

EDUCATION SESSION 11: MYELODYSPLASTIC SYNDROMES



The Myelodysplastic Syndromes: Morphology and Risk Assessment (1999)

John M. Bennett and Peter A. Kouides

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of hematopoietic stem cells inter-related with other clonal bone marrow diseases, such as the acute myeloid leukemias and myeloproliferative syndromes.

A number of investigators gathered in the early 1970s to form the French-American-British (FAB) Working Group. Our 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. We 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 MDS—refractory anemia with excess blasts (RAEB) and chronic myelomonocytic leukemia (CMML).

We knew that 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 we believed a common disease pathway began with a common 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 abnormalities (termed “dysplasia,” although it is a clonal disorder, and hence, neoplastic) of the peripheral blood and bone marrow cells such as ringed sideroblasts, megaloblastic 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 estimating the degree of apoptosis by in situ end-labeling of DNA. Virtually all marrows studied demonstrated apoptosis as well as rapid cell proliferation.

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. Our 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 (CLL).

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

Major portions of this review have appeared in *The Oncologist* 1997;2:389-401 and the Education Book of the 26th Congress of the International Society of Hematology 1996:72-85 (with permission).

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, 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.

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 secondary 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 (epipodophyllotoxins, anthracyclines). These results suggest a 60-times-higher incidence than would be expected in a control population.

Classification

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 we published the FAB classification for MDS in 1982, investigators found 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, including some members of the FAB Working Group, and modifications have been suggested. For example, evidence suggests that patients with greater than 10% leukemic blasts in the bone marrow (11-20%) experience disease progression as often as those who have 20% to 30% blasts. We needed time 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,

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	CR±	CR likely

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

Table 2. FAB Working Group Classification of MDS

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

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

and Romanovsky, iron, and hematoxylin 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%, 11-20%, >20-30%) or if they have CMML, which can be any percentage of blasts with a slight monocytosis of greater than 1,000/uL.

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 illness. These patients may require CML-type treatment with drugs such as hydroxyurea, interferon-alfa, 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.

Diagnostic Evaluation

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 an 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 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 trail that requires such studies.

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 MDS (e.g., t(15;17)), and the same abnormalities seen in both.

Prognostic Factors

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.

We attempted to improve on the existing systems by developing a unique scoring index, the International Prognostic Scoring System (IPSS), which includes a fourth group of patients (Table 4). 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.

We recently responded to letters to the editors of *Blood* questioning whether cytogenetics is a definitive prognostic factor. It clearly is in that it enables us to predict survival and evolution to AML in the low-risk group. This will help us individualize our strategies for treating the patients in whom karyotyping is available.

Abnormal localization of immature precursors (ALIP) is a new 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 normal 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 have 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 (WHO) appointed a committee to revise and update the diagnostic the Lymphomas and the Leukemias diagnostic categories. One of us (John M. Bennett) was privileged to be appointed to the subcommittee for acute leukemias and MDS. Changes have been suggested that will include the following:

1. Eliminate RAEB-t and establish AML when the percentage of marrow blasts is 20% or greater.
2. Eliminate nonproliferative CMML and list "monocytosis" under the other FAB sub groups (total counts >12,000/L will be incorporated under myeloproliferative disorders).
3. List two types of RAEB: RAEB-I (5-10% blasts) and RAEB-II (11-20% blasts).
4. Provide a new category of MDS, unclassified for cases with <5% blasts and moderate to severe dysplasia (>10% dysgranulopoiesis and/or 30% dysmegakaryocytopenia).

These new proposals have the approval of the clinical consultants to the WHO committee and are a reflection of new information on outcome and results of treatment. Publication is planned in several journals.

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.

Table 4. Risk Subgroup

Risk Subgroup	Score	Median survival (years)	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

Score

The score is based on the following parameters:

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%; absolute neutrophil count (ANC) <1,800/ul; platelet count <100,000/ul.

References

1. Aul C, Gattermann N, Schneider W. Age-related incidence and other epidemiological aspects of myelodysplastic syndromes. *Br J Haematol* 1992;82:358-367.
2. Bartl R, Frisch B, Baumgart R. Morphologic classification of the myelodysplastic syndromes (MDS): combined utilization of bone marrow aspirates and trephine biopsies. *Leuk Res* 1992;16:15-33.
3. Bennett JM, Catovsky D, Daniel MT et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982;51:189-199.
4. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick H, Sultan C, Cox C: The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Group [see comments]. *Br J Haematol* 87:746, 1994.
5. DeCillis A, Anderson S, Bryant J et al. Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) on NSABP-25: an update. *Proceedings of A.S.C.O.* 16:130a, 1997.
6. Dickstein JI, Vardiman JW: Issues in the pathology and diagnosis of the chronic myeloproliferative disorders and the myelodysplastic syndromes. [Review]. *Amer J Clin Path* 99:513, 1993.
7. Garand R, Gardais J, Bizet M, Bremond JL, Accard F, Callat MP, de Bouchony ET, Goasguen JE: Heterogeneity of acquired idiopathic sideroblastic anaemia (AISA). *Leukemia Res* 16:463, 1992.
8. Goasguen JE, Bennett JM, Cox C, Hambley H, Mufti G, Flandrin G. Prognostic implication and characterization of the blast cell population in the myelodysplastic syndrome. *Leukemia Res* 15:1159, 1991.
9. Greenberg P, Cox C, LeBeau MM et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079-2088.
10. Hamblin T. Clinical features of MDS. *Leuk Res* 1992;16:89-93.
11. Iwabuchi A, Ohyashiki K, Ohyashiki JH, Kimura Y, Lin KY, Aizawa S, Nehashi Y, Miyazawa K, Yaguchi M, Toyama K: Percentages of bone marrow blasts and chromosomal changes in patients with refractory anemia help to determine prognoses. *Int J Hematol* 60:207, 1994.
12. Kouides PA, Bennett JM. Morphology and classification of the myelodysplastic syndromes and their pathologic variants. *Semin Hematol* 1996;33:95-110.
13. Kouides PA, Bennett JM. Myelodysplastic syndromes. In: Abelloff MD, Armitage JO, Lichter AS, et al., eds. *Clinical Oncology*. New York: Churchill Livingstone, 1995:1977-1998.
14. Mangi MH, Salisbury JR, Mufti GJ: Abnormal localization of immature precursors (ALIP) in the bone marrow of myelodysplastic syndromes: current state of knowledge and future directions. [Review]. *Leukemia Res* 15:627, 1991.
15. Mathew P, Tefferi A, Dewald GW et al. The 5q- syndrome: a single-institution study of 43 consecutive patients. *Blood* 1993;81:1040-1045.
16. Michaux JL, Martiat P. Chronic myelomonocytic leukemia (CMML)—a myelodysplastic or myeloproliferative syndrome? *Leuk Lymphoma* 1993;9:35-41.
17. Raza A, Gezer S, Mundle S et al. Apoptosis in bone marrow biopsy samples involving stromal and hematopoietic cells in 50 patients with myelodysplastic syndromes. *Blood* 1995;86:268-276.
18. Raza A, Mundle S, Iftikhar A et al. Simultaneous assessment of cell kinetics and programmed cell death in bone marrow biopsies of myelodysplastics reveals extensive apoptosis as the probable basis for ineffective hematopoiesis. *Am J Hematol* 1995;48:143-154.
19. Tuzuner N, Cox C, Rowe JM, Watrous D, Bennett JM: Hypocellular myelodysplastic syndromes (MDS): new proposals. *Br J Haematol* 91:612, 1995.
20. Yoshida Y, Anzai N, Kawabata H. Apoptosis in myelodysplasia: a paradox or paradigm. *Leuk Res* 1995;19:887-891.