Understanding the Myelodysplastic Syndromes

PETER A. KOUIDES, JOHN M. BENNETT

University of Rochester School of Medicine and Dentistry, Department of Medicine, Rochester General Hospital, Rochester, New York, USA

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ABSTRACT

The myelodysplastic syndrome (MDS) remains challenging to the clinician in terms of diagnosis and management. The diagnosis is essentially one of exclusion in first ruling out other disorders that can also cause peripheral blood/bone marrow cell dysplasia and cytopenias. The distinguishing biological characteristic of MDS is that it is a clonal disorder of the marrow with impaired differentiation. Recent studies implicate extensive apoptosis as the explanation of the paradoxical observation of marrow hyperplasia but peripheral blood cytopenia. Neutropenia and/or neutrophil dysfunction account for the primary clinical manifestation of MDS in terms of an increased risk for infection, which is the leading cause of death in MDS. The clonal nature of MDS places it also at continual risk for transformation to acute leukemia. Predicting overall survival as well as the risk of AML transformation has been improved by the recent development of a scoring system (International Prognostic Scoring System) that incorporates three laboratory variables: percent of marrow blasts, degree of cytopenias, and presence of chromosomal abnormalities. Based on these variables, four prognostic subgroups can be delineated ranging from low risk with a median survival of 5.7 years, to high risk with a median survival of 0.4 years. Management of MDS can now be based on the patient’s respective prognostic subgrouping, with low-risk patients being considered for hematopoietic growth factor singly or in combination if at the point of red cell transfusion dependence and/or neutropenia with recurrent infections, while high-risk patients should be offered AML-induction therapy or novel agents such as Topotecan. One must individualize further in patients in the remaining intermediate groups, I and II, in choosing the most appropriate therapy. Future advances upon understanding the molecular details of the MDS clone should ultimately improve the care of patients with MDS. The Oncologist 1997;2:389-401

INTRODUCTION

The myelodysplastic syndrome (MDS) has been a most challenging disease for hematologists-oncologists for decades in terms of both diagnosis and management [1-5]. The definition of MDS also has two parts, as it is essentially a clinico-pathologic description. MDS can be defined as a clonal disease of the bone marrow with:

▲ The clinical manifestation of bone marrow failure as well as a tendency to transform into an acute leukemic phase.

▲ The pathological manifestation of morphological abnormalities (termed “dysplasia,” although it is a clonal disorder, and hence, neoplastic) of the peripheral blood and bone marrow cells (Figs. 1A, 1B) such as ringed sideroblasts, megaloblastic erythroid precursors, hypogranulation/hypossegmentation of the granulocytes, and micromegakaryocytes [2, 6, 7].

This review will attempt to further the reader’s understanding of MDS in the framework of this definition, emphasizing relevant features of the presentation, diagnostic work-up, and therapy. We will focus on “primary,” de novo MDS as opposed to “secondary” MDS, i.e., secondary to prior cytotoxic chemotherapy.

ADVANCES IN THE UNDERSTANDING OF THE PATHOGENESIS OF MDS

A major advance toward understanding the pathogenesis of MDS has been the observation of apoptosis, programmed cell death, in MDS [8-10]. The group of Razafi/Preisler et al. have carried out cell kinetic studies from MDS bone marrow biopsies using intravenous infusions of either iododeoxyuridine or bromodeoxyuridine or both and estimating the degree of apoptosis by in situ end-labeling of DNA [9, 10]. Virtually all marrows studied demonstrated apoptosis as well as rapid cell proliferation. Whether apoptosis is the extensive in all cases of
MDS [11] and whether it is specific for MDS and no other clonal—or, for that matter—non-clonal marrow disease (such as folate deficiency) [12] is unclear at this time. However, the observation of increased apoptosis reconciles the seemingly opposing findings of marrow hypercellularity but peripheral blood pancytopenia in MDS patients [13]. Intuitively, this would appear to be related to levels of apoptosis-related oncogene products such as c-myc, which enhances apoptosis, and bcl-2, which diminishes apoptosis, as suggested by a study by Rajapksa et al. [14]. Interestingly, in that study, patients treated with erythropoietin and G-CSF had reduced apoptosis within CD34+ marrow cells [14]. Other cytokines that may play a role in apoptosis in MDS include tumor necrosis factor alpha, transforming growth factor beta, and interleukin-1 beta converting enzyme which are all elevated in MDS patients [15]. These cytokines may exert a dual effect of stimulating proliferation of the early CD34+ MDS progenitors while inducing apoptosis in their progeny [10,15]. Certainly, future therapies are being designed to counter this situation, particularly in terms of blocking the common lipid signaling pathway of phosphatic acid-diacylglycerol that these three cytokines share [16]. Agents that block this pathway include pentoxifylline, lisophylline, and ciprofloxacin [10,16]. Unfortunately, a recent phase II study of ciprofloxacin and pentoxifylline in 14 advanced MDS patients with cytopenias with/without transfusion requirements showed no efficacy [17].

**Clinical Presentation and Diagnosis**

It is uncommon for the patient with MDS to present with physical examination abnormalities that lead to the diagnosis, except perhaps for the MDS subtype, chronic myelomonocytic leukemia (CMML), wherein splenomegaly (20%), hepatomegaly (15%), leukemia cutis (10%), gum hypertrophy, and sterile effusions of the pericardium, pleura, or peritoneum have been noted [18]. A far more common presentation is the discovery of a cytopenia (primarily anemia) in an elderly patient [3]. In a study of anemic patients in a geriatric ward, only iron-deficiency, post-hemorrhagic anemia, and anemia of chronic disease/renal failure were more commonly diagnosed than MDS [19]. Regarding the general population, the best studies to date on incidence are from Europe [20-22], with an overall incidence of approximately 3/100,000/year, rising to approximately 20/100,000/year over age 70. Unfortunately, an incidence has not been established specifically for the United States.

In general, the overall incidence of MDS appears to be increasing over the past decade [23], there also appears to be a slight male preponderance. In general, the over overall incidence probably equals or exceeds the incidence of AML. Certainly, the incidence of MDS markedly exceeds that of AML in older patients. Only 10%-20% of MDS patients are under the age of 60 [21]. Unlike patients with AML, a fair proportion of patients will be asymptomatic despite anemia, although a small proportion (~10%) will present with infection, and probably an even smaller proportion with bleeding [18]. It is not unusual, then, for the patient to be diagnosed because of an incidental hemogram [18]. Anemia (hemoglobin <11 g/dl) is most common (typically isolated), but occasionally isolated thrombocytopenia, and, even less commonly, isolated neutropenia have
been noted. Isolated thrombocytopenia may precede by 2-10 years the development of the features to be discussed below that permit classification as MDS [24, 25]. Another challenge to the clinician confronting a potential case of MDS is that, occasionally, the patient will not present with a cytopenia. Rather, the patient may present with:

- **Leukocytosis**, as a subset of CMML patients can have an increased white blood cell count [26].
- **Thrombocytosis**, particularly in association with refractory anemia or refractory anemia with ringed sideroblasts (often in association with partial deletion of the long arm of chromosome #5 termed “5q−”) [27, 28].
- **Isolated thrombocytopenia**, as above.

Before proceeding with a bone marrow aspirate and biopsy in a patient suspected to have MDS (e.g., an elderly patient with a non-iron deficiency anemia and borderline low WBC and/or platelet count with hypogranular/hypolobulated white blood cells and red cells with basophilic stippling on the peripheral blood smear), it is incumbent that the clinician consider the possibility of the following conditions that can also be associated with cytopenia and peripheral blood cell dysplasia [3]:

- **Vitamin B\textsubscript{12} and/or folate deficiency** since low B\textsubscript{12} levels are not that uncommon in the elderly [29], and hyperlobulation of the neutrophils can be seen as a dysplastic feature in MDS.
- **Proven exposure to heavy metals** [30].
- **Recent cytotoxic therapy**, including patients receiving agents such as methotrexate and azathioprine for rheumatological diseases.
- **Ongoing inflammation**, including HIV infection [31-36] and cancer [37,38], particularly HIV, wherein one study reported dysplastic features of at least one lineage in 105 of 152 patients [32].
- **Chronic liver disease** [39-40], since macrocytosis is common in both entities.

Above all, the first three conditions must be excluded. The latter two could be considered to be relative exclusions as there will be patients with both MDS and a coincidental inflammatory state (such as cancer or rheumatoid arthritis) or MDS with coincidental chronic liver disease/alcohol use. That MDS is a diagnosis of exclusion is illustrated by the not-too-uncommon scenario of a patient referred to the hematologist for further evaluation of a persistent macrocytic anemia despite a trial of vitamin B\textsubscript{12} injections. Such an occurrence reminds one why the term “refractory anemia” was coined.

Thereafter, as the clinician’s pre-test probability for MDS has increased after excluding the above conditions, the bone marrow exam is then done essentially to confirm the diagnosis in terms of identifying at least 10% of cells of either the erythroid, megakaryocytic, or myeloid lineage as dysplastic (Fig. 2), as well as to classify further the disease in terms of the percentage of blasts in the context of the French-American-British (FAB) classification [41] (Fig. 3). The determination of the percentage of blasts is particularly important for prognosis as, intuitively, those patients with ≥5% blasts, termed refractory anemia with excess blasts (and refractory anemia with excess blasts in transformation if there are ≥20% <30%) have a shorter overall survival hand-in-hand with a higher risk of progression of evolution to acute myelogenous leukemia (AML). In those patients with <5% blasts, determination of the percentage of ringed sideroblasts is of value. The percentage of ringed sideroblasts is determined by a Prussian blue stain for assessing the proportion of erythroid progenitors that have iron- (from the Greek sidero) laden mitochondria that encircle the nucleus under the microscope. The classification as refractory anemia with ringed sideroblasts (RARS) is helpful in connoting a

![Figure 2. The dyslastic bone marrow features of MDS.](image-url)

![Figure 3. Steps in diagnosing MDS.](image-url)
“good” prognosis and such patients may be less likely to respond to erythropoietin than those without ringed sideroblasts [42]. On the other hand, RARS patients, albeit a small proportion, may respond to pyridoxine [3].

Occasionally, the diagnosis of MDS by bone marrow (BM) exam can be elusive. This is because of variability in the cellularity from one marrow site sampled to another and variability in involvement of the erythroid, myeloid, and megakaryocytic lineages. Classically there is trilineage dysplasia, but occasionally, particularly in early-onset cases, there can be dysplasia confined to only one or two lineages.

We are often asked by practitioners as well as patients if a BM test is always necessary as in the example already provided (the elderly patient with a non-iron deficiency anemia and borderline low WBC and/or platelet count with hypogranular/hypolobulated white blood cells and red cells with basophilic stippling on the peripheral blood smear). The British are fond of stating that a test should not be ordered if one is not going to do anything differently after obtaining the results. Certainly, one could argue that in an anemic elderly patient with MDS, the treatment is supportive only in terms of red cell therapy. However, as will be discussed in the Therapy section, with the advent of new differentiating agents and the use singly or in combination of hematopoietic growth factors, there are more options available beyond just red cell transfusion therapy, wherein it would be important to confirm the diagnosis of MDS before embarking on such therapies. Most importantly, the marrow exam is necessary for prognosis, particularly in assessing the percentage of marrow blasts as well as obtaining adequate marrow to analyze for chromosomal abnormalities. The cytogenetic testing and the assessment for the percentage of marrow blasts can now be incorporated into a recently developed scoring system that clearly refines the prognosis of MDS, as discussed below.

**PROGNOSIS**

Numerous clinical, pathologic, and biologic factors have been studied in hopes of best predicting the overall survival and acute leukemic transformation risk in MDS patients [44, 45]. These include: the degree of cytopenia, percentage of BM blasts, BM cytogenetics, serum lactate dehydrogenase level, BM histology for abnormal localization of immature precursors, the presence of fibrosis, the marrow immunophenotype, and in vitro bone marrow culture characteristics [44, 45]. None of these factors, either singly or in combination, have clearly led to a prognostic index with adequate precision. This led to the development of the International Prognostic Scoring System (IPSS) for MDS, wherein combined data from seven previously reported studies were analyzed [46]. It was determined that patients could be separated into distinctive subgroups for both median survival and the number of years for the respective subgroup to undergo acute leukemic transformation (Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>Risk subgroup</th>
<th>Score</th>
<th>Median survival (years)</th>
<th>AML risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The score is based on the following parameters:

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score</th>
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<tbody>
<tr>
<td>BM blasts (%)</td>
<td>0</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias (Hemoglobin &lt;10 g%, absolute neutrophil count (ANC)&lt;1,800/µl, platelet count &lt;100,000/µl)</td>
<td>0/1</td>
</tr>
</tbody>
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Stratification by age less than or greater than 60 separates patients further within the low-risk and intermediate-1 subgroups. The IPSS was able to discriminate between the subgroups of other categorization systems [46]. It does appear that this relatively simple prognostic model will be of practical value to the clinician in assessing future clinical outcomes and therapies in MDS patients by allowing for better comparison of therapies by stratifying patients based on the IPSS risk and comparing the subgroups within a study. The role of cytogenetics in prognosis underscores the need for the clinician to request that analysis when the BM examination is done in a patient suspected of having MDS.

**NATURAL HISTORY/CLINICAL COMPLICATIONS**

Since this is disease of the elderly, there are often comorbid conditions that ultimately may shorten the patient’s life expectancy such that ~20% of MDS patients will not succumb to the MDS [47]. Approximately one-third of patients will undergo transformation into AML, which is ultimately fatal. In
the remaining patients, the majority will succumb to infection in part from neutropenia (in one series, 60% of MDS patients had a neutrophil count <2,500/µl [48]), and in part from granulocyte dysfunction, as the MDS clone can have impairment in phagocytic adhesion, chemotaxis, and microbicidal killing [49, 50]. This may also account for slowly resolving abscesses as well as the lack of fever, with such patients often just manifesting malaise [51]. In a study by Pomeroy et al. [47] of 86 MDS patients, infection accounted for 64% of deaths. The risk for infection was about one per year [47]. Bacterial pneumonias and skin abscesses were most common, but unusual/opportunistic-type infections have been reported such as disseminated mycobacterium avium-intracellulare [52], Aeromonas hydrophilia endocarditis [53], bacterial thyroiditis [47], and Epstein-Barr virus hepatitis [47]. The course of these infections can be quite prolonged, in part because of the underlying defects in neutrophil function. Prophylactic antibiotic therapy such as daily trimethoprim-sulfamethoxazole as piloted in other hematological malignancies [54] has not been systematically studied in MDS; neither has the use of intravenous gamma globulin. As for the use of hematopoietic growth factors, they predictably lead to resolution of the neutropenia (78% efficacy with GM-CSF and 90% efficacy with G-CSF) [55]. However, they have not yet been proven in randomized, placebo-controlled, double-blind studies to prolong survival when given prophylactically [56, 57], although one small randomized study of GM-CSF has been reported in abstract form [56] to have decreased the infection rate. A multicenter study of G-CSF (n = 102), also presented only in abstract form, did not report the outcome in terms of the development of infection [57].

Less common than infection but potentially life-threatening is the risk of bleeding in MDS patients. Bleeding can occur even in the absence of thrombocytopenia attributable to platelet dysfunction [58], as evidenced by a prolonged bleeding time [59] and an increase in atypical megakaryocytes [59].

MDS patients can also manifest a wide range of autoimmune phenomena, such as cutaneous vasculitis [60] (Fig. 4), polymyalgia rheumatica [61, 62], necrotizing panniculitis [62], Coombs-positive autoimmune hemolytic anemia [63, 64], remitting seronegative symmetrical synovitis with pitting edema [65], and an inflammatory seronegative arthritis [66, 67]. Acute manifestations of a systemic autoimmune disease, as described in a recent study by Enright et al. [68], include pericarditis, pleural effusions, skin ulceration, seizures, myositis, and peripheral neuropathy. They also reported the following chronic or isolated autoimmune manifestations: glomerulonephritis, polyneuropathy, pyoderma gangrenosum, polyarthritis, and ulcerative colitis [68]. An association of inflammatory bowel disease with MDS had also been reported by other groups [69-70]. It does appear that management of the autoimmune manifestations with immunosuppressive therapy is effective; it may also improve the associated cytopenias [68].

Another clinical feature peculiar to MDS is that these patients have a higher incidence of malignant tumors (as well as lymphoma [72]) than the general population [38]. It has been hypothesized that the increased risk of developing malignant tumors reflects an underlying defect in developing immune surveillance that initially led to the emergence of the MDS clone in the first place [73].

![Figure 4. Cutaneous vasculitis in a patient with MDS.](image-url)
THERAPY OF MDS

Treatment of MDS can be categorized conceptually into three main approaches, as diagrammed in Figure 5. These approaches include:

- Differentiation of the abnormal clone by differentiation-induction agents or perhaps by cytokine therapy.
- Suppression of the abnormal clone by low-dose or standard-dose chemotherapy, perhaps by cytokine therapy via stimulation of residual normal hematopoiesis with subsequent suppression of the malignant hematopoiesis, or by activation of the residual normal host immune system by cytokines/cytokine-activated lymphocytes ("immunotherapy").
- Ablation of the abnormal clone by more intensive therapy via an allogeneic bone marrow transplant (BMT).

The appropriate approach, if any, should depend primarily on three clinical and biological factors:

- Severity of the patient’s cytopenia.
- Degree of leukemic progression (% marrow blasts).
- Patient’s age.

These factors, in turn, are reflected in the IPSS [46] previously described. The main goal in the elderly patient should be to ameliorate their cytopenias when they become transfusion-dependent, wherein the clinician should be reminded of the first principle of medical care: “First do no harm.” However, in the younger patient, the goal may be curative therapy via an allogeneic BMT, wherein the clinician should be reminded of the British maxim: “Desperate diseases deserve desperate measures”.

We will now review treatment in relation to the patient’s IPSS risk grouping, as summarized in Figure 6. The focus will be on those treatments with a fair probability of response (>25%). As such, we will not discuss differentiating agents [74] (e.g., cis-retinoic acid [75,76], all-trans-retinoic acid [77-79], vitamin D3 [80], or hexamethylene bis-acetamide [81, 82]), although they are appropriately still an active area of investigation in combining such agents with various cytokines [83] or new analogs [74].

THE HIGH-RISK OR INTERMEDIATE-2 IPSS GROUP

Since these patients have a median survival of only about a year, it is reasonable to consider relatively aggressive measures. These include allogeneic BMT if the patients are, in general, less than age 50, although there is, of course, no firmly established upper age limit. What is most important is the patient’s “physiological” age which, in turn, considers the patient’s cardiopulmonary, renal, and hepatic reserve. Not surprisingly, the median age of MDS patients transplanted to date...
has been less than 40 years old, so one could argue that even the “best” results are not very applicable for most MDS patients. In these studies, the event-free survival range has been very wide, 20%-70% [84]. This wide range is dependent on the exact age of the patient, the FAB subtype (RA/RARS is better than the other subtypes [85]), the duration of the disease (shorter is preferable [86]), the presence and degree of cytogenetic abnormalities (none, of course, is best [87]), the percentage of marrow blasts (<5% blasts is best [87]), the presence of marrow hypoplasia (better than the other subtypes [85]), the duration of the disease, i.e., faster time to transplant, is a favorable prognostic factor [86]. Since RAEB/RAEB-T patients with a normal karyotype have an apparently equivalent rate of successful remission induction therapy as de novo AML patients [94-96], it may be reasonable to proceed with induction-remission therapy first in these patients prior to autologous BMT in hopes of ultimately reducing the risk of post-BMT relapse as much as possible. Along these lines, Estey, in a cohort of “high-risk” MDS patients (n = 20 RAEB, n = 61 RAEB-T, and n = 3 CMML) treated at their institution with AML-type therapy, noted a profound difference in the CR rate and disease-free survival (DFS) at three years based on the karyotype: “favorable” karyotype (diploid or t(8;21) or inversion 16)—n = 48, CR 79%, DFS 65% versus “unfavorable” karyotype—n = 102, CR 60%, DFS just 5% [96].

In patients without a haploidentical sibling, AML-like induction therapy is certainly reasonable in this high-to-intermediate-2 risk group, particularly if they have a “favorable karyotype”, as above. Nonetheless, even in those achieving CR, the duration of CR is typically quite short, on the order of just a few months [84, 97, 98]. As such, in those patients it may be reasonable thereafter to consider an autologous peripheral blood or BMT. There are now published reports of autologous BMT in the therapy of MDS [99, 100]. However, follow-up is relatively short, precluding conclusions regarding its place in the field of BMT for MDS. Importantly, and counter-intuitively, there has been long-term repopulation by marrow rescue after myeloablation, suggesting that there must be normal stem cells/progenitors present; indeed, polyclonal hematopoiesis has been demonstrated in peripheral blood stem cell harvests [101]. Similar to the situation in chronic phase chronic myelogenous leukemia, it may be appropriate to consider peripheral blood stem cell mobilization relatively early in the course of one’s disease on the assumption that there will be a greater proportion of nonmalignant progenitors.

Other chemotherapy-based options in the high-risk patients include novel agents not previously administered in MDS such as 2-chlorodeoxyadenosine [102] (data are too preliminary), homoharringtonine [103] (mild efficacy), and topotecan [104]. It is the latter, a topoisomerase I inhibitor, which is the most promising given a 28% CR rate in 47 patients (n = 22 RAEB/RAEB-T, n = 25 CMML). This is one of the highest CR rates for single-agent therapy in MDS. Yet, the reason we would reserve its use only for the high/intermediate-2 risk groups is that 19% of the patients died during the induction period, six of these with marrow hypoplasia and three with residual disease. It is hoped that this toxic rate will be abrogated by a lower-dose oral form of topotecan or at lower doses in combination with other agents without compromising efficacy, wherein topotecan-based regimens may be appropriate for most MDS patients.

As for low-dose chemotherapy, the “standard” historically has been low-dose cytosine arabinoside (ARA-C), but the total response rate with low-dose ARA-C (LDAC) has been only one-third (~16% CR~21% partial response, as reviewed by Cheson [105]). Recent studies have attempted to improve upon this by adding additional cytotoxic agents at low doses, such as etoposide [106], 6-TG [107], G-CSF [108], or interleukin 3 (IL-3) [109], and in all cases the response rate is higher than that seen with LDAC alone but typically not significantly greater [107, 109]; usually, the response is of short duration [106]. One study of ARA-C alone deserves particular attention, as all five patients achieved a complete hematological response with low-dose ARA-C. These patients all had deletion of 5q- and were red-cell-transfusion-dependent [110]. Notably, the dysplasia still persisted in the follow-up marrows as the 5q- abnormality
usually did. Neither we nor the authors of that study have any logical explanation to offer as to why there is specificity for response to ARA-C in patients with 5q-.

**The Low-Risk or Intermediate-1 Group**

Intervention in these patients should be primarily predicated on the degree of cytopenia:

- **Anemic to point of red blood cell dependence or hematocrit <28%-30%**: A trial of erythropoietin is worth trying (≥50% probability of response) if patients have the following clinical characteristics: FAB subtype refractory anemia [111-113], baseline serum erythropoietin level <100 IU/l [111, 114-116], red cell transfusion independence [42], and “early” response (i.e., within the first eight weeks) [116]. The dose should be a minimum of 450 u/kg/week total s.c., usually given as a divided dose three times a week [117]. In non-responders, it may be worth retrying the erythropoietin after first pretreating with G-CSF [118,119] or GM-CSF [120-122] daily for six weeks on the presumption that there may be synergy in terms of enhancing normal and MDS erythropoiesis. Sequential therapy has led to a 1.5- to 2-fold increase in the response rate to erythropoietin in terms of increasing the hemoglobin by greater than 2.0 g% and/or reducing the red cell transfusion requirements [118-122]. Besides obtaining a serum erythropoietin level in an MDS patient, a serum ferritin should also be obtained since transfusion dependence may be lessened by s.c. desferrioxamine if patients have a serum ferritin >500 ng/ml and percent iron saturation >60% [123].

- **Thrombocytopenic to <50,000/ml platelets**: In a study by Wattel *et al.* of patients with platelet counts <50,000/ml (as well as <10% marrow blasts), 11/20 patients had at least a 30,000/ml incremental rise in their platelet count after administering either danazol or fluoxymesterone [124]. The greatest hope for the future treatment of the thrombocytopenic MDS patient remains thrombopoietin (*mpl* ligand), now in clinical trials. Other hematopoietic growth factors with megakaryocytic-stimulating properties such as IL-6 [125] and IL-3 [126, 127] have not been very efficacious. On the other hand, there appears to be an inverse relationship of circulating thrombopoietin levels and the platelet count akin to erythropoietin levels to the hematocrit in anemic MDS patients, so it is not clear that thrombopoietin will be effective [128].

- **Neutropenic (<1,000 ANC) with recurrent infections**: One should try G- or GM-CSF from one to seven times per week at standard or low dose [129] s.c. titrated to keep the absolute neutrophil count in the normal range [55].

- **The bone marrow is hypocellular**: In one study, 7/21 patients achieved CR with low-dose melphalan (2 mg p.o. QD). Surprisingly, despite pre-existing marrow hypoplasia, there was not prolonged pancytopenia in the responders, thus suggesting a differentiative or selective antileukemic cell effect than cytotoxicity in general as the mechanism of response [130]. Since hypocellular MDS comprises only 10%-20% of MDS cases [7], the impact of melphalan in MDS may not be substantial. This is also just one study. Cyclosporine [131] with anti-thymocyte globulin has been used in two hypocellular MDS patients with clinical improvement (achieving transfusion independence) and disappearance of the marrow dysplasia.

**Future Advances in MDS**

Fortunately, the study of malignant hematopoiesis is a very active area of research worldwide. It is hoped that the study of the proliferation and differentiation of the MDS clone at the molecular level, including the details of apoptosis, may lead to more effective differentiation-induction/“anti-apoptotic” agents (candidates presently in phase I/II trials include amifostine [132], tamoxifen [133], and recombinant human hemoglobin [134]). The development of molecular “markers” of MDS [135] may also improve the diagnosis of MDS since present methods of detection by “standard” cytogenetics are not very sensitive, as 25%-50% of cases may have a normal karyotype [136]. The study of the cytokines at the cellular/molecular level may lead to more effective trials of combination therapy with differentiation-induction agents, chemotherapy, and/or early-acting cytokines. Further phenotypic characterization of the MDS clone may lead to negative selection of these cells or positive selection of normal stem cells as part of an autotransplant strategy, as is presently being done in chronic phase chronic myelogenous leukemia. The use of agents such as the topoisomerase I inhibitors (e.g., topotecan), with mechanisms of action disparate from agents already used in MDS, may increase the efficacy of chemotherapy for MDS. It is hoped that the further clinical refinements in reducing treatment-related mortality of BMT and the study of T cells at the molecular level may lead to improvement in the prevention and therapy of graft-versus-host disease, in turn increasing the upper age limit of allogeneic BMT for MDS and increasing the feasibility of matched unrelated allogeneic BMT [137].
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