

# The Myelodysplastic Syndromes: Morphology, Risk Assessment, and Clinical Management (2002)

John M. Bennett<sup>a</sup>, Peter A. Kouides<sup>b</sup>, Stephen J. Forman<sup>c</sup>

<sup>a</sup>*Professor of Medicine, Emeritus, James P. Wilmot Cancer Center, Rochester, NY, USA,*  
<sup>b</sup>*Associate Professor of Medicine, Hematology Oncology Unit, Rochester General Hospital,*  
*Rochester, NY, USA,* <sup>c</sup>*Director, Division of Hematology and Bone Marrow Transplantation,*  
*City of Hope National Medical Center, Duarte, CA, USA*

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## Abstract

The Myelodysplastic Syndromes (MDS) represent a group of potentially acute myeloid leukemic disorders. There exists a delicate balance between increased apoptosis and proliferation of the leukemic hematopoietic stem cell that permits many patients to survive for years. When the balance shifts towards proliferation AML develops with a poor outcome for most but not all patients. I will review the latest proposals from the W.H.O. in classification, including pediatric MDS, prognostic factors and response criteria. Then I will present a strategy for the management of low risk patients with supportive care or low intensity treatment (cytokines, Immune modulation, anti-VEGF agents) and finally chemotherapy and intensive therapy with auto and allo BMT.

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## 1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of hematopoietic stem cells. In the early 1970s, a number of investigators gathered to form the French-American-British (FAB) Working Group. The goal was to provide uniform terminology for the myriad of different definitions for the leukemias and related diseases. At the time, new therapies and supportive care measures for hematologic disorders were evolving rapidly. Exciting new drugs were active and more were in clinical development. The group believed strongly that for international groups to be able to exchange information about these different entities, it was critical to agree on common definitions. The FAB Working Group developed a series of proposals and published its first article on the acute leukemias in 1976, which discussed two of the components of what are now called myelodysplastic syndromes (MDS)--refractory anemia with excess blasts (RAEB) and chronic myelomonocytic leukemia (CMML).

It was recognized that some patients could present with

a disease that bore some resemblance to acute myeloid leukemia (AML), but that this entity, unlike AML, did not have many leukemic blasts in the bone marrow. It was associated with some alteration in maturation of the three major cell lines (granulocytes, erythroid precursors, and megakaryocytes), which resulted in pancytopenia and increased risk of infection and bleeding, but did not necessarily progress to acute leukemia. Different terms were applied, including dysmyelopoietic anemias. The FAB Working Group applied the term MDS to these disorders to indicate that the common disease pathway began with a common neoplastic stem cell. The evolution from that stem cell could be highly variable: some patients never evolved to acute leukemia and others evolved quickly.

The definition of MDS also has two parts, as it is essentially a clinico-pathologic description. MDS can be defined as a clonal disease of the bone marrow with:

- The clinical manifestation of bone marrow failure as well as a tendency to transform into an acute leukemic phase.
- The pathological manifestation of morphological ab-

normalities (termed "dysplasia," although it is a clonal disorder, and hence, neoplastic) of the peripheral blood and bone marrow cells such as ringed sideroblasts, megakaryoblastic erythroid precursors, hypogranulation/hyposegmentation of the granulocytes, and micromegakaryocytes.

A major advance toward understanding the pathogenesis of MDS has been the observation of apoptosis, programmed cell death, in MDS. The group of Raza/Preisler et al. have carried out cell kinetic studies from MDS bone marrow biopsies using intravenous infusions of either iododeoxyuridine or bromodeoxyuridine, or both, and estimated the degree of apoptosis by *in situ* end-labeling of DNA. Virtually all marrows studied demonstrated increased rates of apoptosis as well as rapid cell proliferation.

### *1.1. MDS is Primarily a Disease of the Elderly. It is more Common than AML and Appears to be Increasing in Incidence*

Most investigators believe MDS is at least twice as common as AML. Current projections are an annual incidence of approximately 12,000 cases in the United States, which makes it the most common leukemia observed, even more common than Chronic Lymphocytic Leukemia.

One of the limitations in determining the true incidence and prevalence of MDS is the inability of tumor registries to record cases accurately. Most rely on tissue pathology, and many patients with MDS are diagnosed in a hematologist's office where a bone marrow aspirate may be performed without a biopsy, or the diagnosis is made accurately by the process of elimination without ever performing a bone marrow aspirate. This is not the case with AML or any other malignancy.

Addressing the question of whether MDS is increasing in incidence is equally if not more difficult. Older literature is unreliable because different disease classifications existed: idiopathic sideroblastic anemias, refractory anemias, preleukemias, dysmyelopoietic anemias, smoldering acute leukemias, and subacute myeloid leukemias. All of these entities presumably described a similar disease.

We suspect that the incidence and prevalence of MDS are rising, but there are no data to prove this. It makes sense, however, because people are living longer, and MDS is a disease of the aging population. Increasing numbers of people are also developing MDS as a result of exposure to the drugs used to treat patients with solid tumors, the acute leukemias, and autoimmune disorders, as well as in patients receiving bone marrow, liver, and cardiac transplantation.

The acceptance of the FAB classification has facilitated the determination of true age-specific incidences in confined populations, and the best estimates come from selected institutions, cities, and countries that are able to define the entire population at risk. Reports from England, Germany, France, and Thailand have been similar, and there is no evidence to suggest that the incidence

of MDS varies worldwide. The approximate incidence is 6 to 10 cases per 100,000 individuals, with an increasing incidence above the age of 60. This compares with an incidence of AML of approximately 3 cases per 100,000. By age 80, the incidence of MDS may approach 65 to 100 per 100,000.

Despite similar incidences worldwide there is a difference in the median age and subtype classification in Asian vs. American/European countries. Lee and colleagues have published data on a higher incidence of trisomy 1q in MDS patients in Korea (15.2%). In addition there is a lower incidence of Refractory Anemia with Ringed Sideroblasts (RARS) in Korea and Japan and a younger median age (45-50 years).

### *1.2. Like AML, MDS can Occur as a Primary or de novo Disease, or as a Treatment-related or Secondary Event*

A number of retrospective studies suggest a correlation between MDS and occupational exposure to agents such as benzene. Although cigarette smoking has a slight but significant association with the development of AML, data suggesting an effect on the incidence of MDS are sparse.

Two types of secondary leukemias/MDS can occur following treatment with antineoplastic agents (Table 1). The first type, initially recognized in survivors of Hodgkin's disease, generally presents 5 to 15 years after exposure to alkylating agents (i.e., mechlorethamine and procarbazine as part of the MOPP regimen). It shares many of the dysplastic features of MDS, and has a high incidence of chromosomal abnormalities, involving chromosomes 5 and 7 in particular. Patients have trilineage dysplasia and significant marrow fibrosis, and usually progress rapidly to acute leukemia. These secondary leukemias are difficult to classify as one of the FAB subtypes.

The second, more recently recognized type of second-

**Table 1.**  
Secondary Types of Leukemia/MDS.

Characteristic	Class I	Class II
Leukemogen	Alkylating agent	Topoisomerase II Inhibitor
Onset	5-15 yr	<5 yr
Classification by FAB Group	No	Yes
Cytogenetic result	Unbalanced (chromosomes 5 and 7)	Balanced
MDS phase	Yes	No
Response to therapy	Variable	CR likely

CR, complete response; FAB, French-American-British; MDS, myelodysplastic syndromes

ary leukemia is associated with administration of topoisomerase II inhibitors (e.g., etoposide, the anthracyclines, cisplatin). Interestingly, these leukemias are associated with the translocations present in de novo acute leukemia. For example, there are alterations involving chromosome 11 (11q23), translocations involving t(8;21), and translocations of t(15;17).

Survivors of testicular or lung cancer are now presenting with these type II secondary leukemias, and patients previously treated with alkylating agents and anthracyclines as adjuvant therapy for breast cancer are receiving diagnoses of a mix of type I and II secondary leukemias. Recent results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-25, which evaluated high-dose cyclophosphamide combined with doxorubicin as adjuvant therapy in 2,548 breast cancer patients, revealed 16 cases of AML (3 preceded by MDS) and 4 cases of MDS (4-year cumulative incidence of 0.87%), including a mix of both secondary leukemias associated with alkylating agents and topoisomerase II inhibitors (epidodophyllotoxins, anthracyclines). These results suggest a 60-times-higher incidence than would be expected in a control population.

## 2. Classification

### 2.1. FAB Classification Divides MDS into Five Subgroups according to the Percentage of Blasts in the Marrow, Percentage of Ringed Sideroblasts, Presence of Monocytes, and Severity of Dyspoiesis (Table 2)

After publishing the FAB classification for MDS in 1982, investigators found that they could apply it reasonably well. Separations in survival curves, ranging from 5 to 6 years for the most favorable prognostic forms of MDS to less than 1 year for the least favorable forms, were demonstrated. However, the FAB classification has not been without its critics, and modifications have been suggested. For example, evidence suggests that patients with greater than 10% leukemic blasts in the bone marrow (11-19%) experience disease pro-

gression as often as those who have 20% to 30% blasts. Time was necessary to look at the natural survival of the FAB categories and to confirm that the percentage of blasts is an important factor for prognosis.

Classifying MDS, however, continues to be valuable. It is simple. It involves performing a bone marrow biopsy and aspirate utilizing hematoxylin & eosin; reticulin; Romanowsky and iron stains and counting the number of blasts. The percentage of blasts is calculated, and patients are categorized according to this percentage (i.e., <5%, 5-10%, 11-19%, >20-30%) or if they have CMML, which can be any percentage of blasts with a monocytosis of greater than 1,000/uL.

If the absolute percentage of erythroid precursors is 50% or greater, the % blasts is based on the non-erythroid precursors (essentially granulocytes and monocytes). For example, a differential count of 6% blasts, 4% promyelocytes, 15% granulocytes, and 75% erythroid precursors would convert the % of blasts to "24%" blasts (6/25) changing the subgroup from RAEB to RAEB-t (in the FAB system).

Because CMML contains "leukemia" in its name, critics often object to its inclusion with the preleukemic states and myelodysplasia. A similar objection was raised several years ago regarding atypical chronic myeloid leukemia (aCML). A group of patients with elevated white blood cell counts -- usually greater than 12,000/uL -- have disease resembling CML, but with many of the morphologic features of MDS. These patients have an outcome similar to that of RAEB patients. Investigators differ in referring to the diagnosis as proliferative, leukemic, or myelodysplastic; however, the important point is that patients with aCML whose WBC counts are only slightly elevated tend to resemble more closely patients with MDS. Their disease is unlikely to proliferate, and they can be treated successfully in the same way MDS patients are treated. Another small group of patients have an elevated monocyte count (proliferative CMML), dysplastic changes in their peripheral blood and bone marrow, do not have the Philadelphia chromosome or *BCR-ABL* gene rearrangement, and resemble patients with MDS, but have a proliferative

**Table 2.**

FAB Working Group Classification of MDS.

FAB Type	Cases %	Bone Marrow Blasts %	Dyspoiesis	Ringed Sideroblasts, %	Monocytes	Progression to AML, %	Survival Range Yrs.	Survival Median Yrs.
RA	35	<5	+	<15	Rare	10	2-5	4
RARS	15	<5	+	>15	Rare	5	3-10	4
RAEB	20	5-20	++	Variable	Rare	45	0.5-2	1.5
CMML*	15	<20	++	Variable	Increased	20	1-5	2
RAEB-t	15	20-30	++	Variable	Variable	60	<1	0.5

\*Blood monocyte counts must be  $>1 \times 10^9/L$

illness. These patients may require CML-type treatment with drugs such as hydroxyurea, interferon- $\alpha$ , or busulfan.

There are also patients who meet the diagnostic criteria for MDS, but have only granulocytopenia and thrombocytopenia and no anemia. Some authorities justifiably question the diagnosis of RA when the patient is not anemic. A better term for these patients is "uncategorized MDS." The original description of RA was intended to include patients with mild pancytopenias and dysplasia, but since there was no category in which to put other kinds of patients, it has become a catchall phrase.

Despite considerable searching for mutational events in MDS, only a small number have been identified. These include N-ras, present in 10-30% of cases (usually in CMML); p53 tumor suppressor gene (on chromosome 17), recognized in 5-10% of cases; FLT3 oncogene receptor tyrosine kinase (including the absence of the wild type allele) in 5%; p15 ink 4b, a cyclin dependent kinase inhibitor (on 9 p21) and hypermethylation genes that can be seen in as high as 50% of high risk cases.

### 3. Diagnostic Evaluation

#### 3.1. The Diagnosis of MDS is Based on Routine Laboratory and Peripheral Blood Evaluation. Bone Marrow Aspiration and Biopsy Along with Cytogenetic Analyses Should be Performed

The laboratory diagnosis of MDS is prompted by clinical symptoms, such as fatigue, bleeding or infection that indicate the presence of anemia, thrombocytopenia, or severe granulocytopenia. There are no clinical phenomena associated specifically with MDS versus other pancytopenic states, including mild to moderate forms of aplastic anemia, which are occasionally difficult to differentiate from MDS. Sometimes a patient presents with an acellular bone marrow, thereby fulfilling a criterion for aplastic anemia, but the patient also has significant dysplasia, slight macrocytosis, and an abnormal karyotype, such as monosomy 7 or trisomy 8. This patient will eventually develop MDS or acute leukemia if not treated with allogeneic bone marrow transplantation (BMT).

The diagnosis of MDS depends on the process of elimination for half of the patients we observe. For the other half, the diagnosis is not difficult if patients have more than 5% blasts. Having less than 5% blasts and normal cytogenetic and fluorescence in situ hybridization (FISH) results, even in the presence of mild to moderate dysplasia, makes most clinicians reluctant to assign a diagnosis of MDS until a month or two elapses. This allows time to rule out a correctable hematologic process, such as pyridoxine-responsive anemia. If the pancytopenic state is not readily reversible by normal interventions within 1 to 2 months, the chances are overwhelming that the patient has MDS.

Cytogenetic testing should be performed on every

**Table 3.**

Karyotypic Changes Associated with Different Disease Subgroups.

Disease Type	Most Commonly Associated Change
RA	5q-
RARS	+8, 5q-, -7, t/del(11), 20q-
RAEB and RAEB-t	5q-, -7, +8, +5, 7q-, +21, -Y
CMML	-7, +8, t/del(12p), +21, -Y, 7q-
AML (de novo)	t(8:21), t(15:17), t(9:11), inv(16), -7, +8

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; RA, refractory anemia; RAEB, refractory anemia with excessive blasts; RAEB-t, RAEB in transformation; RARS, refractory anemia with ringed sideroblasts.

patient with MDS and cytogenetic and bone marrow evaluations repeated whenever there is a significant alteration in the peripheral blood parameters. Because chromosomal evolution frequently occurs in patients who become more pancytopenic, a different treatment category may be required. However, we are not suggesting a monthly bone marrow biopsy be performed in patients with MDS. Once a diagnosis is established, routine, repeated bone marrow testing is unnecessary, unless there is a valid indication or the patient is on a clinical trial that requires such studies.

#### 3.2. Table 3 Lists the Specific Karyotypic Changes Associated with Different MDS Subgroups and de novo AML

Readable cytogenetic spreads can be obtained in approximately 75% of patients with MDS. Of these, 60% to 65% will be abnormal.

The most common cytogenetic abnormalities occur with chromosomes 5, 7, and 8. There are abnormalities specific to MDS [e.g., 20q- or t/del (12p)] that are rare events in AML, specific translocations unique to AML not observed in primary MDS [e.g., t(15; 17)], and the same abnormalities seen in both.

### 4. Prognostic Factors

#### 4.1. A Number of Indexes have been Proposed to Aid in Predicting Clinical Outcome for Patients with MDS

Every city or country with adequate numbers of MDS patients has developed its own prognostic scoring system. Most of these systems separate patients into three groups, and they all have the same outcome: median survival times of 60, 30, and 15 months for the good-, intermediate-, and poor-prognosis groups, respectively.

Recently an improvement in the existing systems was proposed, referred to as the International Prognostic

Scoring System (IPSS), which includes a fourth group of patients. Greenberg and colleagues performed an analysis of 816 patients with de novo MDS to determine the critical prognostic variables. Patient subgroups were classified according to cytogenetics, percentage of blasts in the bone marrow, and number of cytopenias (Table 4).

In this system cytogenetic availability is important, as it enables one to predict survival and evolution to AML in the low-risk group. This will help to individualize strategies for treating the patients in whom karyotyping

is available.

#### 4.2. Abnormal Localization of Immature Precursors (ALIP) is a Prognostic Factor Being Evaluated in MDS

Using excellent bone marrow biopsy methods, primarily with plastic-embedding techniques, several groups, including investigators in Belgium, described the presence of clusters of immature precursors. Instead of the nor-

**Table 4.**

Risk Analysis (IPSS).

Risk Subgroup	Score	Median survival (years)	Percent AML risk
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	>2.5	0.4	0.2

The score is based on the following parameters:

	Score				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype	Good (normal or 5q- or 20q- or -Y)	Intermediate	Poor (>3 abnormalities or monosomy 7)	11-20	21-30
Cytopenias	0/1	2/3			

(Hemoglobin <10 g/dL, absolute neutrophil count (ANC) <1,800/uL, platelet count <100,000/uL).

**Table 5.**

W.H.O. Classification.

Category	Peripheral Blood	Bone Marrow
1a. RA without dysplasia	Blasts <1%; monos<1,000/ $\mu$ L	Blasts <5% ringed sideroblasts <15%
1b. RA with dysplasia	Same +dysgranulo. and or giant platelets	Same +dysgranulo. and or dysmega.
2a. RARS without dysplasia	Blasts <1% monos<1,000/ $\mu$ L	Blasts<5%; =or>15% ringed sideroblasts
2b. RARS with dysplasia	Same +dysgranulo. and or giant platelets	Same +dysgranulo. and or dysmega.
3a. RAEB-I	Blasts 1-10% monos<1,000/ $\mu$ L	Blasts: 5-10%
3b. RAEB-II	Blasts 11-19% monos <1,000/ $\mu$ L	Blasts:11-19%
4. CMML*	Blasts <1-19% >1,000 monos/ $\mu$ L	Blasts: 0-19%

\*list under myelodysplastic/myeloproliferative category.

mal pattern observed in MDS with blasts located adjacent to the cortical bone, a clustering of these immature cells in the central portions of the bone marrow biopsies, or ALIP, has been observed. The significance of ALIP is strictly related to the potential for MDS patients to evolve to acute leukemia more rapidly than patients who do not ALIP. There is also a strong association between ALIP and the presence of CD34 cells on the cell membrane. ALIP will be most useful in guiding treatment for patients with less than 5% blasts and with RA. Determination of ALIP has not yet played a major role in the United States because bone marrow biopsies are not sophisticated enough to allow pathologists and hematologists to identify ALIP confidently. Nevertheless, we note the presence of ALIP in a bone marrow biopsy.

In 1997 the World Health Organization (W.H.O.) appointed a committee to revise and update the diagnostic categories of the Lymphomas and the Leukemias. One of us (John M. Bennett) was privileged to be appointed to the subcommittee for acute leukemias and MDS. Changes have been suggested that include the following (Table 5):

1. Eliminate RAEB-t and establish AML when the % of marrow blasts is 20% or greater.

2. List CMML in a separate chapter entitled: myelodysplastic/myeloproliferative disorders. Subclassify CMML into CMML-1 and 2, based on the % of blasts in the marrow (1-10 vs. 11-19%).

3. List 2 types of RAEB: RAEB-I (5-10% blasts) and RAEB-II (11-19% blasts).

4. Include under RARS and RA a subtype for dysplasia in granulocytic and (or) megakaryocytic lineage. Dysplasia is defined as 10% or greater dysplastic progeny (granulocytes in peripheral blood and (or) granulocytes, megakaryocytes in bone marrow).

5. Add a new category for cases that do not fit the other subtypes, namely MDS, unclassified.

These new proposals have the approval of the clinical consultants to the W.H.O. committee and are a reflection of new information on outcome and results of treatment.

## 5. Clinical Management

Over the last 10 years, the therapy of MDS has evolved as studies of the biology, classification and natural history have yielded new information. These studies have led to a number of trials designed to improve the effectiveness of supportive care strategies or to use transplantation of allogeneic and autologous stem cells to cure the disease.

### 5.1. Growth Factors in the Treatment of Myelodysplastic Syndrome

Colony stimulating factors including recombinant erythropoietin (Epo), granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) have been utilized to treat patients

with myelodysplasia. In Phase I/II clinical trials, recombinant erythropoietin has been reported to produce erythroid responses manifested by increases in hemoglobin in approximately 10-30% of treated patients. Synergy has been observed between Epo and G-CSF *in vitro*. In general, the treatment with Epo will lead to an increase in the hemoglobin within four to eight weeks of treatment with the response being dependent somewhat on the FAB subtype. The patients who respond are generally those with refractory anemia, whereas patients with refractory anemia with excess blasts in transformation or CMMoL generally do not respond. The response to exogenous erythropoietin is also related to the patients' pre-treatment erythropoietin levels. In patients who have low levels, i.e. less than 200 U/l, the response rate can be as high as 50%. In patients who have high Epo levels, the response rate is low. The predictors of response, therefore, to erythropoietin are as follows:

1. Refractory anemia > RAEB > RARS.
2. Patient not transfusion dependent.
3. No ringed sideroblasts in the marrow.
4. No abnormal cytogenetics.
5. Blast count in the marrow less than 10%.
6. Serum erythropoietin level less than 200 U/l.

Given that some patients have concomitant bleeding disorders from either poor platelet function or low number, it is important to document that patients have adequate iron stores before starting erythropoietin in order to interpret the response appropriately.

G-CSF alone has been utilized to prevent or treat infection in patients with severe neutropenia (<500/ $\mu$ l) with most studies showing a myeloid response. The use of G-CSF and Epo together has also been reported to result in erythroid response rates that are higher. With discontinuation of G-CSF, the erythroid response is often lost. In this setting, the benefit of this combination appeared to be best when high doses of Epo (300 U/kg/day) were utilized. Treatment with G-CSF alone or in combination with Epo is not associated with disease progression or transformation to leukemia.

### 5.2. Standard Chemotherapy for the Treatment of Myelodysplastic Syndromes

A number of chemotherapy drugs have been evaluated in an attempt to achieve hematologic remission in patients with myelodysplasia. Many of the drugs and regimens that have been evaluated were based on the response rates for non-MDS related AML with Cytosine Arabinoside the most commonly studied drug. It appears, through numerous studies, that low dose ARA-C has little, if any, role in the treatment of these patients and in a randomized trial was only marginally better than supportive care. 5-Azacytidine, which can induce cellular differentiation by hypomethylation of DNA, has also been explored in myelodysplasia. The response rate to this agent used as an antiproliferative single agent is under 30% with complete remissions occurring in fewer than 10% of patients. In a randomized trial conducted

by CALGB, a NCI-sponsored cooperative group, there was, in addition, a delay in and a decrease in the % of transformation to AML. Decitabine, a second, closely related compound, has achieved about 50% responses in European trials. A promising new agent in the treatment of MDS is the Topoisomerase inhibitor, Topotecan, which is reported to achieve remission in about 30% of patients. In one trial, Topotecan was administered at a dosage of 2 mg/m<sup>2</sup>/day by continuous infusion for five days. In these pilot studies, 28% of patients with RAEB and CMML went into remission and 13% achieved hematologic improvement. The combination of Topotecan and ARA-C has also been used to treat patients with advanced MDS. In this study, Topotecan was combined with ARA-C (1 g/m<sup>2</sup>/day for 5 days) and 63% of patients with RAEB achieved a hematologic remission. In principle, induction therapy that is effective in achieving remission of MDS could improve the outcome for patients who subsequently undergo allogeneic transplantation (see below).

### 5.3. Alternative Therapies to Improve Hematopoiesis

Amifostine is a phosphorylated organic thiol that has hematopoietic trophic effects on myelodysplastic progenitors and has demonstrated activity in preliminary clinical trials. It is a pro-drug that is dephosphorylated by membrane alkaline phosphatase to the intracellular aminothiol WR1065. This drug is able to protect cells from cellular damage from chemotherapy and radiation, in part due to its antioxidant abilities. Phase I and Phase II trials utilizing Amifostine on a three times per week schedule were performed and showed single or multi-lineage hematopoietic improvement in some patients. Treatment was well tolerated, particularly at doses of less than 200 mg/m<sup>2</sup>, whereas at higher doses nausea becomes limiting. The capacity of Amifostine to alter an unfavorable microenvironment has led to its incorporation into other combination therapies.

Recent studies have suggested that cytokine mediated excessive intramedullary apoptosis may be an important contributing factor to the ineffective hematopoiesis seen in MDS. This has led to studies of agents that decrease proapoptotic cytokines such as TNF, TGF- $\beta$  and interleukin 1 (Pentoxifylline, Ciprofloxacin and Dexamethasone). One study of 35 patients combined Amifostine with Pentoxifylline, Ciprofloxacin and Decadron and had a 76% response rate measured by an improvement in or more cytopenia). Thalidomide has also been tested in MDS based on its anti-angiogenic and anti-TNF activity and appears to show some benefit primarily in improving the hemoglobin level.

### 5.4. Immunosuppressive Treatment of Myelodysplasia

A large number of studies have identified similarities between myelodysplasia and severe aplastic anemia including the high rate of subsequent clonal hematopoietic disorders following immunosuppressive treatment for severe aplastic anemia. Although many patients with aplastic

anemia respond to therapy, most patients do not achieve blood levels that are entirely within the normal range. The risk of progression to clonal disorders was 35% in a large European series of 350 patients who were monitored for 14 years, a figure which includes PNH. The risk of progression to overt myelodysplasia and AML was 9.6% and 6.6% respectively mimicking the evolution over time of myelodysplasia to acute leukemia.

Because of the similarities between the disorders, particularly hypoplastic MDS, immunosuppressive therapy has been utilized for the treatment of myelodysplasia. Some observers have hypothesized that a T cell mediated process can contribute to the pancytopenia associated with myelodysplasia. Recent studies have formally studied the use of immunosuppressive therapy with ATG in patients who were red cell or platelet transfusion dependent for myelodysplasia with marrow cellularities that were either hypo or hypercellular and included all of the different subcategories of myelodysplasia. The vast majority of these patients had failed previous therapy with growth factors and Amifostine. The major criterion of response was transfusion independence. Overall, 35% of the patients responded, half of whom were in the refractory anemia group. The factors that favored a response to ATG were age less than 60, hypoplastic MDS, normal karyotype and a diagnosis of refractory anemia. Thus, patients who have this variant of MDS may benefit from a course of immunosuppressive therapy. Although the response rate is not as high, some older patients and some patients with hypercellular marrows also responded. In addition to ATG, responses have also been seen to other immunosuppressive therapies such as Cyclosporin with transfusion independence the criterion for response. In one small series, Cyclosporin treatment resulted in responses in both refractory anemia with excess blasts and RA patients and in both hypercellular or normocellular marrows. These studies provide evidence to support an immune mechanism of marrow suppression in patients with myelodysplasia independent of the cause of disease. This is consistent with laboratory studies showing T cell mediated BFU-e suppression in myelodysplasia as well as CD8 depletion studies which increase marrow growth in culture.

### 5.5. Autologous Hematopoietic Cell Transplantation for Patients with Myelodysplasia or AML Following Myelodysplastic Syndrome

Survival for patients with refractory anemia with excess blasts, refractory anemia with excess blasts in transformation or therapy-related MDS or secondary AML is very poor with a median survival of less than 12 months. Some patients achieve a remission with intensive chemotherapy but the median duration is usually very short. Interest in the development of autologous hematopoietic cell transplantation for MDS has emerged from laboratory and clinical observations indicating the presence of normal polyclonal hematopoietic stem cells in the marrow of the patients who achieved remission. Some patients with MDS and a well-characterized cyto-

genetic abnormality have achieved both a morphologic and a cytogenetic remission after chemotherapy, suggesting the presence, as in *de novo* AML, of stem cells that are capable of normal hematopoietic reconstitution. Stem cell cultures in patients who achieve remission also demonstrate, on occasion, polyclonal hematopoiesis.

Several groups have reported their results of autologous hematopoietic cell transplantation for MDS that has evolved into AML. In general, it appears that disease-free survival is approximately half of that achieved with autologous transplant for *de novo* AML. Patients with MDS reported in these series are highly selected for the following characteristics:

1. Chemotherapy induced hematologic remission of their secondary AML.
2. The cytogenetic abnormality often disappeared at the time of achievement of remission.
3. Adequate numbers of hematopoietic stem cells could be collected, providing the opportunity for high dose therapy and stem cell reinfusion.

An update of an analysis of the EBMT results for autologous bone marrow transplantation (BMT) was completed for 179 patients who received autologous stem cell grafts for treatment of MDS/AML. The 3-year advanced DFS was 33% with a relapse rate of 55%. Younger patients did better, many due to decreased transplant related toxicity. Thus, patients with MDS and AML who are not eligible for allogeneic transplantation and achieve hematologic remission could be treated with post-remission autologous transplantation that may improve their overall survival. Not surprisingly, the main cause of treatment failure following transplant was not graft failure or post-transplant complications, but a high risk of leukemic relapse. These results are similar to allogeneic transplantation for patients whose disease had already undergone transformation.

### 5.6. Allogeneic Hematopoietic Cell Transplantation for Myelodysplasia

Many groups have reported their results for allogeneic transplantation for myelodysplasia with an average disease-free survival of approximately 40%. The factors that influence long-term, disease-free survival include increasing age, time from diagnosis, advanced versus less advanced disease, intermediate versus good risk cytogenetics, as well as time to transplantation.

The differences in relapse related to marrow morphology have also been studied in patients receiving allogeneic BMT. In patients with advanced disease (increased blasts in the marrow), the risk of relapse was about 30% versus under 5% for patients with low blast counts, resulting in an improved disease-free survival for those with less advanced disease (50% versus 30%). A recent report from Seattle utilized the IPSS scoring system to determine its predictive value on outcome after allogeneic transplantation for MDS. A multi-variable analysis found three factors associated with an increased risk of relapse: Disease duration, morphology (blasts) and cytogenetics. Patients transplanted for refractory ane-

mia or hypoplastic anemia with a cytogenetic abnormality rarely, if ever, relapsed, whereas those with more advanced disease had a significantly increased relapse and decreased survival. Patients with a high risk cytogenetics who underwent transplantation had a greater chance of relapse after transplantation than those with low or intermediate risk cytogenetics. Evaluation of disease-free survival in patients with MDS categorized by IPSS prognostic score, including those up to the age of 65, showed that approximately 60% who had low and intermediate risk 1 categories were disease free, 40% for those with intermediate risk 2 patients and 20% for high risk patients.

### 5.7. Allogeneic Transplantation for Myelodysplastic Syndrome in Older Patients

The mainstay of treatment of myelodysplasia in older patients is supportive care. Given the curative potential of allogeneic bone marrow transplantation in younger patients, this approach has been explored as a therapeutic option in selected older patients with MDS with the goal of preventing leukemic transformation and restoring normal hematopoiesis to prevent infectious or hemorrhagic complications. Although transplantation of marrow or peripheral blood stem cells from a healthy donor is currently the only curative therapy for myelodysplasia, the older age of the patients at diagnosis has generally precluded the generalized use of this approach. Even among younger patients, there is significant morbidity and mortality. With the increasing use of allogeneic peripheral blood stem cells and targeted pharmacokinetic approaches, some older patients with myelodysplasia can be successfully transplanted. One recent study published from Seattle reported a group of 16 patients with MDS between 55-65 who received oral Busulfan targeted to achieve a plasma level of 900 ng/mL combined with Cyclophosphamide followed by bone marrow transplantation. The study indicates that transplantation is feasible and provides excellent survival for certain subgroups of patients. The results were similar to the outcome in younger patients with advanced disease stage and high-risk cytogenetic categories at diagnosis and the highest probability of relapse. Nevertheless, for the appropriate patient in good condition who has a sibling donor, a targeted Busulfan based regimen can be utilized to cure the disease. In this series, only one of 14 with primary myelodysplasia had a recurrence of disease after transplantation. This is consistent with transplant studies which suggest that Busulfan may be a more effective anti-myeloid agent than Cyclophosphamide when combined with total body irradiation.

### 5.8. Therapy-related MDS and AML

There is an increased frequency of therapy-related myelodysplasia in patients who have received curative therapy for Hodgkin's disease, lymphoma, multiple myeloma and breast cancer. Many of these patients have had prior radiation, particularly those with Hodgkin's dis-

ease, and thus do not receive a TBI-related transplant regimen when they develop dysplasia. In addition, the intensity of prior chemotherapy and/or radiation makes such patients at higher risk for post-transplant related complications. An analysis of approximately 150 patients shows that 34% undergoing transplant for therapy-related MDS were long-term, disease-free survivors, 21% relapsed and 45% succumbed to transplant-related complications. These data suggest that allogeneic transplant is potentially successful treatment for patients who develop this complication of cancer therapy. Not surprisingly, the non-relapse mortality rate was higher than for patients with standard myelodysplasia.

### *5.9. Therapy-Related Leukemia and Myelodysplasia as a Complication of Autologous Stem Cell Transplantation*

High dose chemoradiotherapy with stem cell rescue has been the treatment of choice for patients with Hodgkin's disease and non-Hodgkin's lymphoma who have had a suboptimal response to initial therapy or for those with refractory or relapsed disease. With improvement in survival following this kind of therapy, post-transplant therapy-related myelodysplasia and secondary therapy-related AML are emerging as serious long-term complications. The cumulative probability of therapy-related MDS and AML has ranged from 4% at five years to 18% at six years. The risk factors for developing MDS after transplants include: older age at transplant, the use of total body irradiation or radiation therapy as prior treatment and a low platelet count at the time of transplant. In addition, some studies have identified transplant with peripheral blood CD34 cells after chemotherapy priming, particularly with VP-16, as conferring a higher risk of myelodysplasia or AML compared with patients who receive transplants from cells that were obtained from the bone marrow. It is not clear whether this represents a direct causal relationship to the method of priming or whether different populations are mobilized with different mutagenic burdens. The latency period for the development of myelodysplasia after transplantation is short, occurring within a year in approximately a quarter of the patients. However, the overall time for the development of myelodysplasia from diagnosis is very similar to those patients who developed dysplasia unrelated to transplantation.

### *5.10. Innovations in Allogeneic Transplant for Myelodysplasia*

The recent development of minimally ablative or non-ablative transplant regimens has expanded the possibility of performing allogeneic transplantation in older patients with a variety of hematologic malignancies. Initially, these approaches were designed for patients who were older or had concomitant medical conditions that limited the use of allogeneic transplantation in the treatment of their disease. A variety of regimens have been developed, including the combination of Fludarabine and total

body radiation, Busulfan, ATG and Fludarabine and Melphalan/Fludarabine. The use of these immunosuppressive regimens has resulted in donor hematopoiesis, often with significant anti-tumor responses and complete remissions in diseases such as multiple myeloma, lymphoma and chronic myelogenous leukemia in the reported series. Patients with advanced myelodysplasia have also been treated with non-myeloablative regimens and some have achieved a remission. Although long-term results for all of these diseases await longer follow-up, the ability to establish normal hematopoiesis and hematologic remission is an attractive therapeutic strategy, particularly for those with less advanced myelodysplasia and for whom inadequate hematopoietic function is the dominant clinical problem.

The intensity of most high dose transplant regimens results in significant organ toxicity and infections in the hypoplastic phase. The risk of these problems is related to the duration of hematologic recovery. Recent comparative trials of peripheral blood stem cells versus marrow have suggested that both neutropenia and thrombocytopenia are shortened after peripheral blood stem cell transplant. A Phase III trial completed at the Fred Hutchinson Cancer Research Center, Stanford and the City of Hope demonstrated improved overall and disease free survival for patients with advanced hematologic disease, including myelodysplasia, suggesting that this may be the preferred stem cell choice for those with advanced disease.

In addition to post-transplant complications, patients with myelodysplasia who undergo allogeneic transplantation are also at high risk for relapse. Recent advances in the development of BMT regimens include radioimmunotherapy targeted to hematopoietic antigens (CD45 and CD33). Early results suggest that the addition of radioimmunotherapy to the regimen does not increase the toxicity of the regimen and may reduce the relapse rate. The use of individually targeted Busulfan to achieve an anti-tumor response without increasing toxicity has also improved the safety of allogeneic transplantation. Several studies now have been performed that show the utilization of a targeted approach with Busulfan reduces the toxicity of the transplant regimen. In addition, these trials have suggested that the achievement of an appropriate targeted level of drug reduces relapse compared to patients who had lower levels of drug after treatment.

### *5.11. Recent Developments in MDS Management (2002)*

The discovery of enzyme inhibitors introduces a new dimension to the management of patients with MDS. One such program involves the farnesyl transferase inhibitor (R115777) with early Phase I results at MD Anderson Cancer indicating about 25% partial responses. Other agents including the monoclonal antibody (anti-CD33) coupled to calichiomycin (Mylotarg<sup>®</sup>) are under study as well as specific inhibitors of TNF.

In summary there is an increasing number of thera-

peutic options available for patients with MDS. These range from supportive care, cytokine, anti apoptotic agents to intensive chemotherapy±augmentation strategies.

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