Myelodysplastic Syndromes:
DIAGNOSIS AND EMERGING THERAPIES

An Accredited Publication for Health Care Professionals

Editors

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Myelodysplastic Syndromes: Diagnosis and Emerging Therapies

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This activity has been designated to meet the educational needs of hematologists and physicians involved in the management of patients with myelodysplastic syndromes.

MEDIA

Monograph

STATEMENT OF NEED/DESCRIPTION

The myelodysplastic syndromes (MDS) are recognized as a growing disease burden in oncology care within the United States. The increasing incidence of MDS is attributable in large part to the aging of the American population. Improved characterization of these disorders by prognostic variables and pathologic and biologic features has given rise to the development of an exciting array of novel therapeutics and the first FDA-approved agent for the treatment of this disease. For the first time in the history of this disease, physicians have access to a therapeutic agent with the capacity to impact the natural history of the disease. Understanding the selection of patients, proper counseling on side effects, and the potential for development of combination treatments is paramount for optimizing patient outcomes and further drug development for the treatment of MDS.

LEARNING OBJECTIVES

Upon completion of this activity, the participant will be able to:

- Describe myelodysplastic syndromes (MDSs) by prognosis and pathologic features.
- Discuss the goals of therapy for MDS.
- Describe the biology of MDS and translation to new therapeutics.
- Identify the importance of chromatin remodeling as a target for MDS therapy.

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Myelodysplastic Syndromes: Diagnosis and Emerging Therapies

Steven D. Gore and Alan F. List

INTRODUCTION

The myelodysplastic syndromes (MDSs) comprise a hematologically diverse group of stem cell malignancies that have challenged hematologists for decades because of their varied disease course and lack of a taxonomy with therapeutic relevance. In the last decade rapid progress has been made in understanding MDS, and promising new treatments are now emerging that offer a realistic alternative to supportive transfusion therapy. Particularly promising are investigations elucidating the role of epigenetic gene regulation in MDS, which provided the premise for clinical investigation of DNA methylation inhibition. Azacitidine, a DNA methyltransferase inhibitor, restores differentiation capacity in acute myeloid leukemia (AML) cell lines and in patients with poor-risk MDS [Leone 2003, Silverman 2003]. In May 2004, azacitidine was approved by the US Food and Drug Administration (FDA) as the first therapeutic for the treatment of MDS.

The material presented herein is intended to provide physicians and other health care professionals with information that will assist them in treating patients with MDS and in sharing with their patients the hope and optimism that is currently felt by those who are leading the battle against MDS through clinical and translational research.

CHARACTERIZING MDS

The MDSs comprise a spectrum of stem cell malignancies that give rise to ineffective hematopoiesis involving one or more myeloid lineages. Although they are heterogeneous in presentation and natural history, the MDSs are all characterized by progressive cytopenias, functional abnormalities, and bone marrow hypercellularity. Ineffective hematopoiesis in MDS is associated with accelerated apoptosis, with progressive impairment in maturation potential. Currently allogeneic hematopoietic stem cell transplantation, through which the patient's diseased stem cells are replaced by healthy donor cells, is the only potentially curative treatment. Unfortunately this option is a realistic alternative for few MDS patients given the advanced median age of affected patients [Kurzrock 2002, Mufti 2003]. MDS progresses to acute myeloid leukemia (AML) in up to 35% of cases, but even in its absence, these disorders remain lethal owing largely to infectious and hemorrhagic complications as well as sequelae of iron overload. An overview of MDS characteristics is presented in Table 1.

The morphological classification of MDS began as a means of identifying these disorders with reliable specificity and standardizing description of study populations. Recent modifications incorporate features with added prognostic discrimination. Pathologic and prognostic distinction of MDS is important in guiding disease management and defining goals of treatment [List 2003]. In higher-risk disease, the immediate focus of treatment is to extend survival and delay leukemia evolution, whereas in lower-risk disease in which survival is comparatively long, treatment should restore effective hematopoiesis. The newly approved DNA methyltransferase inhibitor azacitidine has been shown to be effective in treating both low- and higher-risk MDS in clinical trials [Silverman 1993, 1994, 2002].

The first case reports of refractory anemia now recognized as MDS date back as early as 1913. The patients described in these reports experienced fatigue, with clinical findings of pallor and anemia unresponsive to treatment, accompanied by bone marrow hypercellularity. The patients in these reports succumbed to complications of progressive cytopenias, eg, infection or acute leukemia. In 1973,

Table 1. Overview of Characteristics of MDS*

• 15,000-25,000 new cases/year
• Median age >60 (70% >50 years)
• M > F
• Clonal disorder: multilineage hematopoietic progenitor
• Ineffective hematopoiesis with peripheral cytopenias
• Symptoms reflect cytopenias (ie, anemia, infection, bruising, hemmorhage)
• Bone marrow failure:
-Majority succumb from infection or bleeding
-Transformation to AML in 35% to 40%
• 50% mortality within 3 to 4 years
• Best supportive care has been the standard treatment

*McNally 1997, Miller 2000, Komrokji 2003, Steensma 2003, Hamblin 2004.

the first literature review of the syndrome referred to it as "preleukemic anemia" [Saarni 1973].

MDS CLASSIFICATION SYSTEMS

The French-American-British System

From 1974 to 1975 a group of hematologists and pathologists, the French-American-British (FAB) Cooperative Group, developed the first systematic nomenclature for the classification of acute leukemias [Phelan 2002]. In a 1976 report, [Bennett 1976] the FAB group identified 2 broad categories of "dysmyelopoietic syndrome," refractory anemia with excess of blasts and chronic myelomonocytic leukemia. In 1982 the FAB group revised this schema to produce the current FAB classification of MDS [Bennett 1982]. Based on specific thresholds in blast percentage, identification of ringed sideroblasts and/or monocytosis, the FAB identified 5 morphologic subtypes of MDS (Table 2 and Figure 1):

- Refractory anemia (RA)
- RA with ringed sideroblasts (RARS)
- RA with excess blasts (RAEB)
- RAEB in transformation (RAEB-t)
- Chronic myelomonocytic leukemia (CMML)

The International Prognostic Scoring System

In an attempt to improve upon the prognostic power of the morphologic classification system, an International MDS Risk Analysis Workshop analyzed numerous prognostic features to define independent variables influencing the natural history of

Table 2. French-American-British Classification System for MDS

Name (Abbreviation)	BM Blast	PB Blasts	RS
Refractory anemia (RA)	0%-5%	0%	No
Refractory anemia with ringed sideroblasts (RARS)	0%-5%	0%	Yes
Refractory anemia with excess blasts (RAEB)	6%-19%	1%-4%	+/–
Refractory anemia with excess blasts in transformation (RAEBT)	20%-29%	5%-29%	+/–

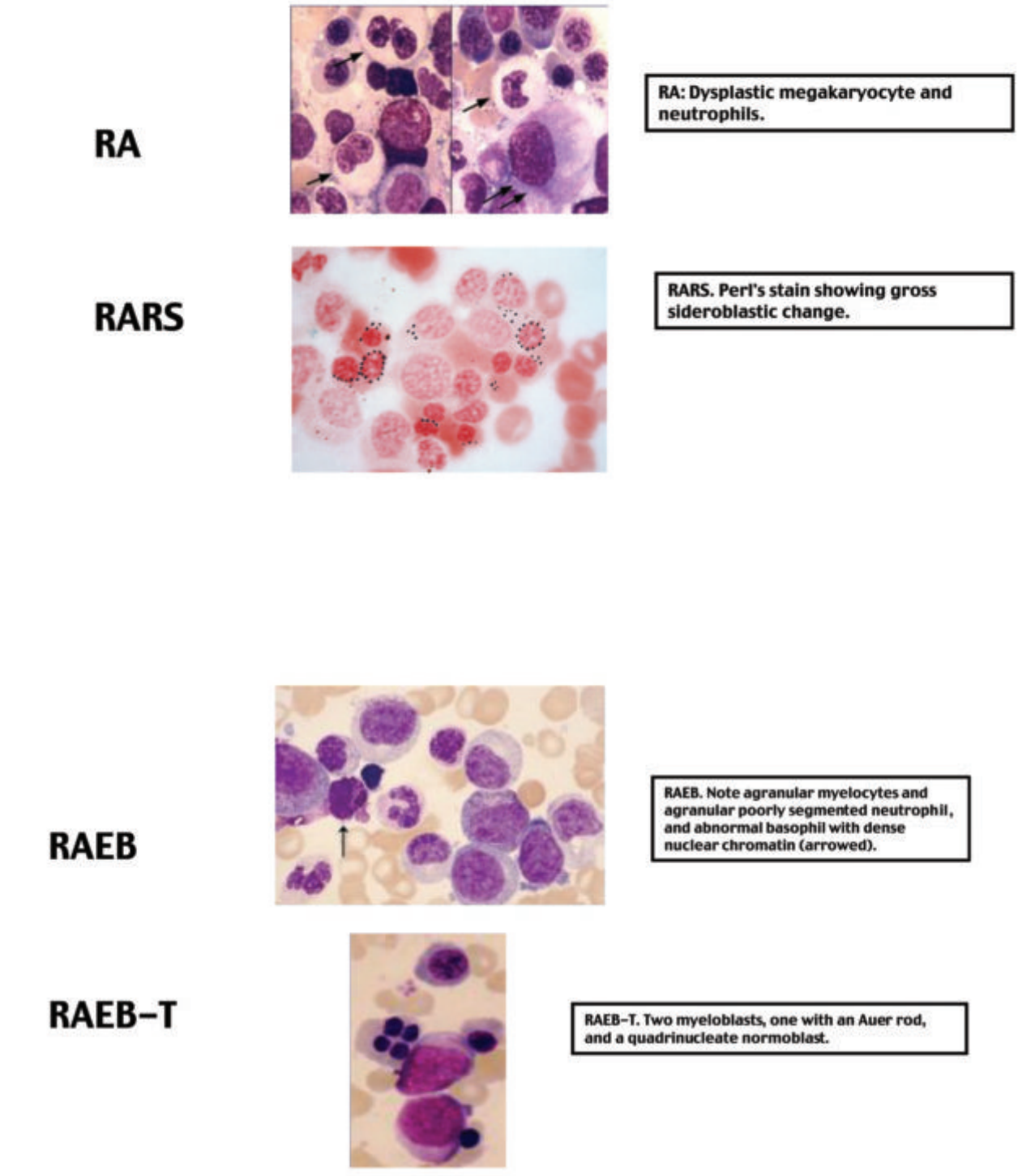

Figure 1. Slides showing pathological characteristics of cells related to French-American-British classification subtypes: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), and RAEB in transformation (RAEB-T).

Table 3. Data Selection Criteria for Development of the International Prognostic Scoring System

- Based on outcomes for 816 untreated de novo MDS patients from large institutional or national trials
- Proliferative CMML (WBC >12,000/μL) excluded
- Intent to define patients with similar outcomes based on risk factors despite disparate morphology
- Risk factors used: cytogenetics, FAB, % blasts, cytopenias, age, sex, and 2 previous scoring systems

the disease. The International Prognostic Scoring System (IPSS) reported in 1997 was the product of this analysis, which included data from more than 800 patients treated by supportive care [Greenberg 1997]. The IPSS combined cytogenetic, morphological, and clinical data from 7 large previously reported studies, with variables selected according to criteria listed in Table 3. The IPSS was formulated through a global analysis and reevaluation of prognostic variables that included the use of prognostically weighted bone marrow cytogenetic categories (Table 4). Three independent prognostic variables were identified that impacted both probability of AML progression and survival: cytogenetic pattern, percentage of bone marrow myeloblasts, and number of cytopenias. Four prognostically distinct groups are identified in the IPSS system (Table 5):

- High risk
- Intermediate-2 risk
- Intermediate-1 risk
- Low risk

The World Health Organization System

The World Health Organization (WHO) attempted to build on previously developed prognostic models with their proposed modifications to the FAB morphologic classification in 2001 [Brunning 2001]. The WHO system preserves 3 elements of the FAB system while introducing novel elements such as number of dysplastic lineages, more refined discrimination in blast percentage, and 1 favorable cytogenetic abnormality recognized by the IPSS system [Bennett 2003] (Table 6). Six subtypes of adult MDS are recognized in the WHO system:

- RARS/RA with dysplasia limited to erythroids
- Refractory cytopenias with erythroid and nonerythroid dysplasia and <5% blasts (ie, refractory cytopenia with multilineage dysplasia [RCMD])
- RAEB 1 (5%-10% blasts)
- RAEB 2 (11%-19% blasts)
- 5q-syndrome, characterized by deletion of the long arm of chromosome 5 as the sole cytogenetic abnormality, characteristic abnormal megakaryocyte morphology, a low frequency of transformation to acute leukemia, and relatively good prognosis
- Unclassified MDS, defined by single-lineage, nonerythroid dysplasia

The distinguishing features from the FAB system include (1) distinction of RA and RARS with single

Table 4. Bone Marrow Cytogenetic Classification Definitions Used in the International Prognostic Scoring System

Cytopenia	Neutrophils <1500/μL
	Hemoglobin <10 g/dL
	Platelets <100,000/μL
Cytogenetic	
Good:	Normal or –5q, -Y, -20q as sole abnormalities
Intermediate:	Other abnormalities
Poor:	–7, complex (≥3 abnormalities)

Table 5. International Prognostic Scoring System Variables and Risk Group Classification

Prognostic Variables	0	0.5	1.0	1.5	2.0
% Marrow blasts	<5	5-10		11-20	21-30
Karyotype	Good	Int	Poor		
Cytopenia	0/1	2/3			

Risk Group Classification	Risk	Score
	Low	0
	Int 1	0.5-1.0
	Int 2	1.5-2.0
	High	≥2.5

lineage dysplasia, (2) separation of refractory cytopenias with <5% blasts and accompanying nonerythroid dysplasia, (3) separation of RAEB into 2 subtypes based on blast percentage, (4) addition of 5q-syndrome as a distinct morphologic subtype of MDS, (5) creation of an unclassified MDS subtype that includes those cases with single nonerythroid dysplasia, and (6) reclassification of RAEB-t and chronic myelomonocytic leukemia (CMML) as new non-MDS categories. CMML is regarded as a myelodysplastic/myeloproliferative disorder, and RAEB-t is eliminated by lowering the threshold for AML to ≥20% blasts. The WHO created a new category of AML with trilineage dysplasia (AML-TLD) [Bennett 2003], which incorporates patients previously categorized as RAEB-t as well as patients who present with AML with no documented history of MDS but whose underlying hematopoiesis is dysplastic and whose disease prognosis is more similar to that of RAEB-t than to de novo AML.

The WHO recommendations for diagnostic tests for MDS are, in order of priority and cost (from least to most expensive): Romanowsky stain

Table 6. Comparison of the French-American-British (FAB) and World Health Organization (WHO) Classification Systems [Germing 2000]

FAB	WHO	Dysplasia(s)
RA	5q-syndrome	Erythropoietic
	RA	Erythropoietic
	RCMD	2-3 Lineages
	MDS-U	1 Lineage
RARS	RARS	Erythropoietic
	RCMD-RS	2-3 Lineages
RAEB	RAEB-1	1-3 Lineages
	RAEB-2	1-3 Lineages
RAEB-T	AML	

(Wright stain, Giemsa stain), bone marrow biopsy, cytochemistry (peroxidase, esterases), immunophenotyping (by flow cytometry or immunoperoxidase), cytogenetics, and molecular genetics. Applied properly, the least expensive method, Romanowsky stain, is generally sufficient for an accurate MDS diagnosis in 90% to 95% of cases [Bennett 2003]. However, it should be emphasized that cytogenetic analysis is necessary for assignment of an IPSS score, which is critical for determining patient prognosis.

The WHO system has continued to gain popularity worldwide. Controversy continues, particularly regarding the distinction between AML and MDS since the differentiation is based upon an arbitrary threshold in blast percentage [Cheson 2002, Young 2002]. Moreover, although one favorable cytogenetic abnormality was incorporated, unfavorable abnormalities with powerful prognostic utility were not considered. However, rather than dictating that RAEB-t cases should be treated as de novo AML with induction chemotherapy, which, as some have argued, is of limited utility for these patients, the reclassification of RAEB-t into AML-TLD encourages the study of RAEB-t and AML with MDS-like features (including cytogenetic abnormalities) separately from de novo AML, which is biologically and clinically very different.

MDS PREVALENCE AND EPIDEMIOLOGY

MDS has the highest annual incidence among hematological malignancies, with approximately 14,000 new cases diagnosed each year. Data from epidemiological studies conducted in Europe indicate that the true annual incidence ranges between 15,000 to 20,000 cases. The underestimation of case rate within the United States relates to lack of capture using traditional coding systems. Unfortunately, MDS is not recorded by the national tumor registry in the United States [Bennett 2003].

MDS incidence is increased with male sex, and exponentially rises with age above 50 years. Men have roughly double the incidence of MDS as women at any age, and incidence increases from 0.5 per 100,000 at <50 years of age to 89 per 100,000 at >80 years, making MDS by far the most common hematological malignancy in elderly individuals [Hamblin 2002].

An opinion poll published in 1991 indicated that most hematologists considered the real incidence of MDS to be increasing owing to improved diagnosis [Reizenstein 1991]. Many factors, both inherited and acquired, have been implicated in the pathogenesis of MDS (Table 7). Certain occupations and chemical and environmental leukemogens are associated with greater risk for development of MDS. Benzene is the best known of these agents, but many others are suspect—including pesticides, fertilizers, petrochemicals and exhaust, and tobacco smoke. At-risk occupations include painters, coal miners, embalmers, shoe and garage workers, hairdressers and cosmetologists, tanker crews, and laboratory technicians [Smith 2002].

A special category of treatment-related MDS, which occurs in patients who have received prior cancer therapy, holds an overall worse prognosis than non–treatment-related, or primary MDS, counterparts. This prognostic distinction is closely linked to the unfavorable chromosomal abnormalities characteristic of treatment-related or secondary MDS [Aul 2002].

MDS in pediatric patients differs from adult syndromes. The incidence of MDS in children is quite low (overall 3.6/million) and, unlike the adult disease, risk inversely correlates with age and is therefore highest among the youngest individuals. Cytogenetic abnormalities are far more common (60%-70%). Moreover, pediatric subtypes such as juvenile myelomonocytic leukemia, myeloid leukemia in Down syndrome, and nonclonal dysplastic disorders have overlapping features, making differential diagnosis challenging. In contrast to elderly individuals, the goal of treatment is cure rather than palliation for most children and younger adults. The classification systems developed for adult MDS offer less discrimination for children. Given these differences in treatment goals and disease biology, separate prognostic stratification has been proposed [Hasle 2002].

MDS PATHOPHYSIOLOGY

The pathophysiology of MDS involves abnormal regulation of cellular proliferation, maturation, and survival. An array of intrinsic and extrinsic factors contribute to or amplify the pathobiology of this complex disorder (Figure 2). MDS is believed to arise and progress as a result of cumulative genomic alterations that promote abnormal cell growth. The initial step may involve changes in cell cycle checkpoint regulation resulting in uncon-

Table 7. Factors that May Be Associated with Predisposition to Development of MDS*

Acquired	Heritable
• Senescence	• Constitutional genetic disorder
	Trisomy 8 mosaicism
	Familial monosomy 7
• Mutagen/genotoxic stress	• Neurofibromatosis 1
Therapeutic	• Embryonal dysgenesis (del1 2p)
Alkylators, Topo-II agents	• Congenital neutropenia
β-Emitters (^{32}P), autoSCT	Kostmann, Schwachman-Diamond
Environmental/occupational (benzene)	• DNA repair deficiencies
Tobacco	Fanconi anemia, AT, Bloom syndrome
Aplastic anemia	• Pharmacogenomic polymorphisims (GSTq1-null)
PNH	

*SCT indicates stem cell transplantation; AT, ataxia telangiectasia; PNH, paroxysmal nocturnal hemoglobinurea.

trolled hematopoietic progenitor proliferation (Figure 3) [List 2004]. Tumor promotion or clonal expansion leads to ineffective hematopoiesis arising from an accelerated apoptotic rate. Disease progression ensues with impaired maturation capacity that gives rise to gradual accumulation of myeloblasts. Current nomenclature denotes AML-TLD when marrow blasts exceed 20%. This advanced stage is associated with a decline of programmed cell death and enhanced survival of leukemic myeloblasts. Although proposed mechanisms of MDS pathophysiology are being investigated, the precise molecular scenario remains to be established; meanwhile, lack of understanding of the fundamental genetic and biological abnormalities in MDS progenitor cells, as well as the biological abnormalities that lead to characteristic phenotypic abnormalities in more differentiated cells, continues to hamper the development of molecularly targeted therapies for the treatment of MDS [Mufti 2003].

Apoptosis is a common cause of cell death in MDS that manifests itself clinically as ineffective hematopoiesis. Evidence indicates that clonal expansion and apoptotic response arise from an interaction between the malignant clone and the microenvironment [Mufti 2003]. The cytokine tumor necrosis factor (TNF)-α is a diffusible amplifier of the MDS phenotype. Apoptotic index is greatest in lower risk or earlier stages of the disease, declining as the disease progresses. In earlier stages of MDS, survival of maturing cells is prematurely extinguished by apoptosis to give rise to peripheral cytopenias [Raza 1996, Young 2002].

The genomic changes accumulated by the clone are likely secondary events that in some cases may confer a proliferative advantage, alter apoptosis threshold, or further impair differentiation. During the last decade much progress has been made in understanding the diversity of biological effectors that underlie ineffective hematopoiesis and leukemic transformation in MDS. Molecular targets have been discovered that are integral to propagation of the malignant phenotype, disease progression, and disease-specific survival signals.

Methylation of DNA is a common epigenetic modification that plays an important role in the control of gene expression in mammalian cells. Hypermethylation of promoter cytosine residues and consequent inactivation of regulatory genes appear to have a pathogenetic role in cancer development. Recent data have shown that DNA methylation is the most frequent heritable molecular change in hematopoietic neoplasms. High-risk MDS shows a high prevalence of inactivation of one tumor-suppressor gene in particular ($p15^{INK4b}$) by

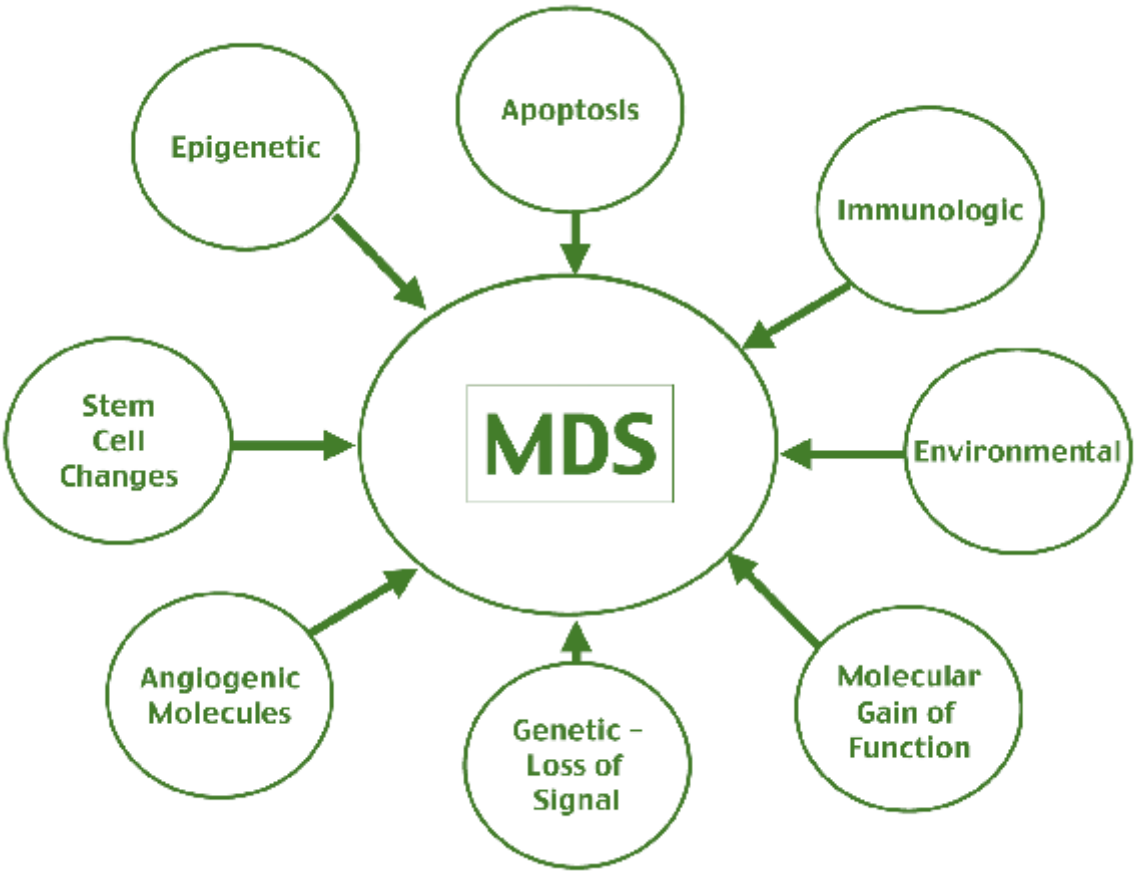

Figure 2. Factors contributing to the pathophysiology of MDS.

promoter hypermethylation. Preliminary data indicate that irreversible DNA methyltransferase inhibitors, such as azacitidine and 5-aza-2′-deoxycytidine (decitabine), offer a promising therapeutic option for the treatment of MDS and represent the first nonintensive treatment that may impact the natural history of disease [Leone 2003].

TREATMENT OF MDS

Treatment Goals

Modern principles of MDS treatment place individualization of therapy as a priority, taking into account natural history of disease, biological features, patient preference, and toxicity limitations. Currently the only curative treatment is allogeneic hematopoietic stem cell transplantation. For the vast majority of individuals in which curative treatment is not an option, the goals include improvement in hematopoiesis, control of infection, and prolongation of survival while preserving quality of life.

Management Considerations

Management decisions must first be guided by estimation, obtained using the IPSS, of the expected survival for the specific individual [List 2003]. Standardized response criteria were established by an International Working Group (IWG) in 1999 to provide uniform measures of clinical benefit for new agents in development that are detailed in Table 8 [Cheson 2000]. Because MDS treatment regimens may not alter survival, but instead focus on amelioration of cytopenias and infection, preservation or improvement in quality of life is paramount. The IWG guidelines recognize this, recommending the use of validated assessment of 5 specific domains of quality of life in clinical trials: physical, functional, emotional, social, and spiritual. An assessment tool that has been used extensively with reproducible results is the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system, which includes the Functional Assessment of Cancer Therapy (FACT) [Webster 2003].

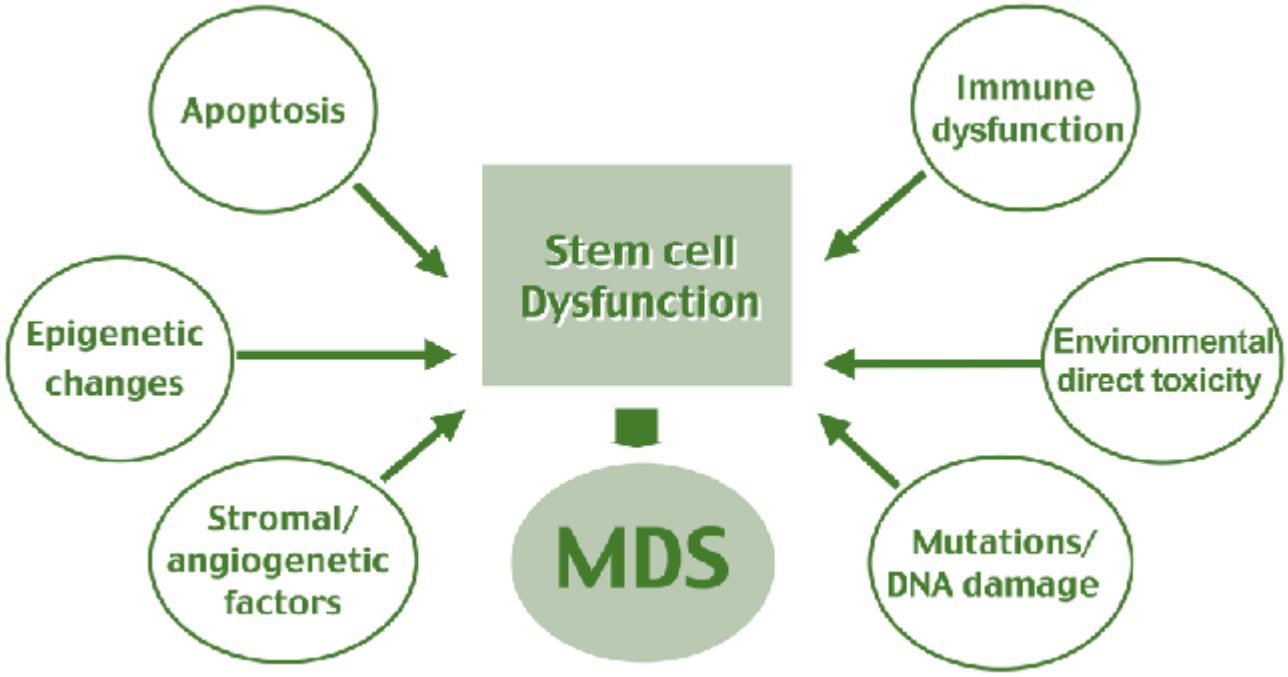

Figure 3. Factors leading to hematopoietic stem cell damage, which in turn leads to MDS.

THERAPEUTIC OPTIONS FOR MDS

Until recently treatment options for MDS were limited to best supportive care, recombinant cytokines, chemotherapy, and stem cell transplantation. With the approval of azacitidine the treatment algorithm must be reevaluated.

Best Supportive Care

Best supportive care is aimed at controlling the symptoms of MDS, preventing and fighting infections, and improving the quality of life of patients with MDS. A summary of best supportive care strategies is presented in Table 9.

Transfusion. The majority of MDS patients will require transfusion support. Transfusion thresholds are based on symptoms, which are influenced by comorbidities. In patients requiring multiple transfusions there is increased risk of alloimmunization and iron overload, and consequent need for iron chelation with deferoxamine to prevent iron overload.

Anemia. Anemia is the most common cytopenia and often has a severe adverse impact on quality of life. Response to recombinant erythropoietin (EPO) can be expected in approximately 20% of patients but infrequently leads to transfusion independence. Anemic MDS patients with low endogenous EPO levels (≤200 U/mL), marrow blasts <10%, and a low transfusion requirement (<2 U/mo) are most likely to have a good response to EPO. Patients should be monitored for the need for iron replacement/supplementation.

Combined administration of myeloid growth factors with EPO increases the response rate to 35% to 40%. In a study of 98 patients, administration of 0.3 to 3 µg/kg per day granulocyte colony-stimulating factor (G-CSF) with 60 to 300 U/kg per day of EPO for 1 week resulted in either a reduction in transfusions or increase in hemoglobin levels of ≥1.5 g/dL in all patients [Hellstrom-Lindberg 1997].

Neutropenia and Infections. Neutropenia occurs in >35% of MDS patients. Only 10% of patients have infection as a presenting or recurring problem, so routine antibacterial prophylaxis is not indicated. Patient education for neutropenic fever precautions, however, is essential.

G-CSF and granulocyte-macrophage–CSF (GM-CSF) have shown effectiveness in promoting neutrophil production in >75% of patients. Patients with

Table 8. International Working Group Treatment Response Criteria for MDS [Cheson 2000]

Complete remission	<5% BM blasts, no dysplasia; Hgb >11; PMN >1.5, PLT >100K
Partial remission	Same as CR; ↓ blasts by 50%
Hematologic improvements (HI)	RBC (HI-E):
	Major: treatment-independent or >2 g/dL ↑ in Hgb;
	Minor: 50% ↓ in tx req 1-2 g/dL ↑ in Hgb
	PLT (HI-P):
	Major: PLT tx indep or ↑ by 30K if <100K at baseline;
	Minor: 50% ↑ PLT count (of at least 10K) if baseline <100K.
	PMN (HI-N):
	Major: if ANC <1500, a 100% ↑ or 500/µL ↑, whichever greater;
	Minor: if ANC <1500, ANC ↑ by 100%, but <500/µL

an absolute neutrophil count <250 can be expected to have a poorer response. Routine use of G-CSF and GM-CSF have not been shown to improve survival of neutropenic MDS patients.

Thrombocytopenia. Medically significant thrombocytopenias affect 25% to 45% of MDS patients. In contrast, thrombocytosis more often occurs in association with the 5q-syndrome. Platelet dysfunction is common and may manifest as prolonged bleeding time, abnormal platelet aggregation results, and bleeding unrelated to platelet count. The use of thrombopoietic cytokines (eg, thrombopoietin, megakaryocyte growth and development factor, interleukin-11) has not as yet been shown to impact transfusion requirements.

Standard Therapy

Chemotherapy. Induction chemotherapy has been applied in the treatment of higher-risk MDS because of the biologic overlap with AML [Estey 1987]. However, although chemotherapy is reasonably well tolerated in patients <60 years old, response rates for nonselected patients range from 15% to 51%. Generally, patients with MDS or MDS/AML have lower complete response rates than patients with de novo AML treated with similar regimens. The higher failure rate in MDS has been attributed to longer duration of hypoplasia after chemotherapy and higher intrinsic drug resistance. When remission is achieved, it is difficult to maintain without transplantation [de Witte 2002].

Gemtuzimab ozogamicin, a humanized anti-CD33 antibody linked to calicheamycin, is approved for the treatment of elderly AML in first relapse. Preliminary investigations indicate that gemtuzimab has lower activity as a single agent in MDS, perhaps owing to the inherent drug resistance [Garcia-Manero 2002].

Bone Marrow Transplantation. Myeloablation followed by matched allogeneic stem cell transplantation is the only treatment that consistently cures adult MDS. Over the 15 years that allogeneic transplantation has been used to treat MDS, patient outcomes have improved, largely because of improved supportive care and histocompatibility matching. Disease-free survival rates range from 23% to 63% depending upon IPSS category, age, and donor compatibility [de Witte 2002].

Reduction in the toxicity of conditioning regimens along with increase of immune suppression is a strategy that is expected to reduce early treatment-related mortality [de Witte 2002]. Nonmyeloablative regimens, designed to be less toxic and to take advantage of graft-versus-leukemia responses, are still under study and widen the range of patients for whom the procedure can be considered [Parker 2000, Anderson 2002]; however, long-term survival and disease-free survival data are not currently available for nonmyeloablative allogeneic stem cell transplantation.

Experience with autologous stem cell transplantation has been limited and largely disappointing. The

Table 9. Synopsis of Best Supportive Care Strategies for MDS [Cheson 2000]

Transfusions	Majority. Lower thresholds. Irradiated only in intensive chemo or transplant.
Anemia	Majority. EPO response 20% to 30%.
	Baseline EPO level. FE support critical.
	Response within 1 to 2 months.
	Weekly dosing not indicated. GCSF helpful in poor EPO responders with lowest levels.
Neutropenia/infections	>50% of patients. 30%-35% have ANC <1000-1500/µL yet only 10% have infection as a problem.
	No indication for routine antibacterial prophylaxis.
	CSF support improves ANC (75% of patients) but has no impact on overall survival.
Thrombocytopenia	25%-50% of patients.
	Thrombopoietic agents have no significant impact on transfusion needs: TPO, MGDF, & IL-11.

most recent update from the European Group for Blood and Marrow Transplantation reports a 46% 3-year disease-free survival resulting from autologous stem cell transplantation after CR in patients aged <20 years. For all patients the rate was 33% after a CR and 18% without CR. The best outcomes were obtained in patients with normal cytogenetics, some of whom may have had smoldering de novo AML rather than bona fide MDS. Treatment failure was mainly due to high relapse risk (55%) [de Witte 2002]. However, trial results to date do not support an overall benefit from AML-type induction chemotherapy prior to stem cell transplantation, especially considering the high morbidity and mortality of these regimens. The median age of patients enrolled in this study was <50 years, indicating this approach, if effective, is appropriate for a limited fraction of MDS patients. Moreover, timing, conditioning regimens, and the balance between the graft-versus-leukemia effect and graft-versus-host disease remain undefined [Hasle 2002].

NEWER APPROACHES TO MDS TREATMENT

Experimental therapies for MDS focus on newly discovered molecular mechanisms such as effectors of apoptosis. Agents under investigation include those targeting vascular endothelial growth factor (VEGF), tyrosine kinase inhibitors, arsenic trioxide, oral matrix metalloprotease inhibitors, farnesyl transferase inhibitors, and imatinib mesylate in select MDS subgroups. One DNA methyltransferase inhibitor, azacitidine, has been approved for treatment of MDS, and its congener, decitabine, has also been demonstrated to be effective against MDS in late-stage clinical trials [van den Bosch 2004]. These new treatments have shown promising results, offering hope for sustained benefit that may halt the relentless progression of MDS and its complications.

AGENTS UNDER INVESTIGATION

Immunomodulatory Agents

The immune system is now thought to mediate ineffective hematopoiesis and bone marrow failure in selected patients with MDS, analogous to its role in aplastic anemia. Approaches to immune modulation are generally aimed at down-regulating aberrant immune activity. Corticosteroids offer limited improvement with increased risk for infection and other side effects [Young 2002].

TNF-α is produced by medullary and splenic macrophages in MDS to promote proliferation and accelerate hematopoietic cell apoptosis [Young 2002]. There are several cell-surface receptors that bind TNF

and initiate apoptosis. One related receptor is the Fas/Fas-ligand complex, which is expressed in increased quantity in certain MDS subtypes [Young 2002]. Antilymphocyte and antithymocyte globulin (ALG and ATG) have produced durable improvements in blood counts and continue to be investigated in selected patient subgroups [Bowen 2002, Milojkovic 2002]. In a pilot study by Killick et al [2003] 10 of 20 evaluable patients (50%) with low-risk MDS (defined as <10% bone marrow blasts) responded to treatment with ATG and became transfusion independent; 8 of 13 patients (62%) with RA responded. The median duration of response was 15.5 months (2-42+ months) at the time of the report. Predictors of response include HLA-DR15 expression, younger age, and low transfusion requirements.

Antiangiogenic Agents

The observation of increased microvessel density, or neovascularity, in the bone marrow of MDS patients led to the rationale for targeting angiogenesis in MDS. VEGF is one of the best-characterized cytokines involved in the development of neoplastic angiogenesis. This angiogenic molecule is overexpressed and elaborated in concordance with its high-affinity, type III receptor tyrosine kinases in myeloid precursors in MDS and AML. Other cytokines that have been implicated include hepatocyte growth factor and basic fibroblast growth factor [List 2003].

Thalidomide, the first antiangiogenic agent to be evaluated for efficacy in MDS [Garcia-Manero 2002; Milojkovi 2002, List 2003], inhibits both TNF synthesis and angiogenic response and promotes cellular cytolytic immune response. Thalidomide treatment has produced erythroid responses in more than 18% of MDS patients. However, treatment is associated with excessive risks of neurological toxicity, particularly in elderly patients. Novel, more potent thalidomide analogues with improved toxicity profiles recently entered clinical investigations. CC5013 is a more potent immunomodulatory derivative of thalidomide that lacks the neurological toxicities of the parent compound. CC5013 inhibits trophic response to VEGF in myeloblasts and endothelial cells and promotes erythropoietin responsiveness in myelodysplastic clones. Among 36 MDS patients with symptomatic or transfusion-dependent anemia who completed 4 or more weeks of treatment with CC-5013, 24 (67%) experienced an erythroid response according to IWG criteria, with 21 patients experiencing sustained transfusion independence or a 2 g/dL or greater rise in hemoglobin [Mufti 2003].

Arsenicals such as arsenic trioxide (ATO) induce apoptosis by forming covalent bonds between proteins with available sulfhydryl groups, disrupting mitochondrial respiration to generate reactive oxygen species that activate the intrinsic pathway of apoptosis. Approved by the FDA for treatment of relapsed acute promyelocytic leukemia, ATO has antiproliferative effects in MDS and AML. Preliminary results of 3 clinical trials indicate that ATO has modest activity in both lower- and higher-risk MDS [List 2003, Mufti 2003].

MOLECULARLY TARGETED MDS THERAPY: DNA METHYLTRANSFERASE INHIBITORS

Cancer research has realized the importance of genomic changes, both in the genetic code itself and in the chemical composition of the DNA-histone complex. Reversible but heritable chemical changes in DNA, termed epigenetic, alter function without necessarily altering the nucleotide sequences. Among the epigenetic modifiers, DNA methyltransferase inhibitors were identified as particularly promising because of the ubiquitous finding of abnormal cytosine methylation in cancer cells. In clinical trials by the Cancer and Leukemia Study Group B (CALGB), the activity of the methyltransferase inhibitor azacitidine was definitively established [Silverman 1993, 1994, 2002, Mufti 2003].

Pharmacology

Abnormalities of cytosine methylation are some of the best-characterized and most common epigenetic changes in cancer cells. Genetic changes such as mutations and deletions are irreversible, but epigenetic changes that lead to altered gene expression are heritable but potentially reversible, a characteristic that makes them particularly attractive therapeutic targets. DNA methylation occurs within the cytosine-guanine dinucleotide (CpG), producing 5-methyl cytosine (5-mC). The DNA of neoplastic cells is characterized by global hypomethylation; dysregulation of DNA methyltransferase I, a key protein for the accurate maintenance of DNA methylation patterns in daughter cells; and regional hypermethylation of CpG dinucleotides in gene promoter regions. These CpG clusters, known as

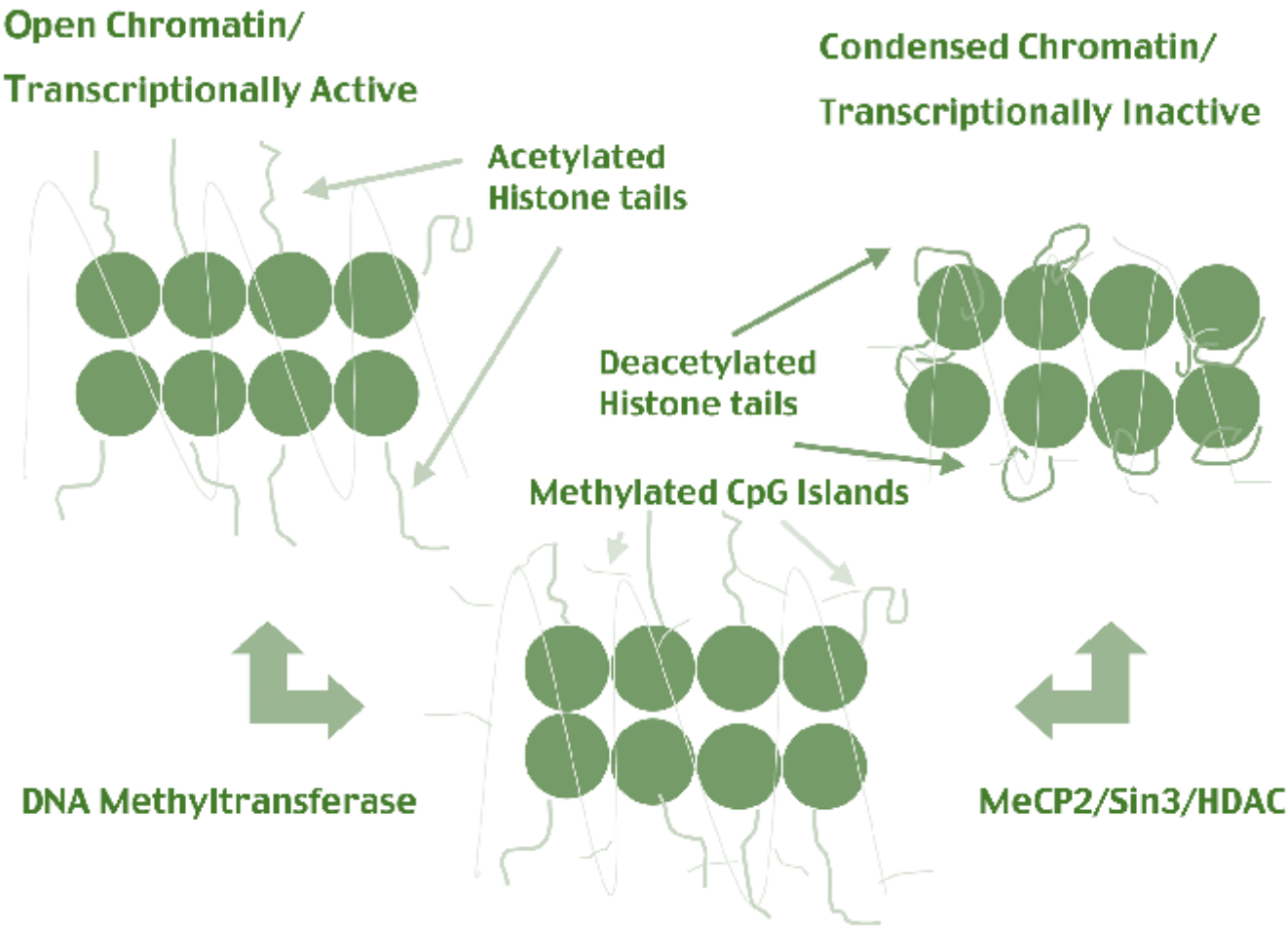

Figure 4. Schematic representation of the mechanism of chromatin inactivation by DNA methyltransferase. Cytosine-guanine dinucleotide (CpG) clusters, known as islands, are usually protected from methylation in normal cells but are often highly methylated in cancer cells. The methylated promoters are bound by specific proteins, such as MeCP2, which recruit transcriptional co-repressors. The co-repressor complexes lead to transcriptional silencing. The deacetylated lysine tails of the histones interact tightly with DNA, rendering the chromatin transcriptionally inactive.

CpG islands, are usually protected from methylation in normal cells, with important exceptions including regions of X chromosome inactivation and imprinted genes. In contrast, CpG islands are often highly methylated in cancer cells. The methylated promoters are bound by specific proteins, such as MeCP2, which recruit transcriptional co-repressors [Mufti 2003]. The co-repressor complexes lead to transcriptional silencing, at least in part through remodeling of nucleosomes into conformations that are prohibitive for transcription. This chromatin remodeling is due in part to histone deacetylases (HDAC). This process is represented schematically in Figure 4. Clinical investigation of HDAC inhibitors as therapeutic targets for the treatment of myeloid malignancies is ongoing.

Extensive studies have demonstrated that promoter methylation of a wide variety of cell regulatory genes in many cancers is associated with silencing of those genes. Promoter methylation of $p15^{INK4B}$ occurs in 60% to 75% of AML patients whose disease evolved from MDS or patients whose MDS carries a significantly higher risk of that evolution (>10% blasts). $p15^{INK4B}$ is an inhibitor of cyclin-dependent kinases 4 and 6, which regulate progression of cells from G1 to S phase [Leone 2002]. Methylation of promoter regions is associated with transcriptionally repressive chromatin and

leads to silencing of a variety of important genes including tumor suppressor genes in a variety of cancers, including myeloid malignancies. Both of the methylation-inhibiting drugs azacitidine and decitabine function at low doses to selectively reactivate suppressed genes.

Clinical Development

Hypomethylating agents were identified in clinical studies as promising cytotoxic nucleosides for the treatment of AML even before their impact on epigenetics was realized [Von Hoff 1976]. When abnormalities of cytosine methylation were identified and their prevalence ascertained, DNA methyltransferase inhibitors were identified as potential therapeutic agents.

In 1985, 2 phase II studies of the safety and efficacy of azacitidine in patients with poor-risk MDS were conducted within the CALGB. Treatment response was demonstrated in 49% of 43 assessable patients (12% in complete remission; 25%, partial remission; and 12%, improved), with an overall median survival of 13.3 months. Transfusion requirements were eliminated in 14 of 17 patients who experienced pathological response to azacitidine and had previously required red blood cell transfusions [Silverman 1993]. The second study showed comparable results with azacitidine administered subcutaneously [Silverman 1994].

On the basis of these findings, azacitidine was considered to have the potential to result in improved quality of life of MDS patients through better palliation, less fatigue, improved physical and social functioning, and less psychological distress. In 1993 a phase III randomized trial was initiated in the CALGB to test this hypothesis. One hundred ninety-one patients (mean age, 67.5 years; 69% male) were randomized to receive either azacitidine (75 mg/m^2 subcutaneously for 7 days every 4 weeks) or supportive care, with supportive care patients crossing over to azacitidine upon disease progression. Quality of life was assessed by centrally conducted telephone interviews. Patients receiving azacitidine experienced significantly greater improvement in fatigue, physical functioning, affect, and psychological distress over the course of the study period than those in the supportive care arm. Improvements in fatigue and psychological state in patients treated with azacitidine compared with those receiving supportive care were particularly striking for patients who remained in the study through at least day 106, corresponding to 4 cycles of azacitidine. Significant differences in quality of life between the 2 groups were maintained even after controlling for the number of red blood cell transfusions, and patients treated with azacitidine showed significantly greater treatment response and delayed time to transformation to AML or death compared with patients on supportive care (Table 10). Based on these results, azacitidine was determined to be an important treatment option for MDS [Kornblith 2002, Silverman 2002], and at a recommended daily starting dose of 75 mg/m^2 administered subcutaneously for 7 days, every 4 weeks, received FDA approval in May 2004 for treatment of patients with all 5 FAB subtypes of MDS.

Table 10. Analysis of Patient Response to Supportive Care (SC) and Azacitidine (AZA) in a Multicenter Randomized Controlled Clinical Trial [Silverman 2002]

	SC	AZA	Crossover
No. evaluated	92	99	49
CR	0 (0%)	7 (7%)*	5 (10%)
PR	0 (0%)	15 (16%)†	2 (4%)
Improved	5 (5%)	38 (37%)†	16 (36%)
Total	5 (5%)	60 (60%)†	23 (47%)

*$P < 0.01$

†$P < 0.001$

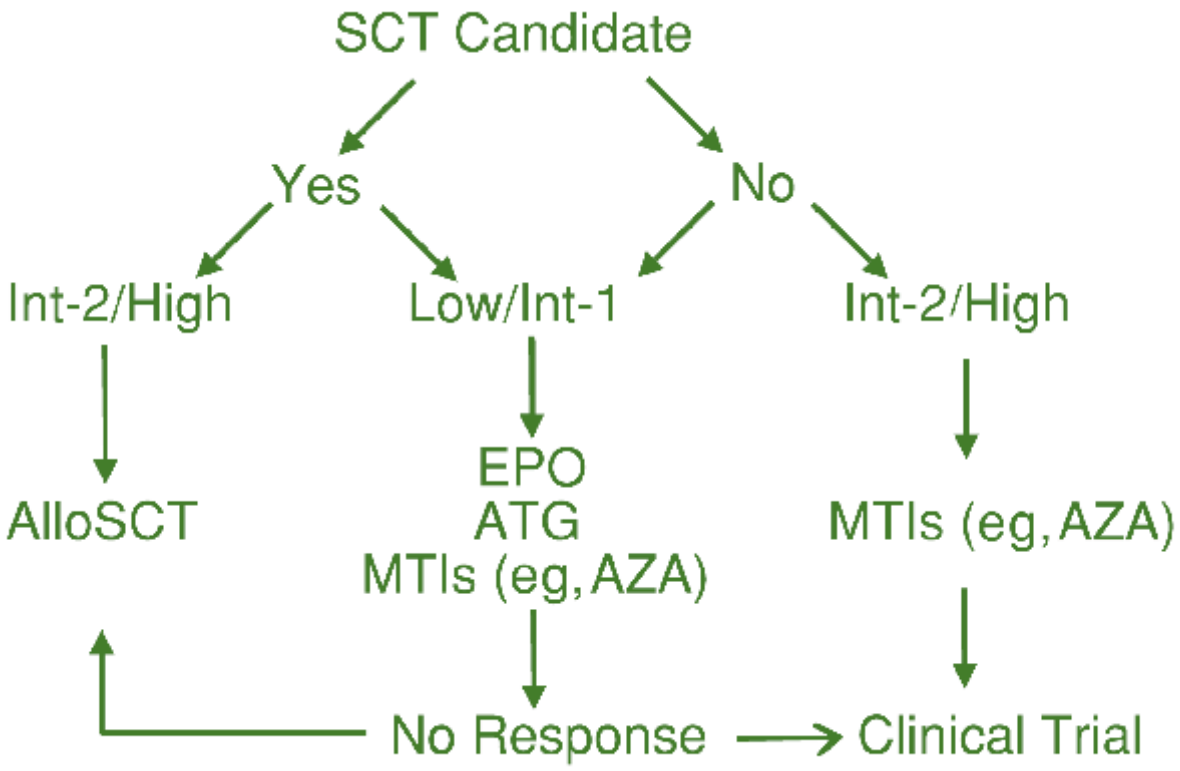

Figure 5. Treatment algorithm for MDS based on IPSS risk groups and currently available therapies. SCT indicates stem cell transplantation; Allo, allogeneic; EPO. erythropoietin; ATG, antithymocyte globulin; MTI, methyltransferase inhibitor; AZA, azacitidine.

The effectiveness of DNA methyltransferase inhibitors in the treatment of MDS has been further substantiated by similarly positive clinical response rates in ongoing late clinical trials of decitabine. Issa et al [2003] reported administration of 10 doses of 5 to 20 mg/m^2 per day intravenously 5 days a week, a dose that is 5- to approximately 30-fold lower than the maximum tolerated dose. The dose of 15 mg/m^2 for 10 days induced frequent responses (11 of 17) with fewer responses seen when the dose was escalated or prolonged (2 of 19). Wijermans et al [2000], in a multicenter phase II study of elderly patients with high-risk MDS who received 45 mg/m^2 per day for 3 days every 6 weeks, reported that low-dose therapy was effective in half of the studied patients and was especially active in the patients with the worst prognoses. More recently, decitabine was shown in 3 consecutive phase II studies to have a clinically significant, often long-lasting effect on the platelet count in a substantial number of high-risk MDS patients [van den Bosch 2004].

AZACITIDINE: PRACTICAL ASPECTS

Preparation

Azacitidine comes in a single-use vial of 100 mg to be reconstituted with 4 mL sterile water (25 mg/mL). The resulting product is a suspension with a cloudy appearance. Azacitidine should be injected within 45 minutes of reconstitution, but if necessary the reconstituted drug may be stored up to 1 hour at room temperature or 8 hours refrigerated. Procedures for handling and disposing of anticancer drugs should be applied [Pharmion 2004].

Administration

The recommended starting dose of azacitidine is 75 mg/m^2 subcutaneously administered daily for 7 days, every 4 weeks. Before injection, the suspension must be resuspended by inverting the syringe 2 to 3 times and rolling the syringe between the palms for 30 seconds. Doses larger than 4 mL should be divided into 2 syringes and administered at different sites [Pharmion 2004].

Table 11. Criteria for MDS Treatment Selection

	Low Risk (Low, Int-1)	High Risk (Int-2, High)
Younger patients (potentially SCT eligible)	Clinical trial	Clinical trial
	Growth factors	MTIs (eg, AZA)
	ATG	Chemotherapy
	Thalidomide	SCT
	MTIs (eg, AZA)	
	CC5013	
	SCT	
Older patients	Clinical trial	Clinical trial
	Growth factors	MTIs (eg, AZA)
	ATG	
	Thalidomide	
	MTIs (eg, AZA)	
	CC5013	

Patient Selection

Azacitidine is indicated for treatment of patients with MDS, including all 5 FAB subtypes. Figure 5 presents a treatment algorithm that incorporates azacitidine with other MDS treatment strategies.

CONCLUSION

In the last decade much progress has been made in understanding the natural history, clinical manifestations, and molecular mechanisms that underlie the complex MDS/AML group of diseases. Efforts continue to refine criteria for each of its many entities in order to improve prognostic capability. The WHO classification and IPSS risk assessment criteria provide reliable diagnostic criteria and can be used to guide treatment selection. Past treatment trials were complicated by a lack of standardized classification and outcome criteria, but consensus regarding these factors is increasing.

The choice of a treatment regimen in each case is based on the individual prognosis and depends on accurate risk classification (Table 11). Although MDS has been curable only through allogeneic hematopoietic stem cell transplantation and other standard treatments have not been highly effective, many new and improved options are available or under investigation. Among the treatment alternatives are agents that impact cell growth and differentiation, immune modulators, TNF antagonists and other apoptosis modifiers, angiogenesis inhibitors, and DNA methyltransferase and histone deacetylase inhibitors.

Three new drugs have been effective against MDS in clinical trials: the angiogenesis inhibitor CC5013 and the DNA methyltransferase inhibitors azacitidine and decitabine. Azacitidine, now approved for use in patients with all stages of MDS, has been demonstrated to be superior to best supportive care, long considered the mainstay of MDS treatment, both in clinical efficacy and in patients' reported quality of life, perhaps the most important indicator of success at the current time.

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POST-TEST
MYELODYSPLASTIC SYNDROMES: DIAGNOSIS AND EMERGING THERAPIES

1. Which of the following statements are true in characterizing MDS?
   a. The MDSs comprise a spectrum of stem cell malignancies that give rise to ineffective hematopoiesis involving one or more myeloid lineages.
   b. MDS progresses to acute myeloid leukemia (AML) in more than 50% of cases.
   c. MDS cases that do not progress to AML are rarely lethal.
   d. All of the above.

2. Which of the following statements are NOT true regarding MDS classification systems?
   a. Multilineage dysplasia identifies patients previously categorized in the FAB as RA or RARS with inferior prognoses.
   b. Patients who have deletion of the long arm of chromosome 5 as a sole cytogenetic abnormality and characteristic abnormal megakaryocyte morphology constitute a unique group of MDS patients with relatively good prognosis.
   c. Patients with trilineage dysplasia and >20% blasts have acute leukemia and should be treated like patients with de novo AML.
   d. Quantification of blast percentage is prognostically important.

3. Which of the clinical and laboratory features listed below are applied in the IPSS for prognostic discrimination?
   a. Marrow blast percentage.
   b. Cytogenetic pattern.
   c. Number of hematologic deficits (cytopenias).
   d. All of the above.

4. Which of the following are true of MDS prevalence and epidemiology?
   a. Women have roughly double the incidence of MDS as men at any age.
   b. Chemical and environmental leukemogens are not believed to be associated with greater risk for development of MDS.
   c. Incidence exponentially rises with age above 50 years.
   d. All of the above.

5. Which of the following treatments are believed to have predictable curative potential that varies by IPSS category and other prognostic variables in higher-risk MDS patients?
   a. Allogeneic stem cell transplantation.
   b. Erythropoietin ± G-CSF.
   c. Thalidomide.
   d. All of the above.

6. Which of the following are NOT true of best supportive care for MDS?
   a. The majority of MDS patients will require transfusion support.
   b. Because of high infection rates resulting from neutropenia, routine antibacterial prophylaxis is required in most MDS patients.
   c. Anemia is the most common cytopenia and often has a severe adverse impact on quality of life.
   d. All of the above.

7. Which of the following therapeutic strategies do NOT offer meaningful potential to improve erythropoiesis in selected lower risk patients?
   a. Erythropoietin ± G-CSF.
   b. Low-dose cytarabine.
   c. Thalidomide, CC5013.
   d. Antithymocyte globulin.

8. Which of the following are true regarding standard therapies for MDS?
   a. When remission is achieved through induction chemotherapy, it is difficult to maintain without transplantation.
   b. Experience with autologous stem cell transplantation for treating MDS patients has been limited and largely disappointing.
   c. Disease-free survival rates for allogeneic stem cell transplantation range from 23% to 63% depending upon IPSS category, age, and donor compatibility.
   d. All of the above.

9. Which of the following statements are NOT true of new and investigational treatments for MDS?
   a. DNA methylation, the most frequent heritable molecular change in hematopoietic neoplasms, is targeted by the irreversible DNA methyltransferase inhibitors azacitidine and decitabine.
   b. CC5013 acts as both an immunomodulatory agent and an angiogenesis inhibitor, and it is less toxic than its analogue thalidomide.
   c. Antilymphocyte and antithymocyte globulin (ALG and ATG) have produced durable improvements in blood counts in all MDS patient subgroups.
   d. All of the above.

10. Which of the following is true regarding azacitidine administration?
    a. Azacitidine should be injected within 2 hours of reconstitution, but if necessary the reconstituted drug may be stored up to 3 hours at room temperature or 12 hours refrigerated.
    b. Doses larger than 4 mL need not be divided into 2 syringes and administered at different sites.
    c. Azacitidine is indicated for treatment of patients with MDS, including all 5 FAB subtypes.
    d. All of the above.

EVALUATION FORM
MYELODYSPLASTIC SYNDROMES: DIAGNOSIS AND EMERGING THERAPIES
PROJECT ID: 04-2205-ES-18

Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgement of participation for this activity.**

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to Which Program Activities Met the Identified Objectives

Upon completion of this activity, participants should be better able to:

• Describe myelodysplastic syndromes (MDSs) by prognosis and pathologic features.	5	4	3	2	1
• Discuss the goals of therapy for MDS.	5	4	3	2	1
• Describe the biology of MDS and translation to new therapeutics.	5	4	3	2	1
• Identify the importance of chromatin remodeling as a target for MDS therapy.	5	4	3	2	1

Overall Effectiveness of the Activity

Was timely and will influence how I practice.	5	4	3	2	1
Will assist me in improving patient care.	5	4	3	2	1
Fulfilled my educational needs.	5	4	3	2	1
Avoided commercial bias or influence.	5	4	3	2	1

Impact of the Activity

The information presented:

(check all that apply)

❒ Reinforced my current practice/treatment habits.

❒ Will improve my practice/patient outcomes.

❒ Provided new ideas or information I expect to use.

❒ Enhanced my current knowledge base.

Will the information presented cause you to make any changes in your practice?

❒ Yes ❒ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

How committed are you to making these changes?

5 (Very committed) 4 3 2 1 (Not at all committed)

Future Activities

Do you feel future activities on this subject matter are necessary and/or important to your practice?

❒ Yes ❒ No

EVALUATION FORM
Myelodysplastic Syndromes: Diagnosis and Emerging Therapies
Project ID: 04-2205-ES-18

Please list any other topics that would be of interest to you for future educational activities:

Follow-up

As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

❒ Yes, I would be interested in participating in a follow-up survey.

❒ No, I'm not interested in participating in a follow-up survey.

Additional comments about this activity:

If you wish to receive acknowledgement of participation for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation and FAX to: (303) 790-4876.

Post-Test Answer Key

1	2	3	4	5	6	7	8	9	10

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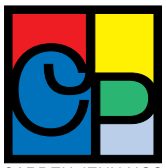

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