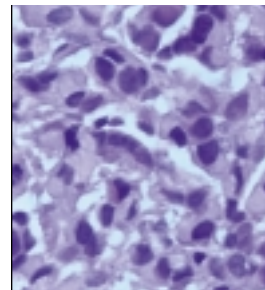


# MYELODYSPLASTIC SYNDROMES IN THE ELDERLY

Hussain I. Saba, MD, PhD

From the MDS Center of Excellence and the Malignant Hematology Program at the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, and the Hematology/Oncology Program at the James A. Haley Veterans Hospital, Tampa, Fla.



## Introduction

Myelodysplastic syndrome (MDS) represents a wide spectrum of diverse clonal bone marrow disorders. It appears to be the most common malignancy worldwide, and it may transform to acute leukemia. The disorders that comprise MDS are characterized by peripheral cytopenias, hypercellular bone marrow in a majority of cases, and dysplastic changes in all cell lines.<sup>1</sup>

MDS originates in the pluripotent stem cell. It involves all myeloid cell lines and may also involve lymphoid cell lines. Alteration of these cell lines leads to ineffective hematopoiesis and peripheral cytopenias. Apoptosis plays a role in the ineffective hematopoiesis. MDS is a highly proliferative disorder with an equally high degree of apoptosis and intramedullary cell death.<sup>2</sup> Using an in situ end-labeling technique and the bone marrow of 21 patients with MDS, more than 70% of the cells were found to be undergoing cell death.<sup>3</sup>

Patients with high levels of apoptosis tend to have higher levels of tumor necrosis factor (TNF). In hypocellular MDS, the possibility of 2 distinct subgroups in MDS has been considered — 1 with cytokine-mediated intramedullary apoptosis and the other with no apoptosis but with stem cell failure,<sup>4</sup> thus giving some clues into the mechanism of cytopenias in MDS. MDS possibly occurs because of a premalignant or malignant transformation of a

multipotent stem cell. The disorder runs a chronic indolent course and often terminates in an acute leukemic transformation. Death also occurs as a result of infection or hemorrhage.

Myelodysplasia is a disease primarily of the elderly, with a median age between 60 and 80 years. The relationship of MDS with anemia has been illuminated by a Belgium study.<sup>5</sup> In a population of 732 elderly patients admitted to geriatric service, 178 (24%) were found to be anemic. MDS caused the anemia in 9% of these patients. A 1998 study also illustrated the relationship between anemia and cancer.<sup>6</sup> In this study, anemia was the most common presenting factor in 99 (85%) of 117 MDS patients. Myelodysplasia is the most common hematologic malignancy in the elderly, with the age-related incidence being as high as 89 in 100,000 for patients older than 80 years of age.

## Classification of MDS

In the past, the disorder currently referred to as “myelodysplastic syndrome” was described as pre-leukemia, oligoblastic leukemia, smoldering acute leukemia, refractory anemia, refractory anemia with excess of blasts, and sideroblastic anemia. MDS patients were identified only by their progression to overt acute leukemia. This led to frequent misdiagnosis since only 20%-30% of cases evolved into acute leukemia.<sup>7</sup> The French-American-British (FAB) classification distinguished acute

*No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.*

Table 1. — FAB Classification of Myelodysplastic Syndromes

Classification	Incidence (%) in Series:	
	1988 <sup>9</sup>	1992 <sup>11</sup>
Refractory Anemia (RA)	28	23
Refractory Anemia with Ring Sideroblasts (RARS)	24	14
Chronic Myelomonocytic Leukemia (CMML)	16	11
Refractory Anemia with Excess of Blasts (RAEB)	23	23
Refractory Anemia with Excess of Blasts in Transformation (RAEB-T)	9	12

leukemia from a group of subacute or chronic disorders that showed some of the characteristics of acute myeloid leukemia (AML). This group of patients with subacute or chronic disorders was typically composed of older patients (>60 years) who rarely needed immediate treatment. The FAB group later coined the term “myelodysplastic syndrome” to describe the disorders of these patients.

Initially, 2 groups in this MDS category were described: refractory anemia with excess of blasts and chronic myelomonocytic leukemia. Subsequent review by the FAB group on specific morphologic fea-

tures and abnormalities in MDS patients in relation to biologic behavior and outcome led to the currently recognized 5 subgroups of MDS<sup>8,9</sup>: refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), refractory anemia with excess blasts (RAEB), chronic myelomonocytic leukemia (CMML), and refractory anemia with excess of blasts in transformation (RAEB-T).

Participants of the 1999 World Health Organization meeting on the classification of hematologic malignancies proposed that CMML is a distinct disease and should be classified in one category only. It was recommended that it be

included in a separately established category of disorders with characteristics of both MDS and myeloproliferative disorders. They also proposed that RAEB-T be removed from the MDS group and reclassified in the AML group.<sup>10</sup> Table 1 shows the incidence of these subgroups from 2 different series.<sup>9,11</sup> The highlights of clinicopathologic differences are presented in Table 2. In general, RA and RARS are considered low-risk MDS subtypes, while CMML, RAEB, and RAEB-T are associated with high risk.

Refractory anemia (RA) is specifically characterized by a hemoglobin level below 11 g/dL. Neutropenia and thrombocytopenia typically accompany this anemia. Other characteristic hematologic findings include the presence of ≤1% myeloblasts in peripheral blood and <5% myeloblasts and <15% ring sideroblasts in the bone marrow. Monocytosis rarely occurs. The bone marrow is usually hypercellular with moderate to marked dyserythropoiesis, dysgran-

Table 2. — Clinical and Pathological Features of MDS

MDS Subtypes <sup>7,9,31</sup>	Peripheral Smear		Bone Marrow		AML Transformation	Median Survival (mos)
	Dyspoiesis	Monocytes	Ring Sideroblasts (%)	Myeloblast (%)		
Refractory Anemia (RA)	+	Rare	<15	<5	11-26	17-64
Refractory Anemia with Ring Sideroblasts (RARS)	+	Rare	>15	<5	5-39	16-52
Chronic Myelomonocytic Leukemia (CMML)	++	Increased	Variable	1-20	15-32	8-22
Refractory Anemia with Excess of Blasts (RAEB)	++	Rare	Variable	5-20	27-66	9-17
Refractory Anemia with Excess of Blasts in Transformation (RAEB-T)	++	Variable	Variable	21-30	50-81	5-10

Saba HI. Myelodysplastic syndromes in the elderly: the role of growth factors in management. *Leuk Res.* 1996;20:203-219. Reprinted with permission.

---

ulopoiesis, and megakaryocytopoiesis. While hypercellularity is more common, approximately 15% of these patients have marrow hypocellularity. Increased bone marrow fibrosis occurs in 10%-15% of patients.

Refractory anemia with ring sideroblasts (RARS) is a subgroup whose name developed from characteristic ring sideroblasts. More than 15% of iron-containing normoblasts in the bone marrow contain iron granules in a perinuclear distribution. A dimorphic population of red blood cells is typically seen in the peripheral blood due to deficient hemoglobinization. The myeloblast counts in the bone marrow should be less than 5%.

Chronic myelomonocytic leukemia (CMML) is a heterogeneous disease with an intermediate survival. CMML is characterized by monocyte counts greater than  $1 \times 10^9/L$  and minimal to marked trilineal dyspoiesis. Cytogenetic abnormalities are common. Less than 5% of blasts are found in the bone marrow, although bone marrow blasts may be as high as 20%.<sup>12</sup> Chronic monocytic leukemia patients are included in this subgroup even though there is poor prognostic correlation between the blast count at the time of initial diagnosis and the prolonged survival after diagnosis. A median survival in the range of 11-66 months was reported in the analysis of 175 patients of CMML from 11 different studies.<sup>9</sup> Other studies, however, suggest a good prognostic correlation in this subgroup with excess of blasts (greater than or equal to 5%) and survival. Differen-

tiating between CMML and chronic myeloproliferative disorders may be difficult because of the occasional occurrence of hepatosplenomegaly, leukocytosis, and myelofibrosis. Some patients with chronic myeloproliferative disorders may have monocytosis of greater than  $1 \times 10^9/L$ .

Refractory anemia with excess of blasts (RAEB) is characterized by the presence of 5%-20% of myeloblasts in the bone marrow. The dysgranulopoiesis (ie, hypogranulation and hyposegmentation of mature neutrophils), dyserythropoiesis, and dysmegakaryocytopoiesis are more marked in RAEB than in RA, RARS, and CMML, and fewer blasts circulate than are detectable in the bone marrow.

Refractory anemia with excess blasts in transformation (RAEB-T) has morphologic abnormalities that are similar to RAEB, but the characteristic finding in this subgroup is bone marrow blast counts of 21%-30%. These patients have a median survival of approximately 5 months.<sup>9</sup> Patients diagnosed with RAEB-T who are <50 years of age respond well to conventional chemotherapy for AML.<sup>13</sup>

## Diagnosis of MDS

Unexplained anemia, leukopenia, and thrombocytopenia with or without monocytosis generally characterize a diagnosis of MDS. Anemia with a hemoglobin level of less than 11 g/dL is the most common finding. Isolated thrombocytopenia or, less commonly, isolated

leukopenia can also be a presenting feature.<sup>8</sup> A diagnosis of MDS may be difficult in patients where dysplastic features are obscure. In these cases, the review of an expert hematopathologist is valuable. Exposure to cytotoxic agents or heavy metals and deficiencies in vitamin B<sub>12</sub> and folate are excluded before a diagnosis of primary MDS is made. Bone marrow smear staining should include the standard stains of Romanovsky and hematoxylin and eosin, as well as Prussian blue stain for iron and reticulin stain for bone marrow fibrosis. In patients with iron deficiency, ringed sideroblasts may be demonstrable with silver staining. Cytochemical staining may be important in determining the origin of blasts from the myeloid cell line (peroxidase and Sudan black B positivity) vs lymphoid blast (terminal deoxytransferase). Early monocytic precursors can be differentiated from poorly granulated myelocytes by using nonspecific or double esterase. Flow cytometry with immune markers is also helpful in analyzing lymphoid and myeloid cells.

## Cytogenetic Findings in MDS

Karyotypic anomalies are seen in 40%-70% of MDS cases at the time of diagnosis and in more than 80% in cases of secondary MDS.<sup>14</sup> These abnormalities are also helpful in the clinical and prognostic aspects of MDS. Chromosomal deletions are more frequent in MDS patients than in those with AML. Major karyotypic aberrations, including rings and dicentrics, are more common in patients with more advanced MDS.

As many as 3 or more chromosomal abnormalities are commonly seen in RAEB and RAEB-T, but more than 1 karyotypic anomaly is rarely seen in RA. Patients with RARS have the lowest incidence of karyotypic aberration. The number and type of chromosomal abnormalities in MDS patients may have prognostic significance<sup>15</sup> by directly correlating with a patient's risk of developing acute leukemia. In general, the more chromosomal aberrations, the more rapid and aggressive the course of MDS will be. In a study of 188 consecutive patients with de novo MDS,<sup>16</sup> the overall incidence of chromosomal aberration was 69%, with the frequency differing according to the subtype. The relative frequency was RAEB-T (100% of patients), RAEB (76%), RA (56%), and CMML (42%). The most common single anomaly in this study was del(5)(q13-q22q33), followed by monosomy 7 or del(7q), del(11)(q14q23), and trisomy 8. Complex karyotypic abnormalities were detected in 33 patients (17.6%). Del(4)(q13q33) was associated with RA and with complex rearrangements in RAEB and RAEB-T. Leukemic transformation occurred in 66 patients (35%). Transformation to acute leukemia did not occur in patients with a normal karyotype MDS or in those with del(5)(q13q33) or del(11)(q14q23) alone. In this study of 188 patients, all cases with complex rearrangements or monosomy 7 or del(7q) developed acute leukemia. The median survival was 31 months in MDS patients without complex abnormalities and 7 months in MDS with complex abnormalities

with 3 or more structural or numerical abnormalities. Patients with del(5)(q13-q33) had the best survival (64 months), and those with monosomy 7 and del(7q) had the worst (7 months) ( $P=0.005$ ).

The 5q- genetic abnormality is highly specific for the subgroup of RA and is highly unusual in CMML. Macrocytic anemia, normal to high platelet count, nonlobulated micro-megakaryocytes, and hypoplastic erythroid series are the morphologic hallmarks of 5q- MDS, which is associated with the least risk for transformation to AML. Patients with monosomy 5 or 5q- have a survival almost similar to those with normal karyotypes. In contrast, the monosomy 7 abnormality is associated with short survival and predisposition for frequent infection. This abnormality is the most frequently encountered karyotypic anomaly of MDS and is encountered most frequently in patients with RA.

### *RAS Gene in MDS*

The RAS gene family encodes signal-transducing proteins that are involved in the regulation of cell growth and differentiation. Gallagher and colleagues<sup>17</sup> investigated the expression of p21RAS and p120GAP in patients with myelodysplasia. Normal bone marrow had low and uniform levels of p21RAS expression. In contrast, 9 of 32 patients with MDS overexpressed p21RAS. Eight of these 9 patients overexpressing p21RAS were found to have low-risk MDS. Twenty-one patients were screened for p120GAP expression, and

no reduction or loss of expression was found. Therefore, p21RAS may represent an alternative mechanism of activation of the RAS signaling pathway that may have a role in leukemogenesis. The occurrence of monosomy 7 and RAS mutations seen in the myeloid progenitors of some congenitally neutropenic patients may predispose them to malignant transformation (eg, MDS or AML).<sup>18</sup>

In a 1997 study, 51 patients with MDS were studied in order to determine the prevalence of activated ras oncogenes.<sup>19</sup> *N-ras* mutations were found in 2 patients with RAEB, in 1 patient with RAEB-T, and in 2 patients with CMML. All but 1 of the patients with *N-ras* mutation developed AML. Thus, mutations at codon 12 of the *N-ras* gene in patients with MDS might be a negative prognostic factor at diagnosis.

Data summarized in 1997 found 627 sequenced point mutations in the RAS and p53 genes in 575 patients with leukemia and myelodysplasia (MDS) out of a total of 4,214 patients investigated.<sup>20</sup> Abnormalities in the RAS gene are common in the pathogenesis of MDS, but they are lost on disease progression, suggesting that RAS mutations may not be a requirement for disease progression.<sup>21</sup> However, a 1998 study by Padua et al<sup>22</sup> does not support this hypothesis. This study showed that oncogene mutation is associated with disease progression and poor survival in MDS. Results of another 1998 study<sup>23</sup> support a link between leukemogenesis in MDS and *N-ras* mutations.

## Clinical Course and Prognostic Factors of MDS

Almost half of MDS patients are symptom-free at the time of diagnosis and are identified only routine clinical and laboratory workups. The symptomatic patient most commonly presents with anemia and has many symptoms such as fatigue and dyspnea that may also be attributed to cardiopulmonary disease. One third of patients' histories include recurrent infection due to either neutropenia or neutrophil dysfunction. A bleeding diathesis, such as petechia, gingival bleeding, and hematomas, is present less often.

Up to 10% of patients with MDS have serious bleeding, including hematuria and gastrointestinal, retinal, and central nervous system hemorrhage. Patients with MDS may also have Sweet's syndrome,

splenomegaly (in 10%-20% of patients), and hepatomegaly (in 5%-26%). In CMML, however, the incidence of splenomegaly and hepatomegaly increases to 30%-50%, and the spleen may be massively enlarged. In general, lymph node enlargement is seen in 5%-15% of these cases.

The course and prognosis of MDS are variable. AML develops in 10%-40% of patients, and 20%-40% die of infection or bleeding or both.<sup>24-26</sup> Attempts have been made to define prognostic factors to predict the course of MDS. These factors include age, level of anemia, neutropenia, or thrombocytopenia, percentage of blasts in the bone marrow, dyspoiesis, central clustering of abnormally localized immature precursors (ALIP), and cytogenetic abnormalities. Other scoring systems such as the Bournemouth score, which assigns numerical values to laboratory data, have been

Table 5. — International Prognostic Scoring System: FAB vs IPSS

FAB Class	IPSS Risk Group
RA	Low, Int-1, Int-2
RARS	Low, Int-1
CMML	Low, Int-1, Int-2, High
RAEB	Int-1, Int-2, High
RAEB-T	Int-1, Int-2, High

devised to provide a more objective assessment of the disease.<sup>24,27</sup> The most important prognostic parameter appears to be the bone marrow "blast" count.<sup>28</sup>

### International Prognostic Scoring System

An International Prognostic Scoring System (IPSS) has been developed to predict the prognosis with more accuracy.<sup>29</sup> The IPSS (Tables 3-5) combined cytogenetic, morphologic, and clinical data from a relatively large group of patients who previously were included in other reported studies.<sup>21,30,31</sup> The IPSS generates risk scores for each variable found to be significant, such as the percentage of bone marrow blasts, the cytogenetic abnormality subgroup, and the number of cytopenias present. In this system, bone marrow blast percentages are scored as follows:

Percent	Score
<5%	0
5-10%	0.5
11-20%	1.5
21-30%	2.0

Karyotypes are graded as good (score 0), intermediate (score 0.5), and poor (score 1.0). The presence

Table 3. — International Prognostic Scoring System

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
BM Blasts (%)	<5	5 - 10	- - -	11 - 20	21 - 30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0 / 1	2 / 3			

Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89:2079-2088. Reprinted with permission.

Table 4. — International Prognostic Scoring System: Scoring and Survival

IPSS Group	IPSS Score	% of MDS Patients	Survival (years)
(1) Low	0	31	5.7
(2) Intermediate - 1	0.5 - 1.0	39	3.5
(3) Intermediate - 2	1.5 - 2.0	22	1.2
(4) High	≥2.5	8	0.4

---

of 1 cytopenia (or none) is graded 0. More than 1 is graded 0.5. By combining the patients' risk score totals for the 3 major variables, 4 risk groups were developed: low, intermediate-1, intermediate-2, and high.<sup>32</sup> Low-risk patients have a total score of 0 and are estimated to have a survival period of 5.7 years. Intermediate-risk patients have scores of 0.5-1.0 (intermediate-1) or 1.5-2.0 (intermediate-2), with an estimated survival time of 3.5 years for intermediate-1 patients and 1.2 years for intermediate-2 patients. High-risk patients have an IPSS score of greater than 2.5 and a projected survival of 0.4 years.

## Management of MDS

Treatment and outcome of MDS are currently unsatisfactory. Treatment modalities have included hormone therapy, chemotherapy, bone marrow transplantation (BMT), and the use of differentiating agents and hematopoietic growth factors.<sup>33</sup> Newer agents include amifostine, cyclosporin A, antithymocyte globulin (ATG), and agents such as topotecan used alone or in combination with other agents.

### *Hormonal Therapy*

Hormone therapy has been used to improve hematologic parameters in MDS patients. Androgens have been suggested to improve anemia, leukopenia, and thrombocytopenia, but results from trials have been inconsistent. Najean and Pecking<sup>34</sup> studied 90 MDS patients and found a possible correlation

between the drug and increasing cytopenia levels, but the efficacy of this androgen treatment was poor. Studies using danazol have been inconsistent; a 1985 study indicated that danazol is effective,<sup>35</sup> but a subsequent study failing to support these findings.<sup>36</sup>

### *Differentiating Agents*

Low-dose cytarabine has been reported to possess the ability to induce differentiation of the leukemic cell line in vitro, and trials have been done on patients with MDS. Buccarani and Tura<sup>37</sup> reported a cellular differentiation response of the bone marrow cells of MDS patients with low dosages of cytarabine (10%-20% of the conventional dose). Wisch and associates<sup>38</sup> continuously infused low-dose cytarabine for 7 to 21 days in 8 patients with MDS, and they reported a response in 6 patients. Many small studies have reported the efficacy of cytarabine in MDS. Careful evaluation of these studies indicates that the overall response rate is more than 15% with no significant improvement in survival time. A randomized study with low-dose cytarabine vs support has been conducted by the Eastern Cooperative Oncology Group and the Southwest Oncology Group. This study showed a complete response with low-dose cytarabine of only 8% with no difference in overall survival in both groups.<sup>39</sup>

Retinoid differentiating activity has been established in studies of promyelocytic leukemia. Trials in MDS, however, have failed to show any impact.<sup>40</sup> Retinoic acid may

also accelerate the transformation of MDS to AML.<sup>41</sup>

Studies on the treatment of MDS patients with other differentiating agents such as vitamin D<sub>3</sub>, interferon alpha, and interferon gamma have been disappointing. Agents such as methyltransferase inhibitors, 5-aza-2'-deoxycytidine (decitabine), and 5-azacytidine have also been studied. These analogues of the pyrimidine nucleoside, cytosine, have been shown to incorporate into the DNA of target cells, forming covalent adducts with the enzyme DNA methyltransferase and inducing inhibition of this enzyme's biochemical activity. Clinical trials of decitabine and 5-azacytidine in patients with leukemia or MDS suggest that they have antileukemic activity and can induce trilineal differentiation in advanced MDS at a rate that is superior to that of other differentiating agents.<sup>42</sup> These agents have been shown to have activity in MDS, with stable normalization of the peripheral blood and bone marrow in some patients.<sup>43</sup> Several early multicenter trials using 5-azacytidine and decitabine have reported initial results showing complete remission (CR) rates of 10%-37% and partial response (PR) rates of 17%-25%.<sup>44</sup> Zagonel et al<sup>43</sup> evaluated the effect of decitabine in 10 patients with advanced MDS (2 with RAEB and 8 with RAEB-T). In this phase I-II study, more than half of the patients had a significant increase in the levels of circulating neutrophils, platelets, and hemoglobin. Complete normalization of blood and bone marrow was reported in 4 of 10 RAEB/RAEB-T patients. Bone

---

marrow hypoplasia or drug-related cytopenia was observed in less than 50% of patients.

In a study of 43 evaluable patients with RAEB or RAEB-T MDS subtypes, Silverman et al<sup>45</sup> administered 5-azacytidine as a continuous intravenous (IV) infusion at a dose of 75 mg/m<sup>2</sup> per day for 7 days every 4 weeks. Five patients had a CR and complete normalization of bone marrow and peripheral blood counts. Eleven had a partial remission, a 50% or more restoration of the deficit from their peripheral blood cell lines, elimination of transfusion requirements, and/or a 50% or more decrease in bone marrow blasts. The median remission duration was 14.7 months. These agents have again caught the attention of MDS investigators, although overall CR rates have been disappointing. In a phase II study,<sup>46</sup> decitabine was administered at a dose of 45 mg/m<sup>2</sup> per day for 3 days every 6 weeks to 66 high-risk MDS patients treated between June 1996 and September 1997. Patients with CRs after 2 courses received 2 additional courses for consolidation, and other responding patients received a maximum of 6 courses. The overall response rate was 49%, with a 64% response in patients with an IPSS high-risk score. Myelosuppression was the only major adverse effect observed.

A 1998 trial by the Cancer and Leukemia Group B (CALGB)<sup>47</sup> on subcutaneous azacytidine in MDS patients included 182 evaluable MDS patients who were randomized to treatment with azacytidine or to observation. Responses

occurred in 63% of the patients receiving azacytidine (6% CR, 10% PR, 47% improved) compared with 7% in the observation group (0% CR, 0% PR, 7% improved). This study failed to show efficacy of azacytidine on survival. The median survival for the azacytidine group was 18 months vs 14 months for the observation group, and the probability of survival at 12 months was 70% for the azacytidine group vs 62% for the observation group. The effect of azacytidine on the quality of life in patients with MDS has also been evaluated.<sup>48</sup> Patients treated with subcutaneous azacytidine at 75 mg/m<sup>2</sup> for 7 days every 4 weeks had less fatigue, greater hematologic response, and delayed transformation to AML or death compared with patients who did not receive azacytidine. Another drug in the cytidine analogue class, 5-AZA-2'-deoxycytidine, has been shown to possess antitumor activity exceeding that of ARA-C and has greater cytotoxicity and inhibition of DNA methylation. Based on this information, a phase III multicenter study to be done in the US has been developed using 5-AZA-2'-deoxycytidine in advanced-stage MDS.

### *Bone Marrow Transplantation*

In the past, BMT was considered an option only for younger MDS patients, and it has a high mortality rate. In their 1998 study, Appelbaum and Anderson<sup>49</sup> investigated posttransplantation outcomes for MDS patients in relation to IPSS risk. A total of 251 patients with a median age of 38 years were studied. The overall DFS rate was

40% with an 18% relapse rate. Mortality not related to relapse was found to be directly associated to older age, duration of disease, mismatched donor, and male gender, and it was also higher in patients who developed MDS as a result of therapy. Morphology, disease duration, and cytogenetics were helpful in predicting relapses in these patients. IPSS scores were found to significantly correlate with relapse and DFS. The 5-year DFS was 60% in low-risk and intermediate-1-risk patients, 36% in intermediate-2-risk patients, and 28% in high-risk patients. It was concluded that IPSS score could be used to predict the possible outcome of BMT in MDS patients.

Other studies have investigated the outcome of BMT in MDS patients. Mattijssen et al<sup>50</sup> studied the outcome of lymphocyte-depleted BMT in 35 patients of MDS with a median age of 41 years. They reported a DFS rate at 2 years of 39%. In 1997, De Witte et al<sup>51</sup> investigated the role of autologous BMT in 79 patients with MDS transformed to AML in their first CR. The 2-year survival rate was 39%, the DFS rate was 34%, and the relapse rate was 64% overall. Age was considered to portend a poor prognosis; patients over 40 years of age had a significantly lower DFS (25%) compared with patients younger than age 40 (39%). A later study further supported this hypothesis regarding age in BMT outcome.<sup>52</sup>

In view of these studies, BMT has been considered to have little applicability as an effective treatment modality in the majority of

Table 6. — Chemotherapy Trials in MDS During the Preleukemic Disease Phase

Investigators	Number of Patients	Combination Chemotherapy Agents	CR (%)	Toxic Deaths (%)
Mertelsmann <sup>55</sup> (1980)	45	Ara-C + 6TG + daunorubicin	51	NR
Armitage <sup>56</sup> (1981)	20	Ara-C + daunorubicin	15	25
Priesler <sup>57</sup> (1986)	15	High-dose Ara-C	13	40+
Tricot and Boogaerts <sup>58</sup> (1986)	15	High-dose Ara-C	53	33
Aul and Schneider <sup>60</sup> (1989)	31	Low-dose Ara-C	16	16
NR = not reported				

patients with MDS, given the higher frequency of this disease in older patients. However, this view is being challenged. In a 1999 French study, Wattel et al<sup>53</sup> reported the outcome of autologous stem cell transplantation as consolidation treatment after a trial of intensive chemotherapy in high-risk MDS patients. The study included 83 patients aged 55 or less. A CR was achieved in 42 of the 83 patients. Three patients underwent allografts in CR, 16 patients received autologous BMT, and 8 received autologous peripheral blood stem cell transplantation after consolidation chemotherapy and granulocyte colony-stimulating factor (G-CSF). After 8 to 55 months, 12 patients were still

in CR. This study shows that transplantation in patients with CR after intensive chemotherapy is a viable option. Deeg et al<sup>54</sup> recently reported on the results of BMT in 50 MDS patients aged 55 to 62 years. Thirteen of the patients had RA, 19 had RAEB, 16 had RAEB-T or AML (RAEB-T/AML), and 2 had CMML. A total of 45 patients were classified for risk according to the IPSS guidelines: 2 were low risk, 14 were intermediate-1 risk, 19 were intermediate-2 risk, and 10 were high risk. Six patients had unrelated volunteer donors, while the rest of the patients had HLA-identical/ nonidentical family members or identical twin donors. All 46 of the transplanted patients survived more than 21 days after

engraftment, and 44% (22) survived 9 to 80 months following BMT. The Kaplan-Meier estimate of survival at 3 years was 59% for the patients with RA, 46% for those with RAEB, and 33% for those with RAEB-T/AML and CMML. These studies illustrate the need for further investigation of BMT in MDS patients.

### Chemotherapy Strategies

Chemotherapy trials for MDS using standard antileukemic drugs in different dosages and combinations are listed in Table 6. Mertelsman et al<sup>55</sup> used the standard daunorubicin, cytosine arabinoside (ara-C), and 6-thioguanine (DAT) regimen in 45 MDS patients and

Table 7. — Chemotherapy Trials During the Acute Leukemic Disease Phase (MDS/AML)

Investigators	Percent of Patients	Chemotherapy Regimen	CR (%)	Toxic Deaths (%)
Aul and Schneider <sup>60</sup> (1989)	20	Low-dose cytosine arabinoside	20	35
	16	Cytosine arabinoside + 6TG + daunorubicin	55	12.5
Keating <sup>59</sup> (1981)	32	Rubidazole, cytosine arabinoside, vincristine, and prednisone	22	53
Priesler <sup>57</sup> (1986)	11	High-dose cytosine arabinoside	18	64
Gajewski <sup>61</sup> (1981)	44	Daunorubicin, cytosine arabinoside, 6TG	41	21

---

reported CR in 51%. Armitage et al<sup>56</sup> used daunorubicin and cytarabine and noted CRs in 15%, with toxic death in 25% of 20 patients. Priesler<sup>57</sup> observed 13% CR with a death rate of more than 40% with high-dose ara-C. Using a comparable high-dose regimen, Tricot and Boogaerts<sup>58</sup> reported a 53% CR rate and a 33% death rate. Similar remission and toxic death rates have been observed with these regimens in MDS patients who were treated as they advanced into frank acute leukemic transformation (Table 7).<sup>57,59,61</sup>

These studies indicate that CRs have occurred (8% to 56%) but at the cost of a high incidence of deaths from toxicity (24% to 64%). Patient age may affect this relationship. Intensive chemotherapy in these patients is complicated by other factors. Fenaux et al<sup>62</sup> studied the role of intensive chemotherapy in MDS patients and found that the prolonged remissions in these patients occurred less frequently. A study by Hirst and Mufti<sup>63</sup> also found that patients with rapidly increasing blasts had higher numbers of remissions, although relapse did occur. Patients with >20% blasts and those with more rapid disease progression had a better rate of CR. CR rates in poor prognosis MDS and secondary AML patients has also been found to be inversely related to the presence of cytogenetic abnormalities. Compared to patients with cytogenetic abnormalities, those with normal metaphases had higher CR rates as well as high DFS rates (33% vs 8%). A 1997 Finnish study reported on 40 MDS patients

with a poor prognosis who were treated with intensive chemotherapy.<sup>64</sup> The median survival of these patients was 12 months, and the median DFS was 8 months. Reports have indicated that intensive chemotherapy can produce increased CR rates in a select group of patients with good Karnofsky score, bone marrow blasts >30%, and normal karyotype.<sup>65</sup>

While the majority of MDS and MDS/AML patients have hypercellular bone marrow, 10%-15% have marrow hypocellularity. Hypocellular MDS patients may have longer survival and may progress to AML less frequently. Once given chemotherapy, these hypocellular MDS/AML patients may have more complications and less chance of achieving remission. In our 1992 study,<sup>66</sup> MDS/AML represented 25% of the acute leukemic population. Of 16 patients with MDS/AML, 5 achieved CR on induction chemotherapy, 4 of whom had hypocellular bone marrow. Hypercellularity was seen in 4 of the 9 MDS/AML patients who failed to achieve CR. MDS cells may be resistant to the cytotoxic actions of chemotherapy due to membrane abnormalities, including high levels of expression of P-glycoprotein (P-gp).

### *Chemotherapy Resistance*

Drug resistance is considered to be a factor in the failure of response to chemotherapy. One reason for chemotherapy resistance is the overexpression of the multidrug resistance (MDR-1) gene product P-gp. P-gp overexpression

has been linked to a number of adverse prognostic variables including CD34 expression, cytogenetic pattern, and secondary leukemia due to prior cytotoxic therapy or MDS. Cells that overexpress MDR-1 are cross-resistant to several drugs commonly used in the treatment of leukemia, such as anthracyclines, mitoxantrone, and etoposide.<sup>67</sup> Attempts have been made to use drug-resistance inhibitors to improve the efficacy of chemotherapeutic agents, including quinine,<sup>68</sup> tamoxifen,<sup>69</sup> cyclosporine,<sup>70</sup> and its stable analogue PSC 833.<sup>71</sup>

In a recent multicenter phase II study,<sup>72</sup> we examined the effectiveness of combination chemotherapy plus PSC 833 (valsopodar) in patients with refractory and relapsed AML. Thirty-seven patients aged 18 to 70 years who were refractory to chemotherapy were treated with a pretreatment loading dose of 2 mg/kg over 4 hours with a concomitant continuous infusion of 10 mg/kg per day for 5 days. A significant number of patients in this study had a background of MDS. Chemotherapy began immediately following loading dose completion and consisted of mitoxantrone (5 mg/m<sup>2</sup> per day IV bolus on days 1-5), etoposide (50 mg/m<sup>2</sup> per day on days 1-5), and cytarabine (1 g/m<sup>2</sup> per day on days 1-5 IV × 1 hr) in the first cohort (6 patients). Due to toxicity, the second cohort of 31 patients were treated with a reduced dose of mitoxantrone (4 mg/m<sup>2</sup>) and etoposide (40 mg/m<sup>2</sup>). Twenty-nine patients also received growth factor support (11 with GM-CSF

and 13 with G-CSF). Patients received a maximum of 2 induction cycles. Those with persistent disease were considered to have failed to respond. Of the 39 patients enrolled in the study, 37

patients were evaluable. Post-chemotherapy marrow hypoplasia was achieved in 33 patients. Twelve patients (32%) achieved CR, 4 achieved partial remission, and 21 failed therapy.

### Growth Factors

Hematopoietic growth factors affect different cell progeny at different stages of development. Interleukin-1, interleukin-3, and

Table 8. — Studies on GM-CSF in MDS

Investigator	GM-CSF Dose/Route	Number of Patients	Subtypes	Improvements in Counts				
				Neutrophils	Reticulocytes	Platelets	↑ BM Blast	AML Onset
Vadhan-Raj <sup>76</sup> 1987	30-500 µg/m <sup>2</sup> continuous IV	8	1 RA 3 RAEB 4 RAEB-T	8	6	3	0	0
Antin <sup>77</sup> 1988	15-48 µg/m <sup>2</sup> IV	7	2 RA 4 RAEB 1 RAEB-T 1 NR	5	5	2	2	1
Thompson <sup>78</sup> 1989	0.3-10 µg/kg SQ	16	7 RA 8 RAEB 1 RAEB-T 1	10	3	1	2	1
Ganser <sup>79</sup> 1989	15-150 µg/m <sup>2</sup> continuous IV	11	3 RA 4 RAEB 2 RAEB-T	8	0	0	4	5
Estey <sup>80</sup> 1989	120 µg/m <sup>2</sup> continuous IV	22	1 RAEB 22 RAEB-T 4 NR	22	NR	2	4	NR
Schuster <sup>81</sup> 1990	3 µg/kg q.d. SQ	26	NR	26	0	0	3	3
Willemze <sup>82</sup> 1990	108 µg/kg b.i.d. SQ 216 µg/kg b.i.d. SQ	33 35	NR	22 22	NR NR	NR NR	1 4	NR NR
Rosenfeld <sup>83</sup> 1991	60-250 µg/m <sup>2</sup> q.d.	20	10 RA 5 RAEB 4 RARS 1 CMML	14	0	0	0	0
Willemze <sup>84</sup> 1992	108 µg b.i.d. SQ 216 µg q.d. SQ	82	22 RA 1 RARS 25 RA 2 RARS 13 RAEB	82	NR	2	NR	2
Takahashi <sup>85</sup> 1993	60-250 µg/m <sup>2</sup> SQ	18	16 RA 1 RARS 1 RAEB	17	3	1	1	NR

NR – not reported

---

GM-CSF affect earlier progeny leading to proliferation of multipotent hemopoietic cell lineage. Others such as G-CSF and M-CSF primarily affect more differentiated progenitors and produce more restricted ranges of progeny.

MDS involves cellular dysfunction as well as defective myeloid maturation of 2 or 3 hematopoietic cell lines. Uncoupling between proliferative and differentiative programs has been proposed as the basic lesion. MDS patients appear to have alterations in biological parameters, including in vitro clonogenic progenitor cell growth, cytogenetics, and enzyme characteristics. In vitro studies have led to the discovery of defective myeloid and erythroid precursor maturation in most patients, which tends to worsen as patients advance toward acute leukemic transformation. Growth factor abnormalities have been implicated in the onset and the progression of MDS. Defective hematopoietic precursor proliferation may involve the decreased responsiveness or impaired production of hematopoietic growth factors.<sup>73</sup> Thus, growth factors could stimulate residual normal hematopoietic progenitor cells in the bone marrow of MDS patients that are unable to proliferate and differentiate at the physiologically available level of colony-stimulating factors. Growth factors also could induce proliferation and maturation of myelodysplastic cell clones that lead to their clonal extinction, such as the actions of GM-CSF and G-CSF on transformed MDS myeloid cells. They

may increase the sensitivity of these transformed malignant clones to chemotherapy and also increase the rate of bone marrow recovery after suppression from chemotherapy.

The uncoupling of genes that regulate proliferation and differentiation as is postulated to occur in MDS patients can be caused by several factors. These include excessive production of growth factors, an increased number or abnormal function of growth factor receptors, and autostimulation by self-generated growth factors. Cells collected from AML patients have been shown to express receptors for GM-CSF and G-CSF. In 1987, Young and Griffin<sup>74</sup> demonstrated the occurrence of autocrine secretion of GM-CSF in acute myeloblastic leukemia. It has also been shown that cells from some patients with MDS or AML can be induced in vitro to differentiate with exposure to G-CSF, GM-CSF, or interleukin-3.<sup>75</sup>

Recombinant hematopoietic growth factors have been used or studied as treatment modalities for MDS patients with the hope that they would induce malignantly transformed cells to differentiate normally. They could be used to combat neutropenia in MDS patients and decrease the infection-related morbidity and mortality. However, concern has been expressed that hematopoietic growth factors could enhance or induce proliferation of malignant hematopoietic progenitors clones, leading to treatment-related onset of acute leukemic transformation.

**GM-CSF** — Studies on the use of GM-CSF in MDS patients are presented in Table 8.<sup>76-85</sup> In 1987, Vadhan-Raj et al<sup>76</sup> reported the results of an initial study showing that the neutrophil count increased in all patients (n = 8) treated with continuous IV infusion of 30-500 µg/m<sup>2</sup> of recombinant GM-CSF. Platelet count improved in 3 of the 8 patients. The percentage of blasts decreased in the bone marrow of the treated patients. None of the patients progressed to acute leukemia during the study period, even though the study included 3 RAEB patients and 4 RAEB-T patients. This led to many subsequent trials of growth factors in MDS.

Most studies reported increases in the neutrophil count, with values reaching normal during treatment with GM-CSF. Increases have also occurred in the eosinophils, monocytes, and lymphocytes as a result of the broad activity of GM-CSF on early hemopoietic progenitor cells. In 1989, Thompson et al<sup>78</sup> reported a phase I-II trial of GM-CSF in 16 patients in which 3 received 0.3 µg/kg per day, 3 received 1.0 µg/kg per day, 4 received 3 µg/kg per day, and 6 received 10 µg/kg per day. The maximum tolerated dose, 10.0 µg/kg, induced rigor, fever, and severe bronchial spasm in 1 patient and produced an increase in white blood cell count to 60,000/µL<sup>3</sup> in another. The most common toxicity reaction was a dose-dependent, flu-like syndrome. One patient with RAEB-T progressed to frank AML and died following 2 doses of GM-CSF. In this study, 11 of 13 patients who received 1.0 µg/kg or more per day responded with 2- to 194-fold

increases in the neutrophil count. This increase was dose dependent and usually returned to the baseline neutrophil count shortly after discontinuing GM-CSF treatment in most of the patients. In 2 patients, the neutrophil count continued to rise for 6 months.

Greenburg et al<sup>86</sup> reviewed the results of 5 studies using short-term GM-CSF (7 to 14 days × 1-5 courses) in 45 patients with MDS. Overall, 38 (91%) of the 45 patients had an increase in neutrophil level, 14 (31%) had an increase in reticulocyte count (with 3 of these patients having decreased the transfusion requirement of red blood cells), and 8 (17%) had a transient increase in their platelet count. Twelve patients (27%) had an increase in the mar-

row blast count, and 7 (15%) developed AML. This occurred in those patients with 15% or more blasts in their bone marrow immediately prior to the administration of GM-CSF. This transient blast count increase was also observed by Ganser et al.<sup>79</sup> Although further studies are needed, evidence suggests that CMML patients treated with GM-CSF may have an increased risk of developing exuberant leukocytosis and an increase in blast cells. Therefore, it has been suggested that GM-CSF should not be considered for patients with CMML.

The dose dependency of GM-CSF treatment was presented by Kurzrock et al<sup>87</sup> in a patient with RAEB-T. A dose of 30-60 µg/m<sup>2</sup> resulted in an increase in circulating

blast cells and a fall in neutrophil count, while a dose of 6 µg/m<sup>2</sup> led to a rise in the platelet count from 50 × 10<sup>9</sup>/L to 185 × 10<sup>9</sup>/L. In a randomized crossover study, subcutaneous injections every 12 hours were more successful in stimulating myelopoiesis than a 2-hour IV infusion. This could be due to a more prolonged and sustained level of circulating GM-CSF after subcutaneous administration.<sup>83</sup>

GM-CSF may also be beneficial in reducing infection rate in MDS patients. In a randomized trial of 133 patients with MDS,<sup>81</sup> GM-CSF was given in a dose of 3 µg/kg per day subcutaneously for 90 days vs observation with support care in excess of 6 months. The patients who received GM-CSF had a sus-

Table 9. — Studies on G-CSF in MDS

Investigator	G-CSF Dose/Route	Number of Patients	Subtypes	Improvements in Counts				
				Neutrophils	Reticulocytes	Platelets	↑ BM Blast	AML Onset
Negrin <sup>89</sup> 1989	0.1-3.0 µg/kg SQ	12	2 RA 7 RAEB 3 RAEB-T	10	5	3	0	0
Kobayashi <sup>90</sup> 1989	60-1600 µg/m <sup>2</sup> IV	7	3 RA 1 RAEB 1 AML	5	0	0	0	NR
Ohyashaki <sup>91</sup> 1989	50-200 µg/m <sup>2</sup> IV	4	3 RA 1 RAEB	4	0	0	0	0
Negrin <sup>92</sup> 1990	0.3-10.0 µg/kg SQ	11	1 RA 6 RAEB 4 RAEB-T	10	4	1	3	3
Yoshida <sup>93</sup> 1991	2.0-10.0 µg/kg IV	41	19 RAEB 2 RARS 17 RAEB 8 RAEB-T	37	0	2	4	1

Saba HI. Myelodysplastic syndromes in the elderly: the role of growth factors in management. *Leuk Res.* 1996;20:203-219. Reprinted with permission.

NR = not reported

---

tained increase in neutrophils, monocytes, eosinophils, and lymphocytes and a decrease in infection rate from 33% to 15%. No effect was seen on platelet counts, hemoglobin levels, or transfusion requirements. In contrast to other studies, progression of RAEB-T to AML in this randomized study was comparable in both the treated and untreated groups. It appears that the transformation from MDS to AML is the natural course of the disease and is not enhanced by GM-CSF. Side effects of GM-CSF treatment include fever, bone pain, local erythema, phlebitis with IV administration, splenomegaly, and adult respiratory distress syndrome (ARDS)-like complications.<sup>88</sup>

**G-CSF** — Studies on the effects of G-CSF on MDS patients are summarized in Table 9.<sup>89-93</sup> Most studies show an increase in the neutrophil count but no changes in monocyte, eosinophil, or lymphocyte counts. Negrin et al<sup>92</sup> observed that MDS patients treated with G-CSF had a sustained rise in the neutrophil count and an accompanying decrease in the incidence of infection. Increases in reticulocyte count and decreased requirement for red blood cell transfusion also occurred in a few patients. Greenberg et al<sup>94</sup> investigated prolonged treatment of 18 MDS patients with G-CSF. The approach resulted in 16 patients normalizing their neutrophil count and having persisting responses for more than 18 months at the time of publication in 1990.

G-CSF also improves granulocyte function, chemotaxis, and

phagocytosis in MDS patients. It also can restore the level of enzyme alkaline phosphates and superoxide-generating ability of neutrophils of MDS patients. The few adverse effects of G-CSF include bone pain with occasional reports of fluid overload and Sweet's syndrome.

**Transformation to Acute Leukemia** — Several investigators have suggested that the use of GM-CSF and G-CSF in MDS patients could enhance acute leukemic transformation rates. In a randomized multicenter study designed to test this hypothesis, Schuster and colleagues<sup>81</sup> studied GM-CSF in MDS patients and found no increase in the progression rate to acute leukemia. A multicenter international study,<sup>95</sup> in which our center was an active participant, studied the effect of chronic G-CSF on the natural history of advanced MDS. This study concluded that chronic administration of G-CSF to MDS patients (RAEB and RAEB-T) did not significantly alter the incidence of AML development. No statistically significant difference was observed in either RAEB (14% vs 18%) or RAEB-T (60% vs 41%) patients. Survival for RAEB-T patients was similar in both arms.

Treatment with either GM-CSF or G-CSF can result in the increase of the granulocyte count in approximately 60% of severely neutropenic (<500/ $\mu$ L) patients with MDS. These growth factors may decrease the incidence of minor life-threatening infections but do not appear to affect the rate of severe life-threatening infections. Results of these studies indicate

that they do not appear to change the median duration of survival time of MDS patients or affect the progression rate to AML.

**Erythropoietin** — Anemia in MDS patients remains a significant problem. Blood transfusion support has been conventionally utilized. Several studies have been conducted using erythropoietin (EPO) to raise the hemoglobin level and reduce the need for transfusion requirement, even in patients with increased plasma EPO levels. It was hypothesized that the administration of EPO in higher dosages could overcome the so-called "maturation block" of red blood cell precursors in the marrow and thus lead to the stimulation of erythropoiesis. Results of clinical trials have shown that the rise in hemoglobin levels has not been significant in the vast majority of patients.<sup>96</sup> In these studies, 23% of patients had an increase in the reticulocyte count, suggesting stimulation of erythropoiesis. Increases in hemoglobin level occurred in 19%. Although the need for red blood cell transfusions decreased in 23%, the criteria used to define a "reduction in transfusion requirements" varied greatly and were often clinically insignificant. The elimination of transfusion requirement occurred in no more than 5% of the patients receiving EPO.

Concerns that EPO administration could also induce a rise in blast cells and disease progression have been unfounded. The transformation to AML has been considered the natural course of the disease rather than the result of EPO admin-

istration. A randomized, placebo-controlled, double-blind trial examined the effects of administration of high-dose EPO (800 to 1,600 U/kg given twice weekly) to 20 patients with MDS (10 had RA and 10 had RARS).<sup>97</sup> Those patients completing the trial were eligible to receive EPO as a part of an open-label study. Eighteen patients (90%) were transfusion dependent. A response to rhEPO was defined as an increase in hematocrit of 4% or more over baseline or the elimination of all transfusion requirements, with the hematocrit stable at the baseline level. One of the patients receiving rhEPO responded, while no responses were seen in the placebo group. An overall response occurred in 4 (24%) of 17 patients receiving rhEPO at a dose of 1,200 to 1,600 U/kg IV twice per week. No responses occurred in terms of platelet or granulocyte counts, and no toxic reactions presented.

In a European study by Hellstrom et al,<sup>98</sup> 12 patients with MDS were treated with recombinant EPO. Five patients had stable anemia with hemoglobin levels of 78-92 g/L, and 7 were transfusion dependent. Recombinant EPO was given at 600 U/kg IV 3 times per week to 11 patients, with dose escalation at 4 weeks and 8 weeks ranging from 1,500 to 3,000 U/kg per week if hemoglobin levels were less than 15 g/L. The 12th patient received 560 U/kg of EPO per week subcutaneously. Three patients had a significant increase in hemoglobin level: 2 had stable anemia prior to treatment, and 1 who had been transfusion dependent became transfusion indepen-

dent. Two of the patients who were transfusion dependent had a reduction in their transfusion needs. All 5 of the patients who responded to EPO did not have marrow sideroblasts, and no patients with sideroblasts had a response. In a nonrandomized study of 19 MDS patients by Aloe Spiriti et al,<sup>99</sup> 17 patients were evaluated, and only 2 (11.8%) had a hematologic response to rhEPO. Their hemoglobin levels rose from mean pretreatment values of 8.5 and 8.4 g/dL to 11.7 and 11.3 g/dL, respectively. One did not require transfusions during rhEPO treatment, while the other's transfusion requirement decreased from 4 to 1.5 units per month.

***EPO and G-CSF Combination Therapy*** — In a 1993 study by Negrin et al,<sup>100</sup> 28 MDS patients were treated with recombinant G-CSF in combination with EPO to determine if this therapeutic approach could improve the anemia observed in these patients. Patients were treated with G-CSF at a starting dose of 1 µg/kg administered subcutaneously. Doses were adjusted to either normalize or double the neutrophil count (dosage range = 0.2-5.0 µg/kg per day). Once the ANC reached the required level, EPO was given subcutaneously at 100 U/kg per day during weeks 1-4, at 150 U/kg per day during weeks 5-8, and at 300 U/kg per day during weeks 8-16. EPO was given simultaneously with the daily administration of G-CSF. Erythroid responses were graded as good, partial, or no response. A good response (GR) was an increase in untransfused hemoglobin levels of

more than 2 g/dL or a 100% decrease in transfusion requirements over the treatment period. A PR was an increase in untransfused hemoglobin levels of 1-2 g/dL or a 50% decrease in transfusion requirements over the treatment period. No response (NR) was anything less than a PR. Myeloid responses were graded as follows: GR = neutrophil count increased to more than 1,800/µL if initially <1,800/µL, PR = neutrophil count increased to 500-1,800/µL if initially less than 1,800/µL or increased by 50%-100% if initially greater than 1,800/µL, or NR. All patients had a myeloid response in the study (26 GR, 2 PR) with both PR patients withdrawing from the study and 2 of the 26 GR patients not evaluable. The combination regimen was well tolerated. Ten of the 24 remaining patients had erythroid responses (7 GR and 3 PR). Six of the patients no longer required transfusions.

In 1996, Negrin et al<sup>101</sup> reported results of another study in which G-CSF and EPO were used in combination to treat MDS patients. Of the 55 patients enrolled in the study, 53 (96%) had a neutrophil response, with 21 (48%) of 44 final evaluable patients having an erythroid response. Seventeen patients continued to respond during maintenance therapy, and a correlation was noted between erythroid response and lower serum EPO levels, higher absolute basal reticulocyte counts, and normal cytogenetics when patients were enrolled in the study.

Hellstrom-Lindberg et al<sup>102</sup> studied anemia in MDS patients treated

with EPO and G-CSF in a phase II randomized trial. Three evaluable patients with MDS and anemia received EPO alone, and 47 were randomized to treatment with G-CSF plus EPO according to 2 arms: patients in arm A received G-CSF for 4 weeks followed by a combination of EPO and G-CSF for 12 weeks, and those in arm B received EPO for 8 weeks followed by combination treatment for 10 weeks. The overall response to G-CSF plus EPO treatment was 38%, with no difference in response rates between the 2 arms. Nine of the patients in arm B responded during the combined treatment part of the regimen, while only 3 responded while on EPO alone. These results suggest that patient pretreatment with G-CSF is not required for the synergistic response to occur with G-CSF plus EPO therapy. The median survival of patients on G-CSF plus EPO was 26 months, and the risk of leukemic transformation during a median follow-up period of 43 months was 28%. The patient IPSS score was effective in predicting survival and leukemic transformation but not in predicting primary response rates.

### *Growth Factors in the Management of AML Transformation of MDS (MDS/AML)*

Transformation to frank AML occurs in a significant number of MDS patients, and induction chemotherapy in MDS/AML patients has been related to a lower incidence of CR (30%-35%) and a higher risk of death from complications of chemotherapy. These effects are most commonly ob-

served in elderly patients. Palliative treatment with hematopoietic growth factors without chemotherapy may be beneficial in the management of these MDS patients. Results obtained during the management of AML patients at our center were evaluated.<sup>103</sup> Of 171 patients evaluated, 70 (41%) had a primary diagnosis of MDS (MDS/AML). Forty-one of the MDS/AML patients received standard induction chemotherapy, 8 received chemotherapy and BMT, and 11 were not actively treated. Five of these MDS/AML patients received no chemotherapy and opted to receive growth factor support (G-CSF or EPO or both) for severe neutropenia and anemia. Four of these 5 patients were alive at 14.9 months, 23.4 months, 21.7 months, and 11.7 months, respectively, following diagnosis of AML. The average survival of the 41 patients who received induction chemotherapy was 8.3 months compared with 14.9 months in MDS/AML patients who were managed with hematopoietic growth factors alone ( $P<0.007$ ). Patients treated with growth factors remained ambulatory and had fewer hospitalizations. This preliminary observation needs further confirmation with controlled studies.

### **Investigational Trials of Other Growth Factors in MDS**

#### *Interleukin-1 Alpha*

Interleukin-1 alpha (IL-1 $\alpha$ ) is a commercially prepared derivative of IL-1 that retains hematopoietic

activity with reduction of the febrile response. It acts on the primitive hematopoietic progenitor cells and also stimulates accessory cells such as marrow stromal cells, T cells, and macrophages producing endogenous growth factors (eg, GM-CSF, G-CSF, and M-CSF). In a phase II trial of IL-1 $\alpha$ , 20 patients with MDS were given IL-1 $\alpha$  subcutaneously at 10 kU or 30 kU  $\times$  14 days.<sup>104</sup> An initial platelet response was seen in 43% of the patients receiving 10 kU and in 33% those receiving 30 kU. The neutrophil response was 40% at 10 kU and 87.5% at 30 kU. The efficacy of 50 kU in the nonresponders was 25% for platelets and 50% for neutrophils. The median time to an initial response and a peak response was 2 weeks and 4 weeks, respectively. These results support the use of IL-1 $\alpha$  in MDS patients.

#### *Interleukin-2*

Cortellezzi et al<sup>105</sup> evaluated the in vitro effects of IL-2 on blast cell proliferation, clonogenic activity, cytokine release, and cell-mediated cytotoxicity in 49 patients with MDS. The number of blast cells decreased in bone marrow after incubation with IL-2. IL-2 increased the granulocyte-macrophage colony-forming unit (CFU-GM) count compared with control patients and increased the amount of IFN-gamma and GM-CSF released by bone marrow mononuclear cells. IL-2 incubation increased the number of CD3 $^-$ /CD56 $^+$  cells in both normal and MDS subjects. Ogata et al<sup>106</sup> also found IL-2 did not induce blast proliferation in most patients. Findings from this study suggest that the IL-2

---

response is heterogeneous in MDS patients. Patients with low blood-soluble IL-2 receptor levels may respond to IL-2 therapy, and low-risk MDS patients may have a better chance of responding to IL-2 therapy. In an in vivo study by Nand et al<sup>107</sup> in 1998, 10 patients with MDS were treated with 1 million units of IL-2 given subcutaneously daily for 12 weeks. The majority of patients improved their CD16+/CD56+ cell counts, but hematologic status and the transfusion requirements of the patients did not change. IL-2 does not appear promising.

### *Interleukin-6*

In a 1995 study of recombinant IL-6, 22 patients with MDS were treated with IL-6 at doses of 1.0, 2.5, 3.75, or 5.0 µg/kg per day given subcutaneously for 7 days.<sup>108</sup> Platelet count improved in 8 patients, and 8 had a transient rise. The number of megakaryocytes did not improve. IL-6 appeared to enhance the maturation of the megakaryocytes already present.

### *Interleukin-8*

Zwierzina et al<sup>109</sup> investigated neutrophils from 23 MDS patients who were treated with IL-8. The patients demonstrated a significant improvement of neutrophil function when the cells were exposed to 10 nm IL-8 as determined by cytochrome C reduction, *Escherichia coli* killing, and chemiluminescence assays. IL-8 was also added to normal and MDS patient bone marrow cultures, with no significant stimulation of myeloid growth noted.

### *Interleukin-11*

IL-11 is a cytokine with thrombopoietic activity. It can work with other hematopoietic growth factors such as IL-6, thrombopoietin, and stem cell factor to induce maturation of megakaryocytes. IL-11 is approved for preventing severe thrombocytopenia and reducing the need for platelet support in some nonmyeloid malignancy patients who have received myelosuppressive chemotherapy. In vivo studies of IL-11 in MDS patients have not yet been conducted. Thrombopoietin is a lineage-specific cytokine for the development and maturation of the megakaryocyte-platelet cell line. It is also known as "megakaryocytic growth and development factor (MGDF)" and "megapoeitin."<sup>110</sup> Thrombopoietin has the ability to enhance the growth of erythroid progenitor cells and directly stimulate primitive hematopoietic progenitor cells in the presence of other cytokines. Conflicting with its use in MDS patients is the suggestion that some megakaryocyte growth factors may play a role in the development of myeloproliferative disorders.

A 1999 in vitro study by Tafuri et al<sup>111</sup> found that IL-11 had little effect on leukemic cell proliferation, cell cycle activation, or programmed cell death. Conversely, this study found that thrombopoietin induced cell cycle activation in a significant number of cases and generally protected the majority of AML blast cells from programmed cell death. These findings may relate to the fact that the receptor number for thrombopoietin (c-

Mpl) is increased in approximately half of the patients with AML and MDS, which is generally associated with a poor prognosis and lower chemotherapy response. Other concerns with the possible use of thrombopoietin include the risk of thrombosis, bone marrow fibrosis, and immunogenicity.

### *Interleukin-12*

In a study involving 11 normal controls and 15 MDS patients, Ogata and associates<sup>112</sup> measured natural killer (NK) cell cytotoxicity in the presence of IL-12 either alone or with IL-2. The NK cytotoxicity of the normal controls and 7 MDS patients increased with IL-12, and the addition of IL-2 further enhanced the increase (type A response). Five of the MDS patients did not respond with IL-12 alone but showed an increase in NK cytotoxicity (type B response) with the combination of IL-12 and IL-2. Three of the MDS patients had low baseline cytotoxicity and did not respond to either IL-12 alone or IL-12 combined with IL-2 (type C response). All of the RAEB-T and RAEB patients in this study had a type B or C response, while 6 of 8 RA patients had a type A response. Most of the RA patients also had an increase in the production of IFN-gamma and TNF-alpha production in conjunction with the increase in NK cytotoxicity in the presence of both IL-12 and IL-2.

### *Mast Cell Growth Factor*

The influence of mast cell growth factor (MGF, c-kit ligand) on bone marrow progenitor cells has

---

been studied in vitro.<sup>113</sup> MGF and EPO increased the CFU-GEMM and BFU-E up to 27-fold in 60% and 80% of the patients, respectively. MGF stimulated CFU-GEMM recovery in 59% of patients with absent growth vs 12% with IL-3 and 8% with GM-CSF. Cytokine combinations did not improve the recovery of EPO-dependent progenitors over that observed with MGF alone. This study suggests that MGF may have the potential to improve the ability of colony-forming units of bone marrow hematopoietic progenitors in MDS patients.

## Newer Approaches in the Management of MDS

### *Amifostine*

Amifostine enhances CFU-GEMM and BFU-E in normal and MDS bone marrow,<sup>114</sup> and it protects normal tissues from radiation or chemotherapy.<sup>115</sup> Amifostine may prevent apoptosis in normal bone marrow cells in vitro while inducing apoptosis in blastic cells. In a phase I-II clinical trial, List and associates<sup>116</sup> used amifostine (100, 200, or 400 mg/m<sup>2</sup>) IV 3 times per week followed by 2 weeks of observation. While 15 of the 18 patients in this study had some type of hematologic response, 3 had an increase in bone marrow blast percentage, and 2 had further progression of disease. Higher doses of amifostine produced significant adverse reactions, while doses of 200 mg/m<sup>2</sup> or less were well tolerated. Side effects were nausea and vomiting. Of the 18 patients in this study, 16 retained

their karyotypically abnormal clone. Route of administration appears to be important in achieving the hematopoietic effectiveness of this agent, and therapeutic response to amifostine may be schedule dependent.<sup>117</sup> While amifostine does not appear to have potential as a curative agent in MDS, further trials of this drug in patients with MDS are indicated.

### *Cyclosporin A*

Cyclosporin A (CsA) is a potent immunosuppressive drug used in patients undergoing organ or bone marrow transplants. CsA has been investigated recently as a possible treatment strategy for MDS patients. In a 1999 report by Berer et al,<sup>118</sup> a patient with transfusion-dependent MDS achieved hematopoietic improvement following CsA therapy and had been transfusion independent for more than 5 years. Jonasova et al<sup>119</sup> reported on results obtained with CsA treatment of 17 hypoplastic MDS patients of RA subtype with differing cellularity of their bone marrow. Fourteen patients had a substantial response, with all transfusion-dependent patients becoming transfusion independent. Complete recovery was observed in 4 patients. Follow-up ranged from 5 to 30 months without failure in these 14 successfully treated patients. Serious side effects occurred in 3 patients, and treatment was stopped with a resultant decrease of the blood count to pretreatment levels. Biesma et al<sup>120</sup> used CsA, ATG, or a combination of both to treat 2 patients with hypoplastic MDS. Following treat-

ment with CsA, ATG, or both, transfusion requirements were eliminated, bone marrow cellularity increased, and dysplastic characteristics disappeared. These studies suggest that CsA may be beneficial in treating some MDS patients.

### *Antithymocyte Globulin*

In a 1997 phase II study with ATG,<sup>121</sup> 25 transfusion-dependent MDS patients with less than 20% blasts were treated with ATG administered at 40 mg/kg per day for 4 days and then followed for a mean of 14 months. Eleven of the treated patients responded and became transfusion independent, with 3 CRs, 6 PRs, and 2 minimal responses. The responders included 9 of 14 patients with RA and 2 of 6 patients with RAEB. The median response was 10 months, and side effects were mild. Molldrem and associates<sup>122</sup> theorized that the hematologic response of MDS patients to ATG treatment is associated with a loss of lymphocyte-mediated inhibition of CFU-GM and with alterations of T-cell receptor V $\beta$  profiles.

Killick et al<sup>123</sup> recently treated 26 low-risk MDS patients with ATG. The subtypes of these low-risk patients (<10% bone marrow blasts) included RA (17 patients), RAEB (6), RARS (2) and childhood MDS (1). The median age was 51 years (range 18-73), with the study end point being 6 months. Patients received antithymocyte globulin (horse ATG) at a daily dose of 1.5 vial per 10 kg for 5 days. The regimen was well tolerated, with only 1 patient experiencing acute pul-

---

monary edema due to fluid overload. Of the 14 patients with adequate follow-up, 6 had a PR (all of the RA subtype), 1 had a complete response, and 7 had no response. One of the patients relapsed at 5 months and was retreated. Six of the 7 RA patients have remained transfusion independent.

### *Topotecan*

Current studies are underway to test other drugs for their effectiveness in treating patients with MDS. Topotecan is currently being studied for its ability to augment responses to other treatment modalities. Investigators at M.D. Anderson Cancer Center also studied the effectiveness of topotecan in combination with ara-C.<sup>124</sup> Topotecan was given at 1.25 mg/m<sup>2</sup> per day for 5 days (continuous infusion), and ara-C was given as a bolus of 1 g/m<sup>2</sup> per day for 5 days. A total of 74 patients (24 RAEB-T, 24 CMML, 14 RAEB, 4 RA, 1 myelofibrosis, and 7 MDS/AML) were evaluated. Of the 45 patients with RAEB, RAEB-T, or AML, 67% had a complete response, with no differences noted in subtype (12 of 14 RAEB patients, 13 of 24 RAEB-T patients, and 5 of 7 AML patients). Thus, topotecan added to the effectiveness of ara-C in RAEB or RAEB-T subtypes of MDS but not in CMML.

Raza et al<sup>125</sup> treated 18 high-risk MDS patients (8 RAEB patients with 15% blasts, 5 RAEB-T patients, and 5 CMML patients) with a regimen consisting of the addition of topotecan (1.25 mg/m<sup>2</sup> IV over ½ hour every 3 weeks) to treatment with A-

PCD (500 mg of amifostine IV for 3 weeks, 800 mg of pentoxifylline orally 3 times per day, 500 mg of ciprofloxacin orally 2 times per day, and 4.0 mg of dexamethasone orally in the a.m. for 5 days every 3 weeks). Twelve of 16 responders achieved either a trilineage response (7 patients) or a PR (5 patients) and 1 patient maintained her counts with improvement in bone marrow blast count. The topotecan was well tolerated. This study suggests the effectiveness of topotecan in combination with A-PCD treatment may be particularly effective in high-risk MDS patients.

In a study of topotecan in combination with fludarabine, ara-C, and G-CSF in patients with aggressive MDS,<sup>126</sup> 11 patients with IPSS scores of higher than 1.5, mean blast counts of 37%, and mean age of 70.5 years were treated with the following T-FLAG regimen: G-CSF (400 µg/m<sup>2</sup> per day from day 1 to recovery) and fludarabine (30 mg/m<sup>2</sup> per day for 4 days IV in ½ hour) followed 4 hours later by ara-C (2 g/m<sup>2</sup> IV on days 1-4 over 4 hours) and then 12 hours later by topotecan (1.5 mg/m<sup>2</sup> dose escalation by 0.5 mg/m<sup>2</sup> in the next 9 patients) IV over ½ hour for 4 days. At a topotecan dose of 1.5 mg/m<sup>2</sup>, there were 3 CRs and 5 PRs among 10 evaluable patients. Three of the PRs were then treated with 2 mg/m<sup>2</sup> of topotecan, and all went into CR. All of the patients with abnormalities in their chromosomes went into cytogenetic remissions.

Beran and Kantarjian<sup>127</sup> also investigated the used of topotecan-

based combination chemotherapy in patients with MDS and CMML. Fifty-nine patients (38 patients with advanced MDS and 21 patients with chronic CMML) were treated with topotecan (1.25 mg/m<sup>2</sup> per day continuous IV for 5 days) and cytarabine (1.0 g/m<sup>2</sup> per day infused over 2 hours for 5 days). Follow-up occurred at a mean of 7 months, and all 59 patients were evaluable. The CR rate in the MDS patients was 66%, with similar rates in both good-risk and poor-risk patients (79% and 58%, respectively). The CR rate in CMML was 48%. Treatment was particularly effective in patients with poor-prognosis karyotypes and secondary MDS, with CR rates of 63% and 69%, respectively. The median duration of CR in MDS patients was 41 weeks, with a median survival of 60 weeks. The median survival in CMML patients was 33 weeks with a median survival of 41 weeks. Although fever of unknown origin occurred in 72% of patients and infection occurred in 59% of patients, this regimen was reasonably well tolerated and had a low mortality rate.

### *Melphalan*

Melphalan has been studied by Denzlinger et al<sup>128</sup> for its ability to induce favorable responses in elderly patients with high-risk MDS. Twenty-one patients with either high-risk MDS (1 CMML, 8 RAEB, and 5 RAEB-T) or secondary AML (7 patients) were treated with melphalan at 2 mg per day given orally. Complete responses were seen in 7 patients (2 patients with RAEB, 2 with RAEB-T, and 3 with

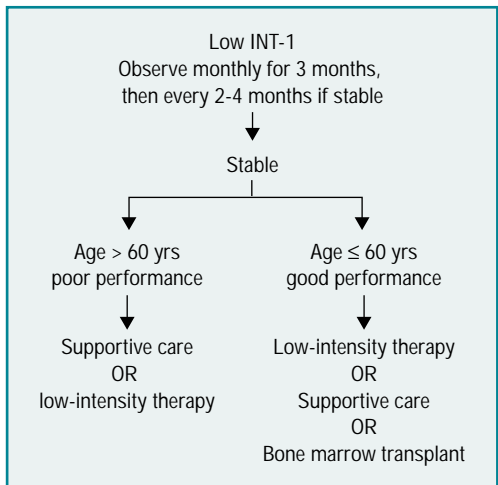


Fig 1. — MDS management: low, intermediate-1 score group (stable group).

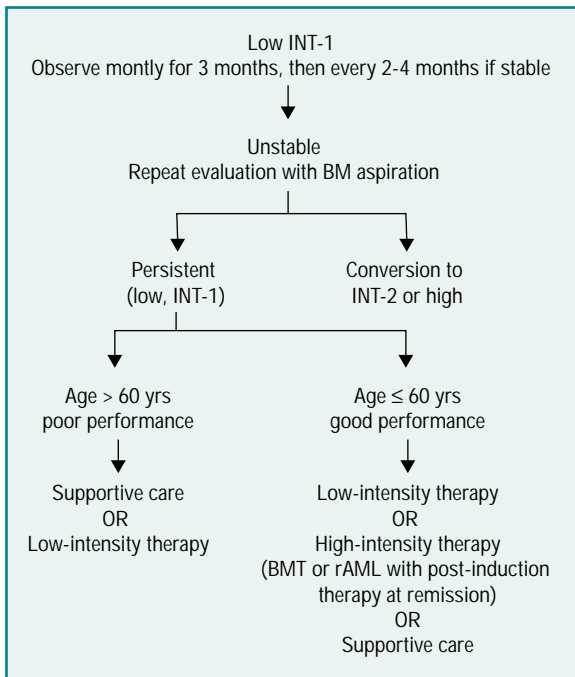


Fig 2. — MDS management: low, intermediate-1 score group (unstable group).

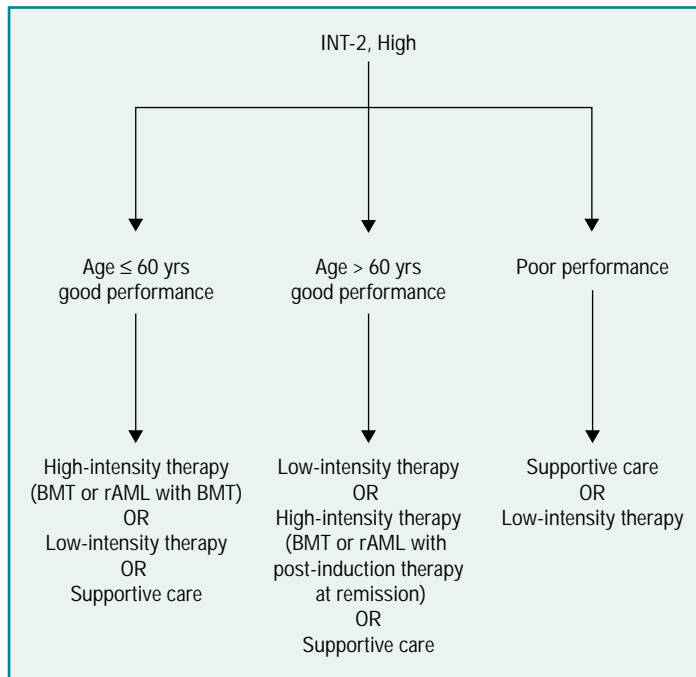


Fig 3. — MDS management: intermediate-2, high score group (unstable group).

secondary AML). However, 5 of these responders relapsed after treatment was stopped. A second complete response was achieved by retreatment in all but 1 patient. Other than a transient initial worsening of their cytopenias, no adverse effects of treatment were noted. The investigators suggest that low-dose melphalan may be a promising treatment for patients with high-risk MDS or secondary AML. They also suggest that the

absence of complex karyotype abnormalities and normal to reduced bone marrow cellularity may predict benefit.

### Thalidomide

Thalidomide is an agent with antiangiogenesis activity that also has the ability to block tumor necrosis factor-alpha (TNF- $\alpha$ ). Cytokine-mediated intramedullary apoptosis of hematopoietic cells has been implicated in the cytopenias observed in MDS, with TNF- $\alpha$  as the main proapoptotic cytokine.<sup>10</sup> Thalidomide has antitumor

*NCCN Statement regarding Figs 1-3: "These guidelines are a work in progress that will be refined as often as new significant data becomes available. The NCCN guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by the NCCN. All rights reserved. These guidelines and illustrations may not be reproduced in any form for any purpose without the express written permission of the NCCN."*

---

activity in patients with myeloma who are resistant to conventional chemotherapy.<sup>129</sup> This information has led to the investigation of thalidomide in MDS patients. Thirty-three patients with MDS are being treated with thalidomide, with oral doses at bedtime starting at 100 mg per day and escalating to a maximum dose of 400 mg per day.<sup>130</sup> At the time of this report, 20 patients had received at least 4-8 weeks of thalidomide and were evaluated. Ten of these patients had shown some type of hematologic improvement, 8 of whom had a 50% or more reduction in red blood cell transfusion requirements or an increase in hemoglobin level by 2 g or more. In 4 of the 10 patients, platelet count increased by more than 30,000/ $\mu$ L, and 1 patient had a increase in absolute neutrophil count by more than 500/ $\mu$ L. Three long-standing transfusion-dependent RA patients have been reported as being transfusion independent.

### *Arsenic Trioxide*

A recent *in vitro* study by Donelli et al<sup>131</sup> investigated the effect of arsenic trioxide on peripheral mononuclear cell cultures and/or bone marrow from 14 patients with MDS or acute leukemia. In this study, cells from 7 (63.6%) of the 11 advanced MDS patients showed increased apoptosis after exposure to arsenic trioxide. Soignet et al<sup>132</sup> reported preliminary results of a multicenter trial of arsenic trioxide in patients with acute promyelocytic leukemia (APL). This study confirmed that arsenic trioxide is safe and effec-

tive in inducing complete remission in patients with APL. In a recent case study, Dutcher et al<sup>133</sup> reported a major hematological response in a 56-year-old woman with high-risk MDS who was treated with arsenic trioxide. Arsenic trioxide (AS203) has also been tested as treatment with relapsed or refractory AML, blast crisis of CML, and MDS.<sup>134</sup> The one MDS patient in this study completed treatment and has remained stable. This approach needs further investigation, and a phase II multicenter study of arsenic trioxide in transfusion-dependent patients with MDS is now being developed.

## Management Approaches and the NCCN MDS Practice Guidelines

At this time, the only potentially curative treatment approach for patients with MDS is BMT. As presented in this review, the precise course of management remains difficult to define in view of the multitude of the processes involving aspects of diagnosis, evaluation, and prognosis. In an attempt to simplify this process, the National Comprehensive Cancer Network (NCCN) has been established. The panel on Myelodysplastic Syndromes Practice Guidelines has suggested approaches for the diagnosis, evaluation, risk stratification, and treatment of patients with MDS, which are being accepted first as the standard of practice. These guidelines suggest observation to determine if the patient has an indolent or progressive course based on IPSS score.

Patients are then categorized by age and by stable vs unstable disease before suggesting specific treatment approaches of supportive care, low-intensity therapy, or high-intensity therapy. Supportive care includes red blood cell and platelet transfusions when needed and iron chelation therapy if necessary. Cytokine support such as G-CSF and GM-CSF is offered when MDS patients are neutropenic with recurrent or resistant bacterial infections, and EPO is prescribed for some anemic patients. Suggestions for low-intensity therapeutic approaches include low-intensity chemotherapy or biologic response modifiers that can generally be administered to outpatients in the context of clinical trials. These include chemotherapy with low-dose ara-C or azacytidine or the use of amifostine, pentoxifylline, IFN- $\alpha$ , ATG, cyclosporine, and retinoids. NCCN suggestions for high-intensity therapy include intensive induction chemotherapy, moderate-intensity chemotherapy, or BMT for high-risk patients. Figs 1-3 depict these suggested NCCN guidelines. While these guidelines are helpful in the treatment of MDS patients, treatment decisions need to be based on all information obtained, including individual patient characteristics.

## Conclusions

MDS represents a group of clonal disorders of the bone marrow characterized by impaired maturation of hematopoietic cell lineage. The morphology of the cell lines are characterized by dysplastic features in all or some lines.

There exists a great diversity in the presentation of this syndrome, manifesting from isolated but persistent mild anemia to a more progressive and aggressive anemia state that accumulates excess blasts in the marrow and leads to fatal AML.

The FAB classification system organizes MDS into 5 subgroups: RA, RARS, CMML, RAEB, and RAEB-T with varying risk of AML transformation. This system further divides low-risk (RA and RARS) and high-risk (CMML, RAEB, and RAEB-T) subgroups. More recently, however, a World Health Organization classification has attempted to exclude RAEB-T from the MDS category and include it in AML. A new classification based on the IPSS is now being accepted to predict the prognosis of MDS patients with somewhat more accuracy. This classifies MDS into 4 risk groups: low, intermediate-1, intermediate-2, and high.

Management of MDS remains difficult, given the heterogeneous and divergent nature of this syndrome. BMT is a viable choice for younger patients, but since MDS remains primarily a disease of the elderly, this option is not an appropriate choice for most patients. New chemotherapeutic and biologic agents are being evaluated, and immune suppressive therapy with ATG and CsA has also shown some promise. Palliation and supportive care are important components to maximizing quality of life. Nevertheless, an emphasis remains on clinical trials designed to discover more effective treatment programs.

## References

1. Mufti GJ, Galton DA. Myelodysplastic syndromes: natural history and features of prognostic importance. *Clin Haematol*. 1986;15:953-971.
2. Raza A, Alvi S, Borok RZ, et al. Excessive proliferation matched by excessive apoptosis in myelodysplastic syndromes: the cause-effect relationship. *Leuk Lymphoma*. 1997;27:111-118.
3. Parcharidou A, Raza A, Economopoulos T, et al. Extensive apoptosis of bone marrow cells as evaluated by the in situ end-labelling (ISEL) technique may be the basis for ineffective haematopoiesis in patients with myelodysplastic syndromes. *Eur J Haematol*. 1999;62:19-26.
4. Goyal R, Qawi H, Ali I, et al. Biologic characteristics of patients with hypocellular myelodysplastic syndromes. *Leuk Res*. 1999;23:357-364.
5. Joosten E, Pelemans W, Hiële M, et al. Prevalence and causes of anaemia in a geriatric hospitalized population. *Gerontol-ogy*. 1992;38:111-117.
6. Intragumtornchait T, Prayoonwiwat W, Swasdikul D, et al. Myelodysplastic syndromes in Thailand: a retrospective pathologic and clinical analysis of 117 cases. *Leuk Res*. 1998;22:453-460.
7. Goasguen JE, Garand R, Bizet M, et al. Prognostic factors of myelodysplastic syndromes: a simplified 3-D scoring system. *Leuk Res*. 1990;14:255-262.
8. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol*. 1982;51:189-199.
9. Recommendations for a morphologic, immunologic, and cytogenetic (MIC) working classification of the primary and therapy-related myelodysplastic disorders. Report of the workshop held at Scottsdale, Arizona, on February 23-25, 1987. Third MIC Cooperative Study Group. *Cancer Genet Cytogenet*. 1988;32:1-10.
10. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. *J Clin Oncol*. 1999;17:3835-3849.
11. Aul C, Gattermann N, Heyll A, et al. Primary myelodysplastic syndromes: analysis of prognostic factors in 235 patients and proposals for an improved scoring system. *Leukemia*. 1992;6:52-59.
12. Storniolo AM, Moloney WC, Rosen CS, et al. Chronic myelomonocytic leukemia. *Leukemia*. 1990;4:766-770.
13. Bennett JM. Myelodysplastic syndromes: a forum for debate and discussion. *Leuk Res*. 1993;17:475.
14. Add Mecucci C, Vanden Berghe H. Cytogenetics. *Hematol Oncol Clin N Am*. 1992;6:523-541.
15. Horiike S, Taniwaki M, Misawa S, et al. Chromosome abnormalities and karyotypic evolution in 83 patients with myelodysplastic syndrome and predictive value for prognosis. *Cancer*. 1988;62:1129-1138.
16. Bernasconi C. Prognostic factors in myelodysplastic syndromes. *Hematol Oncol*. 1993;11:20-26.
17. Gallagher A, Padua RA, al-Sabah A, et al. Aberrant expression of p21RAS but not p120GAP is a common feature of myelodysplasia. *Leukemia*. 1995;9:1833-1840.
18. Kalra R, Dale D, Freedman M, et al. Monosomy 7 and activating RAS mutations accompany malignant transformation in patients with congenital neutropenia. *Blood*. 1995;86:4579-4586.
19. Constantinidou M, Chalevelakis G, Economopoulos T, et al. Codon 12 ras mutations in patients with myelodysplastic syndrome: incidence and prognostic value. *Ann Hematol*. 1997;74:11-14.
20. Parry TE. The nonrandom distribution of point mutations in leukaemia and myelodysplasia: a possible pointer to their aetiology. *Leuk Res*. 1997;21:559-574.
21. Gallagher A, Darley R, Padua RA. RAS and the myelodysplastic syndromes. *Pathol Biol (Paris)*. 1997;45:561-568.
22. Padua RA, Guinn BA, Al-Sabah AI, et al. RAS, RMS and p53 mutations and poor clinical outcome in myelodysplasias: a 10-year follow-up. *Leukemia*. 1998;12:887-892.
23. de Sousa Gernandez T, Menezes de Souza J, Macedo Silva ML, et al. Correlation of N-ras point mutations with specific chromosomal abnormalities in primary myelodysplastic syndrome. *Leuk Res*. 1998;22:125-134.
24. Sanz GF, Sanz MA, Vallespi T, et al. Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: a multivariate analysis of prognostic factors in 370 patients. *Blood*. 1989;74:395-408.
25. Kerkhofs H, Hermans J, Haak HL, et al. Utility of the FAB classification for myelodysplastic syndromes: investigation of prognostic factors in 237 cases. *Br J Haematol*. 1987;65:73-81.
26. Tricot G, Vlietinck R, Boogaerts MA, et al. Prognostic factors in the myelodysplastic syndromes: importance of initial data on peripheral blood counts, bone mar-

row cytology, trephine biopsy and chromosomal analysis. *Br J Haematol.* 1985;60:19-32.

27. Mufti GJ, Stevens JR, Oscier DG, et al. Myelodysplastic syndromes: a scoring system with prognostic significance. *Br J Haematol.* 1985;59:425-433.

28. Aul C, Schneider W. Myelodysplastic syndromes: a prognostic factor analysis of 221 untreated patients. *Blut.* 1988;57:234.

29. Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Haematologica.* 1998;83:358-376.

30. Sanz G, Sanz M, Greenberg P. Prognostic factors and scoring systems in myelodysplastic syndromes: recent advances in myelodysplastic syndromes. *Haematologica.* 1998;83:358-376.

31. Varela BL, Chuang C, Woll JE, et al. Modifications in the classification of primary myelodysplastic syndromes: the addition of a scoring system. *Haematol Oncol.* 1985;3:55-63.

32. NCCN practice guidelines for the myelodysplastic syndromes. National Comprehensive Cancer Network. *Oncology (Huntingt).* 1998;12:53-80.

33. Saba HI, Ballester OF, Balducci L. Hemopoietic growth factors in myelodysplasia. *Hematol Rev.* 1992;37:207-221.

34. Najean Y, Pecking A. Refractory anaemia with excess of myeloblasts in the bone marrow: a clinical trial of androgens in 90 patients. *Br J Haematol.* 1977;37:25-33.

35. Cines DB, Cassileth PA, Kiss JE. Danazol therapy in myelodysplasia. *Ann Intern Med.* 1985;103:58-60.

36. Bassan R, Marini B, Barbui T. Danazol (DZ) treatment for myelodysplastic syndrome (MDS). *Blood.* 1987;70:222a.

37. Buccarani M, Tura S. Differentiation of myeloid leukaemic cells: new possibilities for therapy. *Br J Haematol.* 1979;42:485-487.

38. Wisch JS, Griffin JD, Kufe DW. Response of preleukemic syndromes to continuous infusion of low-dose cytarabine. *N Engl J Med.* 1983;309:1599-1602.

39. Miller KB, Kim K, Morrison FS, et al. Evaluation of low dose Ara-C versus supportive care in the treatment of myelodysplastic syndromes: an intergroup study by the Eastern Cooperative Oncology Group and Southwest Oncology Group. *Blood.* 1988;72:215a.

40. Clark RE, Ismail SA, Jacobs A, et al. A randomized trial of 13-cis retinoic acid with or without cytosine arabinoside in patients with the myelodysplastic syndrome. *Br J Haematol.* 1987;66:77-83.

41. Garewal H, Greenberg P, List A, et al.

N-(4-hydroxyphenyl) retinamide [4-HPR] therapy in myelodysplastic syndromes (MDS): possible disease acceleration by retinoids. *Blood.* 1987;70:228a.

42. Cheson BD. The myelodysplastic syndromes: current approaches to therapy. *Ann Intern Med.* 1990;112:932-941.

43. Zagonel V, Lo Re G, Marotta G, et al. 5-Aza-2'-deoxycytidine (decitabine) is an effective agent for the treatment of advanced myelodysplastic syndromes (MDS). *Proc Annu Meet Am Soc Clin Oncol.* 1992;11:226a.

44. Pinto A, Zagonel V. 5-Aza-2'-deoxycytidine (Decitabine) and 5-azacytidine in the treatment of acute myeloid leukemia and myelodysplastic syndromes: past, present, and future trends. *Leukemia.* 1993;7:51-60.

45. Silverman LR, Holland JF, Weinberg RS, et al. Effects of treatment with 5-azacytidine on the in vivo and in vitro hematopoiesis in patients with myelodysplastic syndromes. *Leukemia.* 1993;7:21-29.

46. Wijermans P, Lubbert M, Verhoef G, et al. Low-dose 5-Aza-2'-deoxycytidine, a DNA hypomethylating agent for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients. *J Clin Oncol.* 2000;18:956-962.

47. Silverman LR, Demakos EP, Peterson B, et al. A randomized controlled trial of subcutaneous azacytidine (aza c) in patients with the myelodysplastic syndrome (MDS): a study of the Cancer and Leukemia Group B (CALGB). *Proc Annu Meet Am Soc Clin Onc.* 1998;17:53.

48. Kornblith AB, Herndon JE, Silverman LR, et al. The impact of 5-azacytidine on the quality of life of patients with the myelodysplastic syndrome (MDS) treated in a randomized phase III trial of the Cancer and Leukemia Group B (CALGB). *Blood.* 1998;92:189a.

49. Appelbaum FR, Anderson J. Allogeneic bone marrow transplantation for myelodysplastic syndrome: outcomes analysis according to IPSS score. *Leukemia.* 1998;12:S25-29.

50. Mattijssen V, Schattenberg A, Schaap N, et al. Outcome of allogeneic bone marrow transplantation with lymphocyte-depleted marrow grafts in adult patients with myelodysplastic syndromes. *Bone Marrow Transplant.* 1997;19:791-794.

51. De Witte T, Van Biezen A, Hermans J, et al. Autologous bone marrow transplantation for patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia following MDS. Chronic and Acute Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. *Blood.*

1997;90:3853-3857.

52. Runde V, de Witte T, Arnold R, et al. Bone marrow transplantation from HLA-identical siblings as first-line treatment in patients with myelodysplastic syndromes: early transplantation is associated with improved outcome. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1998;21:255-261.

53. Wattel E, Solary E, Leleu X, et al. A prospective study of autologous bone marrow or peripheral blood stem cell transplantation after intensive chemotherapy in myelodysplastic syndromes. Groupe Francais des Myelodysplasies. Group Ouest-Est d'Etude des Leucemies aigues myeloides. *Leukemia.* 1999;13:524-529.

54. Deeg HJ, Shulman HM, Anderson JE, et al. Allogeneic and syngeneic marrow transplantation for myelodysplastic syndrome in patients 55 to 66 years of age. *Blood.* 2000;95:1188-1194.

55. Mertelsmann R, Tzvi Thaler H, To L, et al. Morphological classification, response to therapy, and survival in 263 adult patients with acute nonlymphoblastic leukemia. *Blood.* 1980;56:773-781.

56. Armitage JO, Dick FR, Needleman SW, et al. Effect of chemotherapy for the dysmyelopoietic syndrome. *Cancer Treat Rep.* 1981;65:601-605.

57. Preisler HD, Raza A, Barcos M, et al. High-dose cytosine arabinoside in the treatment of preleukemic disorders: a leukemia intergroup study. *Am J Hematol.* 1986;23:131-134.

58. Tricot G, Boogaerts MA. The role of aggressive chemotherapy in the treatment of the myelodysplastic syndromes. *Br J Haematol.* 1986;63:477-483.

59. Keating MJ, McCredie KB, Benjamin RS, et al. Treatment of patients over 50 years of age with acute myelogenous leukemia with a combination of rubidazole and cytosine arabinoside, vincristine and prednisone (ROAP). *Blood.* 1981;58:584-591.

60. Aul C, Schneider W. The role of low-dose cytosine arabinoside and aggressive chemotherapy in advanced myelodysplastic syndromes. *Cancer.* 1989;64:1812-1818.

61. Gajewski JL, Ho WG, Nimer SD, et al. Efficacy of intensive chemotherapy for acute myelogenous leukemia associated with a preleukemic syndrome. *J Clin Oncol.* 1989;7:1637-1645.

62. Fenaux P, Preudhomme C, Hebbard M. The role of intensive chemotherapy in myelodysplastic syndromes. *Leuk Lymphoma.* 1992;8:43-49.

63. Hirst WJ, Mufti GJ. The rate of disease progression predicts the quality of

remissions following intensive chemotherapy for myelodysplastic syndromes. *Leuk Res.* 1994;18:797-804.

64. Ruutu T, Hanninen A, Jarventie G, et al. Intensive chemotherapy of poor prognosis myelodysplastic syndromes (MDS) and acute myeloid leukemia following MDS with idarubicin and cytarabine. *Leuk Res.* 1997;21:133-138.

65. Aul C, Germing U, Minning H, et al. Role of aggressive treatment strategies for myelodysplastic syndromes [in German]. *Schweiz Rundsch Med Prax.* 1999;88:431-438.

66. Saba HI, Shamim F, Ismail R, et al. Acute leukemic transformation in myelodysplastic syndrome. *Blood.* 1992;80:459a.

67. Pirker R, Wallner J, Geissler K, et al. MDR1 gene expression and treatment outcome in acute myeloid leukemia. *J Natl Cancer Inst.* 1991;83:708-712.

68. Solary E, Witz B, Caillot D, et al. Combination of quinine as a potential reversing agent with mitoxantrone and cytarabine for the treatment of acute leukemias: a randomized multicenter study. *Blood.* 1996;88:1198-1205.

69. Berman E, McBride M, Lin S, et al. Phase I trial of high-dose tamoxifen as a modulator of drug resistance in combination with daunorubicin in patients with relapsed or refractory acute leukemia. *Leukemia.* 1995;9:1631-1637.

70. List AF, Spier C, Greer J, et al. Phase I/II trial of cyclosporin as a chemotherapy-resistance modifier in acute leukemia. *J Clin Oncol.* 1993;11:1652-1660.

71. Twentyman PR, Bleehen NM. Resistance modification by PSC-833, a novel non-immunosuppressive cyclosporin. *Eur J Cancer.* 1991;27:1639-1642.

72. Advani R, Saba HI, Tallman MS, et al. Treatment of refractory and relapsed acute myelogenous leukemia with combination chemotherapy plus the multidrug resistance modulator PSC 833 (Valspodar). *Blood.* 1999;93:787-795.

73. List AF, Garewal HS, Sandberg AA. The myelodysplastic syndromes: biology and implications for management. *J Clin Oncol.* 1990;8:1424-1441.

74. Young DC, Griffin JD. Autocrine secretion of GM-CSF in acute myeloblastic leukemia. *Blood.* 1986;68:1178-1181.

75. Delwel R, Dorssers L, Touw I, et al. Human recombinant multilineage colony stimulating factor (interleukin-3): stimulator of acute myelocytic leukemia progenitor cells in vitro. *Blood.* 1987;70:333-336.

76. Vadhan-Raj S, Keating M, LeMaistre A, et al. Effects of recombinant human granulocyte-macrophage colony-stimulating fac-

tor in patients with myelodysplastic syndromes. *N Engl J Med.* 1987;317:1545-1552.

77. Antin JH, Smith BR, Holmes W, et al. Phase I/II study of recombinant human granulocyte-macrophage colony-stimulating factor in aplastic anemia and myelodysplastic syndrome. *Blood.* 1988;72:705-713.

78. Thompson JA, Lee DJ, Kidd P, et al. Subcutaneous granulocyte macrophage colony-stimulating factor in patients with myelodysplastic syndrome: toxicity, pharmacokinetics, and hematological effects. *J Clin Oncol.* 1989;7:629-637.

79. Ganser A, Volkens B, Greher J, et al. Recombinant human granulocyte-macrophage colony-stimulating factor in patients with myelodysplastic syndromes: a phase I/II trial. *Blood.* 1989;73:31-37.

80. Estey E, Kurzrock R, Talpaz M, et al. Therapy of myelodysplastic syndromes (MDS) with GM-CSF. *Proc Annu Meet Am Soc Clin Oncol.* 1989;8:200a.

81. Schuster MW, Thompson JA, Larson R, et al. Randomized trial of subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF) versus observation in patients (pts) with myelodysplastic syndrome (MDS). *J Cancer Res Clin Oncol.* 1990;116:1079a.

82. Willemze R, Visani G, de Witte TH, et al. A randomized phase I/II study with recombinant human GM-CSF in patients (pts) with myelodysplastic syndromes at relatively low risk of developing acute leukemia. *Blood.* 1990;76:337a.

83. Rosenfeld CS, Sulecki M, Evans C, et al. Comparison of intravenous versus subcutaneous recombinant human granulocyte-macrophage colony-stimulating factor in patients with primary myelodysplasia. *Exp Hematol.* 1991;19:273-277.

84. Willemze R, van der Lely N, Zwierzina H, et al. A randomized phase I/II multicenter study of recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy for patients with myelodysplastic syndromes and a relatively low risk of acute leukemia. EORTC Leukemia Cooperative Group. *Ann Hematol.* 1992;64:173-180.

85. Takahashi M, Yoshida Y, Kaku K, et al. Phase II study of recombinant human granulocyte-macrophage colony-stimulating factor in myelodysplastic syndrome and aplastic anemia. *Acta Haematol.* 1993;89:189-194.

86. Greenberg PL, Negrin R, Nagler A. Effects of CSFs in preleukemia. *Bone Marrow Transplant.* 1990;6:121-126.

87. Kurzrock R, Talpaz M, Gomez JA, et al. Differential dose-related hematological

effects of GM-CSF in pancytopenia: evidence supporting the advantage of low-over high-dose administration in selected patients. *Br J Haematol.* 1991;78:352-358.

88. Delmer A, Karmochkine M, Cadion M, et al. Recurrent spleen enlargement during cyclic granulocyte macrophage colony stimulating factor therapy for myelodysplastic syndromes. *Am J Hematol.* 1990;34:73-74.

89. Negrin R, Haeuber DH, Nagler A, et al. Treatment of myelodysplastic syndromes with recombinant human granulocyte colony stimulating factor: a phase I-II trial. *Ann Intern Med.* 1989;110:976-984.

90. Kobayashi Y, Okabe T, Ozawa K, et al. Treatment of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor: a preliminary report. *Am J Med.* 1989;86:178-182.

91. Ohyashiki K, Ohyashiki JH, Toyama K, et al. Hematologic and cytogenetic findings in myelodysplastic syndromes treated with recombinant human granulocyte colony-stimulating factor. *Jpn J Cancer Res.* 1989;80:848-854.

92. Negrin RS, Haeuber DH, Nagler A, et al. Maintenance treatment of patients with myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor. *Blood.* 1990;76:36-43.

93. Yoshida Y, Hirashima K, Asano S, et al. A phase II trial of recombinant human granulocyte colony stimulating factor in the myelodysplastic syndromes. *Br J Haematol.* 1991;78:378-384.

94. Greenberg P, Negrin R, Nagler A, et al. Effects of prolonged treatment of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor. *Int J Cell Cloning.* 1990;8(suppl 1):293-302.

95. Greenberg P, Taylor K, Larson R, et al. Phase III randomized multicenter trial of G-CSF vs observation for myelodysplastic syndromes (MDS). *Blood.* 1993;82(10,S1):196a.

96. Stenke L, Wallvik J, Celsing F, et al. Prediction of response to treatment with human recombinant erythropoietin in myelodysplastic syndromes. *Leukemia.* 1993;7:1324-1327.

97. Stein RS, Abels RI, Krantz SB. Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood.* 1991;78:1658-1663.

98. Hellstrom E, Birgegard G, Lockner D, et al. Treatment of myelodysplastic syndromes with recombinant human erythropoietin. *Euro J Haematol.* 1991;47:355-360.

99. Aloe Spiriti MA, Petti MC, Latagliata R, et al. Is recombinant human erythropoietin treatment in myelodysplastic syndromes worthwhile? *Leuk Lymphoma*. 1993;9:79-83.
100. Negrin RS, Stein R, Vardiman J, et al. Treatment of the anemia of myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor in combination with erythropoietin. *Blood*. 1993;82:737-743.
101. Negrin RS, Stein R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. *Blood*. 1996;87:4076-4081.
102. Hellstrom-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. *Blood*. 1998;92:68-75.
103. Nadeem SO, Saba HI, Nawab U, et al. Is cytokine therapy superior to chemotherapy in the management of acute myelocytic leukemia evolving from myelodysplasia. *Blood*. 1994;84:634a.
104. Yoshida Y. Treatment of the myelodysplastic syndromes: an updated Japanese experience. *Semin Hematol*. 1996;33:246-255.
105. Cortezzi A, Sarina B, Cattaneo C, et al. In vitro effects of IL-2 on NK-activity, clonogenic potential, blast cell proliferation and cytokine release of MDS bone marrow patients. *Leukemia*. 1996;10:1181-1189.
106. Ogata K, Yokose N, Nomura T. Interleukin-2 therapy for myelodysplastic syndrome: does it work? *Leuk Lymphoma*. 1995;17:411-415.
107. Nand S, Stock W, Stiff P, et al. A phase II trial of interleukin-2 in myelodysplastic syndromes. *Br J Haematol*. 1998;101:205-207.
108. Gordon MS, Nemunaitis J, Hoffman R, et al. A phase I trial of recombinant human interleukin-6 in patients with myelodysplastic syndromes and thrombocytopenia. *Blood*. 1995;85:3066-3076.
109. Zwierzina H, Holzinger I, Gaggl S, et al. Recombinant human interleukin-8 restores function in neutrophils from patients with myelodysplastic syndromes without stimulating myeloid progenitor cells. *Scand J Immunol*. 1993;37:322-328.
110. Bartley TD, Bogenberger J, Hunt P, et al. Identification and cloning of a megakaryocyte growth and development factor that is a ligand for the cytokine receptor Mpl. *Cell*. 1994;77:1117-1124.
111. Tafuri A, Lemoli RM, Petrucci MT, et al. Thrombopoietin and interleukin 11 have different modulatory effects on cell cycle and programmed cell death in primary acute myeloid leukemia. *Exp Hematol*. 1999;27:1255-1263.
112. Ogata K, Tamura H, Yokose N, et al. Effects of interleukin-12 on natural killer cell cytotoxicity and the production of interferon-gamma and tumour necrosis factor-alpha in patients with myelodysplastic syndromes. *Br J Haematol*. 1995;90:15-21.
113. Glinsmann-Gibson B, Spier C, Baier M, et al. Mast cell growth factor (c-kit ligand) restores growth of multipotent progenitors in myelodysplastic syndrome. *Leukemia*. 1994;8:827-832.
114. List AF, Heaton R, Glinsmann-Gibson B, et al. Amifostine stimulates formation of multipotent and erythroid bone marrow progenitors. *Leukemia*. 1998;12:1596-1602.
115. Griggs JJ. Reducing the toxicity of anticancer therapy: new strategies. *Leuk Res*. 1998;22:S27-S33.
116. List AF, Brasfield F, Heaton R, et al. Stimulation of hematopoiesis by amifostine in patients with myelodysplastic syndrome. *Blood*. 1997;90:3364-3369.
117. Bowen DT, Denzlinger C, Brugger W, et al. Poor response rate to a continuous schedule of amifostine therapy for "low/intermediate risk" myelodysplastic patients. *Br J Haematol*. 1998;103:785-787.
118. Berer A, Ohler L, Simonitsch I, et al. Long-term improvement of hematopoiesis following cyclosporine treatment in a patient with myelodysplastic syndrome. *Wien Klin Wochenschr*. 1999;111:815-818.
119. Jonasova A, Neuwirtova R, Cermak J, et al. Cyclosporin A therapy in hypoplastic MDS patients and certain refractory anaemias without hypoplastic bone marrow. *Br J Haematol*. 1998;100:304-309.
120. Biesma DH, van den Tweel JG, Verdonck LF. Immunosuppressive therapy for hypoplastic myelodysplastic syndrome. *Cancer*. 1997;79:1548-1551.
121. Mollrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. *Br J Haematol*. 1998;99:699-705.
122. Mollrem JJ, Jiang YZ, Stetler-Stevenson M, et al. Haematological response of patients with myelodysplastic syndrome to antithymocyte globulin is associated with a loss of lymphocyte-mediated inhibition of CFU-GM and alterations in T-cell receptor Vbeta profiles. *Br J Haematol*. 1998;102:1314-1322.
123. Killick AB, Marsh JC, Cavenagh JD, et al. Antithymocyte globulin for the treatment of patients with "low risk" myelodysplastic syndromes. *Blood*. 1999;94:306a.
124. Estey EH. Incorporating new modalities into guidelines. Topotecan for myelodysplastic syndromes. *Oncology (Huntingt)*. 1998;12:81-86.
125. Raza A, Dar S, Borok R, et al. Encouraging response to amifostine, pentoxifylline, ciprofloxacin, dexamethasone (A-PCD) +/- topotecan in patients with myelodysplastic syndromes. *Blood*. 1999;94:305a.
126. Besa EC. A new combination chemotherapy using topotecan, fludarabine, ARA-C and G-CSF for aggressive myelodysplastic syndromes and acute myelogenous leukemia in the elderly: dose finding for topotecan study. *Blood*. 1999;94:307a.
127. Beran M, Kantarjian H. Results of topotecan-based combination therapy in patients with myelodysplastic syndromes and chronic myelomonocytic leukemia. *Semin Hematol*. 1999;36:3-10.
128. Denzlinger C, Bowen D, Benz D, et al. Low-dose melphalan induces favourable responses in elderly patients with high risk myelodysplastic syndromes or secondary acute myeloid leukemia. *Br J Haematol*. 2000;108:93-95.
129. Sabir T, Raza S, Anderson L, et al. Thalidomide is effective in the treatment of recurrent, refractory multiple myeloma. *Blood*. 1999;94:125a.
130. Raza A, Lisak L, Andrews C, et al. Thalidomide produces transfusion independence in patients with long standing refractory anemias and myelodysplastic syndromes (MDS). *Blood*. 1999;94:661a.
131. Donelli A, Chiodino C, Panissidi T, et al. Might arsenic trioxide be useful in the treatment of advanced myelodysplastic syndromes? *Haematologica*. 2000;85:1002-1003.
132. Soignet S, Frankel S, Tallman M, et al. US multicenter trial of arsenic trioxide (AT) in acute promyelocytic leukemia (APL). *Blood*. 1999;96:3084.
133. Dutcher JP, Wiernik PH, Novik Y, et al. Major hematologic response in a patient with myelodysplasia (MDS) to arsenic trioxide (ATO). *Blood*. 2000;96:2606.
134. Wiernik PH, Dutcher JP, Gallagher R, et al. Phase II trial of arsenic trioxide (AS203) in patients (pts) with relapsed/refractory acute myeloid leukemia (AML), blast crisis of CML, or myelodysplasia (MDS). *Blood*. 1999;94:510a.