CONCISE REPORT

Use of Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor in Autologous Marrow Transplantation for Lymphoid Malignancies

By John Nemunaitis, Jack W. Singer, C. Dean Buckner, Roger Hill, Rainer Storb, E. Donnall Thomas, and Frederick R. Appelbaum

The use of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) following autologous marrow transplantation for lymphoid malignancies was explored in a phase I/II dose escalation study. rhGM-CSF was given as a 2-hour infusion daily for 14 days. Treatment was well tolerated at doses up to 240 µg/m²/day. When compared with 86 disease-matched and treatment-matched historical controls, patients receiving ≥60 µg/m²/day rhGM-CSF recovered neutrophil and platelet counts more rapidly, had fewer days with fever, and were discharged from the hospital sooner.

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MATERIALS AND METHODS

Patient selection. Patients with lymphoid malignancies, including acute lymphocytic leukemia, Hodgkin’s disease, or non-Hodgkin’s lymphoma, were undergoing autologous or syngeneic marrow transplantation after standard preparative regimens were eligible for study. Patients were consecutively entered in groups of three at a given dose. This definition was based on our previous experience with 86 patients given autologous grafts for lymphoid malignancies, when only four patients (<5 %) achieved this level of neutrophils by day 14. If no significant toxicity occurred at a dose with suggested biologic activity, we planned to investigate two more dose escalations before closing the study. rhGM-CSF was administered as a single 2-hour intravenous (IV) infusion starting within 1 hour of completion of the autologous marrow infusion (designated as day 0) and repeated daily for a total of 14 days.

Patients. Fifteen consecutive patients with lymphoid malignancy qualifying for autologous or syngeneic marrow transplant were studied. The mean age was 32 years (range 13 to 61 years). There were six females and nine males. Diagnosis, disease state, conditioning regimen, type of marrow transplant, and marrow purging are listed by patient in Table 1. All patients with a fever (T > 38°C) were treated uniformly according to Fred Hutchinson Cancer Research Center protocol with empiric antibiotic therapy and without granulocyte transfusions.

RESULTS

Hematologic responses. The days on which the patients achieved an absolute neutrophil count (ANC) of >500 cells/µL and platelet independence are shown in Table 1. No patient receiving rhGM-CSF at 15 or 30 µg/m²/day achieved an ANC >500 cells/µL before day 14, whereas five of eight evaluable patients receiving ≥60 µg/m²/day did so. Of the five patients who reached 500 neutrophils/µL by day 14, four temporarily decreased their ANC to <500/µL within 24 to 72 hours after stopping rhGM-CSF. The mean maximum reduction of ANC after stopping rhGM-CSF (dose ≥60 µg/m²/day) was 35% (4% to 63%). Table 2 compares the retrospective control group with study patients receiving ≤30 µg/m²/day and ≥60 µg/m²/day rhGM-CSF. Patients receiving ≥60 µg/m²/day showed earlier granulocyte and platelet recovery than the retrospective control group. The average number of days with a temperature ≥38.0°C and the number of platelet transfusions in the first...
30 days after transplantation appeared to be least in patients receiving >60 µg/m²/day of rhGM-CSF.

Two of 14 evaluable patients (UPN 3990 not evaluable) had incomplete engraftment. Both received ≤30 µg/m²/day of rhGM-CSF. One patient, (UPN 3810) now 100 days post-BMT, continues to have an ANC of 400/µL after initially reaching an ANC >1,000 cells/µL on day 24 post-BMT. The other patient (UPN 3647) received a 4-hydroperoxycyclophosphamide (4-HC)-treated bone marrow and has an ANC >2,000 cells/µL but still requires occasional platelet transfusions (~4 U/2 weeks) at day 100. All evaluable patients receiving ≥60 µg/m²/day had complete hematopoietic reconstitution.

Toxicity. rhGM-CSF was well tolerated at all doses. No patient failed to complete courses of rhGM-CSF because of suspected toxicity. The following toxicities related to rhGM-CSF were observed: Three patients had abdominal cramps, two of whom had symptoms associated only with the first dose. One patient had a constant low-grade temperature that resolved when rhGM-CSF was discontinued. One patient had bilateral shoulder pain associated only with the first dose of rhGM-CSF. No hepatic, pulmonary, neurologic, cardiac, or renal toxicities occurred. However, one patient (UPN 3647) developed acute tubular necrosis with a transient rise in creatinine to 2.5 mg/dL believed to be caused by a rapid infusion of acyclovir. He was also receiving rhGM-CSF at the time. The rhGM-CSF was held for 2 days and was restarted without recurrence of renal function abnormalities.

Table 1. Day of Myeloid and Megakaryocytic Engraftment in rhGM-CSF-Treated Patients

<table>
<thead>
<tr>
<th>Unique Patient No.</th>
<th>Diagnosis/Disease State</th>
<th>Conditioning Regimen* TBI Dose (cGy)/days</th>
<th>Type of Marrow</th>
<th>Dose of rhGM-CSF (µg/m²)</th>
<th>Day After Marrow Infusion Patient Independent of Platelet Transfusion</th>
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</thead>
<tbody>
<tr>
<td>3769</td>
<td>NHL/relapse</td>
<td>200 × 6</td>
<td>A None</td>
<td>15</td>
<td>18</td>
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<tr>
<td>3647</td>
<td>ALL/relapse</td>
<td>360 × 4</td>
<td>A None</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>3810</td>
<td>NHL/relapse</td>
<td>200 × 6</td>
<td>A Pan B</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>3806</td>
<td>NHL/relapse</td>
<td>200 × 6</td>
<td>A 4HC†</td>
<td>26</td>
<td>70+</td>
</tr>
<tr>
<td>3854</td>
<td>NHL/relapse</td>
<td>200 × 6</td>
<td>S None</td>
<td>14</td>
<td>13</td>
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<tr>
<td>3895</td>
<td>NHL/relapse</td>
<td>200 × 6</td>
<td>A None</td>
<td>30</td>
<td>31</td>
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<tr>
<td>3919</td>
<td>NHL/remission</td>
<td>200 × 6</td>
<td>A Pan B</td>
<td>30</td>
<td>14</td>
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<tr>
<td>3918</td>
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<td>200 × 6</td>
<td>A None</td>
<td>30</td>
<td>14</td>
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<tr>
<td>3935</td>
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<td>3992</td>
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<td>S None</td>
<td>14</td>
<td>13</td>
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<tr>
<td>3996</td>
<td>NHL/remission</td>
<td>200 × 6</td>
<td>S None</td>
<td>14</td>
<td>13</td>
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<tr>
<td>3908</td>
<td>ALL/relapse</td>
<td>0*</td>
<td>S None</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

NHL, non-Hodgkins lymphoma; ALL, acute lymphocytic leukemia; A, autologous; S, syngeneic.

*All conditioning regimens included cyclophosphamide (60 mg/kg/day × 2 days). TBI, total body irradiation delivered by dual opposing cobalt 60 source. Patient 3945 received TBI by linear accelerator. Patient 3908 received Busulfan (4 mg/kg/day × 4 days) and no TBI.
†Autologous marrow was treated with 100 µg/mL 4-hydroperoxycyclophosphamide.
‡Marrow treated in vitro with a pan-B cell antibody plus complement.
§Death on day 8.

Table 2. Mean Values of Study Parameters

<table>
<thead>
<tr>
<th>rhGM-CSF Dose (µg/m²/day)</th>
<th>No. of Patients</th>
<th>Day of AGN &gt; 100*</th>
<th>Day of AGN &gt; 500*</th>
<th>Day of AGN &gt; 1,000*</th>
<th>Day Platelet Transfusion Independent*</th>
<th>Day of Discharge*</th>
<th>No. of Fabrics Days (T ≥ 28°C)</th>
<th>No. of Platelet Units Transfused (From day 0 to day 301*)</th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>88</td>
<td>16 ± 6 (8-41)</td>
<td>25 ± 10 (10-60)</td>
<td>29 ± 11 (17-64)</td>
<td>38 ± 20 (13-118)</td>
<td>12± 7 (0-30)</td>
<td>84 ± 41 (22-170)</td>
<td>67 ± 16 (82-90)</td>
</tr>
<tr>
<td>≤30</td>
<td>6</td>
<td>13 ± 5 (6-22)</td>
<td>22 ± 10 (14-41)</td>
<td>30 ± 13 (21-53)</td>
<td>30 ± 22 (13-70)</td>
<td>11 ± 6 (3-20)</td>
<td>78 ± 48 (32-154)</td>
<td>67 ± 16 (82-90)</td>
</tr>
<tr>
<td>≥60†</td>
<td>8</td>
<td>10 ± 10 (2-13)</td>
<td>14 ± 2 (12-18)</td>
<td>22 ± 4 (20-24)</td>
<td>29 ± 5 (18-31)</td>
<td>8 ± 2 (1-11)</td>
<td>67 ± 16 (82-90)</td>
<td>67 ± 16 (82-90)</td>
</tr>
</tbody>
</table>

*Mean ± SD (range).
†Retrospective control group of comparably matched patients with lymphoid malignancy who underwent autologous BMT at FHCRC prior to the start of this study.
‡Patient 3990 who died on day 8 was unevaluable and is not included.

DISCUSSION

rhGM-CSF was well tolerated at doses up to 240 µg/m² given by slow IV infusion in patients undergoing autologous marrow transplantation for lymphoid malignancy. Furthermore, more than 90% of patients surviving 14 days treated with rhGM-CSF at doses ≥60 µg/m²/day achieved an ANC of 500 cells/µL before day 14. Because only 5% of 86 patients...
treated in a similar fashion but without rhGM-CSF reached this level before day 14, biologic activity at these doses was strongly suggested. However, a prospective placebo-controlled trial will be necessary to prove this.

rhGM-CSF may also have had an influence on platelet recovery. However, we cannot determine whether this was a direct or indirect effect. In vitro studies have suggested mild stimulation of megakaryocyte proliferation with GM-CSF which could be significantly augmented when combined with other growth factors.8 Other researchers have reported shortened platelet recovery times after autologous BMT in monkeys treated with rhGM-CSF.4 In addition, two of eight patients with myelodysplasia became platelet transfusion independent after treatment with rhGM-CSF.10 However, in other patients with normal baseline platelet counts, GM-CSF had no effect on platelet counts.5 Erythropoietin levels.7-11 No clear effect of rhGM-CSF on erythropoiesis was observed in our study.

Toxicity with rhGM-CSF was mild and predominantly limited to muscle cramps and bone pain. The mechanisms of toxicity are unknown. GM-CSF may induce prostaglandin E production by macrophages.12

Our study raised three concerns. First, a temporary reduction in ANC to <500 cells/μL occurred in four patients within 1 to 3 days after the last dose of rhGM-CSF. This observation is consistent with previous studies showing the short stimulatory effect of rhGM-CSF. Second, not all patients had sustained hematopoietic recovery. This raises the further concern that rhGM-CSF may cause differentiation of early stem cells and interfere with the self-renewal required for long-term reconstitution. Metcalf and colleagues reported data in mice showing reductions in CFU-GM and bone marrow cellularity after mice were given daily intraperitoneal GM-CSF.13 Third, the effect of rhGM-CSF on tumor cell regrowth is unknown. Patients with myeloid leukemia were excluded from this study because myeloid tumors have rhGM-CSF receptors on their cell surface and the effects of exposure to rhGM-CSF on possible surviving tumor cells after transplant have not been determined. Because most lymphoid malignancies are not believed to express rhGM-CSF receptors, we considered it reasonable to explore the molecule in this setting. Nonetheless, some lymphoid tumor cells may express rhGM-CSF receptors or rhGM-CSF may influence tumor growth indirectly.

This study evaluated the short-term effects of rhGM-CSF after autologous BMT for lymphoid malignancy. rhGM-CSF was well tolerated and appeared to have biologic activity when compared with a retrospective control group at doses ≥60 mg/m2/day given as a 2-hour daily infusion. We cannot conclude by this trial whether a particular cytodestruction regimen, marrow-purging technique, or underlying disease affects the responsiveness to rhGM-CSF. Larger prospective randomized phase III trials are needed to define more precisely the possible therapeutic and economic advantages offered by this molecule and to uncover any serious untoward effects.

REFERENCES

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