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The new treatment paradigm for MDS aims to extend leukemia-free and total survival while maintaining hematologic and cytogenetic response.

Changing the Treatment Paradigm in Myelodysplastic Syndromes

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The treatment algorithm for the patient with myelodysplastic syndrome (MDS) is in the process of being revitalized based on recent results of clinical trials. Historically, the goal for lower-risk patients was hematologic improvement, and disease modification was reserved for patients in the higher-risk category. Recent data now favor shifting emphasis away from supportive care alone and toward altering the disease course and prolonging survival, particularly in patients with intermediate-2 and high-risk disease. In addition, there is a greater appreciation for the significant morbidity and mortality resulting from MDS and increased efforts to improve quality of life while pursuing treatment. Immunomodulation with lenalidomide has yielded durable cytogenetic and hematologic responses and also has shown potential to alter disease course. Similarly, immunosuppression with antithymocyte globulin has shown sustained hematologic responses in selected patient subgroups. The methyltransferase inhibitors have demonstrated the ability to alter the natural history of disease and thus prolong time to leukemic transformation. In addition, azacitidine has shown the capacity to extend survival compared with the previous gold standard of conventional care regimens.

With these new data, evaluation of treatment options should no longer focus on response rates as the sole endpoint but rather on time to leukemic transformation and survival. Timing of available therapies, including stem cell transplantation, should be incorporated into the new treatment paradigm, with end goals of prolonging survival and optimizing patient outcomes.

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Abbreviations used in this paper: MDS = myelodysplastic syndrome(s), AML = acute myeloid leukemia, HSCT = hematopoietic stem cell transplantation, RIC = reduced intensity conditioning, alloSCT = allogeneic stem cell transplantation, MTI = methyltransferase inhibitor; IPSS = International Prognostic Scoring System, IWG = International Working Group, DFS = disease-free survival, BSC = best supportive care, QOL = quality of life, CR = complete remission, PR = partial remission.

Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders commonly characterized by a hypercellular and dysplastic bone marrow, cytopenias resulting from impaired peripheral blood cell production, and an increased risk of leukemic transformation. A majority of these patients are over 60 years of age, with median onset occurring in the seventh decade of life.^{1,2} The diverse pathobiology of the disease is manifested by a varied clinical course, with some patients having more indolent disease and longer life expectancy, and others presenting with aggressive variants that rapidly progress to

leukemia. Regardless of initial presentation or disease course, approximately 40% of patients with MDS will transform to acute myeloid leukemia (AML).³

Up until recently, treatment of MDS had been unsatisfactory; traditional chemotherapy yielded poor durable responses and had minimal impact on leukemia progression, and hematopoietic stem cell transplantation (HSCT) was an option for only approximately 5% to 10% of patients due to the high morbidity and mortality associated with HSCT.⁴ The advent of reduced-intensity conditioning (RIC) regimens has broadened the utilization of stem cell transplantation (SCT) by decreasing myelosuppression and increasing the graft-vs-leukemia effect against MDS.⁵ However, even with advancements in this area, SCT has been reserved for patients in whom the benefits outweigh the risks.⁶ The majority of patients with MDS are treated primarily with supportive care measures, including growth factors, platelet and red blood cell (RBC) transfusions, and antibiotics. A select group of patients with lower-risk disease and favorable features may also benefit from immunosuppressive therapy. Historically, treatment goals focused on hematologic improvement for lower-risk patients, which were measured by response rates in clinical trials. In higher-risk patients, the therapeutic aim turned to altering the disease course with the use of high-intensity chemotherapy and SCT.

In the last decade, new therapeutic options have emerged that may offer durable responses and may extend survival with minimal or acceptable toxicities. Lenalidomide (CC-5013; Revlimid®, Celgene Corp, Summit, New Jersey), the newest immunomodulating agent, has shown hematologic and cytogenetic responses, especially in patients with del(5q). Notably, the methyltransferase inhibitors (MTIs) azacitidine (Vidaza®, Celgene Corp) and decitabine (Dacogen®, Eisai Inc, Woodcliff Lake, New Jersey) have demonstrated the ability to not only improve hematologic response, but also prolong overall survival in this challenging patient population. Considering these observations, there appears to be a need to revisit present therapeutic goals as the treatment paradigm for MDS is evolving so that clinicians may select treatment modality based on the desired endpoint. In addition, these emerging data have considerably refined the selection of patients for growth factors or immunosuppressive therapy, immunomodulating agents, MTIs, treatment of iron overload, and HSCT.

In this article, we review outcome definitions for treatment modalities and propose to shift emphasis away from response rates and focus on overall survival as an endpoint. The current prognosis of the patient with MDS and the impact of different treatment options on survival are examined, incorporating recent data from trials with the MTIs, particularly in the higher-risk population. Timing of therapy and the role of

stem cell transplantation are discussed. Also, the effects of various clinical therapeutics on survival and the deleterious effect of inadequate treatment on patient outcomes are examined.

Therapeutic Goals

Consensus practice guidelines recommend that selection of therapy for MDS should consider the patient's age, comorbidities, and International Prognostic Scoring System (IPSS) risk category.^{7,8} Hence, treatment modalities have varied based on whether the goal of treatment was to extend survival or palliate symptoms and improve quality of life (QOL), depending on the patient's risk category and performance status. Treatment of MDS has historically been separated into low-intensity and high-intensity therapies, based on risk of toxicities. Low-intensity therapies, which include immunosuppressive therapy, biologic response modifiers, and cytokines, were targeted at patients with lower-risk disease with the goal of improving cytopenias and QOL without impacting overall survival. Other low-intensity therapies, such as low-intensity chemotherapy and MTIs, and high-intensity therapies, such as leukemia-type induction chemotherapy and high-dose chemotherapy with allogeneic stem cell transplant (alloSCT), aim to alter the course disease or extend survival.

Many patients with MDS receive supportive care alone, particularly lower-risk patients with chronic cytopenias or patients with higher-risk disease who cannot tolerate high-intensity therapy. Lower-risk patients often become dependent on frequent RBC or platelet transfusions and experience repeated infections and bleeding. Regardless of disease status, the heavy physical toll of MDS and its management, including the need for frequent laboratory monitoring and transfusions, physician visits, and the debilitating fatigue experienced by some patients, often leads to significant morbidity and mortality, with associated reduction in QOL.⁹ Thus, improvement in QOL and alleviation of disease-related symptoms are key goals of therapy, and ongoing efforts are needed to provide effective treatment while decreasing the morbidity associated with this challenging disease.

Outcome Definitions

With such variations in the goals of MDS treatment, standardized response criteria became essential to evaluate outcomes of therapy, refine treatment according to patient and disease characteristics, and allow comparisons across clinical trials. In 2000, an International Working Group (IWG) of investigators proposed standardized response criteria to facilitate comparisons across clinical trials, establish risk-based treatment goals, and identify clinically meaningful responses across MDS subgroups (Tables 1–4). These criteria have been widely

adopted into clinical practice and were updated in 2006. The investigators grouped patients into IPSS risk categories and recommended that the major goal of therapy for patients with lower-risk disease (low-risk and intermediate-1 categories) is to achieve hematologic improvement. For higher-risk patients (intermediate-2 and high-risk categories), the focus turns to altering the natural history of disease and prolonging survival.^{10,11}

The IWG criteria define four specific aspects of responses based on treatment goals: hematologic improvement, cytogenetic response, alteration of the natural history of disease, and QOL.¹²

Hematologic response is defined by responses of cytopenias in the three hematopoietic lineages — erythroid, platelet, and neutrophil — and is classified as either a major or minor response (Table 1). Measurement of cytopenias is performed at baseline and takes the averages of at least two separate measurements, irrespective of transfusions (ie, RBC transfusions and platelet transfusions held for 1 week and 3 days prior, respectively). In patients with cytopenias and lower-risk MDS, assessment of hematologic responses is the most relevant clinical endpoint.

Evaluation of cytogenetic responses requires 20 analyzable metaphases to define the extent of the response, by IWG criteria. A major cytogenetic response (MCyR) refers to disappearance of a cytogenetic abnormality, and a minor cytogenetic response (mCyR) is at least a 50% reduction of abnormal metaphases.

The ability of treatment to impact the natural history of disease is measured by complete remission (CR)

or partial remission (PR), disease progression, and transformation (Tables 2 and 3). To achieve CR, there must be less than 5% marrow blasts without evidence of dysplasia and normalization of peripheral blood counts. With the proposed modifications to IWG criteria, lack of dysplasia on bone marrow evaluation is no longer required, and dysplastic changes should consider the normal range of modification. As reported by Ramos et al,¹³ even healthy individuals without MDS showed a variable proportion of dyshemopoietic findings, including erythroid hyperplasia. A marrow CR is achieved if the bone marrow contains less than 5% blasts and decreases by 50% or greater over pretreatment. For a PR, patients must demonstrate all CR criteria if abnormal before treatment except that marrow blasts should decrease by 50% or more compared with pretreatment levels, or they may demonstrate a less-advanced disease classification category than prior to treatment. Cellularity and morphology are no longer relevant with the proposed response criteria.¹⁴

Specific endpoints to survival include overall and event-free survival, progression-free survival (PFS) and disease-free survival (DFS), and cause-specific death (Table 4). With new data emerging on the potential to modify disease and extend survival times, there is now more focus on utilizing overall survival and PFS as endpoints rather than viewing response rates alone. There is also more emphasis on improving QOL, as patients with chronic cytopenias and transfusion dependence experience significant morbidity, particularly the elderly population. The IWG criteria recognize improve-

Table 1. — International Working Group Response Criteria in MDS: Hematologic Improvement*

Criteria	Major Response	Minor Response
Erythroid response (HI-E)	Patients with pretreatment Hgb < 11 g/dL: > 2 g/dL rise in Hgb. RBC-transfusion-dependent patients: transfusion independence.	Patients with pretreatment Hgb < 11 g/dL: 1-2 g/dL rise in Hgb. RBC-transfusion-dependent patients: 50% decrease in transfusion requirements.
Platelet response (HI-P)	Patients with pretreatment platelet count < 100,000/mm ³ : absolute increase of 30,000/mm ³ or more. Platelet-transfusion-dependent patients: stabilization of platelet counts and platelet transfusion independence.	Patients with pretreatment platelet count < 100,000/mm ³ : 50% or more increase in platelet count with a net increase > 10,000/mm ³ but < 30,000/mm ³ .
Neutrophil response (HI-N)	Patients with ANC < 1500/mm ³ before therapy: at least a 100% increase or an absolute increase of more than 500/mm ³ , whichever is greater.	Patients with ANC < 1500/mm ³ before therapy: ANC increase of at least 100%, but absolute increase < 500/mm ³ .
Progression/relapse after HI	One or more of the following: (1) 50% or greater decrement from maximum response levels in granulocytes or platelets (2) reduction in Hgb concentration by at least 2 g/dL (3) transfusion dependence	

HI = hematologic improvement, ANC = absolute neutrophil count, Hgb = hemoglobin.

* Improvements must last at least 2 months in the absence of ongoing cytotoxic therapy. Hematologic improvement should be described by the number of individual positively affected cell lines. This research was originally published in *Blood*. Adapted from Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000;96:3671-3674. © American Society of Hematology. Reprinted with permission.

ment of QOL as an important treatment goal, along with alleviation of disease-related complications. A positive correlation has been noted between hemoglobin level and QOL, with maintenance of higher hemoglobin associated with increased QOL.¹⁴ Along with hematologic improvement and alleviation of symptoms, improvement of QOL is also a benefit of MDS treatment^{13,14} and should be incorporated into clinical trials as a valid endpoint.

Despite standardization and wide utilization and acceptance of IWG response criteria, these criteria are not always applicable to individual patients. In addition, it is understood that clinical response is not easily extrapolated from one patient to another, and assessment of response may be biased based on the clinical course and provider preference.¹⁵ Now that there are data on agents that extend survival rather than inducing CRs or PRs, response rates should no longer be the focal point; rather, clinicians should contemplate survival as an end goal.

Survival in Higher-Risk Patients

The goals of treatment for MDS, whether palliative or curative, are to improve cytopenias and QOL and prolong survival.¹³ With therapeutic options that range from supportive care to more aggressive and toxic therapies, assessment of the patient's prognosis is vital prior to initiating treatment. Prognostic scoring systems in MDS are useful because they can permit comparisons across clinical trials of different treatment approaches and they may guide the clinician in choosing a particular therapy based on individual patient risk assessments.¹⁶ Many collaborative groups have proposed different staging systems to predict prognosis in the MDS patient, including risk of death and leukemic potential. The most widely utilized prognostic score is the IPSS, which was developed from pooling and analyzing patient data from the International MDS Risk Analysis Workshop (IMRAW) database. From univariate analyses performed on these data, the investigators found that the percentage of blasts in the bone marrow, the pres-

Table 2. — International Working Group Response Criteria in MDS: Complete and Partial Remission

Category		Response Criteria	
		Bone Marrow Evaluation	Peripheral Blood Evaluation
Complete remission (CR)	Original criteria*	Repeat bone marrow < 5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia. If erythroid precursors are < 50% of bone marrow nucleated cells, the percentage of blasts is based on all nucleated cells. If there are 50% or more erythroid cells, the percentage blasts should be based on the nonerythroid cells.	1. Hemoglobin > 11 g/dL (untransfused, patient not on erythropoietin). 2. Neutrophils 1500/mm ³ or more (not on a myeloid growth factor). 3. Platelets 100,000/mm ³ or more (not on a thrombopoietic agent). 4. Blasts, 0%. 5. No dysplasia.
	Modified criteria**	Bone marrow: ≥ 5% myeloblasts with normal maturation of all cell lines. Persistent dysplasia will be noted (peripheral blood criteria unchanged).	
		Marrow CR Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment. Peripheral blood: if hematologic responses, they will be noted in addition to marrow CR.	
Partial remission (PR)	Original criteria*	All the CR criteria (if abnormal before treatment), except: Blasts decreased ≥ 50%, or a less advanced MDS FAB classification than pretreatment.	1. Hemoglobin > 11 g/dL (untransfused, patient not on erythropoietin). 2. Neutrophils 1500/mm ³ or more (not on a myeloid growth factor). 3. Platelets 100,000/mm ³ or more (not on a thrombopoietic agent). 4. Blasts, 0%. 5. No dysplasia.
	Modified criteria**	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%. Cellularity and morphology not relevant (peripheral blood evaluation unchanged).	

This research was originally published in *Blood*. *Adapted from Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000;96:3671-3674. **Adapted from Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108:419-425. © American Society of Hematology. Reprinted with permission.

ence and type of cytogenetic abnormality, and the number and magnitude of cytopenias correlated with AML progression and survival (Table 5). These associations were confirmed by multivariable analyses, and they allowed characterization of patient populations and identified patients at high risk of transforming to AML.

Additionally, reanalysis of the IMRAW cohort demonstrated that patients with more severe cytopenias had lower overall survival and a higher risk of AML transformation. Also, as disease risk progressed from low to high, marrow blast percentages correspondingly increased, along with worsening cytopenias.¹⁷

Table 3. — International Working Group Response Criteria in MDS: Altering Natural History of Disease

Category		Response Criteria
Stable disease	Original criteria*/ Modified criteria**	Failure to achieve at least a PR, but with no evidence of progression for at least 2 months.
Failure	Original criteria*/ Modified criteria**	Death during treatment or disease progression characterized by worsening of cytopenias, increase in the percentage of bone marrow blasts, or progression to an MDS FAB subtype more advanced than pretreatment.
Relapse after CR or PR	Original criteria*	<ol style="list-style-type: none"> 1. Return to pretreatment bone marrow blast percentage. 2. Decrement of 50% or greater from maximum remission/response levels in granulocytes or platelets. 3. Reduction in hemoglobin concentration by ≥ 2 g/dL or transfusion dependence.
	Modified criteria**	Same as above, but with reduction in hemoglobin by ≥ 1.5 g/dL or transfusion dependence.
Disease progression	Original criteria*	For patients with: <ol style="list-style-type: none"> 1. Less than 5% blasts: $\geq 50\%$ increase in blasts to more than 5% blasts. 2. 5% to 10% blasts: $\geq 50\%$ increase to more than 10% blasts. 3. 10% to 20% blasts: $\geq 50\%$ increase to more than 20% blasts. 4. 20% to 30% blasts: $\geq 50\%$ increase to more than 30% blasts. One or more of the following: 50% or greater decrement from maximum remission/response levels in granulocytes or platelets, reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.
	Modified criteria**	Same as above, but with <i>any</i> of the following criteria counting towards disease progression: 50% or greater decrement from maximum remission/response levels in granulocytes or platelets, reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.
Disease transformation	Original criteria*/ Modified criteria**	Transformation to AML (30% or more blasts).

This research was originally published in *Blood*. *Adapted from Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000;96:3671-3674. **Adapted from Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419-425. © American Society of Hematology. Reprinted with permission.

Table 4. — International Working Group Response Criteria in MDS: Definitions of Endpoints for Clinical Trials

Endpoint	Response Category	Definition	Point of Measurement
Overall survival	All patients	Death from any cause	Entry into trial
Event-free survival	All patients	Death or failure from any cause	Entry into trial
Progression-free survival	All patients	Disease progression or death from MDS	Entry into trial
Disease-free survival	Complete remission	Time to relapse	First documentation
Cause-specific death	All patients	Death related to MDS	Death

This research was originally published in *Blood*. Adapted from Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000;96:3671-3674. © American Society of Hematology. Reprinted with permission.

Table 5. — International Prognostic Scoring System (IPSS) for MDS: Survival and AML Evolution

	IPSS Risk Category			
	Low	Intermediate-1	Intermediate-2	High
Scores	0	0.5–1.0	1.5–2.0	≥ 2.5
Median time to AML (yrs)	9.4	3.3	1.1	0.2
Median survival (yrs)	5.7	3.5	1.2	0.4

This research was originally published in *Blood*. 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.

While the IPSS allows for better characterization of patients enrolled in clinical trials and identifies those at high risk of AML transformation, it does not provide insight into the pathobiology of MDS, and it does not account for mortality directly relating to disease or disease-related complications, compared to the expected rate of death from other medical comorbidities in the predominantly elderly patient population.¹² In relation to this issue, Della Porta et al¹⁵ analyzed the Pavia database for the impact of comorbidities on non-leukemia-related death and overall survival in MDS patients. The investigators found that comorbidities had the highest impact on patients with lower-risk disease, and transfusion dependence and iron overload independently worsen survival by causing increased cardiac complications and cardiac death.

In order to incorporate immunophenotypic, cytogenetic, and molecular factors into a scoring system for

MDS, Malcovati et al¹⁸ developed a World Health Organization (WHO) classification-based prognostic scoring system (WPSS). The WPSS utilizes WHO subgroups, karyotype, and transfusion requirement as variables and assigns patients into five risk groups for overall survival and AML transformation. The major difference between the IPSS and WPSS is that WPSS uses a time-dependent regression model and, thus, provides prognostic information from initial evaluation through treatment to follow-up. Notably, patients with normal blast counts and those with only erythroid dysplasia have a better prognosis according to the WPSS

model, but this may require more careful evaluation by the clinician for dysplastic changes in other lineages. Patients with del(5q) also had a better prognosis than other WHO subtypes by WPSS, although only in those patients with blasts less than 5% (Fig 1).¹⁹

As Drs Malcovati and Nimer discuss in their article in the first part of this supplement, attempts to improve on these classification systems and refine additional prognostic indices, including cytogenetic abnormalities, are continuing. Recent data have shown that median survival is significantly reduced in patients with 3 or more complex chromosome abnormalities, from 17 months to less than 9 months in patients with 4 or more chromosomal anomalies.²⁰ Multivariate analyses of two large MDS cohorts from the German and M. D. Anderson Cancer Center databases confirmed that complex karyotype had greater prognostic impact than high percentage of blasts (Fig 2).^{20,21} With the emergence of disease-

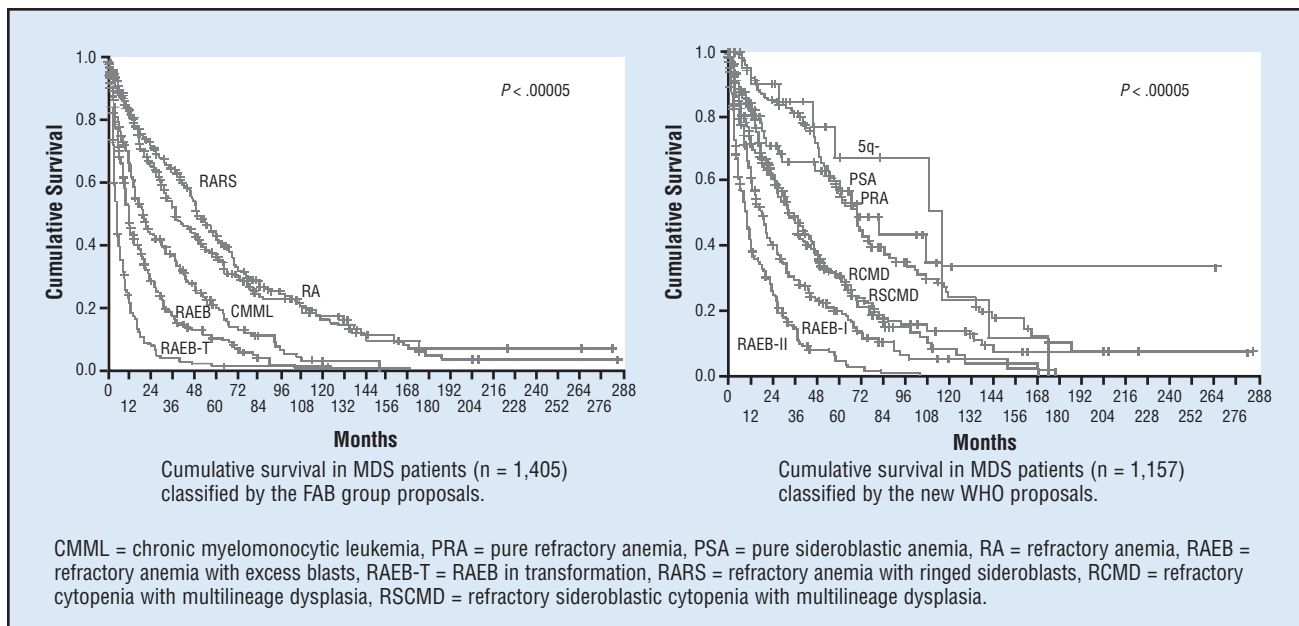


Fig 1. — Cumulative survival in MDS patients classified according to FAB and WHO proposals. From Germing U, Gattermann N, Strupp C, et al. Validation of the WHO proposals for a new classification of primary myelodysplastic syndromes: a retrospective analysis of 1600 patients. *Leuk Res*. 2000;24:983-992. Reprinted with permission from Elsevier.

modifying therapies, there is also an interest in developing a prognostic score for patients with lower-risk MDS to identify patients who may benefit from early interventions.²² It is becoming evident that each risk group requires a different therapeutic approach.

Compared with lower-risk patients, those with higher-risk disease have a higher rate of evolution to AML. Patients tend to die of progressive disease rather than disease-related complications. Greenberg et al¹⁶ assessed survival and AML evolution based on the French-American-British (FAB) classification, bone marrow blast percentage, and number of cytopenias. They found that the progression curve of higher-risk patients overlapped their survival curve. Interestingly, the survival curves for elderly patients (60 years or older) in the high-risk or intermediate-2 groups did not differ substantially from those for younger patients; however, in the lower-risk groups, older age was associated with poorer survival times. With overall survival of only 4 months to a little over 1 year without treatment, therapy for higher-risk patients focuses on altering the disease course and extending survival. With comparable rates of survival in younger and elderly patients in the higher-risk population, this may suggest that both elderly patients and younger patients with high-risk disease should be treated similarly, given their overall prognosis and inevitable progression to leukemia.

Treatment Options and Impact on Survival

Historically, supportive care has been the cornerstone of treatment for MDS for many years due to the scarcity of available treatment options and the toxicities of higher-intensity therapies. While these interventions improve QOL, they neither prolong survival nor modify the disease course. Although immunosuppressive therapy with antithymocyte globulin (ATG) or

cyclosporine may result in hematologic improvement by altering immune-mediated myelosuppression, only a select subset of patients may respond. A recent update of retrospective multivariate analysis of 129 patients from the National Institutes of Health (NIH) cohort showed that younger age, low IPSS score, and presence of HLA-DR15 were the most important predictors of response to immunosuppressive therapy.²³ In addition, patients with trisomy 8 may be particularly responsive, with a significant number of patients (9 of 12) with trisomy 8 achieving transfusion independence in the NIH trials.²⁴ Lim et al²⁵ confirmed that lower IPSS score and younger age were associated with response as well as bone marrow hypocellularity. It is yet to be determined whether immunosuppressive therapy may confer a survival advantage by altering disease natural history.

Although iron chelation therapy (ICT) has been used for many years, only recent data have shown potential benefits in survival. A prospective survey was conducted in 170 French patients who received ICT and were then reevaluated 2 years later. Of 165 evaluable patients, 76 (46%) received ICT for at least 6 months. Patients who received iron chelation had a median overall survival of 115 months compared with 51 months in non-chelated patients ($P < .0001$). The survival advantage was still present after adjustment on other prognostic parameters, including sex, age, IPSS score, and transfusion requirement.²⁶ Although a survival benefit has yet to be demonstrated in prospective, randomized, controlled trials, these promising results support the use of ICT in RBC-transfusion-dependent MDS patients. By regulating body iron levels with iron chelation therapy, the risk of iron overload can be minimized while improving QOL and possibly extending survival.²⁷

In the last 5 years, newly available therapies have altered the manner in which patients with MDS are

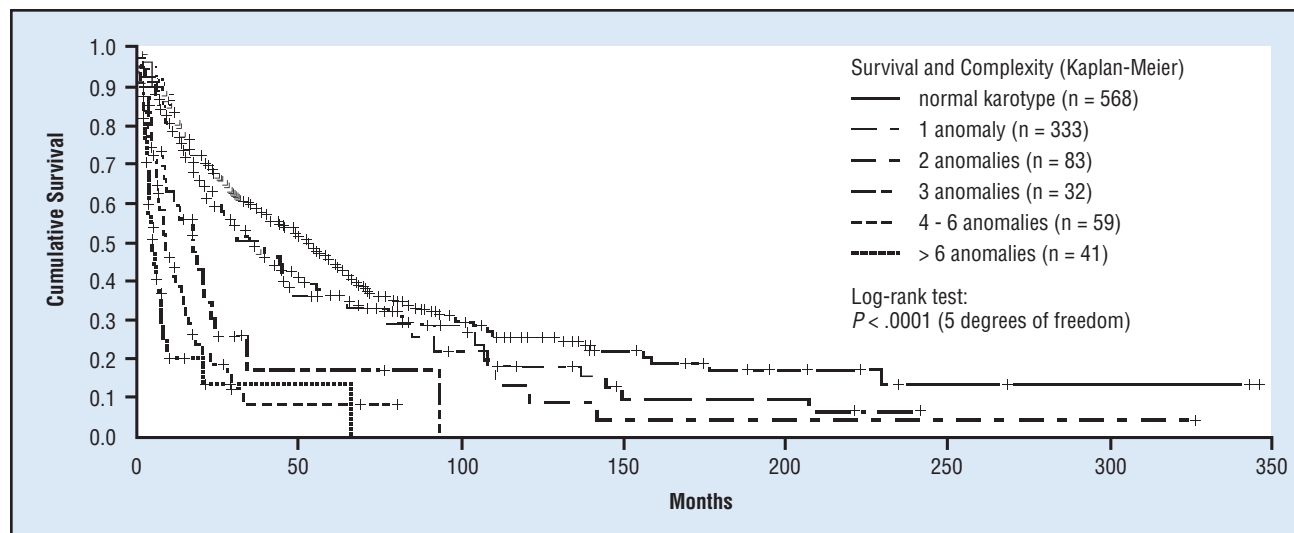


Fig 2. — Impact of degree of karyotype complexity on median survival. This research was originally published in *Blood*. From Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. *Blood*. 2007;110:4385-4395. © American Society of Hematology. Reprinted with permission.

managed. Both the immunomodulating agent lenalidomide and the class of agents known as the MTIs have shown potential to alter the biology of disease and, in the case of the MTIs, improve overall survival. The shift from an emphasis on using best supportive care (BSC) alone to altering the natural history of disease, especially earlier in the disease course, and extending survival has been made possible by the advent of these new therapeutic agents.

Methyltransferase Inhibitors

Promoter hypermethylation of CpG nucleotides in DNA is believed to be a key contributor to the molecular pathophysiology of MDS by inactivating key gene(s) expression essential for control of normal cell growth, differentiation, and apoptosis.²⁸ The mechanism underlying response to therapy with a DNA MTI is via reversal of methylation caused by epigenetic silencing and reexpression of silenced gene products.²⁹ After incorporation into DNA, methyltransferase is inhibited; complete methylation occurs only after several cycles of replication, thus accounting for time to response with MTI therapy (Fig 3).³⁰ Currently, only two hypomethylating agents, azacitidine and decitabine, are approved for the treatment of MDS. Both of these drugs are cytosine nucleoside analogs that were initially developed as cytarabine analogs, but had limited activity and unacceptable toxicities when used at higher doses.³¹ Results of randomized trials with the MTIs have demonstrated improved hematologic response when compared to BSC alone.^{26,32} More recently, treatment with azacitidine has shown not only durable response rates, but also prolongation in survival compared to other conventional therapies for MDS.²⁶⁻²⁸ These data have transformed the

manner in which therapeutic agents are evaluated in this disease and have altered how the MTIs fit into the treatment paradigm for patients with MDS.

Azacitidine

The Cancer and Leukemia Group B conducted the pivotal phase III trial with azacitidine that led to its FDA approval. The CALGB 9221 study randomized patients with all FAB subtypes of MDS to azacitidine 75 mg/m² given subcutaneously per day for 7 days every 28 days or to BSC.³³ After 4 months, patients in the BSC arm could cross over to receive azacitidine if they had worsening disease or transformed to AML. Responses to azacitidine were seen in all FAB subtypes, with 47% of patients achieving significant responses: 10% of patients achieved a CR and 36% of patients demonstrated hematologic improvement. The median time to AML transformation or death for patients receiving BSC was 12 months compared with 21 months for patients receiving azacitidine ($P = .007$). Overall survival also trended toward favoring azacitidine treatment (20 months vs 14 months) but was not shown to be significant due to the crossover design.

A recent phase III randomized multicenter trial with azacitidine demonstrated improvement in overall survival when compared to conventional care regimens in previously untreated intermediate-2 or high-risk patients.³² The AZA-001 study included 358 patients who received either azacitidine ($n = 179$) or one of three conventional treatments: low-dose cytarabine ($n = 49$, 27%), intensive leukemic-like induction chemotherapy ($n = 25$, 14%), or BSC ($n = 105$, 59%). Azacitidine demonstrated a median survival benefit of 9 months ($P = .001$, hazard ratio [HR] = 0.58, 95% confi-

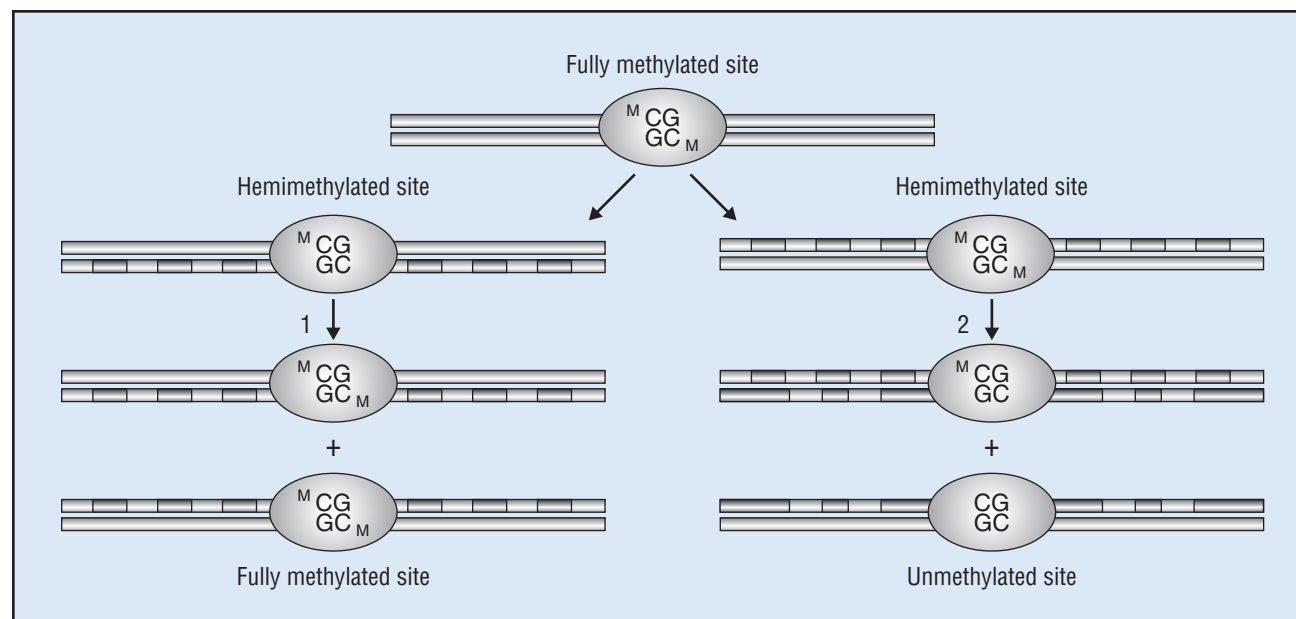


Fig 3. — Mechanism of action of DNA MTIs and their incorporation into DNA. From Silverman LR, Mufti GL. Methylation inhibitor therapy in the treatment of myelodysplastic syndrome. *Nat Clin Pract Oncol*. 2005;2(Suppl 1):S12-S23. © Macmillan Publishers Ltd. Reprinted with permission.

dence interval [CI]: 0.43–0.77) regardless of age, sex, FAB or WHO diagnosis, and karyotype or IPSS category (Fig 4). Azacitidine also demonstrated improved survival when compared with the individual conventional treatment options, ie, low-dose cytarabine and intensive chemotherapy. Survival at 2 years was nearly doubled with azacitidine (51% vs 26%, $P < .0001$, 95% CI: 13–36). Responses with azacitidine were of longer duration when compared with conventional treatment, even though patients who received intensive chemotherapy had a higher CR rate. In addition, azacitidine was more successful at preventing AML transformation and inducing hematologic improvement.

Treatment with azacitidine also confers benefit in higher-risk patients with cytogenetic abnormalities. Subgroup analysis of the study by Mufti et al³⁴ in patients with -7/7q- yielded a 67% reduction in deaths in patients treated with azacitidine, which compared favorably to the HR of 0.58 for azacitidine across all cytogenetic subtypes in the phase III trial. The survival advantage was present even at 2 years, with 33% of azacitidine patients being alive compared with only 8% in patients in the conventional care arm ($P = .03$). Lim et al³⁵ found similar benefit with the use of azacitidine in patients with chromosome 7 abnormalities. Patients with isolated chromosome 7 abnormalities had a median survival of 24.8 months (95% CI: 17.8–31.8) compared with those with complex cytogenetics whose median survival was 17.3 months (95% CI: 8.3–26.3, $P = .10$). In this challenging patient population with complex cytogenetic aberrations, including those with

-7/7q-, azacitidine may serve to induce cytogenetic remissions while transplant-eligible patients await donor selection and diagnostic screening.

With recent data on prolonged survival across IPSS subtypes, there has been an impetus to explore alternative dosing regimens for azacitidine that eliminate weekend administration with the standard 7-day schedule. Lyons et al³⁶ conducted an open-label phase II study in 151 patients in outpatient private practice settings that compared three different dosing schedules: (1) 75 mg/m² for 5 days followed by 2 days off and then 2 days on (AZA 5-2-2; n = 51), (2) 50 mg/m² for 5 days followed by 2 days off and then an additional 5 days (AZA 5-2-5; n = 51), and (3) 75 mg/m² for 5 days only (AZA 5; n = 50). Of IWG-evaluable patients, rates of hematologic improvement were similar in all dosage arms (range 44% to 56%) and were comparable to the established 7-day regimen. Trilineage major hematologic improvements were noted in all three treatment groups, and transfusion independence was achieved in over 50% of patients in all groups. Overall hematologic improvement was achieved in 71 patients (51%). Transfusion independence was obtained in 55% (12 of 22) of AZA 5-2-2 patients, in 60% (12 of 20) of AZA 5-2-5 patients, and in 63% (16 of 24) of AZA 5 patients. In FAB low-risk transfusion-dependent patients, RBC transfusion independence was reached by 60% (9 of 15), 56% (5 of 9), and 61% (11 of 18) in the AZA 5-2-5 group, the AZA 5-2-2 group, and the AZA 5 group, respectively. Of note, grade 3/4 hematologic adverse events tended to be slightly lower for patients treated on the AZA 5 regimen.

The survival data in the CALGB 9221 trial and the AZA-001 trial cannot be directly compared because the CALGB study included patients with all MDS FAB subtypes and IPSS categories, while AZA-001³² included treatment-naïve intermediate-2 and high-risk patients. However, it is apparent that azacitidine confers hematologic improvement and prolongs survival in a wide range of MDS patients. In addition, the comparable rate of hematologic improvement and lower toxicity of the AZA 5 regimen suggests that this dosing schema should be explored outside of the higher-risk population.

Data are also emerging on using azacitidine as maintenance therapy to prolong remission times after intensive chemotherapy. Grövdal et al³⁷ reported preliminary results on 60 patients with high-risk MDS or secondary AML treated with standard doses of daunorubicin and ara-C. Patients in CR were given low-dose azacitidine in the 5-day regimen every 4 weeks until disease relapse. Median duration of

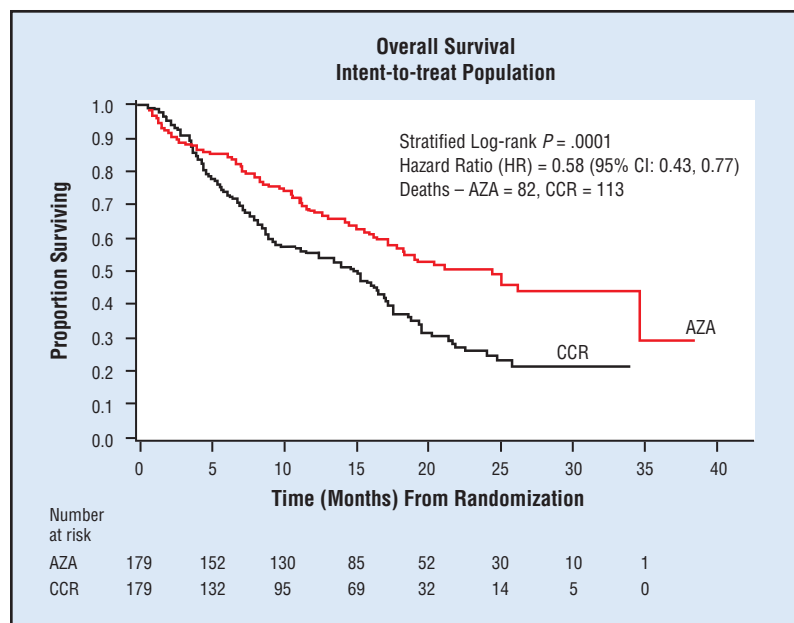


Fig 4. — Overall survival in patients with MDS treated with azacitidine (AZA) compared with conventional care regimens (CCR). This research was originally published in *Blood*. From Fenaux P, Mufti GJ, Santini V, et al. Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients 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.

CR was 13 months (range 2 to 37). A CR duration of greater than 20 months occurred in 30% (7 of 23 patients). However, it is premature to determine if this strategy would be beneficial for all patients. The question of maintenance therapy after alloSCT has yet to be evaluated.

Decitabine

Decitabine was originally studied in elderly European patients with MDS. Based on promising phase II data,^{38,39} a phase III trial was implemented in the United States. A total of 170 patients were randomized to two arms: (1) decitabine 15 mg/m² given intravenously over 3 hours every 8 hours for 3 consecutive days repeated every 6 weeks plus BSC (n = 89) or (2) BSC alone (n = 81). The majority of patients in the decitabine arm had intermediate-2 or high-risk disease, and 74% were transfusion-dependent. The overall response rate was 30% (CR 9%, PR 8%, hematologic improvement 13%), although median time to death or AML transformation was not statistically different between groups. Subgroup analysis demonstrated that certain characteristics were associated with a longer median time to AML transformation or death in patients who received decitabine: *de novo* MDS (12.6 vs 9.4 months, *P* = .04), high-risk disease (9.3 vs 2.8 months, *P* = .01), or treatment-naïve (12.3 months vs 7.3 months, *P* = .08). Cox analysis established that patients who received only supportive care had almost a 2-fold greater risk of AML progression or death compared with those in the decitabine group (Fig 5).⁴⁰

The results of treatment with decitabine were retrospectively compared to two historical cohorts: (1) patients treated with intensive chemotherapy and matched for age, IPSS category, and cytogenetics (n = 115)⁴¹ and (2) patients treated with intensive chemotherapy with similar baseline characteristics as in the phase III trial (n = 376).⁴² For the matched-control analysis, median survival was 22 months for decitabine compared with 12 months with intensive chemotherapy. The 2-year survival rate was also significant at 47% of patients who received decitabine vs 24% of those in the intensive chemotherapy arm (*P* < .001). In the historical control of 376 patients, the 2-year survival rates were 47% with decitabine and 21% for intensive chemotherapy (*P* < .0001).

Similar to azacitidine, an alternate dosing regimen for decitabine has been evaluated and utilized to facilitate outpatient administration and reduce the risk of toxicities. Kantarjian et

al⁴³ studied three schedules of decitabine in 95 patients with intermediate- to high-risk MDS; 32% of patients had secondary MDS, and 55% had higher-risk disease. An intravenous infusion daily for 5 days demonstrated similar results as the original 3-day schedule: the CR rate reached 40%, the overall response rate was 80% and the median response duration was 14 months. A recent update of these results reported a CR and PR

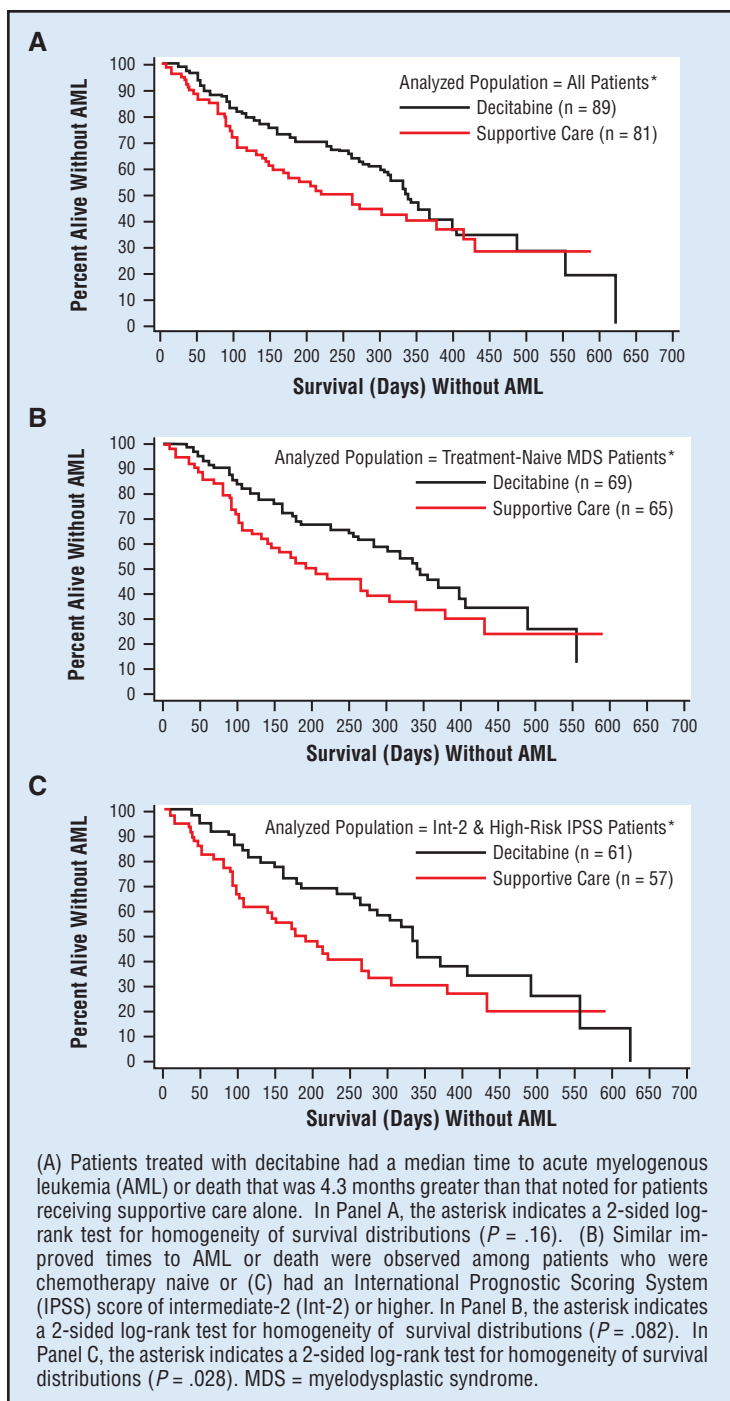


Fig 5. — Survival in patients with MDS treated with decitabine. From Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006;106:1794-1803. © John Wiley & Sons, Inc. Reprinted with permission.

rate of 38% with an overall median survival of 20 months, with 41% of patients alive at 2 years.⁴⁴

Randomized trials involving azacitidine and decitabine have demonstrated significant activity in MDS and prolongation of survival in higher-risk patients. Although study designs with these agents were not identical and cross-study comparisons are not feasible, it is apparent that azacitidine demonstrated a survival benefit compared with conventional care regimens that was still present at 2 years, which had not been achieved with previous studies. In lower-risk patients, the acceptable toxicity profile of the shortened 5-day regimen and the high rates of hematologic improvement make azacitidine an appealing option for those who are not candidates for other therapies. The data now position azacitidine as the preferred MTI in patients with higher-risk disease and also as a viable option in lower-risk patients.

Hematopoietic Stem Cell Transplantation

To date, the only known curative treatment for MDS is alloSCT.⁴⁵ Overall, historical data illustrates that approximately 40% of patients may be cured with alloSCT. Unfortunately, transplantation is feasible for only a select patient population due to advanced age, presence of medical comorbidities, and lack of donor availability. Patients who are less than 65 to 70 years of age, have a good performance status and comorbidity score, and have an HLA-matched donor are the best candidates for transplantation.^{46,47} However, alloSCT can cause a high incidence of morbidity from transplant-related complications (eg, graft-vs-host disease). The DFS rates ranged from 23% to 63% and nonrelapse mortality rates from 20% to 68% in several large prospective studies of more than 700 patients who received myeloablative regimens followed by stem cell rescue.⁴⁸ However, these statistics are no longer accurate since reduced-intensity conditioning (RIC) regimens and nonmyeloablative conditioning are altering the landscape of stem cell transplantation.

RIC regimens are characterized by reduced myelosuppression and an immune-mediated graft-versus leukemia (GvL) effect. These regimens often incorporate fludarabine for its immunosuppressive qualities, with or without cyclophosphamide, along with varying doses of alkylating agents or total body irradiation (TBI). By utilizing lower doses of conditioning chemotherapy or TBI, it is possible to decrease toxicities and reduce the morbidity and nonrelapse mortality while still allowing sustained engraftment. In addition, GvL may lower the risk of disease progression after transplantation.⁴⁹ Therefore, RIC regimens have fulfilled a niche in patients who would benefit from HSCT but would otherwise not be candidates for full myeloablative conditioning given their age and/or comorbidities.

Ho et al⁵⁰ reported their experience with using RIC HSCT in 62 patients with MDS and AML. At a median

follow-up of 474 days for sibling recipients and volunteer unrelated donor (VUD) recipients, 16 of 24 (67%) and 26 of 38 (68%) were alive, respectively. At 1 year, the nonrelapse mortality rates were 5% in sibling recipients and 21% in VUD recipients, and the DFS rates were 61% and 59%, respectively. DFS rates correlated strongly with IPSS risk category, with a DFS rate at 1 year of 86% for intermediate-1 patients, 63% for intermediate-2 patients, and 33% for high-risk patients. In addition, DFS rates correlated strongly with disease status at time of transplantation, with poorer outcomes in patients with relapsed/progressive disease or in PR.

More recently, outcomes of 148 patients with MDS or myeloproliferative disorder who received RIC followed by alloSCT were reported by Laport et al.⁵¹ At a median follow-up of 47 months, 25% of patients (37 of 148) were alive, with a median overall survival of 180 days and a relapse-free survival of 296 days. While transplant-related mortality is lower with RIC regimens, there is an increased propensity to cause relapse. Challenges facing RIC regimens include the diversity in available combinations and the lack of studies comparing standard-intensity with RIC regimens.

To address the optimal timing of SCT, Cutler et al⁵² 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 from diagnosis, but prior to leukemic progression. Analyses were performed across all IPSS categories with adjustments for QOL and then compared to data on nontransplant patients obtained from the International MDS Risk Analysis Workshop database. In lower-risk patients, delaying transplant maximized overall survival, whereas in intermediate-2 and high-risk patients, transplantation at diagnosis maximized overall survival. In the higher-risk groups, time delayed from diagnosis to transplant was associated with loss of survivorship. Although the Cutler model serves as a good generalization, it does not account for low-risk patients who are severely RBC- and platelet-transfusion dependent or are often neutropenic and require regular intravenous antibiotics. In addition, given the recent data with RIC regimens and reduction in treatment-related mortality, the Cutler model may overestimate the negative effects of SCT on survival in lower-risk patients since it is based on standard-intensity conditioning.

Data from de Witte et al⁴ suggested that survival and DFS of patients transplanted at an early stage (untreated refractory anemia, refractory anemia with ringed sideroblasts, or in first CR) were significantly better than the survival and DFS of patients transplanted at a later phase of the disease, ie, those with untreated refractory anemia with excess blasts (RAEB) or RAEB in transformation or those not in first or second CR. The impaired DFS for patients transplanted at an advanced phase of the dis-

ease was attributed to both the higher relapse risk and the higher incidence of treatment-related mortality.

Patient comorbidities were recently shown to be independent, individualized predictors of HSCT outcomes among patients with a variety of hematologic diseases. Sorror et al⁵³ investigated the role of comorbidities, along with other risk factors, in stratifying and comparing patients conditioned with myeloablative and nonmyeloablative regimens. Using a hematopoietic cell transplantation-specific comorbidity index (HCT-CI), patients were stratified into four risk groups incorporating the impacts of both comorbidities and disease risks. Incremental and corresponding increases in nonrelapse mortality were observed in patients with higher comorbidity scores and disease risk. Two-year overall survival and relapse-free survival rates were also markedly improved in patients with lower comorbidity scores and lower-risk disease, with 78% (myeloablative) and 70% (nonmyeloablative) of patients in group 1 surviving at 2 years and 24% (myeloablative) and 29% (nonmyeloablative) of group 4 patients being alive. It appeared that the type of preparative regimen prior to transplantation was not a significant factor across groups (Table 6).

In patients with higher-risk disease, it appears that delaying transplant maximizes survival and that RIC allows more patients to become candidates for HSCT. It is also becoming clear that age alone should not preclude patients from alloSCT, but comorbidity score and disease risk should be incorporated into the decision analysis and selection of patients for transplantation. Also, the use of pretransplant cytoreduction and disease burden may be key factors to consider. Studies have shown that patients with fewer blasts and minimal tumor burden at the time of transplant have a decreased rate of relapse compared to those patients with excess blasts.^{54,55} Future directions should focus on the poten-

tial to incorporate a disease-modifying MTI during screening and donor selection in order to further optimize long-term outcomes in this dynamic population.

Lenalidomide

Immunomodulatory drugs (IMiDs[®]) were investigated as potential MDS therapeutics based on their ability to alter the bone marrow environment and effect on altering the pathogenesis of disease.⁵⁶ Lenalidomide (CC-5013; Revlimid[®], Celgene Corp) is a second-generation IMiD[®] that possesses antiangiogenic activity, suppresses inflammatory cytokine release, and enhances EPO receptor signaling⁵⁷ while generating fewer toxicities than its predecessor, thalidomide (Thalomid[®], Celgene Corp).

Deletions within the long arm of chromosome 5 are one of the most frequent cytogenetic aberrations in MDS.⁵⁸ Lenalidomide was first studied in an open-label, single-center trial in 43 patients with MDS, 38 (88%) of whom had lower-risk disease. Overall, 32 of the 43 patients (74%) were transfusion-dependent and 13 of 43 (30%) had had no response to previous treatment with thalidomide. Patients received lenalidomide in one of three different dosing schedules: 25 mg daily, 10 mg daily, and 10 mg daily for 21 days of each 28-day cycle. Twenty-four patients (56%) achieved an erythroid response according to IWG criteria. Twenty-one of the responders (49%) achieved a major erythroid response, which was characterized as transfusion-independence for 8 weeks or longer or, in patients not transfusion-dependent, a rise in hemoglobin level of ≥ 2 g/dL sustained for at least 8 weeks. Out of 32 transfusion-dependent patients, 20 (63%) achieved freedom from transfusion. Of note, patients with del(5q) had a more marked response compared to patients with normal karyotypes or other cytogenetic abnormalities (83% vs 57% vs 12%, respectively). Cytogenetic response was

Table 6. — Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) Scores and Disease Status Impact on Outcomes Following AlloSCT

Risk Category	Type of Conditioning	Nonrelapse Mortality (%)	Relapse (%)	Overall Survival (%)	Relapse-Free Survival (%)
Group 1 (HCT-CI scores 0–2 and low-risk disease)	Myeloablative, n = 138	11	14	78	75
	Nonmyeloablative, n = 28	4	22	70	63
Group 2 (HCT-CI scores 0–2 and intermediate and high-risk disease)	Myeloablative, n = 176	24	34	51	43
	Nonmyeloablative, n = 34	3	42	57	56
Group 3 (HCT-CI scores ≥ 3 and low-risk disease)	Myeloablative, n = 52	32	27	45	41
	Nonmyeloablative, n = 19	27	37	41	36
Group 4 (HCT-CI scores ≥ 3 and intermediate- and high-risk disease)	Myeloablative, n = 86	46	34	24	20
	Nonmyeloablative, n = 44	29	49	29	23

From Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status-based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2007;25:4246-4254. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

observed in 55% (11 of 20) of patients, defined as a 50% or greater reduction in the number of abnormal metaphases. A complete cytogenetic response was observed in 10 patients, 9 of whom had del(5q).⁵⁹

The MDS-003 clinical trial⁶⁰ was the pivotal study that evaluated the efficacy of lenalidomide on treatment response in 148 lower-risk, transfusion-dependent patients with del(5q) with or without other cytogenetic abnormalities. Among patients who received lenalidomide, 76% had reduced transfusion requirements of 50% or greater, and 67% of those patients became transfusion-independent with an accompanying rise in hemoglobin of 1 g/dL or more. The median time to onset of transfusion independence was 4.6 weeks, and the median duration of transfusion independence had not been reached at 2 years of follow-up. Among 85 evaluable patients, 73% demonstrated cytogenetic improvement. A direct correlation between cytogenetic response and transfusion independence was noted, with all patients who experienced cytogenetic improvement achieving freedom from transfusion.

Cytogenetic response correlated with hematologic response and was not significantly different among patients with isolated del(5q) (49 of 64; 77%), del(5q) +1 (10 of 15; 67%) and del(5q) plus greater than 1 additional chromosomal abnormality (3 of 6; 50%), although the greatest number of patients were those with isolated 5q deletion. The 4-year survival from time of diagnosis — adjusted for time between diagnosis and initiation of lenalidomide — was no different between patients with isolated del(5q) and those with del(5q) and 1 or more additional chromosomal abnormalities.⁴⁹ Long-term follow-up and analysis of patients with del(5q) treated with lenalidomide yielded a durable response to the drug, with median transfusion independence of 2.2 years and some patients exceeding 5 years. Cytogenetic response had the greater predictive power for extended survival and freedom from disease progression (HR = 5.295; $P < .001$).⁶¹ Although there has been promising response in patients with del(5q) and an additional cytogenetic abnormality, the total number of these patients treated with lenalidomide is still relatively small.

Although the exact mechanism of action of lenalidomide in MDS is not known, there are several hypotheses as to its activity in this disease. It is believed that lenalidomide directly targets the clone carrying the del(5q), given the complete rates of hematologic and cytogenetic responses and normalization of platelet counts in responders. Lenalidomide also affects a broad range of ligand-induced responses such as vascular endothelial growth factor (VEGF), which contributes to myeloid precursor self-renewal while exacerbating ineffective erythropoiesis in erythroid progenitors. Lenalidomide may also enhance cell-mediated immunity through potentiation of the production of interleukin-2 and increasing cytotoxic T-cell response. Sekeres et al⁶²

performed multivariate analysis on two phase II trials and reported 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 link between suppression of the MDS clone and erythroid response. In patients without del(5q), multivariate analysis indicated that only the presence of thrombocytopenia at baseline independently predicted for transfusion independence. The specificity of lenalidomide on del(5q) can be explained by two hypothesized mechanisms: (1) selective inhibition of the function of protein(s) encoded by gene(s) on the 5q deleted region critical for cell survival, thus causing apoptosis due to haplo-insufficiency of these gene(s), or (2) stimulation and subsequent overexpression of possible tumor suppressor genes on the 5q common deleted regions. Development of an unrelated, previously undetected, transitory clone harboring the t(1:7) aberration occurred in a single patient with del(5q) treated with lenalidomide, which suggests that lenalidomide may not exhibit specificity for only the 5q- clone and that there may be a population of stem cells with a pre-5q- lesion (unpublished data, A. Mohamedali, MD, 2008).

Another hypothesis is that lenalidomide interferes with one of several proteins encoded by genes located in 5q that has a major role in cell survival. Gene expression profiling of erythroblasts from MDS with del(5q) treated with lenalidomide *in vitro* suggested that lenalidomide upregulates *SPARC* expression, a matrix-cellular protein with antiangiogenic and antiproliferative properties encoded by the 5q common deleted regions.^{63,64} Studies in *SPARC* null mice and comparison to patients with del(5q) suggest that *SPARC* may not be the key gene responsible for the 5q- phenotype, but it may have a cooperative role with other genes for 5q- to be expressed. Currently, the only candidate gene to correct the 5q- phenotype by reexpression in CD34+ cells from 5q- syndrome patients has been the RPS14 gene.⁵⁴

By specifically targeting the 5q clone, lenalidomide may alter the disease course in addition to inducing hematologic and cytogenetic response. In the higher-risk population — those with higher blast percentages and additional cytogenetic abnormalities on top of del(5q) — lenalidomide appears to be effective and may possibly extend survival and alter the biology of disease in responding patients. However, further clinical studies are required to confirm this hypothesis.

Effect of Timing of Therapy on Outcomes

Recent data from clinical trials have demonstrated the possibility of extending survival in patients with higher-risk disease, which until has been a challenging population to treat and a group with poor prognosis. The MTIs, particularly azacitidine, have established that valid endpoints should include prolonging time to leukemic

transformation and improving overall survival. Compared to patients with lower-risk disease, those with intermediate-2 or high-risk MDS are more likely to succumb to disease progression rather than MDS-related complications. As such, the data with the MTIs suggest that earlier treatment may have the potential to alter disease biology earlier in the patient's clinical course and make a greater impact on disease modification, survival, and possibly QOL. As demonstrated by Silverman et al,³³ patients who were treated initially with azacitidine were conferred a survival advantage compared with those who crossed over to the azacitidine arm after receiving BSC first.

Although long-term survival data for lenalidomide are not yet available, promising results with this drug and its disease-modifying effects also suggest impact on survival. Currently available data with lenalidomide and the MTIs are shifting the emphasis away from supportive care alone to active treatment and are altering the approach to patients with MDS. For both lower- and higher-risk patients, it may be possible to treat earlier, alter the course of disease, prevent AML transformation, and extend survival.

Conclusions

In the last decade, the approach to treating patients with myelodysplasia has undergone an evolution with the FDA approval of new therapeutic options that add to the armamentarium of MDS treatments. Historically, treatment goals have varied based on patient risk category, with modification of disease reserved for patients in the higher-risk population and response rates being a primary endpoint. Recent data suggest that the treatment paradigm be reevaluated to focus on prolonging time to leukemic transformation and extending survival while improving QOL. The disease-modifying activity of lenalidomide and the ability of the MTIs to prolong survival are shifting the focus away from response rates alone. Azacitidine has demonstrated a sustained impact on overall survival, separating itself from other available therapies and providing a basis for revising treatment goals. In addition, data suggest that treatment with these therapeutics in patients with lower-risk disease may further extend survival by altering the biology of MDS. The new treatment paradigm should aim for prolonging leukemic-free transformation and extending survival while optimizing QOL and maintaining hematologic and cytogenetic response.

Disclosures

Dr Mufti has served as an advisory board member and consultant for Celgene Corp, Amgen Inc, and Genzyme Corp, and as an advisory board member for Pharmion Corp (now Celgene), and Johnson & Johnson Services, Inc.

Dr Chen reports no significant relationship with the companies/organizations whose products or services may be referenced in this article.

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