



Anne Silber. *Ha Long Bay, Vietnam* (detail). Limited edition serigraph, © 2008. Sheet size 11" × 15".

The classification, diagnosis, treatment goals, clinical experience, guidelines, and therapeutic options for higher-risk MDS patients are reviewed.

Enhancing Survival Outcomes in the Management of Patients With Higher-Risk Myelodysplastic Syndromes

Steven D. Gore, MD, and Evelyn R. Hermes-DeSantis, PharmD, BCPS

The myelodysplastic syndromes (MDS) are a collection of clonal myeloid neoplasms characterized by bone marrow failure and cytopenias. Patients classified with higher-risk disease include those with intermediate-2 or high-risk disease as classified by the International Prognostic Scoring System (IPSS). These patients represent 29% of the MDS population and were originally reported to have a median survival without therapy of only 0.4 for high-risk patients and 1.1 years for intermediate-2 risk patients. The most significant treatment goals in these patients involve prolonging the time to acute myeloid leukemia progression and extending overall survival. Quality of life, symptom control, and transfusion independence are also important.

The National Comprehensive Cancer Network guidelines divide treatment options for this population into high- and low-intensity therapies. High-intensity therapies include cytarabine-based remission induction chemotherapy and hematopoietic stem cell transplantation. Transplantation is the only treatment option with the ability to cure; however, many MDS patients may not qualify due to age or comorbidities. Low-intensity therapies include the DNA methyltransferase inhibitors azacitidine and decitabine. Recently, azacitidine demonstrated the ability to extend survival by as much as 74% despite a modest complete response rate. This review examines the classification and diagnosis of higher-risk MDS patients, the management goals for these patients, clinical experience involved with treatments, guidelines, and recommendations for therapeutic options.

Introduction

The myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal myeloid neoplasms characterized by bone marrow failure that may progress to acute myeloid leukemia (AML). The reported annual incidence is approximately 5 per 100,000 of the general US population.¹ Newer data suggest that MDS may be substantially more prevalent in the population due to under-

diagnosis and underreporting. Additionally, the incidence may be increasing due to improvement in overall life expectancy and better survival of cancer patients who received cytotoxic therapies that may cause MDS.

Recent data have shown that azacitidine (AZA; Vidaza[®], Celgene Corp, Summit, NJ) increases survival in intermediate-2 (Int-2) to high-risk MDS patients by as much as 74%² compared with a combined group of similar patients treated with one of three conventional care regimens. This review specifically focuses on these higher-risk populations, examining treatment goals, options, and directions involved with treatment. Further, it explores how treatment is evolving based on the new survival data and how various therapies fare in the goal of improving survival.

Incidence and Classification

In the United States, MDS was not considered a reportable cancer until 2002. Thus, epidemiological data

From the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland (SDG), and the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey, Piscataway, New Jersey (ERH-D).

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Address correspondence to Steven D. Gore, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 401 North Broadway, Baltimore, MD 21231. E-mail: goresd@jhmi.edu

Table. — IPSS Classification System for Higher-Risk MDS: Survival and AML Evolution

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5	5–10	—	11–20	21–30
Karyotype	Good: Normal –Y alone del(5q) alone del(20q) alone	Intermediate: Other abnormalities	Poor: Complex (≥ 3 abnormalities) or chromosome 7 anomalies		
Cytopenia	0/1	2/3			

Risk Category	Overall Score	Median Survival in Absence of Therapy	25% AML Progression in Absence of Therapy
Int-2	1.5–2.0	1.1 yrs	1.1 yrs
High	≥ 2.5	0.4 yrs	0.2 yrs

This research was originally published in *Blood*. Adapted from Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89(6):2079-2088. © American Society of Hematology. Reprinted with permission.

were not collected by the Surveillance, Epidemiology and End Results (SEER) Program until recently. Current estimates of the incidence and prevalence of MDS range between 15,000 and 20,000¹ but may be low due to underreporting. Based on Medicare billing data, the overall higher annual incidence may be 7 to 8 times higher.³ These data suggest that the overall burden of MDS may be considerably higher than previously reported.

Patients with suspected MDS require a thorough evaluation of both marrow and blood morphology, as well as a careful evaluation of the time over which the abnormal blood counts developed and a cytogenetic analysis of the bone marrow. These assessments allow an accurate diagnosis and classification.⁴ The two classification systems utilized to describe MDS include the French-American-British (FAB) system⁵ and the World Health Organization (WHO) system.⁶ In addition, the International Prognostic Scoring System (IPSS) and the WHO Performance Scoring System (WPSS) assist in predicting survival of MDS patients.⁷

The IPSS is used to assess relative risk and to determine the likely survival of MDS patients treated with supportive care at the time of diagnosis (Table). The IPSS uses a point scoring system based on percent of marrow blasts, the karyotype, and the degree of cytopenias. Patients with higher-risk MDS account for 29% of the patient populations, with 22% presenting with Int-2 MDS and 7% presenting with high-risk MDS.⁸ Based on the IPSS score, median survival in the absence of therapy and the progression to AML have been calculated.⁸¹⁰ For patients with Int-2 and high-risk MDS, the median survival, without therapy, was 1.1 years and 0.4 years, respectively.⁸

While the IPSS is useful at diagnosis, it does not address the assessment over time. Malcovati et al⁷ developed the WPSS to classify patients based on the WHO subgroup, karyotype abnormalities, and transfusion requirements, resulting in five risk groups (very low, low, intermediate, high, and very high). For patients in the high-risk and very high-risk groups, the median overall survival was 21 and 12 months, respectively. In addition,

the probability of AML progression at 2 and 5 years was 0.52 and 0.63 for high-risk patients and 0.79 and 1.0 for very high-risk patients, respectively. When analyzed for its prognostic value, the WPSS was shown to significantly predict overall survival (hazard ratio [HR] = 2.58, 95% confidence interval [CI], 2.5–3.10, $P < .0001$) and risk of AML (HR = 3.63, 95% CI = 2.78–4.74, $P < .0001$).⁷ In contrast to the IPSS, the WPSS was derived using time-dependent covariables so that risk was reassessed upon disease progression. Because of this, the WPSS may be applied at any time during a patient's disease course, whereas the IPSS is more appropriate only at the time of initial evaluation.

Treatment Objectives

For higher-risk MDS patients, the primary goals for treatment involve extending overall survival and altering the course of disease by delaying the time to AML transformation. Other treatment objectives include improving quality of life, providing symptom control and supportive care, and achieving transfusion independence. Appropriate management of this challenging patient population requires a multidisciplinary approach that includes close physician monitoring, frequent laboratory tests, and prudent use of transfusions in order to improve quality of life and provide symptomatic relief.¹¹

Most MDS patients require red blood cell transfusions. Based on a recent survey, 68% of patients with higher-risk disease are dependent on red blood cell transfusions and 33% require platelet transfusions (Fig 1).¹¹ Red blood cell transfusions provide only intermittent relief from fatigue due to the limited half-life of transfused blood, and they expose patients to the risks of transfusion-mediated infections and hypothetical organ damage due to the accumulation of excess iron. Transfusion dependence has been associated with shorter survival; however, this may be due to the association of transfusion-dependence with more advanced disease rather than with transfusion complications per se.⁷

Historically, specific aspects of response to treatment have been based on measurable changes in hema-

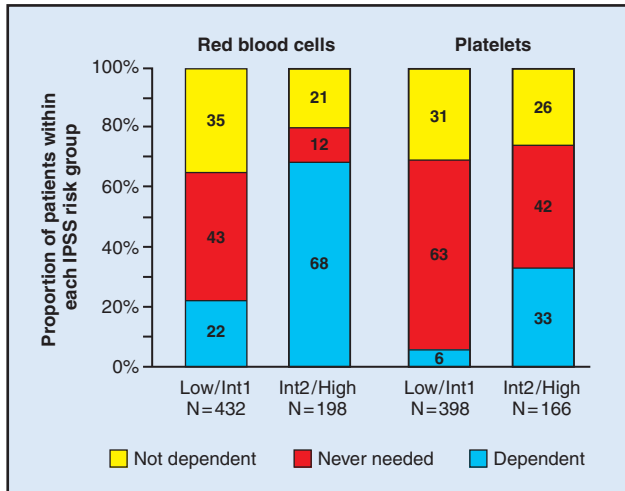


Fig 1. — Percentage of MDS patients requiring transfusions. From Sekeres MA, Schoonen WM, Kantarjian H, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. *J Natl Cancer Inst.* 2008;100(21):1542-1551. Reprinted with permission by Oxford University Press.

tologic parameters. The International Working Group (IWG) recognizes that meaningful response metrics may differ between clinical trials aimed at altering the natural history of the disease and those primarily aimed at improving hematologic function and quality of life (these two goals are obviously not mutually exclusive). Normalization of the hemogram, bone marrow morphology, and bone marrow cytogenetics dominate in therapies aimed at altering the natural history of the disease. In therapies aimed at improving hematologic function and quality of life, issues such as hematologic improvement and improvement in measurable quality of life outcomes may be at least as important.¹²

Because complete response has been considered a required surrogate for improved survival in acute leukemias, this metric has traditionally been considered critical for survival improvement in MDS as well. To date, however, no study has demonstrated an association of complete response (CR) attainment with extended survival.¹³ A recently published randomized trial of AZA vs conventional care has raised questions about the requirement of CR for improved survival in MDS.²

Assessment of Treatment Options

Since the demonstration of longer survival of high-risk MDS patients in response to AZA, best supportive care (BSC) can no longer be considered the standard of care for most patients. The National Cancer Center Network (NCCN) guidelines divide treatment options for this population in two directions: (1) high-intensity therapies such as cytarabine-based remission induction chemotherapy and hematopoietic stem cell transplantation (HSCT) and (2) low-intensity therapies, including the DNA methyltransferase inhibitors (MTIs) — AZA and decitabine (DAC; Dacogen®, Eisai Inc, Franklin Lakes, NJ).¹ Patients not suitable or refractory to any of these therapies can be enrolled in a clinical trial at any point in time.

High-Intensity Therapy

High-dose chemotherapy followed by allogeneic HSCT is currently the only known potentially curative treatment for MDS. The outcomes of allogeneic transplant vary with patient age, patient comorbidities, disease status, type of preparative regimen, and type of donor. In a multivariate analysis of all MDS patients receiving a transplant at the Fred Hutchinson Cancer Research Center between 1981 and 1996, Appelbaum and Anderson¹⁴ noted that increasing age ($P = .0003$), increasing disease duration ($P = .0002$), mismatched donor ($P = .007$), and male gender ($P = .007$) all significantly increased nonrelapse mortality. However, these factors did not affect overall disease-free survival. Deeg et al¹⁵ evaluated 109 patients with MDS treated with busulfan plus cyclophosphamide and HSCT from 45 related donors and 64 unrelated donors. In patients with an IPSS score of 2 or greater, the 3-year relapse-free survival rate was only 29%. Nonrelapse mortality in the same patient population was 31% at 3 years. The observation that relapse-free survival of patients undergoing myeloablative allogeneic transplant varies with IPSS score at the time of transplant has led some investigators to speculate that prior treatment with remission induction chemotherapy or DNA MTIs prior to transplant might improve outcome.¹⁵ This strategy has not been tested in controlled trials.

Determining the optimal timing of allogeneic transplant for MDS for an individual patient can be challenging. Patients with IPSS intermediate-1 (Int-1) disease have a 10% to 20% chance of being alive at 18 years with only supportive care.⁸ The up-front mortality associated with HSCT might encourage patients to delay transplant until disease progression; however, transplant in patients with a higher IPSS score is associated with decreased disease-free outcome. In 2004, Cutler et al¹⁶ analyzed retrospective data from the International Bone Marrow Transplant Registry, the Fred Hutchinson Cancer Research Center, and the International MDS Risk Analysis Workshop (IMRAW) of MDS patients treated with supportive care, which was the population from which the IPSS was derived. Their goal was to use a mathematical model to integrate the competing risks of allogeneic stem cell transplant — treatment-related mortality vs long-term disease control.

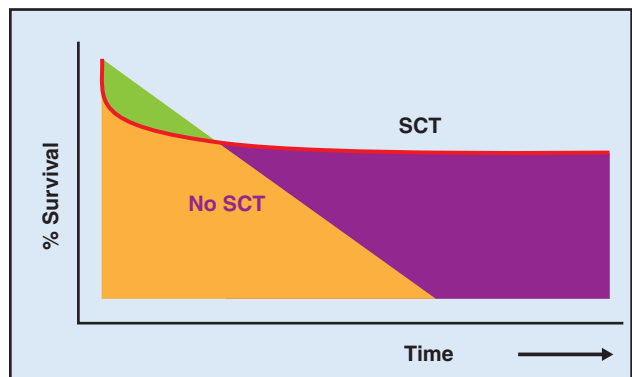


Fig 2. — Decision-making model for transplantation in MDS. SCT = stem cell transplantation. Image provided courtesy of Corey S. Cutler, MD, MPH.

Utilizing a Markov decision analysis model, they examined the overall life expectancy of populations of patients in various IPSS groups transplanted with allogeneic stem cell transplant from HLA-matched siblings if transplanted at various times from diagnosis (Fig 2). For populations of IPSS Int-2 and high-risk patients, transplant at diagnosis maximized average survival, with time delayed from diagnosis to transplant correlating with loss of survivorship for the population. However, no net years of life were lost for patients with lower-risk IPSS MDS if transplant was delayed until disease progression. This analysis was performed based on data derived prior to the availability of DNA MTIs.

Reduced-Intensity Conditioning

Reduced-intensity conditioning (RIC) has been developed to extend allogeneic stem cell transplant to older patient populations and patients with comorbidities. Because RIC does not administer myeloablative conditioning, the success of the transplants requires a robust graft-vs-leukemia effect. While short-term mortality is certainly decreased using these approaches, the incidence of chronic graft-vs-host disease is substantial, and 2-year mortality may approach that of myeloablative stem cell conditioning. The largest study examining the efficacy of RIC in patients with MDS was a retrospective analysis of data from the European Bone Marrow Transplant Registry evaluating patients undergoing HLA-identical sibling donors, with 215 receiving RIC and 621 receiving standard myeloablative (or high-dose) conditioning (SMC).¹⁷ The 3-year relapse rate was significantly higher in patients receiving RIC compared with those receiving SMC (HR = 1.64, 95% CI = 1.2-2.2, $P = .001$). However, the 3-year nonrelapse mortality rate was decreased with RIC (HR = 0.61, 95% CI = 0.41-0.91, $P = .15$). Overall survival and progression-free survival were similar between both groups at 3 years. According to the multivariate analysis, in response to AML-type chemotherapy regardless of receiving RIC or SMC, the hazard ratio of relapse was significantly increased in patients who were treated but not in complete remission compared with patients who were in complete remission prior to transplantation (HR = 2.1, 95% CI = 1.1-3.8, $P = .025$). In contrast, patients who received no disease-modifying therapy prior to transplant had an HR of 1.2 (95% CI = 0.5-2.3, $P = .48$) compared with those in remission.

While these data suggest that remission induction therapy may be beneficial prior to reduced-intensity allogeneic stem cell transplant, successful outcome of remission induction therapy may merely serve as a biomarker of patients with more responsive disease who are more likely to benefit from the reduced-intensity transplant. While allogeneic transplant with RIC represents an important treatment option, particularly for older patients with MDS, its optimal timing and overall efficacy are yet to be established.

In selecting patients who may be candidates for allogeneic HSCT, a thorough evaluation of comorbidities

and other risk factors for poor transplant outcomes must be included. Sorror et al¹⁸ used a hematopoietic cell transplantation-specific comorbidity index (HCT-CI) to stratify patients into four risk groups in order to evaluate the role of risk factors, including medical comorbidities, on patient outcomes in those with hematologic malignancies who underwent HSCT. Patients with higher comorbidity scores and disease risk had incremental and corresponding increases in nonrelapse mortality. The 2-year overall survival and relapse-free survival were also markedly improved in patients with lower comorbidity scores and lower-risk disease, with approximately greater than 50% of patients with lower comorbidity scores being alive at 2-year follow-up.

In patients with higher-risk disease, retrospective data based on untreated patients do not suggest any advantage in delaying transplant. While potential donors are sought for HSCT candidates, some have speculated that therapy may be initiated with a DNA MTI in order to serve as a bridge to transplant. The untested rationale underlying this recommendation presumes that the disease-modifying properties of these therapeutics — AZA in particular — may contribute to optimizing disease control and may potentially lower the risk for subsequent relapse. However, this strategy will need to be studied in prospective controlled trials.¹⁹ In addition, it is becoming apparent that age alone should not be the only determinant for selecting a patient for HSCT; comorbidities and other risk factors should also be considered.

Low-Intensity Therapy With DNA MTIs

DNA MTIs deplete nuclear DNA methyltransferase and promote the synthesis of DNA with methylation marks from the parent DNA strand “erased.” DNA MTIs are

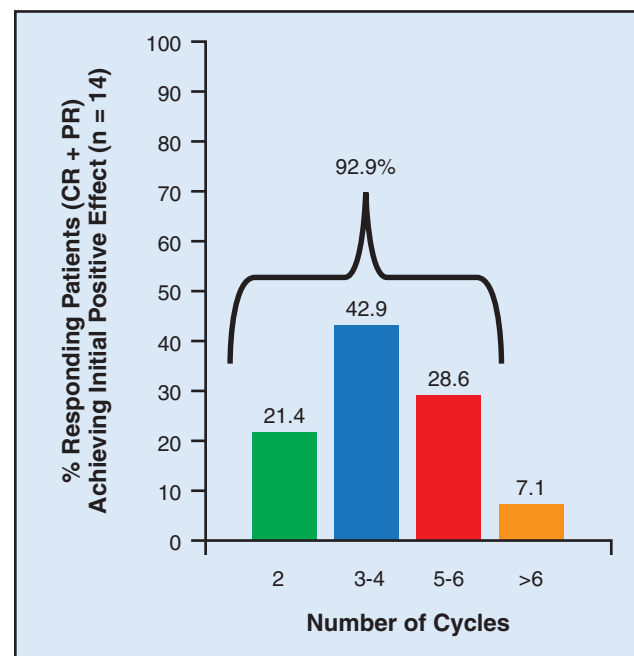


Fig 3. — Mean number of cycles with AZA required to achieve response. Image courtesy of Lewis R. Silverman, MD.

now considered first-line agents in the treatment of MDS, and both AZA and DAC have demonstrated hematologic improvement when compared with BSC. In addition, AZA showed a significant overall survival benefit over a combined cohort of three conventional care regimens. Because the AZA nucleosides must be incorporated into DNA in order to effect methylation reversal, higher concentrations of these agents may sabotage this effect through cell cycle inhibition.²⁰ In vitro, a biphasic dose-response curve for the relationship between methylation reversal and DAC nucleoside concentration has been demonstrated.²¹ The FDA-approved schedules of AZA and DAC were studied empirically and were not derived through careful pharmacodynamically based dose-finding.

Experience With AZA

The approval of AZA was based on results from the Cancer and Leukemia Group B (CALGB) Study 9221. In this trial, Silverman et al²² evaluated AZA 75 mg/m² per day every 28 days for at least 4 cycles compared with BSC in 191 patients with MDS in a randomized controlled study. At month 4, patients receiving BSC alone who had worsening disease or transformation to AML were allowed to cross over into the AZA group. In addition to evaluating CR, partial response (PR), and hematologic improvement, quality of life was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life and the Mental Health

Inventory. Based on reanalysis of the data using the IWG criteria for response, 47% of patients in the AZA arm responded (CR 10%, PR 1%, and hematologic improvement 36%), and 35% of patients who received AZA after BSC responded (CR 6%, PR 4%, and hematologic improvement 25%).²³

The majority of patients who responded (75%) achieved improvement by the fourth cycle, with time to any response occurring with a median number of 3 cycles. The total response increased to 90% by the sixth cycle. This study demonstrated the importance of continuing treatment with a DNA MTI for several cycles before concluding that the patient will not develop a hematologic response (Fig 3).²³ In patients receiving transfusions at baseline, 80% of AZA patients became transfusion-independent.²³ In addition, quality-of-life components of fatigue, physical functioning, dyspnea, psychosocial distress, and positive effect significantly improved in patients treated with AZA compared with BSC.

In this trial, overall survival trended towards favoring AZA treatment (20 months vs 14 months), though this trend was not statistically significant. This was most likely attributable to the crossover design. Notable was a landmark analysis in the original publication. Patients who were randomized to receive AZA had a longer median time to AML transformation or death compared with those who received BSC (21 months vs 12 months, $P = .007$); the comparator includes patients crossed over to AZA (Fig 4).²²

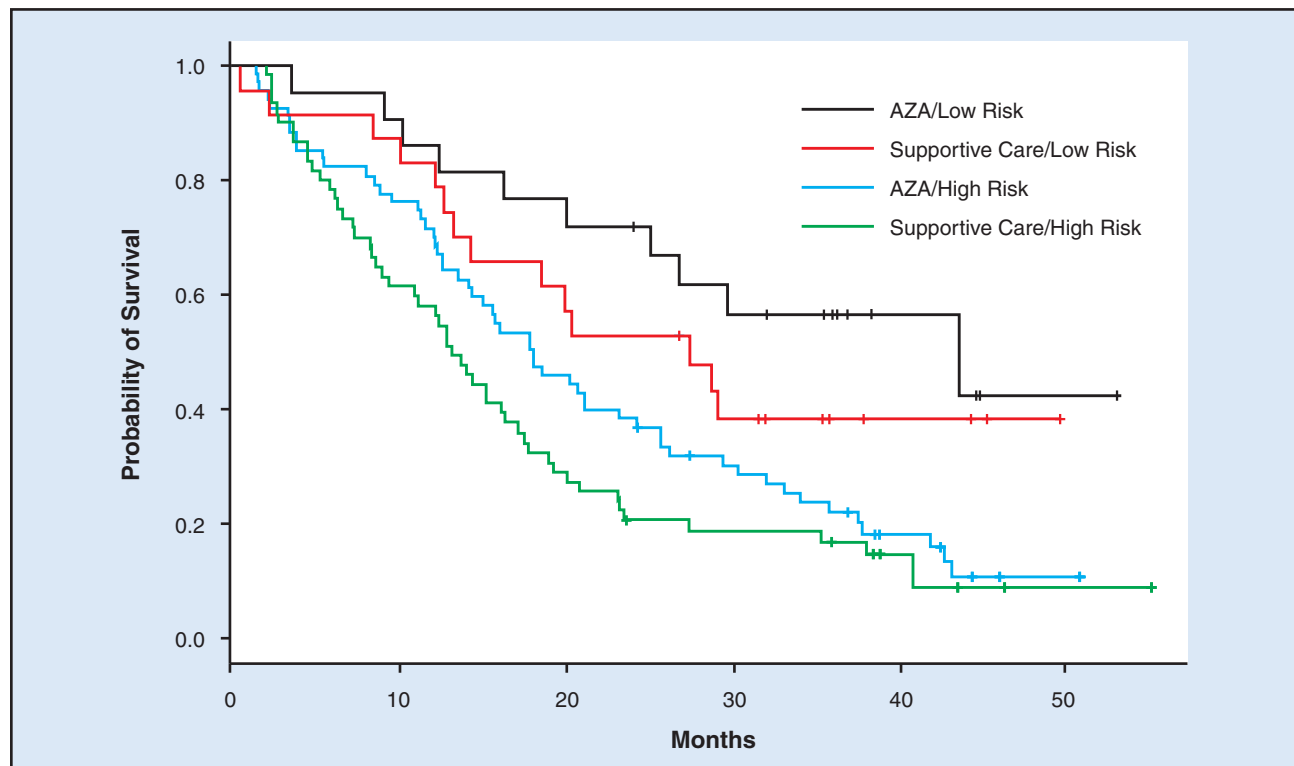


Fig 4. — Overall survival with AZA: survival by randomized arm and FAB subtype. FAB subgroups were divided into low-risk (RAEB, RAEB-T, or CMML) groups. Median survival: AZA/Low, 4 months; Supportive Care/Low, 27 months; AZA/High, 18 months; Supportive Care/High, 13 months. From Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. *J Clin Oncol.* 2002;20(10):2429-2440. Reprinted with permission. © 2002 American Society of Clinical Oncology. All rights reserved.

The most significant data for DNA MTI therapy emerged from an international randomized trial with AZA. In this study, Fenaux et al² evaluated the effect of treatment on overall survival in a phase III, international, multicenter, controlled, randomized, parallel-group, open-label trial. A total of 358 higher-risk MDS patients were randomized to receive either AZA subcutaneously 75 mg/m² per day for 7 days every 28 days for at least 6 cycles (n = 179) or conventional care (n = 179), which included BSC, low-dose cytarabine, or intensive AML-type induction and consolidation chemotherapy. Prior to randomization, the conventional care regimen that was most appropriate for each patient was assigned by the individual investigator based on age, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, and the physician's particular practice. Patients were randomized to receive either AZA or the preselected conventional care regimen. All patients were categorized as Int-2 or high-risk according to IPSS- and FAB-defined refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), or chronic myelomonocytic leukemia (CMML) with at least 10% bone marrow blasts. The average age of the patients enrolled was 69 years. AZA or conventional care was continued until evidence of disease progression or treatment intolerance.²

Efficacy was assessed in an intent-to-treat basis with the primary endpoint of overall survival and secondary endpoints of time to progression to AML, hematologic response, improvement based on IWG 2000, and transfusion independence. After a median follow-

up of 21.1 months (interquartile range, 15.1–26.9), the AZA group had a significantly longer median survival time of 24.5 months vs 15 months for the conventional care group (9.4 months difference, $P = .001$, HR = 0.58, 95% CI = 0.43–0.77, Fig 5). Kaplan-Meier analysis estimated a greater survival at 2 years for of the AZA group (50.8%, 95% CI = 42.1–58.8) compared with patients receiving conventional care (26.2%, 95% CI = 18.7–34.3, $P < .0001$). Median time to progression of AML was also significantly decreased in AZA patients compared with those receiving conventional care (17.8 months vs 11.5 months, HR = 0.50, 95% CI = 0.35–0.70, $P < .0001$). AZA patients also had significantly higher rates of any hematologic response (29% vs 12%, $P = .0001$), CR (17% vs 8%, $P = .015$), PR (12% vs 4%, $P = .0094$), and any hematologic improvement (49% vs 29%, $P < .0001$) compared with those receiving conventional care. The study was neither designed nor powered to compare the outcome of AZA-treated patients with those receiving any of the three individual conventional care regimens. Of the AZA patients who were transfusion-dependent at baseline, 45% became transfusion-independent compared with only 11.4% of the patients receiving conventional care ($P < .0001$). Grade 3–4 peripheral cytopenias were the most common adverse events for all treatments.²

This significant prolongation in survival in patients treated with AZA, despite a modest CR rate, demonstrates that achieving a CR is no longer a sufficient predictor for a therapy's ability to extend survival and alter course of MDS and CMML.

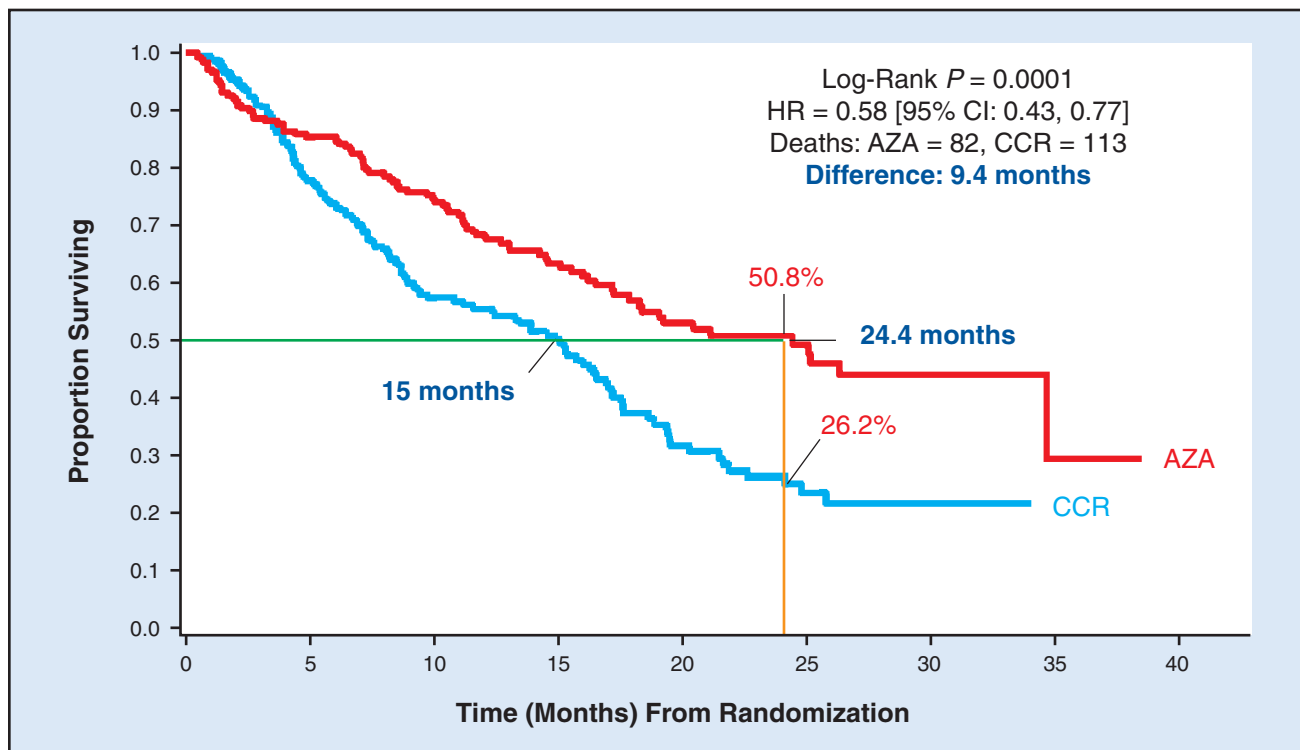


Fig 5. — Overall survival with AZA vs conventional therapy. CCR = conventional care regimen. Reprinted from The Lancet Oncology, Vol 10, Issue 3. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10(3):223-232. Reprinted with permission from Elsevier.

Experience With DAC

DAC is another DNA MTI that has been studied predominantly in higher-risk MDS patients. As with AZA, the most commonly studied dose schedule for DAC was derived empirically rather than through careful dose-finding studies. The FDA-approved schedule of 15 mg/m² intravenously (IV) every 8 hours for 9 doses has been studied in two randomized trials between DAC and supportive care.

In a randomized phase III study, Kantarjian et al²⁴ compared DAC (15 mg/m² IV over 3 hours every 8 hours for 3 days repeated every 6 weeks) to BSC in 170 MDS patients with an IPSS of at least 0.5. Patients in the DAC group had a 17% overall response rate (CR 9%, PR 8%) compared with no patients in the BSC group ($P < .001$). Overall, responses lasted a median of 10.3 months, and all of the responders became transfusion-independent. The median number of courses was 3 (range 0–9), and the time to AML progression or death was not different between DAC and BSC for all patients (12.3 vs 7.3 months, $P = .08$) but appeared improved in patients with Int-2 or high-risk MDS (12 months vs 6.8 months, $P = .03$) in an unplanned retrospective subset analysis.

Wijermans et al²⁵ evaluated the same schedule of DAC among 233 Int-2 and high-risk MDS patients in an EORTC study. The investigators compared DAC (15 mg/m² IV every 8 hours for 3 days of every 6-week cycle for a maximum of 8 cycles) to BSC in a phase III randomized trial. Patients who received BSC were allowed to cross over and receive DAC after transformation to AML. Overall survival and time to progression to AML were the two primary endpoints that were evaluated. The DAC group observed a superior response compared to BSC (CR 13% vs 0%, PR 6% vs 0%, hematologic improvement 15% vs 2%, stable disease 14% vs 22%, progressive disease 29% vs 68%). The median overall survival did not differ between the two groups (HR = 0.88, 95% CI = 0.66–1.17, $P = .83$). Progression-free survival was significantly improved (0.55 years vs 0.25 years, $P = .004$). However, time to AML or death was not improved (0.73 years vs 0.51 years, HR = 0.85, 95% CI = 0.64–1.12, $P = .24$). The median number of cycles was 4, with 40% receiving no more than two cycles. Toxicity included grade 3–4 febrile neutropenia (26% in the DAC group vs 7% in the BSC group). It should be noted that 9 deaths occurred due to toxicity in the DAC group and none due to toxicity in the BSC group. To date, DAC has not achieved the superior survival rates seen in patients on AZA. The lack of difference in overall survival may be due to the small number of cycles administered (median three to four per patient), and the lack of “maintenance therapy” since therapy was limited to 8 cycles.

These studies indicate that while the FDA-approved dose schedule of DAC is active in MDS, survival has not been improved compared to BSC. The M. D. Anderson group has led an effort to study alternative dosing schedules aimed at optimizing methylation reversal and improving tolerability through the use of lower daily dosing of DAC. In a phase I study, Issa et al²¹ evaluated DAC 5, 10, or 20 mg/m² IV for 10 days (5 days on, 2 days off, 5 days on) or 15 mg/m² for 10, 15, or 20 days every 6 weeks in 50 patients with relapsed/refractory leukemia. Responses developed in patients treated at all dosing levels; 15 mg/m² for 10 days was selected for further study based on a response rate (CR, PR, and hematologic improvement) of 65%.

Kantarjian et al²⁶ evaluated three dosing regimens of DAC in 95 patients (77 with Int-1, Int-2, and high-risk MDS and 32 with CMML) in a randomized phase II study. Treatment regimens included DAC 20 mg/m² IV

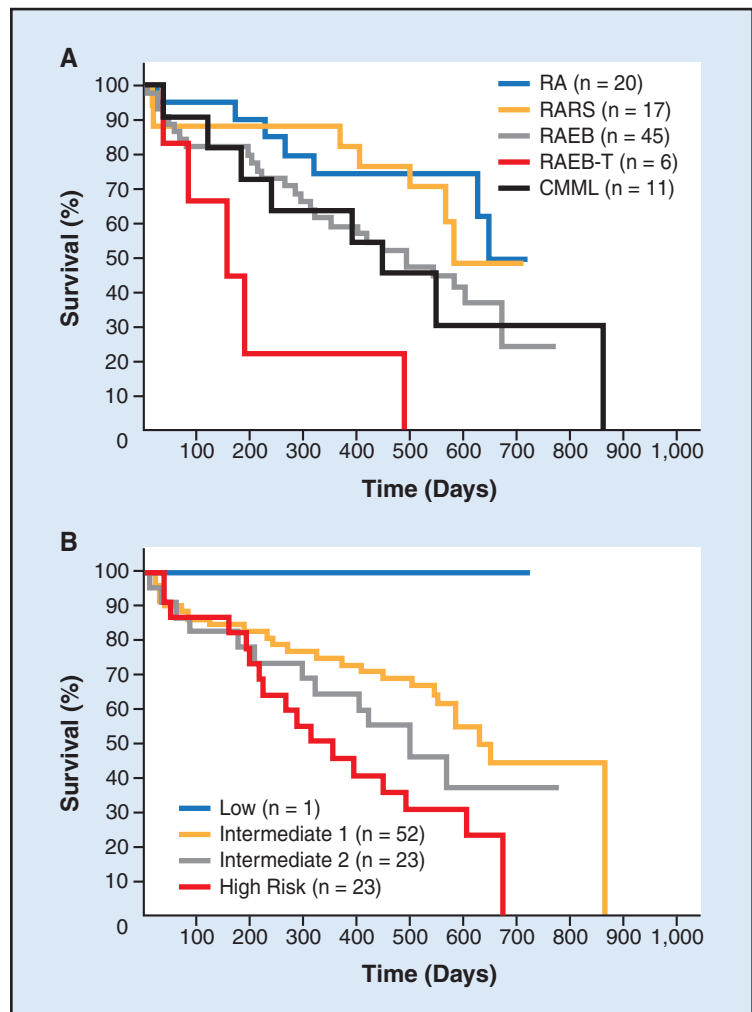


Fig 6. — Outcomes associated with DAC. Kaplan-Meier survival analysis of enrolled patients stratified according to (A) FAB subtype of myelodysplastic syndrome and (B) IPSS score. RA = refractory anemia, RARS = refractory anemia with ringed sideroblasts, RAEB = refractory anemia with excess blasts, RAEB-T = refractory anemia with excess blasts in transformation, CMML = chronic myelomonocytic leukemia. From Steensma DP, Baer MR, Slack JL, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the Alternative Dosing for Out-patient Treatment (ADOPT) trial. *J Clin Oncol*. 2009;27(23):3842–3848. Reprinted with permission. © 2009 American Society of Clinical Oncology. All rights reserved.

for 5 days, DAC 20 mg/m² subcutaneously daily for 5 days, and DAC 10 mg/m² IV daily for 10 days. The treatment cycles were repeated every 4 weeks regardless of counts, and patients were evaluated for response after at least three courses. A total of 32 (34%) CRs were reported, and 69 (73%) showed an objective response by IWG criteria. Of the three regimens, the 5-day IV arm had the best clinical result, with 39% achieving a CR, compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day IV arm ($P < .05$).

Steensma et al²⁷ conducted the Alternative Dosing for Outpatient Treatment (ADOPT) trial, a multicenter phase II study aimed at confirming the activity of this 5-day schedule. The trial enrolled 99 Int-1, Int-2, and high-risk MDS patients. DAC 20 mg/m² IV every day was administered in an outpatient setting for 5 days every 4 weeks. The primary endpoint was the IWG response criteria. Secondary endpoints included evaluating hematologic improvement, CR, overall survival, time to AML or death, transfusion requirements, and toxicity. Overall improvement occurred in 51% of patients, with a CR occurring in 17 patients, marrow completed response in 15 patients, and hematologic improvement in 18 patients (overall response rate 51%, 95% CI, 40%-61%). Median survival was 19.4 months (Fig 6). Patients received a median of 5 cycles (range, 1-17 cycles). In addition, 33% of patients who were transfusion-dependent at baseline became transfusion-independent over the trial.²⁶ The impact of this schedule of DAC on overall survival will require another randomized trial with a survival endpoint, which is not currently planned.

While the hematologic response rates to both AZA nucleosides are similar, the survival advantage demonstrated by the FDA-approved dose schedule of AZA compared with conventional care, as well as the absence of such a survival advantage in response to the FDA-approved dose schedule of DAC in two randomized studies, makes AZA the drug of choice for AZA nucleoside-naïve, high-risk MDS patients. Whether the better-tolerated DAC schedule studied in the ADOPT trial would lead to similar survival advantage due to ease of repetitive administration is unknown.

Treatment Options for Higher-Risk MDS

Overall, treatment options for higher-risk MDS patients include allogeneic HSCT, AML-type intensive chemotherapy, DNA MTIs, or clinical trials. Allogeneic HSCT is the only potentially curative measure for MDS patients, but it remains a complicated choice due to significant risks of morbidity and mortality and a cure rate that does not exceed 40% in high-risk patients.¹

The use of RIC prior to transplantation has overcome some of the complications associated with allogeneic HSCT. Unfortunately, there are still patients who are not candidates for transplantation. For patients who have no HLA-matched donor or for patients whose risk profile for HSCT is unfavorable, DNA MTI therapy (AZA, DAC) may be utilized. If patients fail to respond to such therapy or are not suitable candidates, they can be referred for an

investigational protocol involving new agents or novel combinations with established treatments. The NCCN guidelines also acknowledge the use of intensive remission-induction chemotherapy for high-risk patients. In our opinion, the use of remission-induction therapy is mainly limited to preparation of allogeneic SCT since the duration of chemotherapy-induced remissions for high-risk MDS is brief.

Conclusions

The primary goals in the treatment of high-risk MDS patients focus on lengthening overall survival, prolonging the time to progression to AML, and maintenance of quality of life. The use of proven therapies reduces transfusion dependency in MDS patients and may enhance survival. The treatment algorithm for higher-risk disease includes high- and low-intensity strategies. HSCT is curative and improves overall survival but is appropriate for a limited number of patients. HSCT with RIC cures some patients and extends HSCT as an option to more patients due to the reduction in some of the toxicity. Another alternative involves the use of DNA MTI agents. These treatments can significantly improve functional hematopoiesis, and AZA can lengthen overall survival time for MDS patients. The best response with DNA MTI agents occurs after at least 4 cycles. Optimizing the dosing of these therapies should allow the possibility to treat patients for longer periods of time and with fewer adverse events in order to obtain maximum clinical benefit.

Clinicians today have several options to enhance survival in their higher-risk MDS patients. They should plan treatment accordingly in light of the opportunity to extend lifespan and improve quality of life. Newer approaches on the horizon via clinical study protocols offer further options when patients fail to respond or do not qualify for currently available options.

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