Treatment of Myelodysplastic Syndromes With Hemopoit tic Growth Factors

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THE MYELODYSPLASTIC syndromes (MDS) provide a clinical model for evaluating the evolution of a relatively benign clonal myeloid hemopathy into the frankly malignant neoplasm, acute myeloid leukemia (AML). Because this disease is relatively indolent and predominates in the elderly, a therapeutic challenge has been to provide a treatment modality having adequate support for the patients' dominant cytopenias without causing excessive toxicity. Thus, with the biologic evidence of physiologic relevance and functional specificity of the hemopoietic growth factors and their availability for clinical use in recombinant form, these factors have been used to attempt to improve management of hematologic problems in MDS.

Defective proliferation of hemopoietic precursors within MDS marrow has been suggested as being due to either decreased responsiveness to or decreased production of hemopoietic growth factors. However, as some leukemic cells have enhanced proliferative responses to the colony-stimulating factors **(CSFs)** in vitro[1-3] concern exists regarding the safety of using such agents in responsive neoplastic cells. Further, intrinsic abnormalities of responsiveness occur in the myeloid precursors of these patients. Therefore, in order to evaluate the proliferative versus differentiative responsiveness of hemopoietic precursors in MDS to hemopoietic growth factors and determine the possible clinical utility of CSF treatment, several laboratories, including our own,[4] have assessed in vitro proliferative, differentiative, and regenerative responses of marrow cells from these patients to recombinant human granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (see accompanying article in this issue of the journal[5]). These in vitro findings have suggested the possible efficacy of CSFs in this clinical setting and have led to therapeutic trials with these agents.

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CLINICAL FEATURES

Numerous terms including preleukemia, hemopoietic dysplasia, refractory anemia with **ex**cess of blasts (RAEB), subacute or smoldering myeloid leukemia, oligoleukemia, and myelodysplastic and dysmyelopoietic syndromes[6-10] have been used to describe patients with refractory cytopenias whose marrows showed dysplastic changes in at least two of the three hemopoietic cell lines and **who** have a propensity to undergo transformation into AML. The term "myelodysplastic syndromes" describes the morphologic features of the marrows of these patients, and has been most commonly used to describe this clinical entity. Biologic data, particularly marrow cytogenetics and myeloid clonogenic culture and clonal analysis evaluating restriction fragment length polymorphisms, indicate that MDS patients already have their marrows involved with a myeloid malignant clone despite not having overt leukemia.[4,11,12]

However, heterogeneity of these patients has been recognized regarding variations in their marrow morphology and their differing potential for transforming into AML. Thus, these patients were subclassified by the French, American and British (FAB) Morphologic Group, which formulated a set of criteria based on marrow morphology including the proportion of myeloblasts and degree of derangement of the hemopoietic cell lines.[13] This classification scheme subdivided patients into five subgroups: refractory anemia **(RA),** refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). The first four entities were characterized by abnormal marrow myeloid cell differentiation patterns (dysplasia) with RA or RARS patients having less than 5% blasts associated with

dysplasia of the three hemopoietic cell lines, RAEB having between 5% and 20% blasts and RAEB-T having 20% to 30% blasts. Acute myeloid leukemia was considered to be present if marrows had more than 30% blasts. This morphologic characterization was helpful, although due to evolution of these diseases into aggressive stages, an additional criterion necessary for categorizing these individuals is the pace of such progression. This characteristic is important to distinguish the relative indolence of MDS from the rapid evolution of patients with frank AML. Therefore, relative stability of the patients' peripheral blood counts and marrow morphology for 2 6-week periods aids in categorizing these cytopenic patients as MDS. The inclusion of CMML as belonging to MDS is problematic because this entity is predominantly a myeloproliferative rather than myelodysplastic disorder and appears to be more akin to chronic myeloid leukemia with associated monocytes than with myelodysplasia.

The FAB classification has been useful in determining prognoses in MDS. There has been relative consistency of prognostic findings in seven major large studies evaluating this issue according to FAB morphologic criteria.[13-19] Patients with RAEB and RAEB-t had relatively poor prognoses with median survivals generally ranging from 5 to 12 months in contrast to RA or RARS patients who had median survivals of about 3 to 6 years. The proportion of these individuals who transformed to AML varied similarly, as in the high-risk RAEB and RAEB-t patients this incidence was 40% to 50%, whereas in the low-risk group it was 5% to 15%. In a recent study evaluating time-to-disease evolution, 25% and 55% of patients with RAEB and RAEB-t, respectively, underwent transformation to AML at 1 year, and 35% and 65% at 2 years." In contrast, for patients with RA the incidence was 5% and 10% at 1 and 2 years, whereas none of the RARS patients underwent leukemic transformation within 2 years. Another parameter of negative prognostic significance was an increased proportion of marrow blasts," a finding parallelling data demonstrated for FAB subgroups.

Mortality in these individuals is due to a variety of causes including evolution to AML, infection or bleeding complications related to the patients' dominant cytopenias or, because most of these patients are elderly, concomitant nonhematologic diseases associated with an older patient population. Three large series[14,15,20] have analyzed these data. In RAEB and RAEB-t patients, AML was the cause of death in 20% to 55% of patients, whereas infection and hemorrhage due to marrow failure caused about 36% to 50% of the deaths, and nonhematologic causes caused about 10% to 20%. In RA and RARS, these figures were somewhat reversed, with AML causing death in 0 to 29%, infection and hemorrhage caused 15% to 44% and nonhematologic causes 25% to 42%.

A number of other methods have been used to analyze prognosis for MDS patients based either on biologic features, such as cytogenetic abnormalities and in vitro culture clonogenicity results[4,5] or abnormal clinical features (eg, pancytopenia as opposed to single cytopenia). Patients with abnormal cytogenetics and in vitro marrow myeloid clonal growth patterns, as well as more deranged clinical features have poorer prognoses. These abnormalities generally correlate with the more advanced FAB classifications. Thus, the FAB classification appears to be a useful first approximation of prognoses for these patients. Due to this variability of prognoses in subgroups of patients with MDS, it is necessary to analyze therapeutic outcomes with these parameters appropriately stratified.

A variety of treatment approaches have been used in MDS, with general supportive care being the mainstay of therapy in the community. Thus, patients are treated as needed with antibiotics for infection, and red blood cell and platelet transfusions for anemia and thrombocytopenic bleeding. However, recently other therapeutic approaches are being more frequently used to treat MDS. Considering the direction in which treatment for this disease is now rapidly evolving, major focus of this review will be to evaluate the results of treatment of MDS with hemopoietic growth factors.

HEMOPOIETIC GROWTH FACTORS

The development of in vitro marrow clonogenic culture assays led to discovery of a family of interacting hematopoietic growth factors — the CSFs — which have recently been demonstrated to have critical physiologic roles for

controlling hemopoiesis in vivo.' Interleukin-3 (IL3) and GM-CSF have predominantly proliferative effects on early hemopoietic cell compartments, whereas G-CSF and monocyte-CSF (M-CSF) have major differentiative as well as proliferative effects on later more lineage-restricted precursors cells (for granulocytes and monocytes, respectively). Each hemopoietic cell lineage appears to be regulated by both proliferative and differentiative stimuli. Marrow culture studies in MDS have generally demonstrated subnormal clonal growth and defective cellular maturation of myeloid and erythroid precursors that become more abnormal as these patients evolve toward AML.[4,5,21] The presence of abnormal marrow cytogenetics or defective in vitro myeloid clonogenicity has been shown to have negative prognostic import in MDS.[4,5,11,21] Erythropoietin (Epo) is a relatively late-acting factor that acts predominantly on CFU-E (colony-forming units-erythroid) and on a portion of the earlier BFU-E (burst-forming units-erythroid), which generate CFU-E. Epo acts in synergy with G-CSF[20a] and certain earlier acting factors to enhance in vitro erythropoiesis. Defective in vitro erythropoiesis has been demonstrated in MDS.[4,5]

Treatment with GM-CSF

To date, five therapeutic trials have been reported using recombinant human GM-CSF short-term (generally treatment was administered for 7 to 14 days, with one to five courses of therapy).[23-27] In the study of Vadhan Raj et al,[23] GM-CSF treatment (continuous intravenous infusion) was associated with marked increases in peripheral-blood leukocytes (five- to 70-fold), including granulocytes (five- to 373-fold) in the eight patients evaluated. The absolute number of monocytes, eosinophils, and lymphocytes also increased in all patients. Three of eight patients also had two- to 10-fold increases in platelet counts and improvement in erythropoiesis, with the result that two of three patients who had required red blood cell (RBC) and platelet transfusions no longer needed them (at 20 to 27 weeks of follow-up). Treatment was also associated with increased marrow cellularity and a decreased percentage of marrow blasts in five patients, resulting in an increase in the ratio of differentiated myeloid cells to immature myeloid cells. Patients observed relatively few side effects, but bone pain was dose-limiting when it was associated with high white-cell counts. These results showed that GM-CSF was a potent in vivo stimulator of hematopoiesis and produced short-term hematologic improvement (8 to 32 weeks of observation) in patients with MDS.

In another study,[24] GM-CSF was administered as 1-hour or 4-hour intravenous infusions daily for 7 days or as 12-hour intravenous infusions for 14 days. Temporary improvements were seen in granulocyte counts, monocyte counts, and reticulocyte counts in five of seven patients with MDS, who also had increases in the numbers of eosinophils, immature myeloid cells, and myeloblasts. There was no reduction in RBC transfusion requirements, and no effect was observed on platelet counts. There was minimal toxicity, consisting of transient low-back discomfort, anorexia, myalgias, arthralgias, and low-grade fever.

In a study by Ganser et al,[25] the treatment schedule included dose escalation of GM-CSF administered by continuous intravenous infusion for 7 to 14 days, repeated after a 2-week treatment-free interval. The blood leukocyte and neutrophil counts increased markedly and dose-dependently by 1.3- to 18-fold in 10 of 11 patients. A rise of monocytes and eosinophils occurred in most patients. No sustained increase in reticulocytes or platelets was observed. Lymphocyte counts increased in all patients, affecting both T-helper and suppressor cells; however, the lymphocytes were not activated as analyzed by expression of IL2 receptors. In four of the patients, all with more than 15% blast cells in the bone marrow, the percentage of bone marrow blast cells increased during treatment with GM-CSF and 5 of the 11 treated patients developed AML during or within 1 month of treatment. Another patient developed a chronic myeloproliferative disorder 3 months after treatment. Cytogenetic data indicated induction of both proliferation and differentiation of the leukemic clones by GM-CSF. Toxic side effects were minor with slight fever, phlebitis at the infusion site, and bone pain in the minority of patients.

In another study,[26] GM-CSF was administered by intravenous injections for 5 days to four MDS patients. The treatment courses were

interrupted by a 10-day rest period and repeated two to three times. Granulocyte-macrophage colony-stimulating factor was well tolerated, with only minor side effects seen, which included bone discomfort at the lower back, sternum, and ribs, and constitutional symptoms such as low-grade fever, nausea/vomiting, and mild myalgias. Whereas no increases in platelet and reticulocyte counts were recorded, elevations of absolute neutrophil counts above 100 cells/mm^3 occurred in all patients. However, a striking finding was the development of increases in the number of circulating and bone marrow blast counts that were observed particularly when GM-CSF doses of 500 $\mu g/m^2$ of body surface area were administered.

Thompson et al[27] demonstrated that daily subcutaneous GM-CSF treatment caused increased circulating neutrophil levels in a dose-dependent manner in 11 of 16 patients (two- to 194-fold increments). Although the neutrophils usually returned to pretreatment levels shortly after stopping GM-CSF, two patients continue to exhibit an elevation of neutrophils for 6 months. Dose-related increases in circulating monocytes and eosinophils were also noted. Transient increases in platelet and reticulocyte counts were observed in several patients. Five of the 16 patients later received maintenance therapy with GM-CSF for 2 to 9 weeks. All patients had dramatic increases in neutrophils after 2 weeks. However, thereafter, despite continued therapy, the neutrophil count in 4 patients declined markedly, 1 patient developed antibodies to GM-CSF and 1 patient's disease evolved into AML. This study indicated striking but usually temporary improvement of the neutropenia of MDS with GM-CSF.

The combined data from these five studies[23-27] indicated that 38 of 45 patients treated with GM-CSF had improvements in neutrophil counts, 9 with associated increases in marrow myeloid maturation documented, 14 had increased reticulocyte counts with three of these individuals having decreased RBC transfusion requirements, eight had transient increases in platelets (Table 1). In 12 patients an increase in marrow and/or peripheral blood blasts were noted. Seven patients progressed to AML, particularly individuals with more than 15% marrow blasts (ie, those with RAEB or RAEB-t). In the longer term study reported by Thompson et al,[27] only one of five individuals maintained the increased neutrophil counts.

Table 1. Effects of Recombinant Human GM-CSF and G-CSF in Phase 1/11 Clinical Trials of Patients with Myelodysplastic Syndromes

	GM-CSF[23-27]	G-CSF[31,32]
Short-term treatment duration	7 to 14 days x 1-5 courses daily, IV or subcutaneously 30-750 $\mu g/m^2$	42 to 56 days daily subcutaneously
Daily dose	30-750 $\mu g/m^2$	0.1-3 $\mu g/kg$
Number of patients	45	18
FAB subtypes RA/RAEB-RAEB-t/CMML	14/26/5	2/16/0
Responses		
Neutrophils	38 (84%)	16 (89%)
Reticulocytes	14	5
Platelets	8	1
Marrow maturation	9	16
Increased blasts	12	4
Progression to AML	7	5
Long-Term Treatment Duration	2-9 weeks"	6-28 months[32]
Persistent neutrophil responses/patients	1/5[27]	10/11[27]

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A preliminary report indicates results of a multi-institutional randomized trial of GM-CSF treatment versus observation in MDS, with crossover occurring in patients with infections.[28] Only MDS patients with less than 15% marrow blasts (ie, those with RA, RARS, and some with RAEB) received GM-CSF. To date, 21 MDS patients have received GM-CSF, nearly all of whom demonstrated greater than twofold neutrophil responses, with 8 patients having persisting responses for 6 months. Severe toxicity requiring reduction or discontinuation of GM-CSF dose (initially 3 $\mu g/kg$ per day) occurred in a substantial proportion of the patients. No improvements in the patients' platelet counts or hemoglobin levels were noted. Further patient accrual and follow-up is occurring to determine the impact of this therapy on the incidence of infectious episodes and transformation to AML.

A recent trial using GM-CSF to treat nine patients with secondary MDS (ie, those in whom the MDS developed after prior cytotoxic chemotherapy for other malignancies) indicated neutrophil responses in seven of eight evaluable patients.[29] One patient had a marked

improvement in platelet counts and three had resolution of active infections. Transformation to AML occurred in three patients after 5 to 11 months of therapy and three other patients died of progressive lymphoma (their underlying malignancy).

A recent preliminary study has reported use of GM-CSF in combination with low doses of cytosine arabinoside to treat MDS.[30] A low proportion of the patients (seven of 24 evaluable patients) had persisting improvements in neutrophil counts and marrow maturation patterns, whereas thrombocytopenia often became a major clinical problem. Further follow-up and evaluation of these patients is necessary to determine the value of this therapeutic approach.

Treatment with G-CSF

At Stanford, to date we have treated 18 MDS patients (2 refractory anemia, 9 RAEB, 7 RAEB-t) with daily subcutaneous (SQ) injections of G-CSF, escalating dosage levels every 2 weeks from 0.1-3.0 μg/kg per day for a 6 to 8 week period.[31,32] Sixteen patients had significant elevations in both WBC (two- to 10-fold) and absolute neutrophil counts (ANC, five- to 40-fold). Nine of 11 severely neutropenic patients (ANC < 500/mm^3) had rises in ANC to 1,200 to 16,300 cells/mm^3. All six moderately neutropenic patients (ANC 500 to 1,800/mm^3) had rises in ANC five- to 15-fold. In five patients a greater than twofold rise in reticulocyte counts occurred and 3 of 12 RBC transfusion-dependent patients had a decrease in RBC transfusions. Improved marrow myeloid maturation was noted in 16 of 18 patients. Cytogenetic abnormalities, initially present in 4 responding patients, persisted after treatment, suggesting that enhanced differentiation of the abnormal clone occurred. No significant changes in platelet, lymphocyte, monocyte, or eosinophil counts were found during treatment in 17 of 18 patients. After discontinuing G-CSF treatment peripheral WBCs returned to baseline levels over 2 to 4 weeks.

As a result of the clinical responsiveness and tolerance of these patients to short-term G-CSF treatment, the initial 2 month phase 1/11 trial was extended, using the same dose (generally to 1 to 3 μg/kg per day SQ) for maintenance therapy as that to which the patients initially responded.[32] Eleven patients have received this more prolonged therapy and 10 of the 11 patients had continued improvements of their neutrophil counts, which have persisted for 6 to 28 months to date (Table 1). Marrow granulocytic maturation improved in seven of nine patients. Two of four RBC transfusion-dependent patients had decreases in their transfusion requirements, Platelet counts were generally not altered by this therapy. Neutrophil function (in vitro chemotaxis and phagocytosis), which was maintained or improved after 2 months of treatment, was further augmented in five patients after an additional 6 months of G-CSF therapy.

During the G-CSF treatment study period four patients had eight episodes of clinically significant bacterial infections, seven of which occurred at an ANC ≤ 1,500/mm^3 either before a patient responded or between treatment cycle. Prior to treatment, during an observation period of 2 to 15 months, five patients had developed infections, all of which occurred at an ANC less than 1,500/mm^3. Including this pretreatment period there was a significant reduction in infection risk in responding patients who achieved an ANC greater than 1,500/mm^3 after G-CSF treatment.

Toxicity to G-CSF was minimal, with only two patients stopping G-CSF injections because of side effects related to preexisting clinical conditions (psoriasis, nausea and anorexia).[31,32] Mild fluid overload occurred in one patient. In several patients other medical problems occurred, likely related to their preexisting cardiac or pulmonary disorders. Five of the 18 patients, 4 initially with RAEB-t, converted to AML after 6 to 16 months of the study. In one individual, pretreatment in vitro culture had revealed a marked increase in proliferative sensitivity of his hemopoietic precursors to G-CSF and GM-CSF associated with increased in vitro CFU-GM regeneration and poor myeloid differentiation. These data indicated that G-CSF injected subcutaneously on a chronic basis was well tolerated and effective for eliciting persistent improvement in neutrophil counts and in vitro function, marrow myeloid maturation, and possibly decreasing bacterial infections and RBC transfusion requirements in MDS patients.

Results of a very short-term trial of 40 MDS patients (20 RA, 20 RAEB/RAEB-t) treated with G-CSF has recently been reported." At doses of 2 to 5 μg/kg per day intravenously, 20 of 22 patients (7-day treatment) and 16 of 18 patients (14-day treatment) had substantial neutrophil responses associated with decrements in marrow blasts in 8 of 13 evaluated patients. The treatment was well tolerated.

Evidence of Clonal Responses

Cytogenetic evaluations were performed to determine whether selective responses to CSFs of normal versus abnormal clones occurred in MDS. In the two short-term studies using GM-CSF,[23,25] which perform these analyses, the cytogenetic abnormalities persisted after treatment in the 18 patients having these abnormalities. In the studies of MDS patients treated with G-CSF all six individuals with abnormal karyotypes had persistent cytogenetic abnormalities, three after longer-term (3 to 13 months) therapy.[31,32] The generally persisting cytogenetic abnormalities after treatment with these CSFs suggested enhanced differentiation of the abnormal clone in MDS. Analyzing restriction fragment length polymorphisms of X-linked genes, one patient with abnormal marrow cytogenetics responding to G-CSF showed monoclonality of her neutrophils after treatment.[32] However, another similarly analyzed patient responding to GM-CSF demonstrated polyclonal hematopoiesis after therapy?' Direct evidence of this point will require further analysis of X-linked genetic polymorphisms or of interphase cytogenetics of neutrophils."

Treatment with Interleukin-3

Two studies have reported the effects of IL3 therapy in MDS patients (Table 2). In the first trial, nine patients were treated with one to three 15-day courses of relatively high doses of IL3 (250 to 500 μg/m², subcutaneously).[36] Six of these patients had RA and three had RAEB. All of the patients had leukocyte responses and in seven, neutrophils were elevated. In only three of the patients did an increase occur of their ANC from less than 1,000 to more than 1,000/mm³. Three patients had an increase of reticulocytes, but in only one of nine RBC transfusion-requiring patients was there a decrease in such transfusions. Similarly, three patients had responses of their platelets, and in two of four, there was a transient decrease in platelet transfusion requirements. One of these individuals progressed to AML. In the other study, 13 patients were treated with 28-day courses of varying doses of IL3 intravenously.[37] Five of these individuals had RA, 5 had RAEB or RAEB-t, and 3 had CMML. Eight patients had leukocyte responses, 6 of whom had increases in neutrophils. However, in only 3 patients was there an increase of ANC from less than 1,000 to more than 1,000/mm³ with therapy. Reticulocytes rose in one patient and platelets rose in two. Aside from headaches, bone pain and fever at higher doses, this treatment was relatively well tolerated. These short-term studies indicated modest improvements in neutrophils, which, however, were not as prominent as those demonstrated with G-CSF or GM-CSF. Further, only limited responses occurred in the other cell lines. Thus, it is likely that IL3 will need to be combined with other hemopoietic growth factors to achieve substantial improvement in the cytopenias in MDS patients.

Table 2. Effects of Recombinant Human IL-3 Treatment in Myelodysplastic Syndromes

	Reference 34	Reference 35
Treatment Duration	15 d, X1-3 courses	20 d
Daily Dose	250 to 500 μg/m² SC	30 to 1,000 μg/m² IV
Number of Patients	9	13
FAB Subtypes		
RA/RAEB-RAEB-t/CMML	6/3/0	5/5/3
Responses		
Leukocytes	9	a
Neutrophils	7;3*	6;3*
Reticulocytes	3; ↓ transfusions 1/9	1
Platelets	3t; ↓ transfusions 2|4	2
↑ Blasts	2 PB; 1 BM	1 BM
Progression to AML	1	0

Abbreviations: BM, bone marrow; PB, peripheral blood.
'Increased ANC from less than to more than 1,000/mm³.
†Unsustained.

Treatment with Erythropoietin

Studies have indicated that serum erythropoietin (Epo) levels may be suboptimally elevated in MDS patients relative to their degree of anemia.[38] Recombinant human Epo therapy has been instituted to correct their hypoproductive

anemias and three published reports and several abstracts have detailed the erythroid responses to this form of treatment (Table 3).[39-43] In one study, eight MDS patients were treated with Epo at doses ranging from 200 to 400 units/kg IV three times a week.[39] Erythroid responses to Epo, which were associated with decreases in RBC transfusion requirements or increases in hemoglobin, were found in two of these eight patients. In another study, neither of two MDS patients treated with 50 to 500 units/kg three times a week responded.@In a relatively large study of patients with the low-risk forms of MDS (ie, RA and RARS), 4 of 17 individuals treated with doses ranging from 800 to 1,600 units/kg IV two times per week responded.[41] Generally, the responses took several months to occur but marrow cytogenetics and serum Epo levels did not reliably predict such erythroid responses. These published studies have been corroborated by two recent reports cited in Table 3,[42,43] and thus to date, 11 of 51 (22%) of the patients have responded to Epo. Generally, the patients required relatively high doses of Epo for their responses. This somewhat limited in vivo responsiveness of MDS marrow cells to Epo is not totally unexpected as the defective erythroid clones have demonstrated suboptimal responses to Epo in vitro, particularly for BFU-E responses.[4,5] Thus, as suggested by recent in vitro studies,[5,44] it is likely that a combination of hemopoietic growth factors, which would enhance BFU-E numbers or responsiveness to Epo, may provide more prominent erythroid responses. Such clinical studies are currently in progress.

CONCLUSIONS AND FUTURE DIRECTIONS

The hemopoietic growth factors G-CSF, GM-CSF, and IL3 have been demonstrated to provide marked acute improvement in neutrophil counts and marrow morphology in a high proportion of these patients, and for G-CSF and for some studies with GM-CSF these responses have been quite durable. In a low fraction of such patients, improved hemoglobin levels and decreased RBC transfusion requirements occurred, whereas platelet counts generally remained unchanged. Epo treatment caused improved erythroid responses in about 20% to 25% of MDS patients. Retrospective analysis indicated decreased infectious episodes in patients receiving G-CSF whose neutrophil counts normalized, suggesting possible clinical efficacy for the responding patients.[32] The growth factors appear to be well tolerated with little associated toxicity, and they can be administered subcutaneously, indicating their potential for treating outpatients. These hemopoietic growth factors thus provide encouraging experimental alternatives to chemotherapy or bone marrow transplantation for the generally elderly patients comprising this patient population.

In vitro marrow clonogenic and suspension culture studies suggested the potential therapeutic utility of CSFs for MDS patients. The in vivo and in vitro differentiative responses to CSFs of marrow precursors from these patients indicate that decreased responsiveness and/or decreased intramedullary availability of effective levels of certain hemopoietic growth factors may underlie certain cytopenias in patients with MDS. The use of differentiation-inducing agents such as G-CSF for treating myeloid clonal hemopathies is based on an evolving body of in vitro marrow culture and preclinical data indicating that such agents may diminish self-replication of abnormal cell clones concomitant with enhancing their differentiation.[45-50] Thus, it is of interest that G-CSF has substantial, although

Table 3. Erythroid Responses to Recombinant Human Erythropoietin in Myelodysplastic Syndromes

References	MDS Subtype		Epo Dose (U/kg)	Responses/ Patients	Responder Serum Epo Levels (mU/ml)
	RAIRARS	RAEBIRAEB-t			
39	4	4	200 *to* 400 IV, 3x/wk	2/8 (25%)	694,919
40	2	0	*50* to 500 IV, 3x/wk	0/2	—
41	17	0	800 *to* 1,600 IV, 2x/wk	4/17 (24%)	16,515,589,1030
42	5	5	200 to 1,000 IV. 3x/wk	4/10 (40%)	183 (mean)
43	10	4	80 *to* 640 SO, 3x/wk	1/14 (7%)	1750
Totals	38	13		11/51 (22%)	

subnormal, myeloid differentiating activity for MDS marrow cells.[5,51] This myeloid differentiation-inducing effect of G-CSF is greater than that of GM-CSF, particularly for RAEB/RAEB-t patients and those with normal cytogenetics.[48] Methods are being sought to further enhance differentiation of cells from patients with myeloid clonal hemopathies.

Despite the demonstration of improvements in neutrophil levels and marrow morphology in a substantial proportion of MDS patients with these hemopoietic growth factors, randomized controlled studies are needed to determine whether the natural history of these disorders (survival, evolution to AML, or infectious complications) will be altered by treatment with the CSFs. Still required are growth factors necessary to augment platelet counts in these patients. Investigation is also warranted using erythropoietin in combination with the myeloid CSFs, to determine whether more consistent improvement in hemoglobin levels is achievable in MDS.

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