A Phase I/II Study of Sequential Interleukin-3 and Granulocyte-Macrophage Colony-Stimulating Factor in Myelodysplastic Syndromes

By Sucha Nand, Jeffrey Sosman, John E. Godwin, and Richard I. Fisher

In this phase I/II study, 9 patients with myelodysplastic syndromes (MDS) were treated with interleukin-3 (IL-3) followed by granulocyte-macrophage colony-stimulating factor (GM-CSF). Each treatment cycle was 28 days long and administered as follows: 1 μg/kg/d IL-3 on days 1 through 7 and 3 μg/kg/d GM-CSF for days 8 through 21, followed by a 7-day rest period. IL-3 dose escalations were planned, but the dose of GM-CSF was fixed. Three patients had refractory anemia, 4 had refractory anemia with ringed sideroblasts, and 2 had refractory anemia with excess blasts. Six patients were dependent on red blood cell transfusions, 1 on platelet transfusions, and 2 on both. The absolute neutrophil count improved in 7 (77%) patients and the platelet count improved in 3 (33%) patients during therapy. Hemoglobin levels were unchanged. A clinically relevant response was seen in only 1 patient with thrombocytopenia, and he received five cycles of therapy. The neutrophil count decreased in 2 patients and the platelet count decreased in 4 patients during treatment. The toxicity of the treatment was significant. In the first cohort of 3 patients, 1 patient developed supraventricular tachycardia and congestive heart failure. In the second group, 1 patient developed progressive granulocytopenia and died of gram-negative septicemia. Because of the disparate toxicity, 3 more patients were treated at the same dose level. One of these experienced a high fever and bone pain requiring hospitalization. Because of these adverse effects, the IL-3 dose was not escalated and all patients received 1 μg/kg/d for 7 days. We believe that sequential therapy with IL-3 and GM-CSF at these dose levels causes unacceptable toxicity in patients with MDS. The major toxic events occurred during weeks 4 and 5 after starting treatment and may have been primarily caused by GM-CSF therapy. Although neutrophil counts improve in most patients, the effect on red blood cells and platelets is minimal. At present, this form of therapy remains problematic and appears to have a limited potential in the management of MDS.

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Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders of bone marrow stem cells with a distinct tendency to transform into acute leukemia. These disorders include refractory anemia (RA), RA with ringed sideroblasts (RARS), chronic myelomonocytic leukemia (CMML), RA with excess blasts (RAEB), and RAEB in transformation to acute leukemia (RAEBIT). The clinical expression of the disease is determined by the resulting anemia, granulocytopenia, thrombocytopenia, or any combination of these. At present, there is no satisfactory treatment available for these disorders. Over the last few years, hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-CSF (G-CSF), erythropoietin, and interleukin-3 (IL-3) have been used with short-term improvements in blood counts. Although the responses of GM-CSF and G-CSF were not totally lineage restricted, the effect was predominantly on the granulocytic series. The response to IL-3 was less vigorous, but it appeared to prime and expand a pool of hematopoietic progenitor cells that would then be more responsive to other CSFs. Subsequent studies showed that IL-3 and GM-CSF act synergistically in stimulating hematopoiesis, both in vitro and in the primate models. Early clinical data on the sequential use of IL-3 plus GM-CSF in patients with various malignancies, some of whom had received chemotherapy, shows a superior granulocytic recovery with the combination. The platelet recovery was no better than that seen with the use of IL-3 alone.

We undertook this study to define the optimal dose of IL-3 plus GM-CSF in MDS and to assess the effect of this treatment on the cytopenias. We were also concerned about the effect of this combination on transformation of MDS to acute leukemia.

MATERIALS AND METHODS

Patients. Patients with RA, RARS, CMML, and RAEB with less than 10% blasts in the bone marrow were entered on the study. Patients had to be 18 years of age or older, have a Karnofsky performance status of 70% or more, and have an expected survival of at least 3 months. Patients with a history of asthma, cardiac arrhythmias, congestive heart failure, bleeding disorders, or evidence of human immunodeficiency virus or hepatitis B infection were excluded. Patients also had to have normal levels of serum creatinine, bilirubin, and calcium, and a normal prothrombin time (PT) and partial thromboplastin time (PTT) to enter the study. No therapy with hematopoietic growth factors or biologic response modifiers was allowed during the 4 weeks before treatment on this study.

Source of recombinant hematopoietic growth factors. The recombinant IL-3 and GM-CSF used in this study were provided by Sandoz Pharmaceutical Corp (East Hanover, NJ) and made available to us through the Cancer Therapy Evaluation Program and Division of Cancer Treatment, National Cancer Institute (Bethesda, MD). Both agents were obtained from the bacterial fermentation of a strain of Escherichia coli bearing a genetically engineered plasmid containing the IL-3 or the GM-CSF gene. Nonglycosylated forms of the drugs were used. The drug solutions were prepared and administered according to the manufacturers' guidelines.

Study design. The candidate patients underwent a complete history and a physical examination, in addition to the prestudy laboratory tests, which included a complete blood count (CBC), a chemistry profile, a urinalysis, a PT study, a PTT study, a hepatis
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Marrow Chromosomes</th>
<th>Previous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43/F</td>
<td></td>
<td>RAEB</td>
<td>Del 5 (q13.q33)</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>2</td>
<td>72/F</td>
<td></td>
<td>RARS</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>74/F</td>
<td></td>
<td>RARS</td>
<td>Normal</td>
<td>Interferon α</td>
</tr>
<tr>
<td>4</td>
<td>60/M</td>
<td></td>
<td>RA</td>
<td>Del 5 (q15.q33)</td>
<td>Interferon α</td>
</tr>
<tr>
<td>5</td>
<td>73/M</td>
<td></td>
<td>RARS</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>72/M</td>
<td></td>
<td>RAEB</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>56/F</td>
<td></td>
<td>RA</td>
<td>Del 7</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>63/F</td>
<td></td>
<td>RARS</td>
<td>Normal</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>9</td>
<td>31/M</td>
<td></td>
<td>RA</td>
<td>Normal</td>
<td>GM-CSF</td>
</tr>
</tbody>
</table>

B surface antigen study, an EKG, a chest X-ray, and a bone marrow study with cytogenetics. If the patient met the entry criteria, informed consent was obtained.

Treatment plan. Treatment was administered in the outpatient department. Each treatment cycle was 28 days long. A baseline CBC and a chemistry profile were drawn and patients were started on daily subcutaneous injections of IL-3 for 7 days, followed by GM-CSF for 14 days. This was followed by a 7-day rest period, during which no treatment was administered. The planned IL-3 dose levels, for successive groups of 3 patients, was as follows: group 1, 1.0 μg/kg/d; group 2, 2.5 μg/kg/d; group 3, 5.0 μg/kg/d; group 4, 10.0 μg/kg/d. The GM-CSF dose was fixed at 3.0 μg/kg/d. Standard supportive care was provided.

Patients were seen twice a week, once by the physician and once by the visiting nurse at home. During the study period, a CBC was performed twice a week; a PT, a PTT, and a chemistry profile once a week; and a bone marrow biopsy on day 21. Those who responded had the option of continuing the therapy.

Toxicity of the treatment was graded using the Treatment Common Toxicity Criteria as published by the Division of Cancer Treatment, National Cancer Institute.

For the purposes of this study, the maximum tolerated dose (MTD) was defined as the dose at which fewer than one-third of the patients experienced dose-limiting toxicity (DLT). DLT was defined as any toxicity of the treatment requiring the removal of the patient from the study, or any grade 3 or 4 toxicity. Thus, MTD would be the dose at which 0 or 1 of 6 patients would experience DLT, with the next higher dose having at least 2 of 6 patients encountering DLT.

RESULTS

A total of 9 patients, in three groups, were entered on the study. Four patients were males and the age range was 31 to 73 (median, 66) years. Three patients had RA, 4 had RARS, and 2 had RAEB. Six patients had normal marrow cytogenetics; 2 had deletion 5 (1 had del (5)(q13q33) and the other del (5)(q15q33)), and 1 had deletion 7. Two patients had been previously treated with interferon α, 2 with erythropoietin, and 1 with GM-CSF (Table 1). Six patients were dependent on packed red blood cell transfusions, 1 on platelet transfusions, and 2 on both.

Temporary improvements in white blood cell counts were seen in 7 of 9 patients during treatment, with a maximum response on day 21. In 2 patients (patients no. 1 and 3), there was a decrease in the absolute neutrophil count during treatment. There was no change in the hemoglobin levels or the packed red blood cell transfusion requirement in any patient. Platelet counts temporarily improved in 3 (33%) patients (patients no. 1, 2, and 6) during the treatment. These data are summarized in Table 2. In only 1 of these 3 was the improvement clinically useful. In this patient (no. 6), the baseline platelet count was less than 10,000/μL and he had required weekly platelet transfusions. During IL-3 plus GM-CSF therapy, platelet transfusions were not needed.

Follow-up blood counts, at 1 month posttherapy, were available in 4 patients. Three of these showed a lower absolute neutrophil count and platelet count when compared with pretreatment values. Follow-up blood counts at 6 months after finishing treatment were available in 4 patients. All of these showed a lower absolute neutrophil count when compared with the pretreatment values. The platelet count was lower in 1 patient. This may have been caused by the natural progression of the disease, rather than by delayed effect of therapy.

A repeat bone marrow on day 21 did not show disease progression in any of the 9 patients. Patient no. 6 received five cycles of therapy because of improvement in his platelet count. His peripheral blast count went up to 16% in each of the cycles, but returned to the baseline value during the rest period. However, after five cycles, the blast count remained elevated, requiring treatment with chemotherapy.

The toxicity of the treatment was substantial (Table 3). Grade 1 toxicity in the form of fatigue, anorexia, and flu-like symptoms was common. In the first group of 3 patients, 1 patient (no. 3) developed supraventricular tachycardia and congestive heart failure requiring admission to the Intensive Care Unit on day 22 of the treatment. This accompanied an increase in her absolute neutrophil count to 44,088/μL. In the second group of 3 patients treated at the same dose level, 1 patient (no. 4), who had stable blood counts during the previous year, developed progressive neutropenia and thrombocytopenia. The patient developed gram-negative sepsis on day 31 and died on day 33. In the third group, 1 patient (no. 9) experienced a high fever and severe bone pain requiring hospitalization on day 23. The major toxicities were seen in weeks 4 and 5 after the start of the treatment. Because of the serious toxicity observed, the IL-3 dose was not escalated beyond level 1, and all patients received 1 μg/kg/d for 7 days.

DISCUSSION

The role of CSFs remains uncertain in the management of MDS. Combined data from early studies (on 45 patients) show that GM-CSF improves the granulocyte count in 84%, the reticulocyte count in 31%, and the platelet count in 17% of the patients with MDS.11,19-23 However, blast count also increased in 26% of these patients. The multicenter randomized trial (133 patients) of GM-CSF in MDS showed that the improvement is primarily restricted to the granulocytic series, but the risk of leukemic transformation was not increased.13 Results of treatment with G-CSF in MDS have been similar.24-26 IL-3, in two separate studies involving 22 patients,22,27 was shown to improve granulocyte count in 12, hemoglobin in 1, and platelet count in 5 patients. Erythropoietin improves hemoglobin level in about 20% of patients.
with MDS, mainly in those with a suboptimal endogenous response.28,29

More recently, combinations of hematopoietic growth factors have been used in an effort to obtain a broader hematopoietic response. Greenberg et al29 have reported on the synergistic effect of G-CSF and erythropoietin in vitro. Two separate studies have shown synergism between IL-3 and GM-CSF in vitro and in primates.14,17 This synergism was seen when IL-3 was followed by GM-CSF. Simultaneous administration was not found to be better than a single agent. In a phase I study of IL-3 followed by GM-CSF, Ganser et al31 treated 15 patients with various malignancies, 9 of whom were receiving chemotherapy. Granulocytic responses were superior with the combination, but the effect on the platelets was similar to IL-3 treatments. Two patients developed grade III toxicity in the form of chills, rigors, and dyspnea and treatment had to be stopped in 1 of them.31

Based on the above observations, we decided to perform a phase I/II study of IL-3 plus GM-CSF in MDS. Our results show that granulocyte counts improved in 7 of 9 (77%) patients, that hemoglobin levels and transfusion requirements were unaffected, and that the platelet count improved in 3 patients. However, only 1 of these responses was clinically meaningful. This occurred in patient no. 6, in whom significant improvement in platelet count was noted and platelet transfusions were no longer necessary.

The increments in the absolute neutrophil count and platelet count disappeared within 4 weeks after stopping therapy. During therapy, platelet counts decreased in 4 patients and neutrophil counts decreased in 2. The absolute neutrophil count and platelet count was lower in 3 of the 4 patients that were tested 1 month after stopping therapy.

Toxicity of this regimen was unacceptably high. We saw grade IV toxicity in 2 of the first 6 patients treated with this regimen. Because these two toxicities were so different, we decided to treat 3 more patients at the same dose level. Unfortunately, 1 of these 3 patients also developed grade III toxicity in the form of high fever and severe bone pain. All the major toxic events occurred in weeks 4 and 5 after starting therapy. Therefore, it is possible that the serious toxicity was primarily caused by GM-CSF. In addition, we saw the usual mild side effects associated with the use of CSFs (Table 3). Whether lower doses of IL-3 and GM-CSF would be less toxic and clinically beneficial remains an open question.

In summary, sequential therapy with IL-3 and GM-CSF in doses used in our study is toxic in MDS. Although the neutrophil count improved in 77% and the platelet count in 33% of patients during treatment, hemoglobin levels did not change. In some patients, posttreatment blood counts were lower than the pretreatment counts. Because of the toxicity and of the improvements primarily restricted to granulocytic counts, sequential therapy with IL-3 and GM-CSF appears to have a limited role in the management of MDS, and other approaches need to be considered.

ACKNOWLEDGMENT

The authors thank Ann Marie D’Andrea for expert preparation of this manuscript.

REFERENCES


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