Hematology

MYELODYSPLASTIC SYNDROMES

Medical Grand Rounds

October 6, 1983

R. Graham Smith, M.D.
Division of Hematology/Oncology
Department of Internal Medicine
University of Texas Health Science Center
5323 Harry Hines Blvd.
Dallas, Texas 75235

I. Introduction

A. Definition

Not infrequently the hematologist sees a patient who presents with one or more cytopenias, a cellular bone marrow, and morphologic abnormalities of one or more hematopoietic lineages. Many of these patients are elderly. Usually no apparent cause of the cytopenias is evident. These features define a group of disorders termed the myelodysplastic syndromes (MDS) (1). These conditions are distinguished from aplastic anemia by the presence of a cellular marrow with dysplasia in one or more lineages. MDS differs from acute leukemia since the marrow is not totally replaced with immature (blast) cell forms, although marrow myeloblasts may be increased in some types of MDS. Put another way, the MDS are primarily disorders of hematopoietic cell differentiation while the acute leukemias are characterized by increased proliferation as well as blocked differentiation. Finally, MDS differs from the myeloproliferative disorders (polycythemia vera, myelofibrosis, essential thrombocythemia), which display abnormal proliferation of one or more maturing myeloid lineages as well as reticulin marrow fibrosis. The MDS are about as common as acute myelogenous leukemia (AML) in our patient population and are considerably more common than aplastic anemia. Iatrogenic MDS has become a major problem in clinical oncology as a late complication of exposure to alkylating agents and/or irradiation. These patients present major unsolved problems in management and guaging prognosis.

B. Illustrative Cases

1. Stable refractory anemia - B.A., a 48-year-old housewife (case #3), became lethargic in 1975 and was found to have a macrocytic anemia. The hemoglobin was 9.4 g/dl; mean corpuscular volume 119 μ^3; white blood count 6100/μl with a normal differential; platelets 585,000/μl; reticulocytes <1%. A bone marrow smear revealed decreased cellularity, mildly megaloblastic erythroid changes, and megakaryocytic hyperplasia. The nuclei of the megakaryocytes were unilobular. No ring sideroblasts were seen. Serum B_{12}, folate, iron, and iron binding capacity were normal. Cytogenetic study of the bone marrow revealed a partial deletion of the long arm of chromosome 5 (5q-defect). Over the past 8 years she has required red cell transfusions every 1-4 months. A trial of androgens was unsuccessful in diminishing her transfusion requirement. Repeat bone marrow in February, 1979, revealed increasingly dysplastic megakaryocytic hyperplasia, mildly megaloblastic erythropoiesis, and multiple lymphoid nodules. The 5q-abnormality was found in 40% of metaphases. No increase in myeloblasts was detected. After receiving approximately 60 units of red cells, subcutaneous therapy with the iron chelator desferrioxamine was begun in February, 1980. Febrile transfusion reactions are the major management problem at this time.

Comment - The 5q-abnormality has been described in a number of patients with refractory macrocytic anemia, mild thrombocytosis, non-lobulated megakaryocytes, and a stable course (2,3). In addition, some patients presenting with progressive MDS or AML have been found to have the 5q- lesion together with other karyotypic abnormalities (4,5), and a small number of patients with 5q- MDS may progress to AML (6). Thus, the prognostic significance of this cytogenetic change is uncertain at this time.

2. Evolution of AML after an extended period of myelodysplasia - R.M., a 50-year-old salesman (case #7), was found to have mild anemia and thrombocytopenia in 1980. A spleen tip had been palpable since 1974, and a diagnosis of hereditary spherocytosis was made. A bone marrow revealed mild dyserythropoiesis, left-shifted granulopoiesis and decreased megakaryocytes. Two years later his white count increased to 20,500/μl with a leftward shift and dysgranulopoiesis. A bone marrow revealed clusters of myeloblasts, some containing Auer rods and a diagnosis of AML was made. He was treated with cytosine arabinoside and Adriamycin, resulting in a complete remission except for mild, dysgranulopoiesis. This change progressively worsened, with an increasing leftward shift, over the next 6 months. Three months later his marrow again contained sheets of myeloblasts, and presently he remains in relapse. His erythropoiesis has remained mildly megaloblastoid throughout.

Comment - The gradual progression of dysgranulopoiesis after anti-leukemic therapy suggests his remission was never really complete. In fact, chemotherapy may have promoted granulocyte maturation (Section X).

II. Classification

The classification of MDS currently recommended by the French-American-British (FAB) co-operative group is summarized in Table 1 (1).

TABLE 1. CLASSIFICATION OF THE MYELODYSPLASTIC SYNDROMES

Syndrome	Cytopenias*	Dysplasia*	Blasts PB	Blasts BM	Monocytes
1. Refractory Anemia (RA)	Anemia Reticulocytopenia	Dyserythropoiesis E.H.	<1%	<5%	$<10^3/\mu l$
2. Refractory Anemia with Ring Sideroblasts	Anemia Reticulocytopenia	Dyserythropoiesis >15% Ring Sideroblasts, E.H.	<1	<5	$<10^3/\mu l$
3. Refractory Anemia with Excess Blasts (RAEB)	Anemia Reticulcytopenia Neutropenia	Dyserythropoiesis Dysgranulopoiesis G.H., left shift, E↑, G↑	<5	5-20	$<10^3/\mu l$
4. Chronic myelo-monocytic Leukemia (CMML)	[Monocytosis] [Granulocytosis]	Dysgranulopoiesis	<5	<1-20	$>10^3/\mu l$
5. RAEB in Transformation	Anemia Reticulocytopenia Neutropenia Thrombocytopenia	Dyserythropoiesis Dysgranulopoiesis Dysmegakryocytopoiesis	>5	20-30 Auer Rods*	$<10^3/\mu l$

*All the listed features need not be simultaneously found, but some evidence of dysplasia must be present. E↑, erythroid hyperplasia; G↑, granulocytic hyperplasia. From Ref. 1.

Many hematologists use the terms subacute or smoldering granulocytic leukemia for RAEB and RAEB in transformation. Additional clinical characteristics of these syndromes are given in Sections IV and V.

III. Etiology and Pathogenesis

A. Clonal Nature of MDS

A key observation has been the recognition that many, if not all, of these syndromes originate in an altered stem cell. First, the disorders that progress to AML are panmyelopathies, involving all 3 myeloid lineages. In addition, both cytogenetic (7) and isoenzyme (8) analysis demonstrate that the dysplastic hematopoietic cells are clonal in origin. Often a mixture of cytogenetically normal and abnormal cells is found, suggesting the presence of competing stem cell clones. These observations suggest that somatic mutation or other genetic alterations play a major role in the pathogenesis of MDS. In most instances the cause of these stem cell alterations is unknown. It has become clear, however, that mutagenic influences such as alkylating agents and ionizing radiation may lead to MDS-like syndromes as well as to AML.

B. Cytogenetic Abnormalities in Marrow Cells from Patients with MDS

Several non-random cytogenetic changes have been observed in marrow cells taken from patients with MDS. About 25 to 50% of such patients harbor cytogenetically abnormal marrow clones (7-9). These abnormalities involve chromosomes 5 (5q- or monosomy), 7 (7q- or monosomy), 8 (trisomy), and 20 (20q-). Changes frequently seen in de novo AML and CML (t(8;21), t(15;17)), have not been seen in MDS although the Ph^1 chromosome (t(9,22)) has been reported in a single case (10). Conversely, changes common in MDS, with the exception of +8, are unusual in de novo AML. These differences suggest that the pathogenesis of MDS differs from that of unheralded AML--that is, AML presenting without a cytopenia prodrome (9).

TABLE 2. CYTOGENETIC ABNORMALITIES IN MARROW CELLS FROM PATIENTS WITH MDS (7)

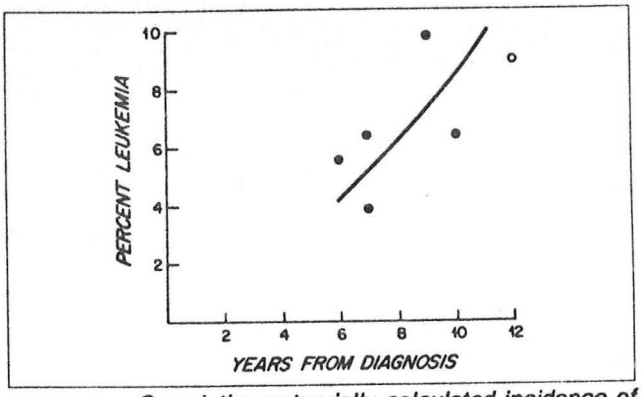
Abnormality	Number of Patients	%
None	119/244	49
Any	125/244	51
+8	21/125	17
-7,7q-	29/125	23
-5,5q-	20/125	16

C. MDS in Patients Treated with Cytotoxic Chemotherapy

Development of acute nonlymphocytic leukemia in patients with a broad range of malignancies and non-malignant disorders after therapy with cytotoxic drugs, usually alkylating agents, has been well recognized for a number of years (11). In many of these patients AML evolves from an MDS of varying (often short) duration. The risk of these disastrous complications may be substantial. Patients given the MOPP regimen and irradiation for Hodgkin's disease have a cumulative risk of AML of 6-10% at 10-12 years (12) (Figure 1). Marrow cytogenetic abnormalities in this group of patients are similar

to those seen in other patients with MDS (Table 2), except that multiple abnormalities are more commonly seen in the therapy-related group of patients (9).

Figure 1.



Cumulative actuarially calculated incidence of acute nonlymphocytic leukemia after treatment of Hodgkin's disease with the MOPP combination and irradiation. O = present study; ● = figures from the recent literature [3-5, 7, 9]; see text for details.

D. MDS in Patients Exposed to Ionizing Radiation

The leukemogenic effects of ionizing radiation are well-known (13). MDS-like syndromes were seen in the atom bomb survivors (14). In patients irradiated for control of Hodgkin's disease, the risk of MDS or AML appears to be minimal (15). Nonetheless, the development of MDS and AML in patients who receive radiotherapy without chemotherapy is a measurable risk of treatment (16).

E. MDS Following Benzene Exposure

Exposure to benzene can lead to MDS as well as to aplastic anemia (17). Of 44 pancytopenic patients with occupational exposure to benzene who were followed for 2-17 years, 23 patients recovered completely, 14 died of complications of pancytopenia, 1 died of myeloid metaplasia, and 6 developed AML. Leukemia was commoner in patients with initially hypoplastic marrows, compared to those with normocellular marrows. Leukemia developed 6 months to 6 years after the onset of pancytopenia (17).

IV. Morphologic Features of Myelodysplastic Syndromes

A. Peripheral Blood

In MDS cytopenias are due to ineffective hematopoiesis, due to defective cytodifferentiation. Any one, two, or three lineages may be involved. Cytopenias are accompanied by morphologic evidence of dysplasia, as outlined below (1).

1. Dyserythroporesis - macrocytosis, anisopoikilocytosis, basophilic stippling, circulating normoblasts

2. Dysgranulopoiesis - agranular or hypogranular cytoplasm; basophilic cytoplasm in mature granulocytes, hyposegmentation (Pelger-Huet anomaly = bilobed granulocytes); occasionally hypersegmentation with bizarre shapes
3. Dysmegakaryocytopoiesis - giant platelets, hypogranular platelets, circulating megakaryocytes
4. Monocytes - monocytosis (>1000/μl), immature monocytes

Dysplasia is evident at the functional level as well. Shortened red cell survival (18,19) neutrophil dysfunction (20,21), and platelet dysfunction (22) are common findings.

B. Bone Marrow

The diagnosis of MDS is confirmed by examination of the marrow, which reveals characteristic dysplasia. The marrow cellularity is decreased to increased, but by definition is not aplastic.

1. Dyserythropoiesis- ringed sideroblasts, multinuclearity, nuclear fragments or budding, lobed nuclei, megaloblastic or megaloblastoid forms, PAS positivity, clear cytoplasmic areas, basophilic stippling; erythroid hyperplasias, hypoplasia
2. Dysgranulopoiesis - left shift; granule abnormalities (apparent absence of granules or giant granules), peripheral cytoplasmic basophilia, abnormally segmenting nuclei, asynchronous cytoplasmic/nuclear maturation, nuclear blebs, giant nuclear lobes, hypersegmentation; "paramyeloid" cells with morphology intermediate between myelocytes and monocytes (especially in CMML); Auer rods
3. Dysmegakaryocytopoiesis - micromegakaryocytes including nonlobated or bilobed nuclei, large mononuclear forms, multiple small separated nuclei, giant or abnormal cytoplasmic granules

C. Excess of Myeloblasts

Up to 30% blasts may be found in the marrow, according to the FAB classification. Typical (type I) myeloblasts or blasts with a few primary (azurophilic) granules (type II) may be found. The occasional presence of Auer rods emphasizes the relationship of these disorders to AML.

V. Recapitulation: Presenting Clinical Features of MDS

Patients with MDS will usually come to the attention of physicians because of unexplained anemia. Occasionally they present with isolated neutropenia or thrombocytopenia (23). Commonly there is bicytopenia or pancytopenia. Uncommonly, as in CMML, a leukocytosis is found. An important clue is the finding of a cellular marrow in the face of these cytopenias. As noted above, morphologic evidence of dysplasia in one or more cell lineage is found in both the peripheral blood and bone marrow.

Another common feature in the marrow is a left shift in granulopoiesis, with or without elevated numbers of myeloblasts; this immaturity falls short of the extensive blastic replacement seen in AML. Clinical problems relate to

the various cytopenias, which do not respond to nutritional replacements. The course and prognosis of the various syndromes is discussed in Section VIII.

VI. Differential Diagnosis

Before a diagnosis of MDS is made, certain treatable disorders which can superficially resemble MDS should be excluded.

A. Megaloblastic Anemias

These anemias characteristically present with macrocytic anemia and megaloblastic erythroid hyperplasia. In severe cases other cytopenias can be seen. Marrow iron accumulation with occasional ring sideroblasts may be found, especially in alcoholics. Predominant erythroid hyperplasia, classic megaloblastic dyserythropoiesis at all levels of maturity, megaloblastic metamyelocytes and bands, hypersegmented polys, and the absence of a striking left shift in granulopoiesis help distinguish these anemias from MDS. Nonetheless, certain cases may be sufficiently confusing to justify laboratory studies to exclude vitamin B_{12} or folate deficiency. Megaloblastic dyspoiesis may be seen during antimetabolite therapy and in copper deficiency states. In the adult, copper deficiency has been seen most often in chronic gastrointestinal diseases or when trace metals are not given to patients on parenteral hyperalimentation.

B. Sideroblastic Anemias

Secondary (treatable) sideroblastic states include those caused by drugs (isoniazid, cycloserine, pyrazinamide, chloramphenicol), lead intoxication, and ethanol. Sideroblastic anemia may also be associated with a variety of chronic inflammatory and neoplastic diseases; successful therapy of the chronic disease may ameliorate the anemia. Finally, certain sideroblastic states are heritable and rarely, if ever, progress to leukemia. All of these conditions involve primarily the erythroid lineage. In contrast, many patients with MDS harbor dysplasia in 2 or all 3 myeloid lineages. Idiopathic acquired sideroblastic anemia, however, is classified as an MDS and is often accompanied by entirely normal granulopoiesis and thrombopoiesis. In making this diagnosis, known causes of sideroblastic anemias must be excluded.

C. Immunologic Blood Cell Injury

Autoimmune hemolytic anemia, thrombocytopenia, and leukopenia may cause cytopenias with marrow hyperplasia. Usually, dysplasia of blood and marrow cells is absent or minimal in these conditions. Occasionally, however, co-existant folate deficiency or alcoholism may cause enough marrow dysplasia to create confusion with MDS. Acquired pure red cell aplasia (PRCA) may result from autoimmune destruction of committed red cell precursors (25). PRCA is rarely a preleukemic condition. Chromosomal abnormalities may provide a clue as to which few cases of PRCA may progress to leukemia (26).

D. Toxic Marrow Injury

Arsenic poisoning may cause severe dyserythropoiesis. During recovery from a variety of drug- or toxin-induced marrow injury, a certain degree of dysplasia may be seen. These changes are transient.

VII. Summary of Cases of MDS seen at PMH and DVAH

The presenting clinical features and course of 37 patients with MDS seen at PMH and the DVAH over the past 8 years are summarized in the Appendix and Table 3. Of 8 patients presenting with refractory anemia, 2 have remained stable over a 7 to 12 year follow-up. One has progressed to AML, while 5 died during the period of refractory anemia of causes related to cytopenias. Patient 8, although remaining clinically stable, has developed signs of dysgranulopoiesis.

Of the 9 patients with refractory anemia with ring sideroblasts, 2 progressed to AML and 1 to RAEB. One of these patients (#10) displayed only dyserythropoiesis on presentation 5 years before developing AML; multilineage dysplasia or granulocyte lineage immaturity was not seen. Three of these patients remained stable over a 2 to 6 year follow-up period.

Nine patients presented with refractory anemia with excess blasts. Three of these patients progressed to frank AML, while 3 died of causes directly related to cytopenias. Nine patients presented "in transformation" by the FAB classifications. Four of these patients developed overt AML, while 4 died of causes related to cytopenias 6 to 18 months after diagnosis.

Two patients fit the category of chronic myelomonocytic leukemia. One of these patients has remained hematologically stable over a follow-up period of 4 years, while one died of unrelated causes one month after diagnosis.

Six patients received alkylating agents prior to the onset of MDS and, therefore, may have had iatrogenic disease. Two of these patients (#19 and #37) were given alkylating agents for non-neoplastic disease.

TABLE 3. PATIENTS WITH MDS AT PMH-DVAH 1975-83: SUMMARY

Disease	Number	Progression to AML	Deaths
RA	8	1 (24)*	5 (5-36)*
RARS	9	2 (4,60)	4 (1-42)
RAEB	9	3 (1-6)	7 (1-60)
CMML	2	0	1 (1)
RAEB-T	9	4 (2-12)	7 (4-18)

RA, refractory anemia; RARS, refractory anemia with ring sideroblasts; RAEB, refractory anemia with excess blasts; CMML, chronic myelomonocytic leukemia; RAEB-T, refractory anemia with excess blasts, in transformation.

*The figures in parenthesis are the times in months from diagnosis to progression or to death.

VIII. Prognosis

A. Clinical and Morphologic Guides

Patients with MDS may survive for years with stable anemia, die of complications of cytopenias, or progress to AML. As exemplified by our cases, prediction of natural history is often a difficult matter. Greenberg has recently reviewed this issue (27). Unfortunately, he does not address patients with isolated refractory anemias without bi- or trilinege abnormalities. Most hematologists agree that patients with isolated refractory anemias have a good prognosis, with fewer than 10% progressing to AML (28). The risk of progression may be lowest in subjects with abundant complete ring sideroblasts (29). Some have argued that this condition (idiopathic acquired sideroblastic anemia) is not a preleukemic condition (30). Two of our patients fitting this description, however, progressed to AML (#10) or RAEB (#16). Considering patients with more advanced MDS, including patients with dysplasia in more than one lineage or with increased blasts, reported median survivals range from 6 to 30 months (27) (Table 4). The abundance of blasts is probably the most important prognostic factor. Patients with >10% marrow blasts have survivals ranging from 6 to 12 months (27). A wide divergence in the frequency of transition to AML is reported. It is Greenberg's thesis that morphologic features fail to predict natural history with any accuracy and that biologic variables such as marrow cytogenetics and <u>in vitro</u> growth patterns correlate better with prognosis (27).

TABLE 4. CLINICAL FEATURES OF THE SMOLDERING MYELOID LEUKEMIC STATES

	Preleukemia	RAEM	SML
DX criteria, marrow	Hemopoietic dysplasia	Blasts + Pros* 5%-40%	Blasts 10%-40%
References	2, 3, 15, 39-42	8, 10, 43-45	4, 5, 7, 18, 36, 39, 46, 47
No. patients	312	220	212
Age >50 yr	63%-85%†	60%-90%	58%-75%
Male	60%-88%	59%-73%	60%-70%
Transformation to AML	23%-44%	14%-64%	25%-59%
Median Survival (mos)	18-20	13-30	6-12
Anemia	15%-90%	27%-100%	82%-100%
Neutropenia	37%-53%	50%-54%	20%-60%
Thrombocytopenia	40%-68%	41%-65%	33%-76%
Pancytopenia	30%-44%	40%-65%	38%-41%
Monocytosis	0%-40%	10%-30%	2%-40%
Peripheral Blasts	0	0-+	0-+ +
Splenomegaly	20%-40%	—	10%-60%

*Percent marrow blasts and abnormal promyelocytes.

†Range of incidences of the features in the cited references.

RAEM, refractory anemia with excess myeloblasts; SML, smoldering myeloid leukemia

B. Cytogenetic Studies

Among the patients reported in the Second International Workshop on Chromosomes in Leukemia (7), about twice as many with a chromosomally abnormal marrow clone progressed to AML as those without such an abnormality

(Table 5). Similar results have been reported by several independent groups (reviewed in ref. 27) (Table 6). Multiple cytogenetic abnormalities (involving more than 2 chromosomes) may connote a particularly bad prognosis. Twelve of 14 such patients studied by Nowell's group were dead within 4 months of study. Nine of these patients progressed to AML, while 3 died of complications of cytopenias (9). Patients with chemotherapy-linked MDS frequently display such multiple cytogenetic abnormalities (9). Unfortunately, in limited prospective studies patients exposed to chemotherapy have not developed detectable cytogenetic abnormalities prior to the development of clinical MDS (9). Apparently, by the time the abnormal clone is large enough to permit detection by cytogenetic examination, marrow dysfunction has already reached an advanced stage.

One point should be emphasized: The finding of a normal karyotype does not exclude the possibility of progression to AML (Table 5)

TABLE 5. CLASSIFICATION OF PATIENTS BY NN, AN, AND AA AND PROGRESSION TO ANLL

Chromosome category	Total No.	With progression to ANLL		Without progression to ANLL	
		No.	%	No.	%
NN	119	18	15.1	101	84.9
AN	78	21	26.9	57	73.1
AA	47	13	27.7	34	72.3

NN, normal metaphases only; AN, normal and abnormal metaphases; AA, abnormal metaphases only

TABLE 6. PROGNOSIS OF SMOLDERING MYELOID LEUKEMIC STATES: UTILITY OF MARROW CYTOGENETIC STUDIES

Karyotype	Incidence (%)	Transformation to AML (%)	Median Survival (mo)
SML, RAEM—15 patients[43,62]		60	15
Normal karyotype	33 (0-55)*	40	30
Abnormal karyotype	67 (40-100)	70	10 (8-21)
Preleukemia—135 patients[12,42,58,59]		42	9
Normal karyotype	66 (64-79)	31 (22-39)	12 (10-19)
Abnormal karyotype	34 (21-36)	72 (66-77)	4 (3-5)

*Mean values and ranges of means for cited studies.

C. Bone Marrow Culture Studies

Granulocyte-macrophage progenitors in bone marrow will form colonies of differentiating granulocytes and macrophages in soft agar cultures containing appropriate growth factors. Decreased formation of normal granulocyte/macrophage colonies, with increased growth of small, poorly differentiating clusters has been reported to correlate with an adverse prognosis in MDS (reviewed in ref. 27) (Table 7). Other studies have demonstrated substantial overlap in colony formation between favorable and unfavorable prognostic groups, making predictions about individual patients unreliable (31). Thus, the utility of marrow culture studies as a prognostic guide is uncertain at this time.

TABLE 7. PROGNOSIS OF SMOLDERING MYELOID LEUKEMIC STATES: UTILITY OF IN VITRO MYELOID GROWTH PATTERNS

Growth Patterns	Incidence (%)	Transformation to AML (%)	Median Survival (mo)
SML, oligoblastic leukemia —80 patients[47,66]		51 (45-56)*	9 (7-11)
Nonleukemic growth	33 (27-38)	31 (29-33)	20 (15-25)
Leukemic growth	68 (62-73)	60 (50-70)	7 (5-8)
RAEM—17 patients[43]		41	14
Nonleukemic growth	70	29	21
Leukemic growth	30	100	10
Preleukemia—82 patients[15-17]		40 (35-44)	16 (9-20)
Nonleukemic growth	54 (30-74)	29 (21-40)	34 (9-50)
Leukemic growth	46 (26-70)	64 (50-80)	9 (4-10)

*Mean values and ranges of means for cited studies.

X. Treatment

A. Refractory Anemia

These patients are frequently transfusion-dependent. Responses to androgens, corticosteroids, lithium, and pyridoxine are incomplete at best. Management centers around preventing or ameliorating complications of long-term transfusions--including transfusion reactions and iron overload. Iron chelation therapy with subcutaneous Desferol becomes necessary after about 50 units (12 g Fe) have been administered in order to prevent lethal complications of transfusional hemochromatosis (32).

B. Refractory Anemia with Excess Blasts

These patients often are pancytopenic. During the preleukemic phase of their illness, they will require occasional support with platelet transfusions and antibiotics in addition to chronic transfusion therapy. Glucocorticoids may increase blood cell counts in 10-15% of patients (33).

Some debate has focused on the best management of patients with progressively increasing blast cell burdens. The traditional view held that AML following a preleukemic phase responded poorly to standard cytoreductive therapy, and that such patients were best managed with supportive care only. This view emerged from the experience that many patients given antileukemic therapy died promptly of infection, bleeding, or both (34-36). Recently, complete remissions have been reported in a small subset of these patients (37,38). In therapy-linked AML these remissions were brief (37). Many of these patients are elderly and, therefore, tolerate standard remission induction therapy poorly.

The mechanism of remission in these patients is of some interest. Some patients appear to achieve a true complete remission with the return of normal hematopoiesis (38). Others, such as our patient #7, are simply returned to a more stable MDS, with residual cytopenia(s) and dysplasia. Few cytogenetic studies to document eradication of abnormal clones have been done, and some "remissions" may result from temporary induction of maturation rather than complete suppression of the abnormal clone (Section X.C.1., below).

In summary, standard remission induction therapy may be of value in some of these patients who progress to overt AML. The problem remains the selection of patients most likely to benefit from this therapy. At the present time, this selection is based on estimates of patient tolerance for the rigors of induction therapy, as well as the wishes of the well-informed patient. Clearly, remission induction therapy should be reserved for patients with a poor prognosis, generally those who have progressed to AML.

C. Experimental Therapy

Newer approaches to therapy of MDS are clearly needed (27). Recent interest has focused on two areas: differentiation inducers and bone marrow transplantation.

1. Differentiation inducers - Stimulated by Charlotte Friend's observation that murine erythroleukemia cells could be induced to differentiate with dimethyl sulfoxide (39), many investigators have demonstrated that a variety of cultured rodent and human leukemic cells can be made to differentiate in vitro in response to a broad range of compounds including many chemotherapeutic agents (40), retinoids (41), and 1α,25-dihydroxy-vitamin D3 (42). This differentiation is usually aberrant and incomplete, but most importantly, is often accompanied by loss in self-renewal capacity. Treatment with these compounds, therefore, represents a quite different approach to these disorders--an approach not based on direct cell destruction but upon restoration of a normal genetic program of the cell, namely differentiation and loss of self-renewal capacity.

Several clinical trials in MDS patients with these agents have begun. These drugs include low-dose cytosine arabinoside (43-45), retinoids (46), and vitamin D analogues (47). To summarize, meaningful responses have been achieved in a minority subset of patients in both preleukemic and leukemic categories (44-47). Since these therapies are relatively nontoxic, further trials are certainly warranted. This approach, if effective, would be particularly appropriate for elderly individuals who are unable to withstand aggressive remission induction therapy.

2. Bone marrow transplantation - Recent trials have shown that allogeneic transplantation following marrow ablation is potentially curative in AML developing out of MDS (48,49). Transplantation would seem to be an ideal approach to many MDS, since defective hematopoietic clones are replaced by normal clones. Unfortunately, the vast majority of patients are too old to be considered for bone marrow transplantation, since the cutoff age for transplantation in most centers is 40 years.

XI. Summary and Conclusions

MDS is a loosely knit group of bone marrow disorders characterized by cytopenias and morphologic abnormalities (dysplasias) in one or more hematopoietic lineages. Based on cytogenetic evidence, the pathogenesis of these disorders may differ from that of AML presenting de novo, even though both disorders result from an outgrowth of abnormal stem cell clones. It is clear that alkylating agents and related cytotoxic agents may induce MDS. This risk must be kept in mind when these agents are used to treat patients with non-neoplastic diseases. Certain patients with isolated refractory anemia

may remain stable for years, while other patients, generally with multiple cytopenias or dysplasias, either die of complications of marrow failure or progress to overt AML in a matter of months. Treatment for anemia or the preleukemic phase of these disorders is supportive. Management of overt leukemia following MDS is unsatisfactory. Standard remission induction therapy may yield remissions in a small subset of these patients. For many others, alternate means of therapy are badly needed. Therapy with differentiation inducers is one new approach now undergoing clinical trial. This approach is attractive because the toxicity is minimal.

REFERENCES

1. Bennett JM, Catovsky D, Daniel MT, et al. Br J Haematol 51:189, 1982.
2. Sokol G, Michoux JL, Van den Berghe H, et al. Blood 46:519, 1975.
3. Mahmood T, Robinson WA, Hamstra RD, et al. Am J Med 66:946, 1979.
4. Rahman F, Brown CH. Proc Am Assoc Cancer Res 19:309, 1978.
5. Kerkhofs H, Hasemeijer A, Leeksma CH, et al. Br J Haematol 52:365, 1982.
6. Jume'an HG, Libnoch JA. Ann Intern Med, 91:748, 1979.
7. Van den Berghe H, et al. Cancer Genet Cytogenet 2:108, 1980.
8. Fralkow P. Ann Rev Med 30:135, 1979.
9. Nowell PC. Cancer Genet Cytogenet 5:265, 1982.
10. Roth DG, Richman CM, Rowley JD. Blood 56:262, 1980.
11. Kyle RA. Semin Oncol 9:131, 1982.
12. Aisenberg AC. Am J Med 75:449, 1983.
13. Lillienfeld AM. Yale J Biol Med 39:143, 1966.
14. Kamada N, Uchino H. Blood Cells 2:57, 1976.
15. Pedersen-Bjergaard J, Larsen SO. N Engl J Med 307:965, 1982.
16. Pedersen-Bjergaard J, Philip P, Pedersen NT. Proc Am Soc Clin Oncol 2:C-674, 1983.
17. Aksoy M, Erdem S. Blood 52:285, 1978.
18. Helmstadter V, Arnold H, Blume KG, Uhl N, Hunstein W. Acta Haematol 57:339, 1977.
19. Riedler GF, Straub PW. Blood 40:345, 1972.
20. Ruutu P, Ruutu T, Vuopio P, et al. Scand J Haematol 18:317, 1977.
21. Breton-Gorius J, Coquin Y, Vilde JL, Dreyfus B. Blood Cells 2:187, 1976.
22. Lintula R, Rasi V, Ikkala E, et al. Scand J Haematol 26:65, 1981.
23. Tricot J, Criel A, Verwilghen RH. Scand J Haematol 28:243, 1982.
24. Hines JD, Grasso JA. Semin Hematol 7:86, 1970.
25. Krantz SB, Moore WH, Zaentz SD. J Clin Invest 52:324, 1973.
26. Dessypris EN, Pogo A, Russell M, et al. Blood 56:421, 1980.
27. Greenberg PL. Blood 61:1035, 1983.
28. Geary CG. Br J Haematol 55:1, 1983.
29. Hast R. Scand J Haematol 21:396, 1978.
30. Heimpel H. Preleukemia, Springer, Berlin, 1979, pp 139-146.
31. Milner GR, Testa NG, Geary CG, et al. Br J Haematol 35:251, 1977.
32. Schafer AI, Cheron RG, Dluhy R, et al. N Engl J Med 304:319, 1981.
33. Bagby GC, Gabourel JD, Linman JW. Ann Intern Med 92:55, 1980.
34. Joseph A, Cinkatal K, Hunt L, et al. Br J Cancer 46:160, 1982.
35. Cohen JR, Creger WP, Greenberg PL, et al. Am J Med 66:959, 1979.
36. Armitage JO, Dick FR, Needleman SW, et al. Cancer Treat Rep 65: 601, 1981.
37. Duane SF, Peterson BA, Bloomfield CD, et al. Proc Am Soc Clin Oncol 2:177, 1983 (abstr. C-688).
38. Murray C, Cooper B, Kitchens LW, Jr. Cancer 52:967, 1983.
39. Friend C, Scher W, Holland JG, et al. Proc Natl Acad Sci USA 68: 378, 1971.
40. Schwartz EL, Ishiguro K, Sartorelli AC. Adv Enzyme Regulation 21: 3, 1983.
41. Breitman TR, Selonick SE, Collins SJ. Proc Natl Acad Sci USA 77: 2936, 1980.
42. Abe E, Miyaura C, Sakayami H, et al. Proc Natl Acad Sci USA 78: 4990, 1981.

43. Najean Y, Pecking A. Cancer 44:1976, 1979.
44. Housset M, Daniel MT, Degas L. Br J Haematol 51:125, 1982.
45. Castaigne S, Daniel MT, Tilly H, et al. Blood 62:85, 1983.
46. Moore M, personal communication, 1983.
47. Koeffler P, personal communication, 1983.
48. Gyser M, Perreault C, Boileau J, et al. Blood 61:1275, 1983.
49. Perreault C, Gyser M, Boileau J, et al. N Engl J Med 308:777, 1983.

APPENDIX

MYELODYSPLASTIC SYNDROMES: PMH & DVAH PATIENTS SEEN 1975-1983

#	Age/Sex	Previous History	Cytopenias	Smear	Marrow Dysplasia	Marrow Other	Course
I.	RA						
1	62/F	Hodgkin's MOPP	A,G,T		[dry tap]	60% Cellular	Died 5 mos post-diagnosis severe pancytopenia, red cell alloantibodies
2	70/M	EtOH	A,T		E	G↓	Persistent thrombocytopenia, GI bleeding. Died 8 mos post-diagnosis
3	42/F	Marshall Islands	A	Macrocytic	E,M		Stable anemia over 7 yr Febrile transfusion reactions, iron overload
4	60/F	WDLD Lymphoma Cytoxan, chlor-ambucil	A,G,T	Pelgeroid	E,G	Lymphoma	Died 8 mos post-diagnosis Progressive pancytopenia, sepsis
5	78/M	Splenomegaly	A,G,T		E	Left shift G	Died 3 yrs post-diagnosis Sepsis with splenectomy
6	78/M		A,G,T	Pelgeroid Left shift	E,G,M	M↓	Died 6 mos post-diagnosis Sepsis, bleeding Terminal neutrophilia with left shift
7	50/M	Splenomegaly	A,T		E,G,M	M↓	Progression to AML 2 yrs post-diagnosis
8	50/M		A		E	E↓	Stable mild anemia over 12 yrs Recent Pelgeroid changes
II.	RA with Ring Sideroblasts						
9	60/M	Anemia 1 yr Exposure to gasoline, kerosine, naphtha, benzene (auto mechanic)	A,G,T	Pelgeroid	E,G,M	Left shift G	Progression to AML 4 mos post-diagnosis, died 2 mos later
10	68/M	PCDUS	A		E		Progression to AML 5 yrs post-diagnosis
11	72/F	Anemia 3 yrs Chronic renal failure	A		E		Died 1 mo post-diagnosis CVA
12	71/M	Myeloproliferative disorder, HN_2, busulfan, ara-C	A,G		E	G↓, M↑	Developed 5q- 2 yr post-alkylating agent therapy
13	87/M		A		E	G↓	Died 3.5 yrs post-diagnosis Unknown causes
14	81/M	Cirrhosis, splenomegaly, 30 yr history anemia	A		E		Stable anemia. Died 3 yrs post-diagnosis - unknown cause
15	/M		A		E		Stable anemia 6 yrs Pyridoxine - refractory
16	56/M		A		E		Progression to RAEB 8 yr post-diagnosis
17	86/M		A	Macrocytic	E,G	M↑	Died 20 mos post-diagnosis Unrelated causes

#	Age/Sex	Previous History	Cytopenias	Smear	Marrow Dysplasia	Marrow Other	Course
III.	RAEB						
18	77/M	? insecticides	A,G,T	Rare blast	G,M		Died 5 mos post-diagnosis Cause of death - acute leukemia
19	33/F	Myasthenia gravis 11 yrs. Cytoxan, Imuran, Prednisone	A,G,T			G↑	Died 1 mo post-diagnosis Autopsy: AML
20	58/M		A,G	Pelgeroid	E,G,M		Stable cytopenias over 2 yrs, iron overload
21	98/F		A,G	Macrocytosis Rare blast	G	E↓	Died 2 mos post-diagnosis Progressive pancytopenia
22	75/F		A,G	Pelgeroid Left shift	E,G		Died 5 yrs post-diagnosis Fever, renal failure
23	44/F		A		E,G,M		Developed S.L.E., Stable counts over 1 yr
24	79/M	GI bleeding, PCDUS	A	Pelgeroid Rare blast	E		Died 7 mos post-diagnosis Gastric carcinoma, terminal neutrophilia
25	59/M		A,G,T				Progression to AML 6 mos post-diagnosis. Died 2 mos later - sepsis
26	64/M		A,G,T		E	E↓, G↓, M↓	Died 7 mos post-diagnosis GI bleeding
IV.	CMML						
27	61/M	Intermittent macro anemia 10 yrs, ? nutritional in origin	A	Monocytosis WBC 15,300 Macrocytosis		10-15% immature monocytes	Died 14 d post-diagnosis Arrhythmia
28	50/F		A	Monocytosis			Stable over 4 yrs
V.	RAEB, in transformation						
29	42/M	Perirectal abscess	A,G,T		G		Progression to AML 3 mos post-diagnosis. Died 1 mo later post-HIDAC induction course
30	72/M	Service station cashier	A,G,T		G		Died 6 mos post-diagnosis bleeding, sepsis
31	76/M		A,G		E,G		Progression to AML 2 mos post-diagnosis. Died 2 mos. later
32	45/M	Worked in rubber factory - ? benzene exposure		Pelgeroid 6% blasts	E,G	M↓, 30% blasts	Progression to AML 4-6 mos post-diagnosis
33	65/M	Myeloma, 20 courses Alkeran Radiotherapy T11	A,T	Pelgeroid Rare blast	G	E↓	Died 11 mos post-diagnosis subdural hematomas
34	55/M		A,T	NRBC Left shift Pelgeroid	E,G	M↓	Died 18 mos post-diagnosis Progressive dysplastic neutrophilia
35	81/M		G		E		Died 1 yr post-diagnosis Sepsis after chemotherapy
36	67/M	GI bleeding, Fe deficiency, 10 yr before onset	A,T	Left shift 14% blasts			Progression to AML with leukemia cutis 1 yr post-diagnosis. Died 5 mos later
37	45/M	Renal transplant Cytoxan, Imuran	A,G,T	Pelgeroid	E,G,M		Progressive thrombocytopenia 6 weeks post-diagnosis, now on low-dose ara-C

A, anemia; G, granulocytes; T, thrombocytopenia; E, erythroid; M, megakaryocyte; ↓, hypoplasia; ↑, hyperplasia