy, patients treated with ESAs in sequential Nordic group trials were compared to patients who did not receive ESAs.¹⁶ Patients were matched for prognostic variables such as frequency and number of RBC transfusions, WHO classification, and IPSS categories. Patients receiving less than 2 units of RBC transfusions per month had a survival benefit (hazard ratio

[HR] = 0.57, $P = .015$) with ESA, but this benefit was not observed in patients with a higher transfusion requirement.¹⁶ The GFM reported similar results from their analysis of more than 400 patients treated with ESAs in clinical trials performed between 1988 and 2005. These patients were compared with case-matched controls who received only supportive care in the IPSS/International MDS Risk Analysis Workshop database.¹⁷ Similarly, Golshayan et al¹⁸ conducted a pooled analysis of 1,869 MDS patients with low-risk disease according to ESA treatment. A survival benefit was observed for patients who received an ESA, with this difference maintained even after outcomes were corrected for FAB (French-American-British) type, baseline transfusion requirements, IPSS category, prior treatments, and interval from diagnosis.

Treatment with ESAs has come under scrutiny in the past year. As a result, the US Food and Drug Administration (FDA) strengthened safety warnings based on safety concerns in solid tumor trials showing increased mortality from the underlying disease and increased risk for thromboembolism, particularly in studies targeting hemoglobin levels greater than 12 g/dL.¹⁹⁻²¹ These safety concerns prompted the Centers for Medicare and Medicaid Services (CMS) to limit coverage for ESAs for treatment of chemotherapy-induced anemia in select solid tumors but elected to exclude MDS from the national coverage decision.

Available data involving the use of ESAs in MDS show that these agents improve symptoms and decrease transfusion needs. In addition, the Nordic/Pavia case studies

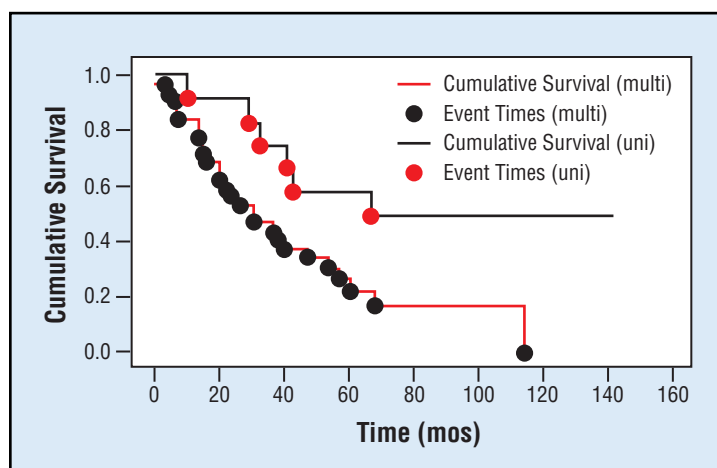


Fig 3. — Survival of MDS patients with less than 5% bone marrow blasts treated with EPO and G-CSF within the Nordic MDS Group trials. Unilineage dysplasia (uni; median survival, 67 months) vs multilineage dysplasia (multi; median survival, 28.5 months), $P = .03$, is shown. This research was originally published in *Blood*. From Howe RB, Porwit-MacDonald A, Wanat R, et al. The WHO classification of MDS does make a difference. *Blood*. 2004;103(9):3265-3270. © American Society of Hematology. Reprinted with permission.

also indicated that ESAs lessen the risk for AML transformation in responding patients and extend survival in patients with low transfusion requirements receiving an ESA. These observations support the notion that restoration of erythropoiesis and MDS maturation potential in ESA responders alters the natural progression of disease. In light of these findings, low-risk and intermediate-1-risk patients with symptomatic anemia who have low endogenous erythropoietin levels and low transfusion requirements should receive an ESA as primary therapy, reserving the addition of granulocyte colony-stimulating factor (G-CSF) for suboptimal responders.

Lower-Risk Patients With Poor ESA Response Profile and ESA Failures

Treatment with ESAs can decrease transfusion requirements and improve erythropoiesis in patients with low transfusion burden. They are, however, ineffective in the vast majority of MDS patients with transfusion requirements of two units per month or greater and appropriately elevated endogenous erythropoietin production.²² In such patients with either an unfavorable ESA response profile or who fail ESA therapy, the NCCN guidelines recommend evaluation for immunosuppressive therapy (IST) (Fig 1A). For patients who do not respond to IST or are not candidates for IST, treatment with an MTI should be considered.

Immunosuppressive Therapy

Hematopoietic impairment in MDS may arise in part from an aberrant autoimmune process linked to clonal expansion of hematopoietic inhibitory T lymphocytes.^{23,24} IST with antithymocyte globulin (ATG) and/or cyclosporine can relieve hematopoietic suppression, resulting in hematologic improvement in a select population of patients. In an initial prospective study by Molldrem et al,²⁵ transfusion-dependent MDS patients were treated with ATG and prednisone. One 4-day course of ATG induced transfusion independence in 21 (34%) of 61 patients within 8 months of treatment. Median time to response was 2.5 months, with 76% of responding patients maintaining freedom from transfusion at 5 years of follow-up. Nonerythroid cytopenias improved as well, with 90% of responders achieving platelet and neutrophil count recovery. The majority of IST responders had lower-risk disease, and Cox regression analysis showed that younger age and lower platelet count were associated with higher probability of response to ATG.

Recent results of a retrospective analysis of 96 patients treated with ATG by Lim et al²⁶ confirmed lower IPSS score as a predictor of response as well as bone marrow hypocellularity. Hematologic response was similar to results from the National Institutes of Health (NIH) experience, in which 75% of patients who responded to ATG sustained a durable response lasting a median of 31.5 months.

Table 1. — Predictive Probability to Response (PPR) to Immunosuppressive Therapy

Age in Years + Duration of RCTD (mos)		Predictive PPR
DR15 ⁻ Patients	DR15 ⁺ Patients	
> 58	> 72	Low (0–40%)
50–58	64–72	Intermediate (41%–70%)
< 50	< 64	High (71%–100%)

RCTD = red cell transfusion dependence.

This research was originally published in *Blood*. Adapted from Sauntharajah Y, Nakamura R, Wesley R, et al. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. *Blood*. 2003;102(8):3025-3027. Epub 2003 Jun 26. © American Society of Hematology. Reprinted with permission.

The proportion of patients with MDS responsive to IST is greatest in younger individuals, suggesting an age-dependent difference in disease pathobiology. In univariate analysis of covariates from the NIH experience,²⁷ younger age (60 years or less), marrow hypocellularity, presence of a paroxysmal nocturnal hemoglobinuria (PNH) clone, HLA-DR15 phenotype, and duration of RBC transfusion-dependence were associated with IST response. Multivariate analysis found that younger age, shorter transfusion duration, and presence of HLA-DR15 retained independent predictive power, allowing incorporation of these variables into a predictive model to identify patients with the greatest probability of benefit from IST (Table 1). MDS with trisomy 8 may be particularly responsive to IST, with 9 of 12 patients with trisomy 8 having achieved transfusion independence following IST in the NIH trials. Interestingly, trisomy 8 progenitors are more resistant to apoptotic signals, suggesting that autoimmune hematopoietic immune response selects for clonal expansion of trisomy 8 populations, perhaps explaining the clonal expansion following IST.^{28,29} While the optimal regimen and schedule of IST have not yet been determined, IST in younger patients can yield durable hematologic responses that may modify adverse effects of RBC transfusion dependence on survival and AML potential.³⁰

Lenalidomide

The pathogenesis of MDS involves a complex biological cascade that includes increased angiogenesis³¹ and overproduction of proinflammatory cytokines, accelerated apoptosis of hematopoietic progenitors, and autocrine stimulation by vascular endothelial growth factor (VEGF).^{32,33} Immunomodulatory drugs (IMiDs[®]) were investigated as potential MDS therapeutics based on their ability to alter the bone marrow environment. Thalidomide (Thalomid[®], Celgene Corp, Summit, New Jersey) was the first IMiD[®] to undergo clinical investi-

gation in MDS, but it demonstrated only modest activity and excess neurosedative toxicities.

Lenalidomide (CC-5013; Revlimid[®], Celgene Corp), is a second-generation amino-substituted thalidomide analog with greater potency and less neurologic toxicity than thalidomide.³⁴ The NCCN Panel recommends treatment with lenalidomide in patients with lower-risk MDS and del(5q) with or without additional cytogenetic abnormalities. The most common cytogenetic abnormality in MDS is del(5q), occurring in approximately 15% of patients.

The MDS-003 clinical trial³⁵ was the pivotal study that evaluated the efficacy of lenalidomide in lower-risk, transfusion-dependent patients with del(5q) with or without other cytogenetic aberrations. Overall, 76% of patients who received lenalidomide had a 50% or greater reduction in transfusion requirements, and 67% became transfusion independent with an accompanying rise in hemoglobin of 1 g/dL or more. The median time to onset of transfusion independence was 4.5 weeks, with a median duration of transfusion independence that exceeded 2 years. Transfusion response rate was independent of karyotype complexity, with comparable frequency of response in patients with isolated del(5q) or accompanied by multiple cytogenetic abnormalities. Unlike cytokine therapy, lenalidomide acts to suppress the del(5q) clone with a corresponding high frequency of cytogenetic response. Among 85 evaluable patients, 73% had cytogenetic improvement after 24 weeks of lenalidomide treatment, with all cytogenetic responders achieving freedom from transfusion. Consistent with lenalidomide's action to suppress the del(5q) clone, the most common adverse events were early neutropenia and thrombocytopenia. Grade 3 or 4 myelosuppression (by National Cancer Institute Common Toxicity Criteria) generally occurred within the first 8 weeks of treatment, with neutropenia occurring in 54.7% of patients and thrombocytopenia in 43.9% of patients. Multivariate analysis showed that the most important variable limiting transfusion independence response was pretreatment thrombocytopenia.

Sekeres et al³⁶ analyzed the relationship between lenalidomide-induced cytopenias and hematologic improvement in two phase II trials. Treatment-induced thrombocytopenia occurred more often in patients with del(5q). Multivariate analysis showed that treatment-related thrombocytopenia and neutropenia (in patients with normal baseline absolute neutrophil count) correlated with response to lenalidomide in patients with del(5q), supporting the linkage between suppression of the clone and erythroid response, whereas in patients without del(5q), no relationship was seen.

Lenalidomide has also been evaluated in lower-risk patients without del(5q). In a large multicenter trial, 56 (26%) of 214 patients achieved RBC transfusion independence with a rise in hemoglobin of 1 g/dL or more,

and an additional 17% had reduction in transfusion requirements of 50% or greater. Response to treatment occurred after a median of 4.8 weeks; however, duration of response was not as prolonged as in del(5q) responders (median 41 weeks). Unlike del(5q) MDS, histologic remissions were rare, suggesting that lenalidomide's actions on both the malignant clone and the microenvironment restores erythropoietic potential in responding patients.³⁷

Long-term outcome with lenalidomide treatment in del(5q) MDS was analyzed in 168 patients participating in four clinical trials.³⁸ These data show that transfusion-independence response to lenalidomide is durable, with a median duration of 2.2 years, and some patients are now exceeding 5 years. Multivariate analysis showed that cytogenetic response had the greater predictive power for extended survival and freedom from disease progression (HR = 5.295; $P < .001$). These data suggest that lenalidomide may alter the natural history of disease and perhaps extend survival in responding patients.

Methyltransferase Inhibitors

Hypermethylation of cytosine residues on DNA and consequent chromatin condensation are key characteristics of the malignant phenotype that lead to epigenetic silencing of genes involved in the control of normal cell growth and differentiation.³⁹ The MTIs are a class of anti-neoplastics that deplete nuclear DNA methyltransferase, the enzyme responsible for the methylation of DNA, and as a consequence, promote demethylation in newly synthesized DNA. Two MTIs are approved for the treatment of MDS: azacitidine (Vidaza[®], Celgene Corp, Summit, New Jersey) and decitabine (Dacogen[®], Eisai Inc, Woodcliff Lake, New York). Both are cytosine analogs that are distinguished by their sugar moieties, which may account for differential activity: azacitidine contains a ribose sugar, and decitabine contains deoxyribose, leading to DNA specificity.

Azacitidine Trials

Azacitidine was first studied in MDS by the Cancer and Leukemia Group B (CALGB) in two phase II trials that involved patients with advanced MDS.^{40,41} Encouraging results from these trials led to the pivotal phase III study (CALGB 9221) that compared treatment with azacitidine (75 mg/m² per day × 7 every 28 days) to best supportive care (BSC) in patients with MDS of any FAB type.³ Patients in the BSC only arm were allowed to cross over to azacitidine treatment if they experienced progression of disease. Responses to azacitidine were observed in all FAB types, with a complete response (CR) or partial response (PR) and hematologic improvement rate of 47% (CR + PR, 11%) using the International Working Group 2000 response criteria.⁴ Median time to AML transformation or death for patients receiving BSC was 12 months compared with

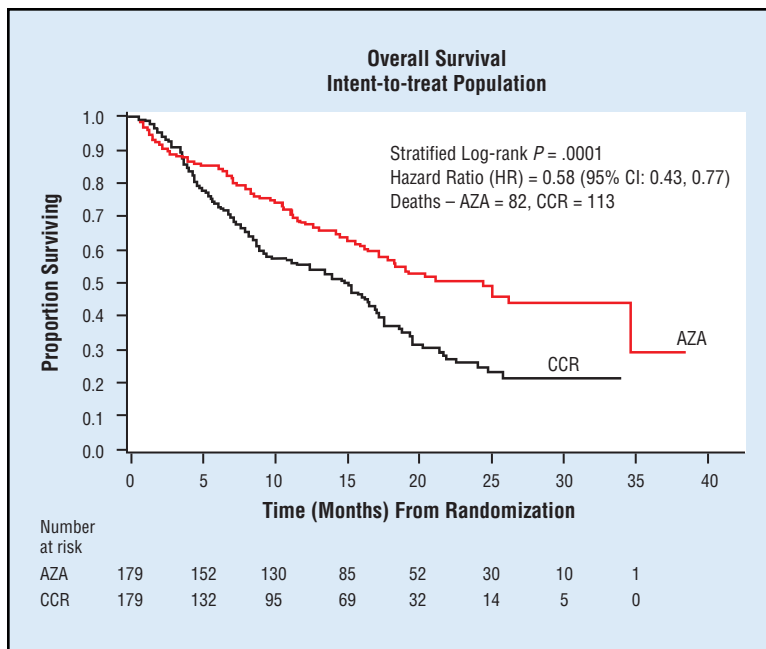


Fig 4. — Overall survival with azacitidine (AZA) compared to CCR. Treatment with azacitidine demonstrated increased overall survival of 24.4 months vs 15 months with CCR ($P = .0001$). This research was originally published in *Blood*. From Fenau P, Mufti GJ, Santini V, et al. Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): results of the AZA-001 phase III study. *Blood*. 2007; 110:250a. Abstract 817. © American Society of Hematology. Reprinted with permission.

21 months in the azacitidine arm ($P = .007$). Overall survival favored azacitidine treatment (20 vs 14 months) but did not reach statistical significance owing to the crossover design.

The NCCN guidelines recommend considering treatment with an MTI in patients with lower-risk disease who do not respond to ESA therapy, in patients who are not candidates for IST, and in patients with multilineage cytopenias. In patients with intermediate-2 or high-risk disease who are not candidates for HSCT, treatment with MTIs is now positioned as primary therapy.

Recent results of randomized trials with azacitidine may change the utilization of MTIs and the schedule and duration that these agents are applied. An FDA-mandated phase III randomized, multicenter trial (AZA-001) compared treatment with azacitidine at the FDA-approved dose and schedule to conventional care regimens (CCRs) in previously untreated intermediate-2 or high-risk patients with refractory anemia with excess blasts (RAEB), RAEB in transformation (RAEB-t), or chronic myelomonocytic leukemia (CMML).⁵ Prior to randomization, patients selected one of three CCR management strategies: BSC only, low-dose cytarabine at 20 mg/m² per day for 14 days of every 28-day cycle,

or standard AML-type induction and consolidation chemotherapy. Azacitidine was continued until evidence of disease progression or treatment intolerance. A total of 358 patients were randomized to either azacitidine or CCR (179 patients per arm) with a primary endpoint of overall survival. Azacitidine was administered for a median of 9 cycles and yielded a significant improvement in overall survival (median 24.4 months vs 15 months with CCR, $P = .0001$, HR = 0.58) across IPSS categories (Fig 4). Survival at 2 years was nearly doubled with azacitidine (51% vs 26%, $P < .0001$). Azacitidine treatment was superior to all CCRs with corresponding extension in median overall survival of 12.9 months vs BSC, 9.1 months vs low-dose cytarabine, and 8.7 vs standard induction therapy (Table 2). Response rates also favored azacitidine, with more patients achieving major and minor hematologic improvement than with any CCR. Grade 3/4 toxicities were primarily hematologic and were either comparable or lower with azacitidine.⁶ This improvement in overall survival with azacitidine treatment despite a modest CR rate (17%) indicates that this agent acts by a mechanism that is distinct from conventional cytotoxics and leads to reduction in leukemia potential.

Standard dosing of azacitidine for 7 consecutive days requires weekend administration, which is often problematic in the community setting. Lyons et al⁴² conducted an open-label, randomized phase II study that compared alternate dosing schedules. Azacitidine was administered subcutaneously (SC) on one of three schedules: 75 mg/m² for 5 days followed by 2 days off and 2 days on (AZA 5-2-2); 50 mg/m² for 5 days followed

Table 2. — Median Overall Survival (OS) With Azacitidine in AZA-001

Patient Groups	Azacitidine Median OS (mos)	Conventional Care Regimen Median OS (mos)	P Value
All Patients	24.4	15	.0001
Conventional Care Regimen	24.4	BSC 11.5	.003
		LDAC 15.3	.016
		Std CT 15.7	.19
IPSS Cytogenetic Group			
Good	Not reached	17.1	.03
Intermediate	26.3	17	.017
Poor	17.2	6	.011

BSC = best supportive care, LDAC = low-dose ara-C, Std CT = conventional induction/consolidation.

This research was originally published in *Blood*. From Fenau P, Mufti GJ, Santini V, et al. Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): results of the AZA-001 phase III study. *Blood*. 2007;110:250a. Abstract 817. © American Society of Hematology. Reprinted with permission.

by an additional 5 days after a weekend hiatus (AZA 5-2-5); and 75 mg/m² for 5 days only (AZA 5). Rates of hematologic improvement were similar across the three dosing schemas (range 44% to 56%) and were comparable to the established 7-day schedule. Major hematologic improvement occurred in all hematopoietic lineages in each treatment group. Transfusion independence was achieved in 55% of AZA 5-2-2 evaluable patients, in 60% of AZA 5-2-5 patients, and in 63% of AZA 5 patients. Grade 3/4 hematologic adverse events were lowest in AZA 5 patients (44% vs 33% vs 18%). Although CR, PR, and overall survival were not endpoints of the trial, the high rate of hematologic improvement and lower toxicity of the AZA 5 regimen supports its routine application outside of the higher-risk setting.

Decitabine Trials

Decitabine (5-aza-2'-deoxycytidine) was initially studied in Europe in elderly patients with AML and MDS with promising results.^{43,44} A subsequent phase III randomized trial⁴⁵ led to its approval by the FDA for the treatment of intermediate-1, intermediate-2, and high IPSS risk MDS. Patients were randomized to receive either decitabine 15 mg/m² intravenously (IV) over 3 hours every 8 hours for 3 consecutive days repeated every 6 weeks for up to 6 cycles, or BSC alone. Patients who received BSC were allowed to cross over and receive decitabine after transformation to AML. Co-primary endpoints for the trial were CR and PR and time to AML transformation or death. The overall response rate was 30% (CR 9%, PR 8%, hematologic improvement 13%); however, there was no difference in the median time to death or AML transformation between the treatment arms. Subsequent subgroup analysis revealed that patients on the decitabine arm had a longer median time to AML transformation or death than those who received supportive care if they had *de novo* MDS (12.6 vs 9.4 months, $P = .04$), had high-risk disease (9.3 vs 2.8 months, $P = .01$), or were treatment naive (12.3 months vs 7.3 months, $P = .08$). Moreover, patients who achieved the best response to decitabine (CR or PR) had a significantly longer median time to AML progression or death (17.5 vs 9.8 months for nonresponders, $P = .01$) with corresponding longer median survival (23.5 months vs 13.7 months; $P = .007$).⁴⁵ Overall mortality in patients treated with decitabine was 10%, with grade 3 or 4 neutropenia or thrombocytopenia developing in 87% and 85% of patients, respectively. Myelosuppression was the most common reason for dose delay, dose reduction, or discontinuation of therapy.⁶

Recently, an alternate dose and schedule of decitabine has been popularized based on results of a randomized phase II trial that now permits outpatient administration at a lower cumulative dosage than that applied in the registration trial (100 mg/m² vs 135 mg/m²).⁴⁶ Kantarjian et al⁷ studied three schedules of

decitabine in patients with intermediate to high-risk MDS; 32% of patients had secondary MDS, and 55% had intermediate-2 or high-risk disease. Patients were randomized using a Bayesian adaptive design to one of three treatment schedules: 20 mg/m² IV over 1 hour daily for 5 days, 20 mg/m² SC daily for 5 days, or 10 mg/m² IV over 1 hour daily for 10 days. After enrollment of 15 patients per arm, the 5-day IV schedule yielded a CR rate higher than the other regimens (39% vs 21% with 5-day SC administration and 24% with 10-day IV), thereby triggering allocation of subsequent participants to the 5-day IV arm.⁷

An update of the results with the 5-day regimen reported a CR and PR rate of 38% with an overall median survival of 19 months, and 41% of patients were alive at 2 years.⁴⁷ A recent multicenter trial testing the 5-day regimen in 99 patients with intermediate and high-risk MDS yielded a lower rate of CR and PR (17%) with hematologic improvement in 18% and a median survival mirroring the M. D. Anderson experience (19.4 months).⁴⁵ A median of only five treatment cycles were administered in the multicenter trial compared with 10 cycles in the Kantarjian study. Patients who achieved a CR had prolonged survival (median not reached). However, for all other response measures, including marrow CR, PR, and hematologic improvement, no discernable difference was seen in survival compared with patients whose best response was stable disease.

The addition of recent data with the MTIs raises the question of how these agents should be positioned in the treatment paradigm for MDS. Given the high rate of hematologic improvement and manageable toxicity of the 5-day azacitidine regimen, it appears best suited for the treatment of lower-risk patients who are not candidates for or have failed ESAs, IST, or lenalidomide use. In the setting of higher-risk disease, the 7-day regimen used in the AZA-001 trial yielded improvement in overall and 2-year survival that has not been achieved in prior MTI studies. This now perhaps positions azacitidine as the lead agent for primary treatment of patients with higher-risk disease.

Bridging to Transplantation

High-dose chemotherapy followed by allogeneic HSCT is currently the only treatment with curative potential in MDS. Historical experience has shown that approximately 40% of patients may be cured with HSCT, although advanced age, medical comorbidities, procedure morbidity and mortality, and lack of donor availability limit the procedure to a select minority.^{48,49} Cutler et al⁵⁰ constructed a Markov decision model to examine three different transplant strategies for newly diagnosed MDS: transplantation at diagnosis, transplantation at time of progression to AML, and transplantation at an interval of 2 years from diagnosis. Analyses were performed across IPSS categories with

adjustments for quality of life, and the results were compared to data from the International MDS Risk Assessment Workshop database. For lower-risk IPSS categories (low-risk and intermediate-1), delayed transplantation maximized overall survival, with transplantation prior to AML transformation associated with better survival than at time of leukemic progression. For intermediate-2 and high-risk patients, transplantation at diagnosis maximized overall survival, with delay from diagnosis yielding inferior outcome (Fig 5). The Cutler model has been adopted by the NCCN, but the powerful disease-modifying effects of the MTIs — azacitidine in particular — suggest that treatment with an MTI should be initiated during donor selection and medical screening in HSCT candidates to optimize disease control and potentially lower the risk for subsequent relapse. Only prospective studies will show if the latter strategy is successful.

Iron Chelation Therapy

The relatively recent recognition of the adverse impact of chronic RBC transfusion dependence on overall survival in lower-risk patients with MDS has raised the awareness of the potential benefit of effective iron chelation. The Pavia study found that for every 500 ng/mL increase in serum ferritin above 1,000 ng/mL, there is a corresponding 30% decrease in overall survival.¹⁰

Iron chelation therapy (ICT) in MDS historically has been underutilized, owing to the need for parenteral administration of deferoxamine, (Desferal®, Novartis Oncology, East Hanover, New Jersey), poor compliance, and limited understanding of the adverse effect of transfusional hemosiderosis. More recently, long-term efficacy and safety of oral deferasirox, (EXJADE®, Novartis Oncol-

ogy, East Hanover, New Jersey), were demonstrated in a phase II, open-label, 3-year trial⁵¹ in which preliminary 1-year results of treatment in 176 lower-risk, transfusion-dependent MDS patients were reported. Patients received deferasirox at doses of 20 to 40 mg/kg per day, which resulted in a decrease in mean serum ferritin by 859 $\mu\text{g/L}$ ($\pm 1,548$) after 12 months of therapy compared with 3,400 $\mu\text{g/L}$ at baseline. Labile plasma iron (LPI) concentration, the toxic form of iron, normalized in all patients within 3 months and was sustained throughout the first year of treatment. ICT was discontinued in 6 patients (3.4%) due to adverse events including rash, pneumonia, thrombocytopenia, and gastric carcinoma. Reversible elevation in serum creatinine was common, occurring in 25% of patients with normal serum creatinine at baseline. This study is the first to show that chelation with deferasirox at the approved dose range leads to sustained suppression of LPI and effectively lowers iron stores.⁵¹

The potential survival benefit of ICT was shown in a prospective survey of 170 patients referred for RBC transfusion at 18 treatment centers in France during a 1-month period in 2005. Patients received a standard ICT with SC deferoxamine, deferiprone, or deferasirox, or they received low-dose iron chelation with subcutaneous bolus deferoxamine or intravenous deferoxamine after RBC transfusions. The median overall survival from time of diagnosis was 115 months in chelated patients and 51 months in nonchelated patients ($P < .0001$). After stratification by prognostic variables including IPSS category, age, sex, and transfusion requirements, the survival difference favoring the ICT group remained highly significant. ICT intensity was an important determinant of outcome in multivariate analysis. Lower-risk patients who received a standard iron chelation regimen had a median survival of 120 months compared with 69 months for patients who received low-dose chelation ($P < .0001$), while survival for patients who did not receive ICT survival was only 50 months.⁵²

These recent results support the benefit of ICT in lower-risk, RBC transfusion-dependent MDS patients. The optimal time to initiate ICT, however, has not been established. The NCCN recommends that ICT be considered in lower-risk transfusion-dependent patients when iron stores exceed storage site saturation, ie, after 20 to 30 units or a serum ferritin of $\geq 2,500$ ng/mL. Given the compelling data from the Pavia experience showing incremental decline in survival above a ferritin of 1,000 ng/mL, the latter lower threshold appears more appropriate. The potential impact of earlier ICT intervention must await results of prospective studies.

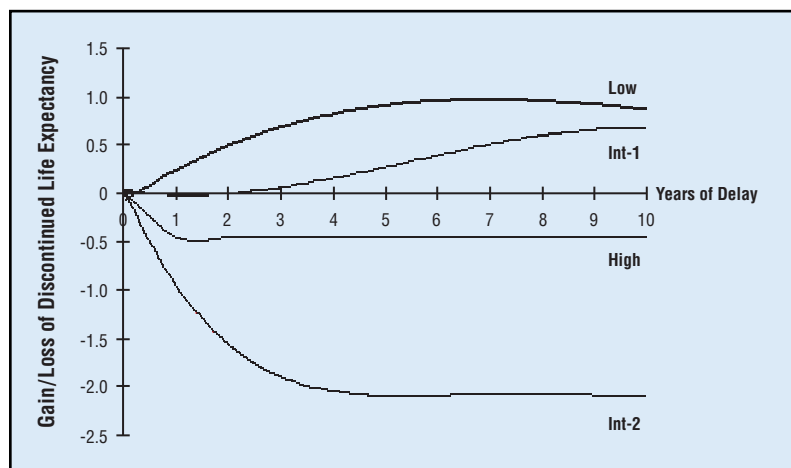


Fig 5. — Net benefit or loss of overall discounted life expectancy for HSCT. A net benefit for delaying transplantation is noted for lower-risk patients. In the higher-risk groups, any delay in time to transplantation is associated with loss in life years. This research was originally published in *Blood*. From Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for lower-risk myelodysplasia is associated with improved outcome. *Blood*. 2004;104(2):579-585. © American Society of Hematology. Reprinted with permission.

Conclusions

The past 5 years have ushered in the first FDA-approved MDS therapeutics that are changing the manner in which these disorders are managed. The shift from an emphasis on supportive care to that of active treatment has shown that these new treatment strategies can alter the natural history of disease while ameliorating symptoms. The role of HSCT is now reserved for higher-risk patients or those with progressive disease. Lower-risk anemic patients with a favorable response profile should be managed with ESAs, while IST, lenalidomide, and MTIs should be reserved for those who are ESA-insensitive. Azacitidine in particular has filled a therapeutic void for both lower- and higher-risk patients and can serve as a bridge to transplant for patients with higher-risk disease who are not immediate transplant candidates. For each of these treatments, evidence is accumulating showing that a disease-modifying effect is possible even in patients with lower-risk disease, whether by suppressing the malignant clone or by promoting hematopoietic maturation competence.

Disclosures

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