Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome

John A. Thompson, D. Gary Gilliland, Josef T. Prchal, John M. Bennett, Kay Larholt, Richard A. Nelson, Esther H. Rose, Margaret H. Dugan, and the GM/EPO MDS Study Group

This randomized, placebo-controlled trial was designed to assess the efficacy and safety of therapy with granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin (epoetin alfa) in anemic, neutropenic patients with myelodysplastic syndrome. Sixty-six patients were enrolled according to the following French–American–British classification: refractory anemia (20), refractory anemia with excess blasts (35), refractory anemia with ringed sideroblasts (9), and refractory anemia with excess blasts in transformation (2). Patients were stratified by their serum erythropoietin levels (less than or equal to 500 mU/mL, n = 37; greater than 500 mU/mL, n = 29) and randomized, in a 2:1 ratio, to either GM-CSF (0.3-5.0 μg/kg-d) + epoetin alfa (150 IU/kg 3 times/wk) or GM-CSF (0.3-5.0 μg/kg-d) + placebo (3 times/wk). The mean neutrophil count rose from 948 to 3831 during treatment with GM-CSF ± epoetin alfa. Hemoglobin response (increase greater than or equal to 2 g/dL, unrelated to transfusion) occurred in 4 of 45 (9%) patients in the GM-CSF + epoetin alfa group compared with 1 of 21 (5%) patients with GM-CSF + placebo group (P = NS). Percentages of patients in the epoetin alfa and the placebo groups requiring transfusions of red blood cells were 60% and 92%, respectively, for the low-endogenous erythropoietin patients and 95% and 89% for the high-endogenous erythropoietin patients (P = NS). Similarly, the average numbers of units of red blood cells transfused during the 12-week study in the epoetin alfa and the placebo groups were 5.9 and 9.5, respectively, in the low-endogenous erythropoietin patients and 9.7 and 8.6 in the high-endogenous erythropoietin patients (P = NS). GM-CSF ± epoetin alfa had no effect on mean platelet count. Treatment was well tolerated in most patients, though 10 withdrew from the study for reasons related predominantly to GM-CSF toxicity. (Blood. 2000;95:1175-1179) © 2000 by The American Society of Hematology

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of disorders characterized by the abnormal proliferation and differentiation of hematopoietic precursor cells, ineffective hematopoiesis, and, in some patients, evolution to acute leukemia. The disorders are of varying severity, with some patients having chronic, mild anemia whereas others have severe abnormalities in the production of all cell types.

There is, at present, no standard therapy for MDS. Aggressive chemotherapy or radiotherapy followed by allogeneic bone marrow transplantation may induce durable complete remission, but many patients are not eligible for transplantation because of age or lack of a suitable donor. Because pancytopenia, anemia, and thrombocytopenia are common in patients with MDS, the potential role of hematopoietic growth factors in the management of hematologic disorders in patients with MDS is under investigation.

Erythropoietin regulates erythropoiesis, particularly of mature red blood cells (RBCs). Endogenous erythropoietin levels vary widely among patients with MDS, even those with similar hemoglobin levels, but overall there is an inverse relationship between the severity of anemia and the level of endogenous erythropoietin. Clinical studies evaluating the efficacy of recombinant human erythropoietin (epoetin alfa) as a treatment for MDS have produced variable results. Responses, defined as a reduction in transfusion requirement (more than or equal to 30% to 50%), increases in hemoglobin levels (1 to 2 g/dL), or both have been reported in 0% to 56% of patients. Various predictors of response have been proposed, including low endogenous erythropoietin levels before therapy and the need for RBC transfusion.

The limited therapeutic use of epoetin alfa in MDS may be attributed to a deficiency in these patients of the burst-forming unit-erythroid (BFU-E) pool, the most immature erythroid progenitor cells, leading to insufficient influx of epoetin alfa-sensitive cells. Multi-lineage growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) are needed for optimal growth of BFU-E cells. GM-CSF has been shown to expand this pool in the bone marrow of patients with MDS. Treatment of MDS with GM-CSF may increase the pool of BFU-E cells and thereby could potentially be further stimulated by erythropoietin. An open-label study involving 13 patients with MDS examined the effects of administering GM-CSF for 6 weeks, followed by epoetin alfa plus GM-CSF for 12 weeks. Combined therapy appeared to...
stimulate erythropoiesis and to correct or improve anemia in some patients. A double-blinded, placebo-controlled, randomized study to assess the safety of combination therapy with GM-CSF and epoetin alfa after autologous bone marrow transplantation found that the combination treatment was well tolerated in patients with MDS and that it caused no severe or unexpected toxicities and no withdrawals from adverse effects.12

We investigated the use of combined therapy with low doses of GM-CSF and epoetin alfa in patients with MDS. The objective of the study was to assess 3 primary aspects: (1) the efficacy and clinical benefit of combined GM-CSF–epoetin alfa therapy in the restoration of normal hematopoiesis in these transfusion-dependent patients; (2) the safety of the combination therapy in anemic, neutropenic patients with MDS; and (3) the effect of patients’ pretreatment endogenous erythropoietin levels on their responses to the combination therapy.

### Patients and methods

This was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study in patients with a diagnosis of MDS and refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), or refractory anemia with excess blasts (RAEB). At the screening examination, patients provided written informed consent and full medical histories, and they underwent physical examinations that included hematologic assessment. Eligible patients were neutropenic (absolute neutrophil count [ANC] less than 1500 cells/mL) and anemic (hemoglobin less than or equal to 10 g/dL), and they had platelet counts (unrelated to transfusion) greater than or equal to 15,000/mL. Patients had to be transfusion dependent (requiring at least 4 U RBC in the previous 3 months) and older than 17 years of age, and they had to have a performance status less than or equal to 2 (on the Zubrod scale) and normal renal and hepatic function. Patients were not to have undergone cytotoxic treatment for MDS for at least 30 days before the study. Criteria for exclusion included history of malignancy (except basal or squamous cell skin cancer or cervical carcinoma in situ); recent (within 1 year) history of thromboembolic disease; acute leukemia or refractory anemia with excess blasts in transformation (RAEB-t); 2 patients (1 from each treatment group) with French–American–British classifications (FAB) of RAEB-t were allowed to continue in the study because their conditions remained stable for a considerable time.

Primary efficacy measures were change in hemoglobin from baseline to endpoint (last value recorded), RBC transfusion rate in months 2 and 3, and proportion of patients requiring RBC transfusion during study. Secondary measures included determining the proportion of patients showing increases in hemoglobin (unrelated to transfusion) greater than or equal to 2 g/dL above the baseline value (hemoglobin responders), the proportion of patients becoming ANC correctors (ANC greater than or equal to 2000 cells/mL), and a change in platelet count from baseline to endpoint.

Significance was set at 0.05, and most tests were 1-sided. Tests of interaction were 2-sided and had a significance level of 0.10. Linear model analyses (least-squares mean) were performed to assess the effects of possible covariables (baseline hemoglobin, baseline RBC transfusion rate, and FAB classification of MDS at diagnosis) for hemoglobin level, RBC cumulative transfusion rate, platelet cumulative transfusion rate, and RBC transfusion rate in months 2 and 3. Two-sample t tests were used to test differences in monthly platelet transfusion rates. Differences in the proportion of patients transfused with RBCs and platelets were assessed using the 1-sided Fisher exact test. For the secondary variables, summary statistics were provided for weekly ANC and white blood cell counts, and 2-sample t tests were used to analyze changes in hemoglobin and platelet count. Proportions of patients showing increased (greater than or equal to 2 g/dL) hemoglobin or becoming ANC correctors were compared using the 1-sided Fisher exact test. Analysis of efficacy was based on the intent-to-treat population. Analysis of safety included data from all patients who received study medication.

### Results

Of the 66 patients enrolled, 45 received epoetin alfa and 21 received placebo. Demographic and baseline characteristics were similar in both treatment groups (Tables 1 and 2). Thirty-seven patients (25 epoetin alfa, 12 placebo) had baseline endogenous medication, and blood chemistry, serum iron profiles, and liver and spleen size evaluations were repeated monthly (days 29, 57, and 85). On the last day of the study (day 85), bone marrow aspirates and biopsy procedures were repeated. Transfusions were given to patients whose hematocrit was less than or equal to 25% and, at the investigator’s discretion, to patients whose hematocrit was between 25% and 30%. Serum erythropoietin levels were measured using a modified competitive radioimmunoassay with a limit of quantitation of 5 mU/mL.

Criteria for withdrawal included a World Health Organization grade 3 adverse event attributable to GM-CSF and the development of acute leukemia or refractory anemia with excess blasts in transformation (RAEB-t). Two patients (1 from each treatment group) with French–American–British classifications (FAB) of RAEB-t were allowed to continue in the study because their conditions remained stable for a considerable time.

### Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>GM-CSF + Epoetin Alfa</th>
<th>GM-CSF + Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Race</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>44</td>
<td>20</td>
<td>64</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mean age (y) (± SD)</td>
<td>62.4 (±14.9)</td>
<td>62.9 (±14.2)</td>
<td>62.5 (±14.6)</td>
</tr>
<tr>
<td>Age range (y)</td>
<td>21-95</td>
<td>25-84</td>
<td>21-95</td>
</tr>
<tr>
<td>FAB classification</td>
<td>RA</td>
<td>RAEB</td>
<td>RAEB-t</td>
</tr>
<tr>
<td>RA</td>
<td>13</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>RAEB</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>RARS</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

FAB, French-American-British group; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RAEB-t, refractory anemia with excess blasts in transformation.
erythropoietin levels less than or equal to 500 mU/mL. Baseline endogenous erythropoietin levels were greater than 500 mU/mL in 29 patients (20 epoetin alfa and 9 placebo). Mean baseline hemoglobin levels for both baseline endogenous erythropoietin groups (treatment groups combined) were 9.4 and 8.6 g/dL, respectively. Forty-eight patients completed the study (34 in the epoetin alfa group and 14 in the placebo group).

Efficacy analyses

Changes in hemoglobin levels over the course of the study are shown in Table 3. In patients treated with GM-CSF and placebo, hemoglobin levels tended to decrease during the study despite transfusion, whereas hemoglobin levels were maintained at approximately baseline levels in patients on GM-CSF and epoetin alfa. For patients with more than 500 mU/mL endogenous erythropoietin, the mean change in hemoglobin level from baseline to endpoint was greater in the epoetin alfa group than in the placebo group. The adjusted mean change in hemoglobin level was 0.07 g/dL in patients who received epoetin alfa compared with −0.96 g/dL in those who received placebo ($P = .048$).

Hemoglobin responses occurred in 4 of 45 (9%) patients in the GM-CSF + epoetin alfa group, compared to 1 of 21 (5%) patients in the GM-CSF + placebo group ($P = .59$). All 5 hemoglobin responders had baseline endogenous erythropoietin concentrations less than or equal to 500 mU/mL. All 4 hemoglobin responders who received epoetin alfa had RAEB, whereas the hemoglobin responder who received placebo had RARS. The durations of hemoglobin response were 9, 13, 13, 13, and 75 weeks.

The percentage of patients transfused during the study and the mean number of units of blood transfused during months 2 and 3 are shown in Table 3. In the less than or equal to 500 mU/mL endogenous erythropoietin group, only 15 of 25 (60%) epoetin alfa patients were transfused with RBCs compared with 11 of 12 (92%) placebo patients. This difference approached statistical significance ($P = .051$). In the more than 500 mU/mL endogenous erythropoietin group, 19 of 20 (95%) epoetin alfa patients and 8 of 9 (89%) placebo patients were transfused. Among patients who received epoetin alfa, the percentage transfused with RBCs was significantly lower in the less than or equal to 500 mU/mL endogenous erythropoietin group (60%) than in the more than 500 mU/mL endogenous erythropoietin group (95%), $P = .0069$.

For all treatment groups, the overall mean ANC rose from 948 cells/µL at baseline to 3831 cells/µL by week 12. In the less than or equal to 500 mU/mL endogenous erythropoietin group, 83% of epoetin alfa patients and 92% of placebo patients were classified as ANC correctors. The corresponding values for the more than 500 mU/mL endogenous erythropoietin subgroup were 80% and 75%, respectively.

Analysis of mean change in platelet count from baseline to endpoint revealed no significant differences between the 2 treatment groups. The mean pretreatment platelet count was 108 000/µL in the placebo patients and 120 000/µL in the placebo group. In the low endogenous erythropoietin group, the mean change in platelet count from baseline to endpoint was −14 640/µL in the epoetin alfa patients and −32 920/µL in the placebo patients ($P = .12$). In the high endogenous erythropoietin group, the mean change in platelet count from baseline to endpoint was −17 750/µL.

Table 3. Change in mean hemoglobin level, percentage of patients transfused during the study, and mean number of units of blood transfused during months 2 and 3 of the study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Endogenous EPO (mU/mL)</th>
<th>N</th>
<th>Mean Baseline Hb (g/dL)</th>
<th>Mean Final Hb (g/dL)</th>
<th>Mean Hb Change (g/dL)*</th>
<th>Number (%) Hb Responders</th>
<th>% Patients Transfused with RBCs</th>
<th>Mean Units of RBC Transfused During Months 2 &amp; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM-CSF + epoetin alfa</td>
<td>≤500</td>
<td>25</td>
<td>9.34</td>
<td>9.40</td>
<td>+0.04</td>
<td>4 (16)</td>
<td>60§</td>
<td>5.9†</td>
</tr>
<tr>
<td>GM-CSF + placebo</td>
<td>≤500</td>
<td>12</td>
<td>9.38</td>
<td>8.45</td>
<td>−0.92</td>
<td>1 (8)</td>
<td>92</td>
<td>9.5</td>
</tr>
<tr>
<td>GM-CSF + epoetin alfa</td>
<td>&gt;500</td>
<td>20</td>
<td>8.49</td>
<td>8.60</td>
<td>+0.07†</td>
<td>0</td>
<td>95</td>
<td>9.7‡</td>
</tr>
<tr>
<td>GM-CSF + placebo</td>
<td>&gt;500</td>
<td>20</td>
<td>8.67</td>
<td>7.62</td>
<td>−0.96</td>
<td>0</td>
<td>89</td>
<td>8.6</td>
</tr>
<tr>
<td>All epoetin alfa patients</td>
<td>—</td>
<td>45</td>
<td>8.96</td>
<td>9.04</td>
<td>+0.06</td>
<td>4 (9)</td>
<td>76</td>
<td>7.6</td>
</tr>
<tr>
<td>All placebo patients</td>
<td>—</td>
<td>21</td>
<td>9.08</td>
<td>8.09</td>
<td>−0.95</td>
<td>1 (5)</td>
<td>90</td>
<td>9.1</td>
</tr>
</tbody>
</table>

*Adjusted according to linear model analysis (least-squares mean).
†Significantly different from <500 mU/mL endogenous erythropoietin/placebo group, $P = .048$.
‡Marginally lower than in >500 mU/mL endogenous erythropoietin + placebo group, $P = .051$.
§Statistically significantly lower than in >500 mU/mL endogenous erythropoietin + epoetin alfa group, $P = .0069$.
|†| $P = .09$; epoetin vs. placebo for endogenous erythropoietin 500.
‡| $P = .62$; epoetin vs. placebo for endogenous erythropoietin >500.

RBC, red blood cells; ANC, absolute neutrophil count; SD, standard deviation.
Table 4. Incidence of adverse events with probable or definite relationship to study medication

<table>
<thead>
<tr>
<th>Category</th>
<th>GM-CSF + Epoetin Alfa* N (%)</th>
<th>GM-CSF + Placebo† N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin reaction at injection site</td>
<td>15 (33)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>3 (8)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>2 (5)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Erythema/pruritis/rash/urticaria</td>
<td>3 (6)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (6.7)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (11.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (2)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain in extremities</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Allergic</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

FAB, French-American-British; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation.

* N = 45.
† N = 21.

in the epoetin alfa patients and −12 330/µL in the placebo patients (P = 62).

Safety analyses

A total of 243 adverse events were reported, 165 in the 45 epoetin alfa-treated patients and 78 in the 21 placebo-treated patients. Injection site reactions were most common (62% epoetin alfa and 86% placebo). Of the adverse events, 57 (36 epoetin alfa and 21 placebo) were deemed to have a probable or definite relationship to study medication (Table 4). Nine of the adverse events were rated as severe—5 in the epoetin alfa patients (1 pain in extremities, 3 thrombocytopenias, and 1 stroke) and 4 in the placebo patients (1 myalgia, 1 erythema, and 2 injection-site reactions).

At the doses used, combination therapy with GM-CSF and epoetin alfa was well tolerated in most patients. However, 18 of 66 patients withdrew during the course of therapy. In 8 of these 18 patients, the reason for withdrawal was thought to be disease related: infection (3), evolution to acute leukemia (2), second malignancy (1), gait disturbance (1), and asthenia (1). The other 10 patients who withdrew did so because of side effects that were thought to be drug related: thrombocytopenia (3), myalgia (2), skin erythema (2), fever (1), pericarditis (1), and stroke (1).

Changes in laboratory test values from baseline to endpoint were similar for epoetin alfa-treated and placebo-treated patients. Systolic and diastolic blood pressure values remained fairly constant in both groups. Most patients did not experience changes in liver or spleen size. Of the 36 patients on epoetin alfa who did not have liver enlargement at baseline, 3 (8.3%) experienced liver enlargement during the study. Three of 19 (15.8%) patients in the placebo group experienced liver enlargement during the study (complete liver and spleen data were available for all; none had liver enlargement at baseline). Two of 38 (5.2%) patients in the epoetin alfa group with normal spleens at baseline experienced spleen enlargement during the study, in comparison with 4 of 19 (21.1%) patients on placebo; 1 patient on epoetin alfa who had an enlarged spleen at baseline experienced a reduction in spleen size.

Transformation to acute leukemia occurred in 1 patient in the GM-CSF + epoetin alfa group and in 1 patient in the GM-CSF + placebo group. There were 3 deaths on the study (all in the GM-CSF + epoetin alfa group). The causes of death were pericarditis, stroke, and thrombocytopenia.

Discussion

The objectives of this randomized, double-blinded, placebo-controlled study were to assess the efficacy (in terms of restoring normal hematopoiesis) and tolerability of combined therapy with GM-CSF and epoetin alfa in anemic, neutropenic patients with MDS and to assess the effect of pretreatment endogenous erythropoietin level on response to therapy. Hemoglobin response (an increase in hemoglobin of at least 2 g/dL unrelated to transfusion) occurred in 4 of 45 (9%) patients in the GM-CSF + epoetin alfa group, compared with 1 of 21 (5%) patients in the GM-CSF + placebo group, a difference that was not statistically significant. Although all the hemoglobin responders had levels of endogenous EPO less than or equal to 500 mU/mL, no statistically significant effect of endogenous EPO on hemoglobin response was demonstrated. The median duration of hemoglobin response was 13 weeks.

GM-CSF in combination with epoetin alfa appeared to offer benefits over GM-CSF and placebo in terms of maintaining hemoglobin levels and in reducing transfusion requirements in patients with low baseline endogenous erythropoietin levels. Low (less than or equal to 500 mU/mL) endogenous erythropoietin levels have previously been suggested to be predictive of response to epoetin alfa in patients with MDS.6,7 This is consistent with our finding that, among previously transfusion-dependent patients treated with GM-CSF and epoetin alfa, those with low erythropoietin levels were less likely to require RBC transfusion than those with high (more than 500 mU/mL) endogenous erythropoietin levels. However, the apparent effect of epoetin alfa was not observed solely in the low endogenous erythropoietin group. The difference in mean hemoglobin over the course of the study in the epoetin alfa versus placebo recipients reached statistical significance only in the more than 500 mU/mL endogenous erythropoietin group.

Other studies have shown that GM-CSF can increase leukocyte counts in patients with MDS.14-16 In agreement with these findings, our study indicated that in anemic and neutropenic patients with MDS, treatment with GM-CSF, with or without concurrent epoetin alfa, increased the ANC approximately 3-fold. An ANC increase of this magnitude may help overcome infection. Moreover, GM-CSF, with or without epoetin alfa, had no apparent effect on mean platelet counts.

Eighteen patients withdrew from the study. Withdrawal was for disease-related reasons in 8 of them. Withdrawal from the protocol for disease-related reasons in 8 of 66 patients is not surprising in this population of neutropenic, transfusion-dependent patients with MDS. The other 10 patients who withdrew did so because of side effects, including thrombocytopenia, myalgia, skin erythema, fever, and pericarditis, that were thought to be drug related. The occurrence of myalgia, skin erythema, fever, and pericarditis was likely to be GM-CSF-related because they have been reported in other studies of GM-CSF treatment and they do not commonly occur in side effects of epoetin alfa. The thrombocytopenia observed was likely...
related to both GM-CSF and epoetin alfa therapy. The 3 cases of
treatment withdrawal because of thrombocytopenia occurred in the
GM-CSF + epoetin alfa group, whereas there were no cases of
treatment withdrawal because of thrombocytopenia in the
GM-CSF + placebo group. Six patients had documented enlarge-
ment of the spleen during the study, a side effect that has previously
been reported with GM-CSF therapy. The development of spleno-
megaly may contribute to worsening thrombocytopenia in this
patient population.

In conclusion, combination therapy with GM-CSF and epoetin
alfa offers benefit over GM-CSF alone with respect to maintenance
of hemoglobin levels and reduction of transfusion requirements in
patients with MDS who have less than or equal to 500 mU/mL
baseline endogenous erythropoietin levels. GM-CSF, with or
without epoetin alfa, can also substantially increase ANC in
anemic, neutropenic patients with MDS. For transfusion-dependent
patients with MDS who are not candidates for bone marrow
transplantation, a therapeutic trial of GM-CSF and epoetin
alfa for 3 months may be indicated to determine the response to
cytokine therapy.

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facts of recombinant human granulocyte macro-
phage colony stimulating factor in patients with

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