Treatment of the Anemia of Myelodysplastic Syndromes Using Recombinant Human Granulocyte Colony-Stimulating Factor in Combination With Erythropoietin

By Robert S. Negrin, Richard Stein, James Vardiman, Kathleen Doherty, Jill Cornwell, Sanford Krantz, and Peter L. Greenberg

We treated myelodysplastic syndrome patients (MDS) with both recombinant human granulocyte colony-stimulating factor (G-CSF) and recombinant human erythropoietin (EPO) to determine whether such combination therapy resulted in improvement of their anemia. Twenty-four of 28 patients began on study completed the protocol and were evaluable for erythroid responses. Therapy was initiated with G-CSF at 1 μg/kg administered by daily subcutaneous injection and adjusted to either normalize or double the neutrophil count. EPO was then administered by daily subcutaneous injection at a dose of 100 U/kg and dose-escalated to 150 and 300 U/kg every 4 weeks while continuing the G-CSF. Changes in absolute reticulocyte count, hematocrit level, and need for RBC transfusions were compared with pretreatment values as well as other blood cell counts. Ten of 24 patients (42%) had erythroid responses, whereas all patients had neutrophil responses. Six previously transfused patients no longer required RBC transfusions during the treatment period. Erythroid responses were found to be independent of patient age, French-American-British subtype, duration of disease, prior RBC transfusion requirements, or cytogenetic abnormalities at presentation. Pretreatment serum EPO levels were lower in erythroid-responding as compared with nonresponding patients (median 157 v 600 U/L; P = .05). The combined treatment modality was generally well tolerated. We conclude that a substantial percentage of MDS patients had both erythroid and myeloid responses when treated with the combination of G-CSF and EPO.

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MATERIALS AND METHODS

Patients. Twenty-eight patients with MDS were enrolled in this study, 16 at Stanford University Medical Center and 12 at Vanderbilt University Medical Center. All patients had histologically confirmed MDS evaluated both at the treating institution and by central pathology review (by J.V.) at the University of Chicago Medical Center before entering the study. Bone marrow aspirates were classified according to French-American-British (FAB) criteria as either refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), or refractory anemia with excess blasts in transformation (RAEB-T).20 The clinical characteristics of the patients are shown in Table 1. All 28 patients were evaluable for myeloid responses and toxicity. Four patients did not complete the dose escalation of EPO because of bone pain (1), splenic pain (1), splenic pain with progression to AML (1), and gastrointestinal bleeding (1). These four patients were therefore not eligible for evaluation of erythroid responses. Written informed consent was obtained from all patients according to guidelines established by the Human Experimentation Committees at either Stanford University or Vanderbilt University.

THE MYELODYSPLASTIC syndromes (MDS) are characterized by chronic cytopenias that predispose patients to symptomatic anemias requiring RBC transfusions, infection, bleeding, and a high incidence of conversion to acute myeloid leukemia (AML).1,4 These patients have limited treatment options and often respond poorly to cytotoxic chemotherapy.5,6

Recently, a series of studies have been reported using recombinant human colony-stimulating factors (CSFs) to treat MDS patients. Both granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been used in this patient population,7,14 as well as preliminary studies with interleukin-3,15,16 With these growth factors the majority of patients have improvements in neutrophil counts that in some studies using G-CSF and GM-CSF, has been correlated with a decrease in infection risk.12,13

Despite the improvements in myeloid cell numbers in these patients, the majority of patients who were anemic and thrombocytopenic remained so. A low proportion of these patients had erythroid responses to either G-CSF or GM-CSF.7,12 Because many patients with MDS have ongoing needs for RBC transfusions and often have serum erythropoietin (EPO) levels that are lower than would be expected relative to the degree of anemia,17 investigators have explored the use of recombinant human EPO treatment in this patient population. These studies have shown that approximately 10% to 25% of patients demonstrated erythroid responses.16-25 Generally, the doses required for erythroid responses were high and responding patients had variable serum EPO levels before treatment. In vivo, narrow erythroid hematopoietic precursor cell (burst-forming unit-erythroid [BFU-E]) responses to EPO in MDS patients have also been suboptimal.26,27 Recent studies have demonstrated in vitro synergy between G-CSF and EPO for normal and MDS erythropoiesis.28,29 Thus, we have evaluated combination therapy with G-CSF and EPO in patients with MDS to determine whether treatment with both agents resulted in erythroid as well as myeloid responses.

From The Department of Medicine, Stanford University Medical Center, Stanford, CA; the Department of Medicine, Vanderbilt Medical Center, Nashville, TN; the Department of Pathology, University of Chicago Medical Center, Chicago, IL; the Veterans Administration Medical Center, Nashville, TN, and the Veterans Administration Medical Center, Palo Alto, CA.

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Address reprint requests to Robert S. Negrin, MD, Room H1353, Bone Marrow Transplant Program, Stanford University Medical Center, Stanford, CA 94305.

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Table 1. Characteristics of MDS Patients Enrolled in the G-CSF Plus EPO Clinical Trial

<table>
<thead>
<tr>
<th></th>
<th>No. evaluable for erythroid responses</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (range)</td>
<td></td>
<td>71 (34-84)</td>
</tr>
<tr>
<td>Male/female</td>
<td></td>
<td>21/7</td>
</tr>
<tr>
<td>FAB subtype:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>RARS</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>RAEB</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>RAEB-T</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Anemic</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>RBC transfusion dependent</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Neutropenic</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyto genetic abnormalities</td>
<td></td>
<td>9/26</td>
</tr>
</tbody>
</table>

Study design. All patients were evaluated before study entry with complete history and physical examinations. Eligibility criteria included histologically confirmed MDS performed by our central pathology reviewer, hemoglobin level ≤10 g/dL, hematocrit level ≤31% or symptomatic anemia, serum creatinine <2.0 mg/dL, and bilirubin less than 2.5 times the upper limit of the institutional normal value. Patients were excluded if they had received cytotoxic or radiation therapy within 4 weeks of study entry. Patients were receiving current therapy with lithium, vitamin A or D, steroids or danazol, or had cardiac disease with decompensated congestive heart failure, active gastrointestinal bleeding, or uncorrected iron deficiency anemia (defined as absence of marrow iron, transferrin saturation of <16%, serum iron <40 μg/dL or serum ferritin <20 μg/L). Patients previously treated with other hematopoietic growth factors within 4 weeks of study entry were also excluded. Eligible patients underwent baseline laboratory evaluation including a complete blood cell count (CBC) with reticulocytes and platelets, serum EPO, B12 and RBC folate levels, stool guaiac determinations, chest radiograph, and electrocardiogram. B12 and RBC folate levels were normal in all patients.

G-CSF was administered as a daily subcutaneous (SC) injection with a starting dose of 1.0 μg/kg. CBC counts were obtained twice weekly until stabilization of the absolute neutrophil count (ANC) occurred. The dose of G-CSF was adjusted to normalize the ANC if the pretreatment ANC value was less than 1,800/μL, or to double the ANC if above 1,800/μL. The dose required to achieve this ranged from 0.2 to 5.0 μg/kg/d. EPO administration was then begun by daily SC injection while continuing the daily G-CSF injections. The EPO dose was started at 100 U/kg/d and increased every 4 weeks to 150 and finally 300 U/kg/d. The 300 U/kg/d dose was continued for a total of 8 weeks. CBC counts were obtained weekly once the EPO was begun and a chemical survey panel was obtained monthly. Bone marrow aspiration with cyto genetic was performed at study entry and at either the end of 8 weeks of the 300 U/kg/d EPO treatment or the time of erythroid response.

Patients were questioned weekly concerning possible adverse events. Patients were instructed to draw up the appropriate amount of G-CSF and EPO into a syringe and self-inject the drugs SC. Treatment was discontinued if severe side effects occurred or at the patient’s request.

Recombinant human G-CSF was supplied by AMGEN, Thousand Oaks, CA, and recombinant human EPO was supplied by Ortho Biotech, Raritan, NJ. The factors were provided to the Cancer Therapy Evaluation Program (CTEP), Investigational Drug Branch, National Cancer Institute, which then distributed them to the participating medical centers. Statistical analyses were performed by Student’s t-test.

Response criteria. Erythroid responses were defined as being a good response (GR), partial response (PR), or no response (NR). A GR was defined as an increase in untransfused hemoglobin values of >2 g/dL or a 100% decrease in RBC transfusion requirements over the treatment period. A PR was defined as an increase in untransfused hemoglobin values of 1 to 2 g/dL or a greater than 50% decrease in RBC transfusion requirements. NR was defined as responses less than a PR. Pretreatment RBC transfusion requirements were calculated over the months before study entry when accurate data were available. This ranged from 1 to 36 months (median 7 months), and was stable for 1 to 2 months before study entry. Myeloid responses were categorized as being either a complete response (CR), PR, or NR. A CR was defined as normalization of the ANC (>1,800/μL) if initially <1,800/μL, or if the pretreatment ANC was >1,800/μL then increased by 100%. A PR was defined as an increase in ANC to between 500 and 1,800/μL if initially <1,800/μL, or a 50% to 100% increase in ANC if initially >1,800/μL. NR was defined as changes in ANC less than a PR.

RESULTS

Patients. The clinical characteristics of the 28 enrolled patients are shown in Table 1. The median age was 71 years (range 34 to 84) with 21 males and 7 females. Thirteen patients had RA, 8 RARS, 5 RAEB, and 2 RAEB-T. All patients were anemic and 25 were RBC transfusion dependent. Eighteen patients were neutropenic (≤1,800/μL) and 12 were thrombocytopenic. Twenty-six patients had cytogenetic studies performed, of whom 9 patients showed abnormalities, primarily involving chromosomes 5 and 8. All 28 patients were evaluable for toxicity and myeloid responses. Four patients did not complete the dose escalation of EPO, and thus, were not evaluable for erythroid responses.

Myeloid responses. Treatment was started with daily SC G-CSF injections beginning at 1.0 μg/kg. All patients had a myeloid response (26 CR, 2 PR), with all patients but one requiring between 0.2 and 1.0 μg/kg/d to maintain this neutrophil level (Table 2). One patient required dose escalation to 5.0 μg/kg/d. Both PR patients withdrew from the study early because of toxicity (patients no. 112 and 209).

Erythroid responses. Once a myeloid response occurred, EPO was begun by daily SC injection while continuing the G-CSF injections. The EPO dosage was initially 100 U/kg/d, with escalation every 4 weeks to 150 and finally 300 U/kg/d, which was continued for a total of 8 weeks. A representative responding patient’s course is shown in Fig 1. This patient (no. 102) had been dependent on approximately four units of RBCs per month for 12 months and was chronically neutropenic, with an ANC of 1,400/μL before therapy. Treatment was initiated with G-CSF at 1.0 μg/kg/d, which resulted in a prompt increase in a total white blood cell (WBC) count and ANC to the 6,000 to 12,000/μL range. Two weeks later, EPO administration was started at 100 U/kg/d. Increases in absolute reticulocyte counts and untransfused hematocrit levels were noted at the 150 U/kg/d EPO dose, although these values were not sustained. At the 300 U/kg/d EPO dose, a sustained increase in hematocrit level was noted, and the patient did not require any...
RBC transfusions for 4 months of subsequent treatment. Platelet counts did not change.

The response of a second patient (no. 110) is shown in Fig 2. This patient had a prior diagnosis of idiopathic he- 


cmochromatosis with chemical and clinical evidence of iron overload. His anemia was caused by MDS, which precluded 


ephlombotom therapy. At the time of protocol initiation, the 


patient had a stable hematocrit level of 30% and was neutro- 


tenic, with an ANC of 1,330/uL. On initiation of G-CSF, 


an increase in WBC count and ANC was promptly noted, 


with an ANC in the 6,000 to 10,000/uL range. EPO adminis-


tration was begun at 100 U/kg, resulting in an increase in 


able reticulocytes and hematocrit level from 30% to 


1. 2% over a 10-week period. This patient’s treatment was 


maintained on 100 U/kg of EPO and did not undergo dose 


escalation. The scheduling of EPO administration was 


decreased to three times weekly and courses of therapeutic 


phlebotomies were initiated for his hemochromatosis.

Erythroid responses of the 24 evaluable patients are 


shown in Tables 2 and 3. Ten of the 24 patients (42%) had 


erithroid responses. Seven patients had a GR and three had 


a PR. Of the 10 responding patients, 9 required the 300 


U/kg/d dose of EPO, whereas 1 patient (no. 110 discussed 


above) responded at a dose of 100 U/kg/d. In all patients the 


responses were maintained over the course of the protocol. 

Six responding patients of the 22 evaluable patients (27%) 


who were previously dependent on RBC transfusions to 


control symptoms no longer required transfusions. 

A variety of clinical features were compared in an effort to 


evaluate retrospectively possible correlations with ery- 


thropoietin responses (Table 4). No correlation was noted 


between erythroid responses and age, FAB subtype, disease 


duration, prior RBC transfusion requirements, reticulocyte, 


neutrophil, or platelet counts at study entry, presence of 


cytogenetic abnormalities, or the pretreatment or posttreat- 


ment relative myeloid or erythroid differentiation indexes 


of the bone marrow. The only pretreatment laboratory pa- 


rameter that was different between the responding and nonresponding patients was the serum EPO levels. Re- 


sponding patients had lower levels, with a median value of 


157 (range 18 to 948) U/L as compared with nonresponding 


patients, with a median value of 600 (range 92 to 3,010) 


U/L (P = .05), although there was significant overlap of 


these values between the two groups (Fig 3). Platelet counts 


were generally unaffected by treatment. However, two pa- 


tients had significant decreases in platelet counts, one of 


whom was found to have evolved to AML. Five patients had 


previously received treatment with EPO alone (without re-
Fig 1. Hematologic response of MDS patient no. 102 to combination therapy with G-CSF plus EPO. Baseline hematocrit (●), absolute reticulocyte count (○); WBC count (●), absolute neutrophil count (○) are shown. RBC transfusions are denoted by the solid bars. G-CSF was started as a daily SC injection denoted by the arrow. Two weeks later, EPO was begun, initially at 100 U/kg, with doses escalated to 150 and 300 U/kg/d.

Responses) at least 2 months before enrolling in this study. The EPO for these patients had been administered in a variety of doses and schedules, generally between 50 to 1,000 U/kg three times per week by either intravenous (IV) or SC injection. One of these patients, who had previously received 1,000 U/kg of EPO IV three times weekly for over 4 weeks, responded to G-CSF plus EPO.

Serum ferritin values were >400 μg/L at study entry in 27

Fig 2. Hematologic response of MDS patient no. 110 to G-CSF plus EPO therapy. EPO was administered by a daily (hatched area) SC injection of 100 U/kg for 10 weeks and then decreased to three times weekly for an additional 4 weeks. Response of blood counts is demonstrated.
TREATMENT WITH RBC transfusions. Marrow myeloid and erythroid responses, probably reflecting their continued thyroid dysplasia and the presence of ringed sideroblasts persisted in patients who had demonstrated these morphologic abnormalities, independent of their clinical responses.

Cytogenetic studies. Twenty-six patients had marrow cytogenetic studies performed before study entry. Nine patients had abnormal cytogenetics, of whom five patients had all abnormal cytogenetics (AA) and four patients had a mixture of normal and abnormal chromosomes (AN). These cytogenetic abnormalities were either 5q−, monosomy 7 or trisomy 8 in 6 of these patients. Identical marrow chromosomal patterns were found in all patients tested after the treatment protocol. Of the patients in whom cytogenetics were performed, 7 of 9 responders had normal cytogenetics as compared with 8 of 14 nonresponders (Table 4; P = NS). The two patients with cytogenetic abnormalities who had erythroid as well as myeloid responses (patients no. 102 and 204) had trisomy 8 as their karyotypic abnormality, one of whom also had a 5q− lesion. These two patients had persistence of their karyotypic abnormalities during their responses, suggesting responsiveness of their abnormal hematopoietic clones. Two other patients with the 5q− abnormality (no. 201 and 202) did not respond.

Toxicity. The combined treatment with G-CSF and EPO was generally well tolerated. There were no significant lesions at the injection sites and all patients were treated as outpatients. Two patients (no. 202 and 208) progressed to AML over the 4- to 5-month treatment period. In all other patients bone marrow aspirations at the end of the treatment protocol showed the same FAB classification as that noted before initiating treatment. As stated above, four patients did not complete the treatment protocol. These individuals were patient no. 112, who developed severe bone pain shortly after beginning the G-CSF injections before EPO administration, no. 203, who developed splenic pain, no. 208, who developed splenic pain and evolution to AML, and no. 209, who developed gastrointestinal bleeding before administration of EPO. Patient no. 212 also developed splenic pain, but was able to continue the protocol after decreasing the dose of G-CSF. Patient no. 211 also developed bone pain following G-CSF administration but completed the protocol.

DISCUSSION

In this report, we have evaluated the clinical efficacy of combination therapy with G-CSF and EPO in an effort to improve the anemia in MDS patients. Previous phase I-II studies have documented that the majority of MDS patients had neutrophilic responses to G-CSF11−13 and a small subset of patients also had erythroid responses when treated with G-CSF or GM-CSF alone.11,12 In a prior study of G-CSF treatment of MDS patients, 4 of 18 (22%) patients had erythroid responses,12 all of whom would have been classified as PRs by the criteria used here.

Treatment with EPO alone has also been widely studied in MDS patients.18−23 In the eight reported trials, a total of 84 patients have been treated with EPO alone, of which there have been 19 responders (23%). In our current study, 10 of 24 patients (42%) had erythroid responses, a finding that compares favorably to results with either G-CSF or EPO alone. However, direct comparisons of results from our study with those obtained with EPO alone is not possible, because EPO dose, scheduling, and mode of administration differed. Further, MDS patients are heterogeneous, and it is possible that selection factors could contribute to these different response rates.

The rationale for using G-CSF and EPO in combination

### Table 3. Erythroid Responses of MDS Patients Treated With G-CSF Plus EPO

<table>
<thead>
<tr>
<th>FAB Subtype</th>
<th>GR</th>
<th>PR</th>
<th>NR</th>
<th>Total</th>
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<tr>
<td>RA</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>11</td>
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<tr>
<td>RARS</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>RAEB</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7</td>
<td>3</td>
<td>14</td>
<td>24</td>
</tr>
</tbody>
</table>

Overall response rate (GR plus PR) 10/24 (42%).

### Table 4. Comparison of Pretreatment Clinical Characteristics With Erythroid Responses in MDS Patients Treated With G-CSF Plus EPO

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Median (Range)</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 10</td>
<td>n = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>70 (61-84)</td>
<td>71 (64-84)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior RBC transfusion requirements (units per month)</td>
<td>11 (1-84)</td>
<td>16 (3-102)</td>
<td>NS</td>
</tr>
<tr>
<td>Reticulocytes × 10³/µL</td>
<td>2.3 (0-6)</td>
<td>2.6 (1-6)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils × 10⁹/µL</td>
<td>23 (13.6-49.2)</td>
<td>14.1 (2.5-46.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets × 10⁹/µL</td>
<td>1.6 (1.1-5.1)</td>
<td>1.3 (0.3-7.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum EPO, U/L</td>
<td>188 (2-740)</td>
<td>168 (32-566)</td>
<td>NS</td>
</tr>
<tr>
<td>Relative erythroid differentiation index*</td>
<td>18.9 (18-948)</td>
<td>600 (92-3,010)</td>
<td>P = .05</td>
</tr>
<tr>
<td>Relative myeloid differentiation index†</td>
<td>1.8 (0.73-4.44)</td>
<td>2.6 (0.16-11)</td>
<td>NS</td>
</tr>
<tr>
<td>Cyto genetic findings (abnormal/normal karyotypes)</td>
<td>10.2 (0.92-15.7)</td>
<td>4.65 (2.87-10.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as medians (range).
* Orthochromatic + polychromatic normoblasts/basophilic + pronormoblasts.
† Neutrophils + bands + metamyelocytes + myelocytes/promyelocytes + myeloblasts.

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was the documented in vitro synergy for erythropoiesis of these agents, both for normal and MDS erythroid presursors and the in vivo responses stated above following the use of either agent alone. Further, the data of Leary et al demonstrated that G-CSF enhanced the development of early precursors into EPO-responsive progenitor cells, supporting the possibility that clinical responses may reflect in vivo synergy of these agents. Alternatively, the in vivo responses could relate to the relatively high EPO doses or the daily dosing used in this study. To distinguish between these possible explanations we plan to discontinue the G-CSF in our responding patients to determine the possible persistence of the in vivo erythroid responses. Preliminary evaluation of in vitro-in vivo correlations of patients in whom in vitro erythroid clonogenicity (ie, marrow BFU-E) were evaluated indicated that patients with responsive marrow BFU-E in vitro were the in vivo responders as compared with those patients lacking detectable in vitro BFU-E growth. The persistence of cyogenetic abnormalities in two of the erythroid and myeloid responders does not support the hypothesis that more responsive normal hemopoietic clones emerged during treatment. However, for more precise assessment of the issue of clonality evaluation of X-linked gene homozygosity using restriction-length polymorphisms analysis is needed.

The only pretreatment clinical characteristic of the patients that was predictive of erythroid responses was the serum EPO level. However, there was substantial overlap of these values between the responding and nonresponding patients. Other features including age, sex, FAB subtype, duration of disease, duration of RBC transfusional needs, absolute reticulocyte count, ANC, platelet count, marrow morphology, and cytogenetics did not correlate with erythroid response. Of interest was the general lack of alteration in the qualitative marrow morphologic features (dysplasia, ringed sideroblasts) in the responding patients. This finding and the persisting cyogenetic abnormalities in two responders suggests that a quantitative increase of responsive (though abnormal) erythroid precursors occurred in these patients. The in vitro correlation studies showing increments in BFU-E are consistent with this requirement for adequate numbers of responsive erythroid precursors.

The combination of therapy with G-CSF and EPO was generally well tolerated. Two patients progressed to AML. However, it is not known whether G-CSF or EPO impact on the rate of transformation in this disease, which has a potential for evolution to AML. An ongoing phase III study comparing G-CSF with supportive care is aimed at definitively answering this question. Of interest was the observation that three patients developed splenic pain without splenomegaly, a finding which has not previously been noted using either G-CSF or EPO in MDS patients. Splenomegaly has been reported in a portion of the children with congenital agranulocytosis (Kostmann’s syndrome) who were chronically treated with G-CSF.

In summary, we have evaluated the utility of combination therapy with G-CSF and EPO in MDS patients. One important aspect of this study was the determination that it is possible to administer two cytokines together without a negative interaction. A substantial proportion of the patients had clinically beneficial erythroid and myeloid responses, possibly related to synergy between these two agents for stimulating hemopoiesis. The durability of these responses and determination of factors that are predictive for both erythroid and myeloid responses are currently under study. The results would be important to predict which patients are likely to respond to such therapy because of the potential relatively high cost of treating such patients with both cytokines.

ACKNOWLEDGMENT

The committed administrative efforts of Drs Sherri Brown (AM-GEN), David Gordon (Ortho), and Langdon Miller (CTEP/NCI) are greatly appreciated. The expert secretarial assistance of Sara Clarke and Vibeke Cleaver, and the statistical analysis by Byron Brown, PhD, Stanford University Biostatistics Department, are also appreciated.

REFERENCES

Treatment of the anemia of myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor in combination with erythropoietin [see comments]

RS Negrin, R Stein, J Vardiman, K Doherty, J Cornwell, S Krantz and PL Greenberg