A Phase II Study of Continuous Infusion Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor as an Adjunct to Autologous Bone Marrow Transplantation for Patients With Non-Hodgkin’s Lymphoma in First Remission


Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) clearly hastens myeloid recovery in patients with relapsed hematologic malignancies undergoing autologous bone marrow transplantation (ABMT). In efforts to further improve neutrophil engraftment and shorten hospital stay in ABMT patients, rhGM-CSF was administered by a potentially more potent route (continuous infusion) to non-Hodgkin’s lymphoma (NHL) patients with better BM reserve (first remission). Time to myeloid engraftment was compared with that of NHL patients treated in first remission at our institution on a similar ABMT protocol but without growth factor support (controls). Median neutrophil engraftment (absolute neutrophil count, 500 cells/μL) in first remission patients treated with rhGM-CSF was 14 days, compared with 22 days in controls (P = .0001). Hospital stays were also significantly reduced for rhGM-CSF patients (P = .0003). Platelet engraftment did not differ between the two groups. Persistent fever and generalized serositis were the primary toxicities. rhGM-CSF, delivered by this route, was efficacious but more toxic than 2-hour rhGM-CSF infusions previously reported by other investigators. Future alterations in both dose and schedule may retain comparable efficacy yet diminish toxicity.

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WIDESPREAD use of myeloablative therapy has been limited by severe aplasia and its attendant toxicities. Recombinant hematopoietic growth factors have limited the length and severity of myeloid aplasia, and thus become critical adjuncts to high-dose therapy. One such growth factor is recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), a regulatory glycoprotein that both promotes the proliferation and differentiation of myeloid progenitor cells and enhances the function of mature neutrophils and monocytes. After a phase III trial in 1991, rhGM-CSF was approved for use in patients with relapsed lymphoid malignancies undergoing autologous bone marrow transplantation (ABMT). Patients treated with rhGM-CSF on this and subsequent phase III ABMT studies all demonstrated more rapid myeloid engraftment by 7 to 10 days. In contrast, rhGM-CSF did not augment platelet recovery despite in vitro data suggesting that rhGM-CSF was capable of modest stimulation of megakaryocyte proliferation and differentiation. The clinical impact of these studies was evident in shorter hospitalizations and fewer serious infections in most trials. Although rhGM-CSF is now a standard adjunct to ABMT, several critical issues remain unresolved, including the optimal route and schedule of administration, as well as determining which patient subgroups will benefit most from its use.

The superiority of myeloablative therapy compared with conventional dose salvage therapy for relapsed hematologic malignancies remains controversial. However, the potential efficacy and relative safety of high-dose consolidation has led to its introduction into the primary treatment of poor-risk patients with leukemia or lymphoma. We, and others, have begun to evaluate ABMT as consolidation therapy for patients with poor prognosis non-Hodgkin’s lymphoma (NHL) at the time of first complete or very good partial remission (upfront patients). Historically, upfront patients at our institution have not received rhGM-CSF during ABMT, yet have comparable time to myeloid engraftment and length of hospital stay as relapsed patients who receive rhGM-CSF during similar transplant regimens. Comparable engraftment without growth factor support in upfront patients is likely caused by less pretransplant therapy resulting in the relative sparing of committed and early myeloid progenitor cells.

Our present study is designed to determine whether rhGM-CSF improves the time to myeloid engraftment in upfront NHL patients undergoing ABMT. An additional goal is to determine the feasibility of delivering continuous infusion rhGM-CSF during ABMT. rhGM-CSF has been administered by 2-hour bolus infusion during ABMT with acceptable toxicity. However, in vitro and in vivo human studies suggest that continuous infusion or subcutaneous delivery of rhGM-CSF is more efficacious than bolus infusions. In the results presented below, we show that rhGM-CSF can significantly hasten the time to myeloid engraftment in upfront NHL patients undergoing ABMT. However, continuous infusion administration of rhGM-CSF resulted in greater toxicity than reported in previous studies using 2-hour bolus administration.

MATERIALS AND METHODS

Selection of patients and treatment protocol. Study patients initially presented with stage III or IV low-grade or intermediate-grade
(National Cancer Institute Working Formulation) B-cell non-Hodgkin’s lymphoma. To be eligible for induction chemotherapy, patients with stage III low-grade lymphoma were required to have at least one mass greater than 5 cm. All patients with stage IV low-grade lymphoma were eligible except those with very limited disease, defined as one or two lymph node masses on the same side of the diaphragm (<5 cm) and focal BM involvement (<5%). Intermediate-grade lymphoma patients included stage III or IV diffuse small cleaved cell or diffuse mixed, small and large cell. Patients with diffuse large-cell lymphoma (DLCL) were eligible only if they had an incomplete response to four cycles of primary chemotherapy.

To be eligible to proceed to ABMT, all patients were required to achieve a minimal disease state (lymph nodes <2 cm, intratrabecular BM involvement with lymphoma =20%, and the absence of hepatosplenomegaly) after the administration of primary combination chemotherapy, and, in a few cases, involved field radiotherapy. Lymphoma cells were required to express the CD20 (Bl) antigen. Consecutive patients were accrued. Informed consent, conforming to the Food and Drug Administration and Dana-Farber Cancer Institute standards, was required for participation.

Further eligibility requirements included a Karnofsky score greater than 80%, serum bilirubin less than 1.5 mg%, serum creatinine less than 1.5 mg%, and normal pulmonary diffusing capacity of carbon monoxide as well as cardiac ejection fraction within 4 weeks of BM harvesting. Before BM harvest, patients were required to have a total white blood cell count greater than 3,000 cells/μL, a hematocrit greater than 28%, and a platelet count greater than 100,000/μL. Patients with a history of myocardial infarction, conges-
tive heart failure, or clinically significant cardiac dysrhythmia were excluded from the study. Patients were also excluded if central ner-
vous system involvement with lymphoma was shown within 4 weeks of the BM harvest.

The controls included all lymphoma patients at Dana-Farber from 1988 to the time of the present study who received an ABMT in first remission. Study and control patients were treated on similar upfront ABMT protocols, including eligibility requirements, ablative regimen, purging technique, and supportive care. Control patients did not receive rhGM-CSF or any other cytokine growth factor during the BMT.

The ABMT preparative regimen for both study and control pa-
tients included cyclophosphamide (60 mg/kg of body weight, admin-
istered on each of 2 successive days) and 1,200 cGy of total body irradiation (TBI; administered in 200 cGy fractions twice a day over a 3-day period). All patients received ABM purged with a cocktail of B-cell monoclonal antibodies (B1, B5, and JS) plus complement. Supportive care. BM rooms had positive pressure laminar air flow. Reverse isolation was observed. All study and control patients received prophylactic oral antibiotics starting on the day of admission. Prophylactic acyclovir was administered to all patients at a dose of 400 mg/kg orally three times daily or 5 mg/kg intravenously three times daily beginning on the day of admission and continuing for 1 year after ABMT.

Intravenous antibiotics were initiated when fever greater than 101°F occurred for a 4-hour duration, unrelated to blood product infusions, in the setting of a total neutrophil count less than 500 cells/μL. Mezlocillin and gentamycin were the initial intravenous antibiotics unless the patient had a penicillin allergy, in which case cotrimoxazole was instituted in place of mezlocillin. Amphotericin was added, at the discretion of the clinician, if fever persisted for 3 to 7 days despite broad spectrum antibiotics. If a neutrophil count of greater than 400 cells/μL was attained for 2 consecutive days, in the absence of fever, all antibiotics were discontinued except for acyclovir. Once intravenous antibiotics were discontinued, if oral hydration was adequate and there were no other complications of ABMT requiring hospitalization, patients were discharged from the hospital. If fever persisted after the neutrophil count reached 400 cells/μL, treatment decisions concerning intravenous antibiotics and rhGM-CSF were left to the discretion of the clinicians.

Patients received routine transfusions for a hematocrit less than 30% and a platelet count less than 20,000/μL. Daily complete blood counts and biweekly renal and liver serum tests were performed on these patients.

Study design. This was a phase II prospective trial with a target accrual of 25 patients. A total of 27 consecutive patients were ac-
crue. One relapsed patient was incorrectly registered to this study. She was declared ineligible, and is not included in the analysis.

Study medication. Study patients received yeast rhGM-CSF (Sargramostim) by continuous infusion through a central venous catheter at a fixed dose of 250 μg/m²/day (specific activity, 5 × 10⁷ colony-forming units/mg; Immunex, Seattle, WA; supplied by Hoechst-Roussel Pharmaceuticals, Somerville, NJ). rhGM-CSF was reconstituted with 50 mL of normal saline and 0.1% human serum albumin and administered at a rate of approximately 2 mL/h by an infusional pump (Cadd-I, Pharmacia Deltic, Inc, St Paul, MN). The infusion began within 2 hours of marrow reinfusion and was administered for a total of 21 days. The drug was discontinued if a patient developed a serious allergic reaction or a life-threatening adverse reaction (grade IV), wanted to be withdrawn for any reason, or the clinician decided grade II/III toxicity was unaccept-

Definition of neutrophil engraftment. Engraftment was defined as an absolute neutrophil count (ANC) greater than or equal to 500 cells/μL on 2 consecutive days. Time to neutrophil recovery was calculated from the day of marrow reinfusion to the first of the 2 required consecutive days. In addition, the time to first neutrophil was measured from the day of marrow reinfusion to the appearance of the first neutrophil.

Definition of platelet engraftment. Engraftment was defined as the time from marrow reinfusion to the first of 2 consecutive days with a platelet count greater than or equal to 20,000/μL followed by at least 7 days without an intervening platelet transfusion. Patients also were considered to have engrafted if their platelet count was greater than 20,000/μL independently increasing for at least 5 days, and if further follow-up was not available.

Definition of documented infection. Infection was defined as the occurrence of at least two positive blood cultures for coagulase-negative staphylococcus or a single blood culture positive for any other organism. Patients with invasive infection in a closed body fluid or organ that was documented either histologically or by culture were considered to have documented infection.

Definition of hospital stay. Hospital stay was defined as the number of days from the day of marrow reinfusion to the day of discharge.

Toxicity data. Toxicity data from study patients and historical controls were collected by retrospective chart review.

Statistical methods. Engraftment in rhGM-CSF patients and controls was compared using the Wilcoxon test. Time to engraftment was considered censored if the patient did not achieve the stated criteria during a period in which consecutive daily measurements were obtained. Median engraftment times were calculated according to the method of Kaplan and Meier, as were plots of time to engraftment. The number of patients developing the first neutrophil before 10 days was compared with the Fisher exact test.

RESULTS

Patient characteristics. The characteristics of study pa-
tients and historical controls are shown in Table 1. The me-
Table 1. Characteristics of Study Patients and Historical Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study (n = 26)</th>
<th>Historical (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr) (range)</td>
<td>45.5 (35-56)</td>
<td>41.0 (19-57)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Disease histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular predominantly small cleaved cell</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Follicular mixed, small cleaved, and large cell</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse small cleaved cell</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Diffuse mixed, small cleaved, and large cell</td>
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<td>1</td>
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<tr>
<td>Diffuse large cell</td>
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<td>4</td>
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<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>Percentage of BM involvement at ABMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>≤5%</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>&gt;5% and &lt;20%</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Disease status at ABMT</td>
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<td></td>
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<tr>
<td>Minimal disease</td>
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<td>32</td>
</tr>
<tr>
<td>Complete remission</td>
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<td>14</td>
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<tr>
<td>Prior history of extranodal involvement</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>Prior history of radiation therapy</td>
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</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Median no. of BM cells infused (×10^7)/kg</td>
<td>3.55</td>
<td>3.46</td>
</tr>
</tbody>
</table>

The median age of the 26 study patients was 45.5 years (range, 35 to 56). Twenty patients had follicular, predominantly small cleaved cell lymphoma; 4 patients had follicular mixed, small cleaved cell lymphoma; and 2 patients had diffuse small cleaved cell lymphoma. Seven patients had stage III and 19 patients had stage IV disease. Twenty-four of 26 patients received 6 to 8 cycles of CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy before transplantation. One patient received 6 cycles of CHOP followed by 3 cycles of CVP (cyclophosphamide, vincristine, prednisone) and 1 patient received 5 cycles of CHOP followed by 2 cycles of CVP. Fourteen patients achieved a minimal disease state and 12 patients achieved a complete clinical remission at the time of ABMT.

The 43 historical control patients were comparable with regards to age, stage, previous chemotherapy, remission status, and number of BM mononuclear cells per kilogram infused at the time of BMT. The control group included 34 patients with low-grade lymphoma (follicular, predominantly small cleaved cell and follicular, mixed, small cleaved cell) and 9 patients with intermediate-grade lymphoma (diffuse small cleaved cell; diffuse mixed, small and large cell; and diffuse large cell).

Hematologic responses. Both the time to the appearance of the first neutrophil as well as the time to 500 and 1,000 neutrophils/μL was more rapid in the study patients treated with continuous infusion rhGM-CSF compared with those of control patients. As shown in Fig 1, the median time to first neutrophil was 9 days for study patients compared with 11 days for controls (Wilcoxon, P < .0001). The first neutrophil was observed before day 10 in 15 of the 26 rhGM-CSF patients (58%) compared with 3 of the 43 controls (7%; Fisher’s exact, P < .0001). The median time to engraftment of 500 neutrophils (Fig 2) was 14 days for the study patients compared with 22 days for the controls (Wilcoxon, P = .0001). The median time to engraftment of 1,000 neutrophils (Fig 3) was 16 days for rhGM-CSF patients compared with...
Fig 3. Kaplan-Meier estimate of the probability of the time to an ANC of 1,000/µL from the day of BM reinfusion for 26 patients with NHL in first remission treated with rhGM-CSF after ABMT compared with 43 first-remission historical controls who underwent ABMT but did not receive rhGM-CSF ($P < .0001$).

27 days for controls (Wilcoxon, $P < .0001$). Platelet engraftment to 20,000/µL (Fig 4) was not statistically different in rhGM-CSF and historical control patients (Wilcoxon, $P = .11$; 22 and 19 days, respectively).

Infections. Documented infection developed in none of the 26 study patients but was observed in 6 of the 43 control patients. Although there was a trend for a reduction in documented infections on rhGM-CSF, it was not statistically significant (Wilcoxon, $P = .0764$). Four streptococcal and two staphylococcal infections were documented in control patients and were limited either to central line sites or blood. The median number of days on intravenous antibiotics for rhGM-CSF patients was 7, compared with 13 days for control patients (Wilcoxon, $P = .0004$).

Duration of hospitalization. Length of hospitalization from the day of BM reinfusion was shorter for rhGM-CSF-treated patients than for controls. As shown in Fig 5, the median duration was 24 days for rhGM-CSF patients compared with 28 days for control patients ($P = .0003$). Four of the 26 study patients and 5 of the 46 control patients required brief readmissions (median, 4 days; range, 2 to 9 days) within 30 days of discharge. In only 1 case (control patient) was readmission caused by fever and neutropenia. These readmission days were not included in the hospitalization analysis.

Toxicity. Thirteen of 26 patients (50%) completed the full 21-day course of continuous infusion rhGM-CSF. Duration of rhGM-CSF infusion for the 13 patients who did not complete the full course ranged from 9 to 18 days (median, 12 days). Eight of these 13 patients had less than 500 neutrophils at the time of rhGM-CSF discontinuation and were changed to a different schedule or growth factor. Six of the 8 patients were changed from rhGM-CSF to rhG-CSF, and 2 patients were changed to 2-hour bolus infusion of rhGM-CSF.

A comparison of fever as well as other toxicities during ABMT between study patients and historical controls is shown in Tables 2 and 3. Fever greater than 101°F during the transplant was common and similar in both rhGM-CSF patients (96%) and controls (83%). However, the pattern of fever differed markedly. In patients who experienced fever, onset during agranulocytosis was more common in controls patients (95% vs 48%), whereas onset of fever after the appearance of the first neutrophil was more common in rhGM-CSF patients (52% vs 5%). In addition, 72% of febrile rhGM-CSF patients experienced persistent fever, despite recovery of 500 neutrophils and broad spectrum antibiotics, compared with only 11% of the controls. Fourteen of the 18 persistent fevers in rhGM-CSF patients (78%) resolved within 24 to
Cl GM-CSF POST-ABMT IN FIRST-REMISSION NHL

48 hours of discontinuing the growth factor. Generalized rash (excluding folliculitis) was similar in rhGM-CSF patients (42%) and controls (41%). Isolated peripheral edema was more common in rhGM-CSF patients (23% v 4%). In addition, generalized serositis was uncommon but seen exclusively in rhGM-CSF patients (3 patients, 12%). One of these cases was complicated by pericarditis and atrial fibrillation. Veno-occlusive disease (VOD) occurred in 1 control patient and was fatal. Diffuse alveolar hemorrhage (DAH) occurred in 2 control patients and 1 case was fatal.

DISCUSSION

TRI-containing myeloablative therapy followed by BM rescue alone results in 4 to 6 weeks of severe neutropenia and thrombocytopenia in patients with relapsed hematologic malignancies.14-17 In this setting, neutropenia can be reduced to approximately 3 weeks with the addition of rhGM-CSF.6 Importantly, this results in shorter hospital stays and fewer life-threatening infections. We have previously shown that, by selecting patients for ABMT with better BM reserve (first remission), neutrophil engraftment can be achieved in 3 weeks without growth factor support.17

The results of this study show that first remission NHL patients treated with rhGM-CSF during ABMT have a substantial reduction in the median time of neutropenia compared with historical controls not receiving growth factor. This was reflected in both a shorter period of agranulocytosis as well as more rapid engraftment after the appearance of the first neutrophil. It should be noted that control patients used for comparison in this study are comparable to study patients, and the results presented here must be interpreted accordingly. Fourteen-day neutrophil engraftment (ANC, >500/µL) observed in our patients approximates the neutrophil engraftment achieved when mobilized peripheral blood stem cells (PBSCs) are combined with BM in patients with solid tumors receiving non-TBI-containing ablative therapy.26-31 Shortened neutropenia combined with antibiotic prophylaxis resulted in no documented infections in our patients. In fact, neutropenia was so short that the hematologic toxicity of ABMT no longer became the rate-limiting determinant of hospital stay. This was evident as the median hospital stay was reduced by only 4 days in rhGM-CSF–treated patients compared with controls despite an 8-day and 11-day improvement in median time to recovery of 500 and 1,000 neutrophils/µL, respectively. In most cases, the hospital stay was limited by persistence of nausea, vomiting, or diarrhea associated with the preparative ABMT regimen.

The results from this study are notable because toxicity attributed to rhGM-CSF precluded completion of the full 21-day continuous infusion schedule in 50% of the study patients. It is clear from previous clinical studies that toxicity related to rhGM-CSF is dose-, route-, and duration-dependent.20-24 Two- and 6-hour infusions of rhGM-CSF have been common schedules with acceptable toxicity in ABMT patients.6,19 Continuous infusion administration of rhGM-CSF is more potent but frequently more toxic than shorter bolus infusions.20,21 The toxicity related to rh-GM-CSF is reversible and presumably mediated by endogenous secondary cytokine release (interleukin-1 [IL-1], IL-6, tumor necrosis factor, and interferon) from rhGM-CSF–activated mononuclear cells.20-24 Milder toxicities manifest as “cytokine flu” (low-grade fever, malaise, myalgias, and bone pain). More severe toxicities include generalized serositis, high fevers, and erythromedra.7,8,21

The toxicities of patients on our study were rapidly reversible but considerable. Fever is a common complication of neutropenia during ABMT and was similar in rhGM-CSF patients and ABMT control patients who did not receive any growth factor. However, it was striking that the pattern of fever was very different between rhGM-CSF and control patients. Control patients had the onset of fever almost exclusively during the period of agranulocytosis (95%) and few patients (11%) experienced persistent fever after neutrophil engraftment (ANC, >500/µL). In contrast, a significant proportion of rhGM-CSF–treated patients (52%) had the initial onset of fever after the appearance of the first neutrophil (ANC, >0/µL) and a large proportion (72%) had persistent fever after neutrophil engraftment (ANC, >500/µL) despite broad spectrum antibiotics. We attribute the persistent fevers primarily to rhGM-CSF because this pattern of fever was not observed in control patients, documented infections were not observed in rhGM-CSF–treated patients, and the fevers resolved rapidly after discontinuing growth factor. In addition to persistent fever, peripheral edema (23% v 4%) and generalized serositis (12% v 0%) were seen more commonly in rhGM-CSF–treated patients than in historical controls. Generalized serositis was present in 3 rhGM-CSF patients on our study, with pericarditis and atrial fibrillation complicating 1 of these cases. Persistent fever and generalized sero-

Table 2. Fever During ABMT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of GM-CSF Patients (n = 26)</th>
<th>No. of Historical Controls (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 101°F</td>
<td>25 (96)</td>
<td>38 (83)</td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC = 0</td>
<td>12 (48)</td>
<td>36 (95)</td>
</tr>
<tr>
<td>ANC &gt; 0 (after nadir)</td>
<td>13 (62)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Persistent fever*</td>
<td>18 (72)</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

Percentages are in parentheses.

* Not related to documented infection.

Table 3. Nonfebrile Toxicities During ABMT

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of GM-CSF Patients (n = 26)</th>
<th>No. of Historical Controls (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash*</td>
<td>11 (42)</td>
<td>19 (41)</td>
</tr>
<tr>
<td>Peripheral edema (alone)</td>
<td>6 (23)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Generalized serositis</td>
<td>3 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>4 (15)</td>
<td>0</td>
</tr>
<tr>
<td>VOD</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>DAH</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Death†</td>
<td>0</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Percentages are in parentheses.

* Excluding folliculitis.
† One death caused by DAH and one by VOD.
sis were not significant toxicities reported in the US phase III trial using a similar dose of yeast-derived rhGM-CSF by 2-hour bolus administration. Study drug in that trial was discontinued in only 1 patient in each study arm because of persistent fever. Generalized serositis was not reported in either study arm. In contrast, two European phase III trials using similar doses of Escherichia coli-derived rhGM-CSF by continuous infusion reported generalized serositis infrequently (7% and 13%), but solely on rhGM-CSF treatment arms.

Persistent fever was the primary reason physicians chose to take patients off the study. If patients remained neutropenic at the time rhGM-CSF was discontinued, they were changed to either 2-hour infusions of rhGM-CSF or bolus infusion recombinant human granulocyte colony-stimulating factor (rhG-CSF). The favorable experience with 2-hour rhGM-CSF administration in previous studies at our institution and the ready availability of rhG-CSF may have biased some clinicians to prematurely discontinue growth factor. This may partially explain why a large number of patients did not complete the full 21-day course of therapy.

The trade-off between the clear efficacy of rhGM-CSF by continuous infusion delivery and the observed toxicity poses a dilemma for future dosing and delivery in ABMT trials. The efficacy of continuous infusion delivery of rhGM-CSF might be maintained, and its toxicity minimized, by lowering the daily dose (ie, 125 μg/m²/d). This modified continuous infusion regimen could be compared with 2-hour infusion of rhGM-CSF that has a more favorable toxicity profile. Subcutaneous dosing of rhGM-CSF is an alternative schedule. Dose-intense chemotherapy trials have shown this schedule to be equally efficacious and less toxic than continuous infusion delivery. Theoretical concerns about bleeding and infectious complications of subcutaneous dosing during the severe aplasia of ABMT may not be clinically relevant. Regardless of the route of delivery of rhGM-CSF, early engraftment of upfront patients treated with cytokine therapy may make a shorter duration of treatment possible. Because rhGM-CSF toxicities are primarily duration-dependent, side effects might be reduced by shorter courses of therapy. Decisions to reduce the duration of cytokine therapy should account for an immediate reduction in neutrophil count commonly observed in the first few days after discontinuing growth factors. A practical treatment endpoint might be to stop cytokine therapy when the ANC reaches 1,000 to 1,500/μL. This should ensure that the ANC remains safely above 500/μL after stopping the growth factor, thereby minimizing potential infectious complications.

Prolonged thrombocytopenia after TBI-ablative therapy remains problematic. Patients with persistent thrombocytopenia are exposed to the risks of platelet transfusions (infec-
tious diseases, alloimmunization) and are frequently unable to receive potentially beneficial posttransplant therapies. Despite the fact that rhGM-CSF alone has been unable to augment platelet recovery in this or other trials, it remains an attractive cytokine to support ABMT because it may act synergistically with other multilineage cytokines (IL-3, IL-11, stem cell factor, and leukemia inhibitory factor) to stimulate thrombopoiesis. Preclinical work is promising and early clinical studies using rhGM-CSF in combination with other cytokines (rhGM-CSF and IL-3) or rhGM-CSF fusion products (PIXY321) are now underway. In addition to combining different cytokines to stimulate thrombopoiesis, another strategy has been to use mobilized PBSC infusions to hasten platelet recovery. PBSC infusions after non-TBI ablative chemotherapy regimens have yielded impressive platelet engraftment results. Whether PBSC infusions will lead to equally successful platelet engraftment after TBI-containing ablation regimens remains uncertain and deserves further study.

High-dose, myeloablative therapies are becoming common strategies in earlier stages of treatment for hematologic malignancies. Hematopoietic growth factors as adjuncts to high-dose therapy in these patients can reduce neutropenia substantially so that serious infections occur rarely, and determinants of hospital stay change to nonhematologic toxicities. Current research efforts are directed toward maximizing the efficacy/toxicity profiles of these cytokines and devising combinations that will result in full trilineage hematopoietic recovery.

ACKNOWLEDGMENT

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A phase II study of continuous infusion recombinant human granulocyte-macrophage colony-stimulating factor as an adjunct to autologous bone marrow transplantation for patients with non-Hodgkin's lymphoma in first remission