Maintenance Treatment of Patients With Myelodysplastic Syndromes Using Recombinant Human Granulocyte Colony-Stimulating Factor

By Robert S. Negrin, Douglas H. Haeuber, Arnon Nagler, Yukio Kobayashi, Jeffrey Sklar, Timothy Donlon, Martha Vincent, and Peter L. Greenberg

Myelodysplastic syndromes (MDS) are characterized by chronic refractory cytopenias resulting in increased risk of infection, bleeding, and conversion to acute leukemia. In an effort to improve these cytopenias we have treated 18 patients over a 6- to 8-week period with increasing daily subcutaneous doses of recombinant human granulocyte colony-stimulating factor (G-CSF). Sixteen patients responded with improvement in neutrophil counts. On cessation of treatment these counts returned to baseline values over a 2- to 4-week period. To maintain these improved blood counts 11 patients were treated with G-CSF for more prolonged periods. Ten patients again responded with an increase in total leukocyte counts (1.6- to 6.4-fold) and absolute neutrophil counts (ANC) (3.6- to 16.3-fold), with responses persisting for 3 to 16 months. A significantly decreased risk of developing bacterial infections was noted during periods with ANC $> 1.500/mm^3$ as compared with periods of time with ANC $< 1.500/mm^3$. Two anemic patients had a greater than 20% rise in hematocrit over the study period, and 2 additional patients had a decrease in red blood cell transfusion requirements during G-CSF treatment. Bone marrow myeloid maturation improved in 7 of 9 maintenance phase patients. Three patients progressed to acute myeloid leukemia during treatment. The drug was generally well-tolerated and no severe toxicities were noted. These data demonstrated that G-CSF administered to MDS patients by daily subcutaneous administration was well-tolerated and effective in causing persistent improvement of the neutrophil levels and marrow myeloid maturation. These effects were associated with a decreased risk of infection and, in some patients, with decreased red blood cell transfusion requirements.

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The MYELODYSPLASTIC syndromes (MDS) consist of a group of disorders of hematopoiesis characterized by chronic cytopenias and cytopenias leading to frequent infections, transfusional requirements, and increased risk for conversion to acute myeloid leukemia. Treatment options are limited due to the relatively refractory nature of this disease to chemotherapy and the general advanced age of this patient group.

The emergence of recombinant human colony-stimulating factors (CSFs) as therapeutic modalities has led to the possibility that these agents may improve the cytopenias that characterize this disease. In vitro studies in MDS have shown the potential of granulocyte-CSF (G-CSF) to enhance myeloid cell differentiation without causing increased clonal self-generation. In vivo and in vitro studies in mice have provided evidence for decreased leukemogenicity of leukemic cells after exposure to G-CSF. Accordingly, several clinical trials using either G-CSF or granulocyte-macrophage CSF (GM-CSF) have demonstrated that patients with MDS are responsive to these agents and that neutrophil counts can be improved in the majority of patients. Our initial phase I/II study demonstrated well-tolerated dose-dependent increases in neutrophil counts in 10 of 12 MDS patients treated with G-CSF over a 6- to 8-week period. In these trials, improvements in blood counts were dependent on continued treatment, as upon cessation of the CSFs blood counts rapidly reverted to baseline values. Therefore, the chronic nature of this disease would require longer-term, perhaps indefinite administration of these agents to attempt to alter the natural history of MDS, ie, diminish infectious risk and transfusional needs as well as alter the risk of conversion to acute leukemia and improve survival.

Little is known about the chronic administration of these drugs in humans. To evaluate the long-term efficacy, tolerance, and toxicity of G-CSF in MDS patients, we describe results of maintenance subcutaneous administration of this drug to such patients for periods up to 16 months.

MATERIALS AND METHODS

Patients. Eighteen patients with MDS were enrolled in the dose-escalation phase, and 11 of these patients received maintenance treatment. Of the seven patients in the short-term study who did not receive maintenance treatment, four had died (two of MDS-related events) and three patients declined further treatment. All of these patients had responded with an increase in absolute neutrophil counts (ANC) during the dose-escalation phase of treatment. Inclusion and exclusion criteria were the same as those described previously. The clinical characteristics of the patients are listed in Table 1. Written informed consent was obtained from all patients according to guidelines established by the Stanford University Human Experimentation Committee.

Study design. The initial dose-escalation phase of this study has been described previously. Patients were treated by subcutaneous injection of G-CSF beginning at 0.1 µg/kg/d and increased every 2 weeks to 0.3, 1.0, and 3.0 µg/kg/d until normalization of the ANC occurred. On completion of the 8-week dose escalation phase, the G-CSF injections were discontinued and a bone marrow examina-
MAINTENANCE TREATMENT OF MDS WITH G-CSF

Table 1. Profiles of MDS Patients

<table>
<thead>
<tr>
<th>MDS Classification</th>
<th>Dose-Escalation Phase</th>
<th>Maintenance Phase</th>
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<tr>
<td>RA</td>
<td>2</td>
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<tr>
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<tr>
<td>Total</td>
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Hematologic characteristics

<p>| | |</p>
<table>
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</tr>
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<tbody>
<tr>
<td>Anemia</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia (&lt;1,800/mm(^3))</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(500/mm(^3))</td>
</tr>
<tr>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15</td>
</tr>
<tr>
<td>Cytogenetic abnorm.</td>
<td>6</td>
</tr>
</tbody>
</table>

Ages: 62 to 78 years; sex: 14 male, 4 female.
Abbreviations: RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation.

Statistical analysis of the relative risk of infectious episodes was performed by testing the hypothesis that two Poisson events were the same when based on different time intervals. The \( P \) values were calculated using two-tailed analyses that were corrected for continuity.

RESULTS

Hematologic responses. Eighteen patients were entered into the 6- to 8-week dose-escalation phase of treatment with G-CSF. The short-term hematopoietic responses of the first 12 patients have been reported previously.\(^{20}\) Sixteen of 18 patients responded with a rise in white blood cells (WBC) (1.9- to 12-fold) and ANC (5- to 40-fold). In all patients blood counts returned to the pretreatment baseline values over 2 to 4 weeks on discontinuation of the G-CSF injections.

Eleven patients enrolled in the long-term maintenance phase of the trial. The hematopoietic responses of these patients are shown in Table 2 and Fig 1. In this group 10 patients had a rise in WBC (1.6- to 6.4-fold) and ANC (3.6- to 16.3-fold) over baseline pretreatment levels. A positive neutrophil response was defined as being either a normalization of the ANC (eight patients), a rise in ANC to above 1,000/mm\(^3\) if the ANC was initially less than 500/mm\(^3\) (one patient), or a greater than 100% increment if the ANC was initially normal (one patient). These positive responses have been maintained during therapy for periods to date of 6 to 16 months in eight of the patients, and the other two responding patients have been maintained for 3 months (Table 2, Fig 1). The ANC responses of the maintenance phase patients are shown in Fig 1. Five patients began the maintenance phase of treatment with less than 500 neutrophils/mm\(^3\), four responded with increases to greater than 1,300 neutrophils/mm\(^3\).

In six patients the G-CSF injections were discontinued after 6 months as per protocol. In all patients there was a decline in both WBC and ANC toward the pretreatment baseline value (Fig 1). This occurred over a 4- to 8-week period, which was slightly longer than after the initial dose-escalation phase of the trial. Five patients were restarted on the G-CSF (one patient declined retreatment) and again had persistent responses of both the WBC and ANC. In the remaining five patients the G-CSF was continued without interruption. The dose of G-CSF required to maintain these increased neutrophil counts for different patients was variable, ranging from 0.3 to 10 \( \mu \)g/kg/d, although the dose was relatively constant for each patient. The doses required to maintain the neutrophil counts in the normal range are listed in Table 2. Most patients continued to respond to the initial dose used, which resulted in normalization of the neutrophil count during the dose-escalation study that ranged from 1 to 3 \( \mu \)g/kg/d. Patient no. 12 required up to 10 \( \mu \)g/kg/d to normalize the ANC; however, he has been maintained on 5 \( \mu \)g/kg/d for over 6 months. Patient no. 18 initially responded to 3 \( \mu \)g/kg/d with an ANC > 1,800/mm\(^3\); however, after 4 months his ANC dropped to less than 500/mm\(^3\) and the dose was increased to 5 \( \mu \)g/kg/d with a rise in ANC to 1,300/mm\(^3\). There was no apparent relationship between French-American-British (FAB) classification and dose required for a neutrophil response. None of the 10
patients tested has developed antibodies to G-CSF, including the two nonresponding patients.

Red blood cell (RBC) responses were more variable. Of the 10 anemic patients treated in maintenance phase, two patients without a transfusion requirement had a greater than 20% increase in hemoglobin levels (Table 2, patient nos. 10 and 13). Two more severely anemic individuals (patient nos. 1 and 6) had decreases in transfusion requirements.

![Neutrophil responses of maintenance phase MDS patients to G-CSF](image_url)

**Fig 1.** Neutrophil responses of maintenance phase MDS patients to G-CSF. Absolute neutrophil counts are plotted for all maintenance phase patients. The solid and broken lines denote periods of time on and off G-CSF therapy, respectively.
Patient no. 1 initially required 3 to 4 U of RBCs every 4 to 6 weeks, which temporarily decreased to 5 U during 6 months of treatment concomitant with doubling of his reticulocyte count. In patient no. 6, RBC requirements decreased from 2 to 4 U of RBCs every 4 to 6 weeks before G-CSF treatment to 4 U of RBCs during 13 months of G-CSF treatment. Platelet counts generally remained stable during the treatment period; however, patient no. 6 had an increase in platelet count from 32,000 to 83,000/mm³ and patient no. 17 had a decrease in platelet count from 67,000 to 30,000 (Table 2). There were no significant changes in monocyte, lymphocyte, basophil, or eosinophil counts during treatment.

Six patients had circulating myeloblasts at the beginning of the maintenance phase (Table 2). After several weeks of treatment these cells were no longer detected in four individuals (patient nos. 1, 6, 18, and 19). Three patients (nos. 1, 16, and 17, one initially with RAEB and two with RAEB-T, respectively) progressed to AML during the maintenance phase after 16, 3, and 6 months of treatment, and died 1, 2, and 8 months later, respectively.

Bone marrow morphology was evaluated in nine patients before the study, after the dose-escalation phase, and after 6 months of maintenance treatment. In seven responding patients there was improved marrow myeloid maturation, with a decrease in the number of myeloblasts and an increase in the number of neutrophils (Table 3). To further quantify these findings a relative myeloid differentiation index was calculated. This index was defined as the percentage of neutrophils, myelocytes, and metamyelocytes divided by the percentage of myeloblasts and promyelocytes. There was an increase in this index, indicating enhanced marrow myeloid cell maturation, in the seven responding patients after both the cytogenetic studies after 6 and 12 months of maintenance treatment (Fig 2, Table 3).

Cytogenetic analysis was performed on marrow cells from 10 maintenance phase patients; 7 of whom had all normal karyotypes, 1 had a mixture of normal and abnormal chromosomes (AN), and 2 of whom (patient nos. 6 and 19) had all abnormal metaphases (12 and 3 metaphases, respectively) at the beginning of the study (Table 2). In addition, patient no. 7, who completed only the dose-escalation study, had complex karyotypic abnormalities including a del (5)(q13,p33) in all 21 metaphases before treatment with G-CSF. All of these patients, except for the AN patient, responded with increased ANCs while on G-CSF (reference 20, Table 2). In responding patient nos. 7 and 19, the initial cytogenetic abnormalities persisted (19 and 8 metaphases, respectively) after the dose-escalation phase of treatment. Patient no. 6 developed one normal metaphase out of seven after the dose-escalation phase. This patient had additional cytogenetic studies after 6 and 12 months of maintenance treatment in which the same abnormal clone was found in 19 of 20 metaphases in both studies. A fourth individual (patient no. 17), initially with all normal cytogenetics, developed a mixture of normal (15) and abnormal (3) metaphases during treatment.

To further analyze the issue of the clonal nature of the responsive cells, RFLP analysis was performed on two X-linked genes (PGK and HPRT) using DNA from the four female patients. Three individuals were not polymorphic at these genes, whereas one individual (patient no. 7) was polymorphic at the PGK gene. After triple digestion of this patient's DNA with BglII, BgIII, and EcoRI, two bands appeared on Southern blot autoradiograms using the PGK probe at 1.7 and 1.3 kilobases ([kb], Fig 3). After digestion with the methylation sensitive enzyme HpaII, the 1.3-kb band disappeared in all bone marrow and blood cell populations, indicating clonal hematopoiesis before treatment. After treatment with G-CSF, in which this patient responded with an increase in ANC from 1,100/mm³ to 5,600/mm³, an identical clonal pattern was observed in both the mononuclear cell and neutrophil fractions (Fig 3).

Infectious episodes. In four maintenance phase patients there were eight episodes of clinically significant bacterial infections after beginning the G-CSF injections (Table 4). These infections were defined as either having positive cultures or a source of infection identified and being signifi-
patients who achieved an ANC > 1,500/mm³ with G-CSF treatment (0.08 compared to 0.01 episodes per month, \( P < .04 \)).

**Toxicity.** Relatively little toxicity was associated with the chronic use of G-CSF. There were no infections or rashes at the injection sites, although local bruising was noted on occasion in two thrombocytopenic patients. Bone pain was not reported. Several patients had fever over the course of the study. However, in most cases this resolved over 1 to 3 days, consistent with a viral-like illness. In our previous dose-escalation trial several patients with preexisting cardiac and pulmonary disease had these clinical problems during G-CSF treatment. Although it was not felt that these episodes were related to the G-CSF, cardiac radionuclide ventriculograms and pulmonary function with diffusion studies were performed on four patients at the beginning, during, and after 6 months of maintenance treatment to evaluate the impact of G-CSF on cardiac and pulmonary function. No changes were noted in cardiac ejection fraction, lung diffusion capacity, or pulmonary function in these patients (data not shown).

**DISCUSSION**

In this report we have evaluated relatively long-term tolerance, efficacy, and toxicity of G-CSF in MDS patients, extending our initial observations on the short-term efficacy of this treatment. Ten of 11 maintenance-phase MDS patients had persistent improvements in neutrophil counts for periods up to 16 months (8 patients have responded for greater than 6 months to date). Continued treatment was necessary to maintain improved ANCs as blood counts reverted to the pretreatment baseline values over 4 to 8 weeks after stopping the drug.

Improvement in marrow myeloid maturation, as quantified by the relative myeloid differentiation index, was also demonstrated in responding patients. This was noted in all six of the patients with the subclassification of RAEB, and 1 of the 3 RAEB-T patients evaluable for morphologic assessment. The other two RAEB-T patients had decreased myeloid maturation concomitant with their progression to AML. In this regard, combined data of MDS patients treated with GM-CSF indicate that 7 of 45 patients have progressed to AML in five short-term studies, particularly in those individuals with greater than 14% marrow blasts. Extending our initial observations on the short-term efficacy of this treatment.* Ten of 11 maintenance-phase MDS patients had persistent improvements in neutrophil counts for periods up to 16 months (8 patients have responded for greater than 6 months to date). Continued treatment was necessary to maintain improved ANCs as blood counts reverted to the pretreatment baseline values over 4 to 8 weeks after stopping the drug.

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Fig 3. RFLP analysis of clonality. Pretreatment bone marrow cells from patient no. 7 were separated into nonadherent, adherent, mononuclear (MNC), and intermediate myeloid/erythroid fractions. Posttreatment peripheral blood was separated into MNC and neutrophil (PMN) fractions. After preparation of DNA, restriction fragments were generated and half of the sample was further digested with the methylation sensitive enzyme $Hpall$. The samples were probed with an 800-bp fragment from the 5' end of the PGK gene. All pretreatment bone marrow fractions show 1.7- and 1.3-kb fragments when not subjected to digestion with $Hpall$ (lanes 2, 4, 6 and 8), whereas only the 1.7-kb fragment remains after digestion with $Hpall$ (lanes 1, 3, 5, and 7), indicating clonality of the cells. After treatment with G-CSF, identical patterns are seen using peripheral blood mononuclear cells (MNCs) and neutrophils (PMNs, lanes 9 through 12).

In retrospective analysis there was a significant reduction in bacterial infection risk during periods with an ANC > 1,500/mm$^3$ with G-CSF therapy, as compared to periods with an ANC < 1,500/mm$^3$ (Table 4). We previously showed that in vitro neutrophil function in MDS patients after G-CSF therapy demonstrated enhanced phagocytosis and maintained chemotaxis in the majority of patients. These data indicate that in addition to increasing neutrophil counts, G-CSF treatment was associated with possible clinical efficacy. However, an apparent although statistically insignificant increase in infection risk was noted in patients who were treated with G-CSF but had not yet achieved an ANC > 1,500/mm$^3$ (Table 4, A vs B). This may be merely a reflection of the small number of infectious episodes that

25 Other patients will need to be evaluated in this way to determine the proportion of patients with clonal responses after growth factor treatment.

Analysed in this fashion who was treated with GM-CSF.

Patient had a dramatic and persistent rise in neutrophil count while on G-CSF. Two other patients, both with all abnormal metaphases, also had persistence of these abnormalities after responding to G-CSF with an increase in ANC. These data suggested that differentiation of the abnormal clone occurred with treatment. Further support for the induced differentiation of the abnormal clone by G-CSF was obtained using RFLP analysis of X-linked genes. Using this type of evaluation, clonal hematopoiesis has previously been demonstrated in approximately 35% of patients with MDS. One of four responding female patients was polymorphic at the PGK gene locus and the clonal nature of her neutrophils was demonstrated before and after treatment with G-CSF (Fig 3). These data indicate that the neutrophil response in this MDS patient treated with G-CSF was due to maturation of the abnormal clone rather than stimulation of residual normal hematopoiesis. This result is in contrast to the finding of polyclonal hematopoiesis in one recently reported patient analyzed in this fashion who was treated with GM-CSF.

Patients will need to be evaluated in this way to determine the proportion of patients with clonal responses after growth factor treatment.
Table 4. Relative Risk of Bacterial Infections in MDS Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>A + B v C</th>
<th>P Values†</th>
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<td></td>
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<tr>
<td></td>
<td>A v B</td>
<td>NS</td>
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</table>

Abbreviations: A, patients 6, 12, 16, 18, and 19 had infections before G-CSF therapy; B, patients in this group had either not yet had neutrophil responses (early in treatment), or had decreased neutrophil levels after discontinuing G-CSF as per protocol; C, patients in this group had persistent neutrophil responses to G-CSF.

*Ten neutropenic patients were retrospectively evaluated for 2 to 15 months before treatment and during 4 to 16 months of treatment with G-CSF.

†P Values for the relative risk of infections were calculated as a test for differences between two Poisson variables, corrected for continuity, two-tailed.

REFERENCES


ACKNOWLEDGMENT

The authors thank Dana Bangs; Jan DiJulio, RN, MSN; Maureen O'Hara, RN; Claudia Rupp, PharmD; Byron Brown, PhD; Valerie Cannon; Jane Pelton; and Shirley Gray, Stanford University Medical Center, for expert assistance. The superb care given by the nursing staff on the Clinical Research Center of Stanford University Hospital is also greatly appreciated.


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