Recombinant Granulocyte-Macrophage Colony-Stimulating Factor After Autologous Bone Marrow Transplantation for Relapsed Non-Hodgkin’s Lymphoma: Blood and Bone Marrow Progenitor Growth Studies. A Phase II Eastern Cooperative Oncology Group Trial

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Sixteen patients with relapsed non-Hodgkin’s lymphoma underwent autologous bone marrow transplantation and infusion of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF). Treatment consisted of involved-field radiotherapy, cyclophosphamide 60 mg/kg/d intravenously (IV) for 2 days, and fractionated total body irradiation (1,200 cGy). Autologous bone marrow was thawed and infused IV, followed 3 hours later by the first infusion of IV rhGM-CSF 11 μg/kg/d for 4 days. Infusions of rhGM-CSF were continued daily until either both neutrophil count exceeded 1,500/μL and platelet count exceeded 50,000/μL, or until 30 days after marrow re-infusion. Toxicities encountered were mild and included fever, chills, hypertension, alopecia, rash, diarrhea, stomatitis, myalgia, and synovial (knee) effusions. Neutrophil recovery greater than 500/μL occurred a median of 14 days (range, 9 to 30 days) after marrow infusion, significantly earlier than in a comparable group of historic controls who recovered counts at a median of 20 days (range, 12 to 51 days) (P = .00002). Median time to self-sustaining platelet counts greater than 20,000/μL was 23.5 days (range, 12 to 100 days), comparable with the historic group (P = .38). One bacteremia (central venous catheter exit site infection with Staphylococcus epidermidis) and one local infection (Giardia lamblia in stool) occurred. Patients received a median of 11.4 (range, 4.4 to 20.2) × 10^8 colony-forming unit granulocyte-macrophage (CFU-GM) progenitors per kg. Stem cell progenitors CFU-GM, CFU-granulocyte, erythroid, monocyte, megakaryocyte (CFU-GEMM), and burst-forming unit-erythroid (BFU-E) were detected in the bone marrow as early as 7 days after marrow re-infusion, and increased in proportion to peripheral blood counts, but by 30 to 60 days still remained much lower than before transplant. Neutrophils transiently decreased in 13 of 16 patients (median decrease, 42%) within 24 to 72 hours of discontinuing rhGM-CSF infusions. These data suggest that rhGM-CSF therapy enhances neutrophil recovery by forcing stem cells to produce mature elements at an enhanced rate but may not affect marrow stem cell and early progenitor population sizes.

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PATIENTS AND METHODS

Patient population. Patients 15 to 60 years of age with histologically confirmed non-Hodgkin’s lymphoma in relapse were eligible to participate as part of protocol EST P-Z488 of the Eastern Cooperative Oncology Group (ECOG). Pretreatment evaluation included history and physical examination; chest radiograph; pulmonary function tests; electrocardiogram; radionuclide gated blood-pool scanning; measurement of 24-hour urine creatinine clearance; and external imaging tests for determination of tumor size and location. Patients with an ECOG performance status of greater than 1, central nervous system metastases, serum creatinine greater than 1.5 mg/dL, 24-hour creatinine clearance less than 60 mL/min, carbon monoxide lung diffusion capacity less than 60% of predicted, cardiac ejection fraction less than 50% of predicted, and serum aspartate aminotransferase or serum total bilirubin greater than twice normal were excluded from participation. In addition, patients shown to have lymphoma involving the BM (on routine histologic examination) and patients who received previous extensive local radiation (eg, mantle or large mediastinal configuration, pelvic radiation therapy, etc) were ineligible for this trial. Patients gave written informed consent, and the protocol was approved by the Institutional Review Board for Human Investigation at each participating institution.

BM transplant protocol. BM was aspirated under general or regional anesthesia at least 4 weeks since exposure to cytotoxic therapy, except in the case of treatment with nitrosoureas, in which case at least 6 weeks must have elapsed. BM was cryopreserved with a controlled-rate liquid nitrogen freezing apparatus using previously published methods. BM was not treated in vitro with

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Supported, in part, by Grants P30CA43703, CA4548, CA45609, and CA21115 from the National Institutes of Health, the National Cancer Institute, the United States Public Health Service, and Sandoz Research Institute, East Hanover, NJ. S.L.G. is a recipient of a Mallinckrodt Foundation Scholar Award.

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was frozen in a final concentration of 10% dimethylsulfoxide and was stored in the liquid phase of a liquid nitrogen refrigerator (−196°C) until used. All patients received a multi-lumen central venous catheter for venous access. The intensive chemo-radiation therapy or conditioning regimen has been reported previously. Briefly, treatment consisted of 1,200 to 2,000 cGy involved-field radiation therapy days T-17 through T-6 (eg, 17 through 6 days before marrow infusion) to previously bulky (>5 cm diameter) or active disease sites in 10 fractions over 14 days, intravenous (IV) cyclophosphamide 60 mg/kg/d on days T-5 and T-4, and 1,200 cGy fractionated total body irradiation (200 cGy twice daily 6 to 10 hours apart at 20 to 30 cGy/min) on days T-3 through T-1. Through one dedicated lumen of the central venous catheter, intravenous therapy with rhGM-CSF fractions over 14 days, intravenous (IV) cyclophosphamide 60 mg/kg/d on days T-5 and T-4, and 1,200 cGy fractionated total body irradiation (200 cGy twice daily 6 to 10 hours apart at 20 to 30 cGy/min) on days T-3 through T-1. Through one dedicated lumen of the central venous catheter, intravenous therapy with rhGM-CSF at a dose of 11 µg/kg/d was begun 3 hours after completion of marrow infusion (day T-0). rhGM-CSF was administered IV daily thereafter for 4 hours until either (1) recovery of both neutrophil count (>1,500/µL) and platelet count (>50,000/µL, untransfused) occurred, or (2) colony-stimulating factor therapy was administered for a total of 30 days.

Complete blood counts, measurements of serum electrolytes, and serum tests of liver and renal function were obtained at least thrice weekly. Patients were treated in single hospital rooms equipped with high-efficiency particulate air filters and placed on a diet low in bacterial and fungal content. The hematocrit was maintained in the 25% to 30% range by transfusion of packed, irradiated red blood cells, and the platelet count was maintained above 20,000/µL by platelet concentrate transfusions. All blood products received 1,500 to 3,000 cGy of irradiation. Parenteral alimentation and broad-spectrum antibiotic support were used as clinically indicated. Toxicity grading was according to the Common Toxicity Criteria of the National Cancer Institute.

Historic controls. A historic control group consisted of our previously published multi-institutional experience; 52 patients received involved-field radiation therapy, intravenous cyclophosphamide, and fractionated total body irradiation with autologous BM support.1 Of these patients, 47 patients remained alive at least 30 days after marrow re-infusion and were used to construct the historical data for this comparison.

rhGM-CSF. Complementary DNA encoding GM-CSF was cloned and expressed by Genetics Institute (Cambridge, MA).3 Glycosylated rhGM-CSF was formulated as a lyophilized powder by Sandoz Pharmaceuticals (Basel, Switzerland), and was supplied by Sandoz Research Institutes (East Hanover, NJ). A historic control group consisted of our previously published multi-institutional experience; 52 patients previously were exposed to one of several conventional combination chemotherapies, five patients heretofore were treated with two differing regimens, and one patient eventually failed three different chemotherapy combinations. Before beginning cyclophosphamide and total body irradiation therapy, all patients received involved-field radiation. Thirteen of 16 patients were exposed to at least one radiation treatment field that involved a large marrow-bearing area, such as the entire mediastinum, entire para-aortic and celiac region, or whole pelvis or whole abdominal field. Other patient characteristics are shown in Table 1.

In vitro peripheral blood and BM cultures. Immediately before beginning involved-field radiation therapy, 2.5 mL BM aspirates from the posterior iliac crests and 20 mL peripheral blood samples were collected for hematopoietic stem cell assays. Thereafter, 20 mL blood samples were collected twice weekly beginning 1 week before transplant and continued until discharge; BM aspirates (2.5 mL) were performed weekly beginning the day of BM re-infusion (day of BM transplantation, ie, day T-0). All samples were collected in sodium heparin without preservatives at a final concentration of 30 U/mL (Sigma Chemicals, St Louis, MO). BM and peripheral blood mononuclear cells were prepared by Ficoll-Hypaque as previously described.18 BM cells were plated at 2 x 10^6 cells/mL and blood cells at 5 x 10^6 cells/mL as follows:11 cells were suspended in a mixture of Iscove's modified Dulbecco's medium containing 0.1% deionized bovine serum albumin, 0.8% methylcellulose (Fluka, Buchs, Switzerland), 30% selected fetal bovine serum (Hy Clone Labs, Logan, UT), 10^4 mol/L α-thioglycolic acid, 10 mmol/L hemin (Kodak, Rochester, NY), 4 U/mL recombinant human erythropoietin (rhEpo; kindly provided by N. Crerand, Johnson & Johnson, Raritan, NJ), 200 U/mL rhGM-CSF (kindly provided by Dr D. Oette, Sandoz Research Institute, East Hanover, NJ), and 100 U/mL recombinant human interleukin-3 (rhIL-3; kindly provided by Dr E. Liehl, Sandoz Forschungsinstitut, Vienna, Austria). Hematopoietic stem cells were plated in 1 mL aliquots in triplicate 35-mm gridded plastic plates at 37°C, 5% carbon dioxide for 14 days. The number of erythroid burst-forming units (BFU-E), granulocyte-macrophage colony-forming units (CFU-GM), and mixed granulocyte-erythroid-macrophage-megakaryocyte colony-forming units (CFU-GEMM) were counted.11 The variation between plates in CFU number was less than 12%. Data were recorded as the mean of triplicate values for individual assays and as mean ± SD for the group as a whole.

Statistical methods. The Peto Wilcoxon test was used to compare recovery of neutrophil and platelet count between the study population and historic controls. Linear regression analysis was used to compare hematopoietic variables before and after marrow transplant.

RESULTS

Patient characteristics before initiating transplant conditioning regimen. Sixteen patients entered this study between January 1989 and February 1990. These patients were treated at the Ireland Cancer Center, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH; Shands Hospital, University of Florida, Gainesville; and the Hospital of the University of Pennsylvania, Philadelphia.

All patients treated on this protocol either had relapsed lymphoma or had tumor resistant to cytotoxic drug therapy. Ten patients previously were exposed to one of several conventional combination chemotherapies, five patients heretofore were treated with two differing regimens, and one patient eventually failed three different chemotherapy combinations. Before beginning cyclophosphamide and total body irradiation therapy, all patients received involved-field radiation. Thirteen of 16 patients were exposed to at least one radiation treatment field that involved a large marrow-bearing area, such as the entire mediastinum, entire para-aortic and celiac region, or whole pelvis or whole abdominal field. Other patient characteristics are shown in Table 1.

Efficacy. Patients received a median of 26 days rhGM-CSF therapy (range, 13 to 30 days). Recovery to neutrophils greater than 500/µL was significantly faster (median, 14 days; range, 9 to 30 days) than in controls (median, 20 days; range, 12 to 51 days) (P = .00002, Peto Wilcoxon test). Time to self-sustaining platelet count greater than 20,000/µL was 23.5 days in the rhGM-CSF group (range, 12 to 100 days) comparable with 26 days in the control group (range, 7 to 149 days) (P = .38, Peto Wilcoxon test). This is not a randomized comparison and the tests have not been adjusted for differences in patient characteristics between the two groups that might be relevant to hematopoietic reconstitution. However, even with this caution, it is clear that rhGM-CSF therapy resulted in a significant shortening of
the time to neutrophil recovery. Patients were hospitalized for a median of 37 days, which ranged from 27 to 57 days. During the hospital stay, a median of 8 U of red blood cells (range, 4 to 25 U) were infused, and a median of 72 U of platelets (range, 12 to 217 U) were transfused. Data from the historic control group regarding duration of hospital stay and transfusion exposure are not available for comparison.

Cessation of rhGM-CSF was accompanied by a transient but marked decrease in granulocyte count in most patients. In 13 of 16 patients the neutrophil count decreased a median of 42% (range, 10% to 73%) within 72 hours of discontinuing rhGM-CSF therapy. Neutrophil count did not decrease below 500/µL and no patients developed infection during this temporary decrease in neutrophils.

**Toxicity.** Despite the use of rhGM-CSF infusions for up to 30 days (median, 26 days), infusions of rhGM-CSF therapy were well-tolerated, even in some patients who had already recovered normal neutrophil count but not adequate platelet count. Mild to moderate reversible toxicities were noted in most patients, but rhGM-CSF infusions were not discontinued because of toxicity in any patients. Three patients developed grade 2 myalgias, and two patients developed synovial (knee) effusions. These effusions occurred during the first week of rhGM-CSF therapy, were transudates on examination, and resolved within 1 week without specific therapy despite continuing rhGM-CSF infusion. Three patients experienced unexplained weight gain (grade 1 in two patients and grade 2 in one patient). One patient developed a marked increase (grade 2) in systolic blood pressure in association with rhGM-CSF infusions.

Other toxic effects observed in our patients included mucositis, diarrhea, neutropenia, fever, and infection, all of which are recognized concomitants of the BM transplant preparative regimen. Twelve patients experienced grade 1 or 2 mucositis and one patient had grade 3 mucositis. Twelve patients developed diarrhea usually grade 1 or 2, but one patient each experienced grade 3 and grade 4 toxicity. In the historic control group, the frequency was similar but the severity worse.

All patients developed neutropenic fever and required the institution of broad-spectrum parenteral antibacterial agents. Patients had a median of 8.5 days of fever defined as oral temperature greater than 38°C (range, 2 to 26 days), and combination parenteral antibacterial agents therapy was administered for a median of 14.5 days (range, 8 to 32 days). In addition, 12 of 16 patients received amphotericin B therapy administered in empiric fashion for persistent neutropenic fever despite the use of broad-spectrum antibacterial agents. The amphotericin B cumulative dose administered ranged from 150 to 930 mg (median, 480 mg), which was administered over a median 10-day period (range, 3 to 26 days).

Only one patient developed a bacteremia, due to *Staphylococcus epidemidis* central venous catheter exit site infection. This infection occurred the day of marrow reinfusion when the neutrophil count was 650/µL, and the infection resolved with the use of parenteral antibacterial agents. Another patient developed a mild, transient *Giardia*
*lamblia* gastrointestinal infection. One patient experienced pneumonia, which progressed despite vigorous supportive care. This patient subsequently was thought to have radiation pneumonitis, demonstrated at autopsy.

**Hematopoietic reconstitution.** Patients received a median of 2.5 \times 10^8 nucleated BM cells/kg (range, 1.1 to 2.8 \times 10^8 cells/kg), similar to the historic control group in which a median number of nucleated marrow cells reinfused was 2.0 \times 10^6 cells/kg (range, 1.0 to 8.0 \times 10^6 cells/kg). Ten patients were evaluated for circulating and BM hematopoietic stem cells, CFU-GM and BFU-E, before and after preparative chemo-radiation therapy, autologous BM re-infusion, and administration of GM-CSF therapy. Changes in hematopoietic stem cells were compared with the duration of neutropenia and with evidence of late BM regeneration. This group of 10 patients received a median of 2.0 \times 10^5 progenitors/kg (range, 4.4 to 20.9) and experienced a median of 14 (range, 9 to 30) days of less than 500 neutrophils/μL. Ten patients were evaluated for circulating and BM hematopoietic stem cells, CFU-GM and BFU-E, before and after preparative chemo-radiation therapy, autologous BM re-infusion, and administration of GM-CSF therapy. Changes in hematopoietic stem cells were compared with the duration of neutropenia and with evidence of late BM regeneration. This group of 10 patients received a median of 2.0 \times 10^5 progenitors/kg (range, 4.4 to 20.9) and experienced a median of 14 (range, 9 to 30) days of less than 500 neutrophils/μL. (Table 1). The median number of CFU-GM progenitors infused was 11.4 (range, 4.4 to 20.2) \times 10^3/kg and of BFU-E infused was 14.4 (range, 10.9 to 20.9) \times 10^3/kg.

All patients showed early regeneration of hematopoietic precursors in the BM between days 10 and 22 after transplantation (Table 2). During this early regeneration phase, the recovery of BM stem cells reached a median of 54% (range, 13% to 83%) of pretreatment BFU-E. However, two patients had less than 25% of pretreatment BFU-E concentrations and five patients had BFU-E of less than 25% pretreatment values. The two patients with the most severe late neutropenia had the lowest numbers of BFU-E in their BM. Between 60 and 90 days after transplant, three patients maintained moderate neutropenia in the range of 396 to 1,150 neutrophils/μL. However, these three patients may have benefitted from GM-CSF.

### Table 2. Hematopoietic Progenitor Cell Recovery After Marrow Transplant

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<th>Days to Early Hematopoiesis (days 0-30)</th>
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Numbers in parentheses refer to percentage of control pretreatment values in each patient. Abbreviations: PMN, neutrophil count; UPN, ECOG accession number; ND, not determined.
levels of CFU-GM and BFU-E in the BM, whereas those with the least recovery of neutrophil counts had the lowest levels of BFU-E in the BM and tended to have the lowest levels of BM CFU-GM as well.

There was a statistically significant correlation between the pretreatment BFU-E BM concentration and the "late" (ie, 60 days after transplant) CFU-GM (but not BFU-E) concentration in the marrow ($r^2 = .502, P < .05$, linear regression analysis). As might be expected, a correlation was noted between the number of days of rhGM-CSF therapy and days until recovery of neutrophils in excess of $500/\mu L$ ($r^2 = .472, P < .05$, linear regression analysis). However, no correlation was noted between the number of CFU-GM per kilogram or BFU-E per kilogram infused during autologous BM transplantation, or the pretreatment stem cell concentration in the blood or BM and recovery of hematopoiesis posttransplant. There also was no correlation between the length of GM-CSF treatment and either the early or late increase in stem cells present in the BM, nor was there a correlation between the time to reach an absolute neutrophil count of $500/\mu L$ and either the early or late regeneration of CFU-GM. These observations suggest that GM-CSF therapy is able to promote hematopoiesis as well as encourage early production of neutrophils even in patients who later show long-term deficiencies in hematopoiesis.

Most patients had a decrease in both peripheral blood neutrophil count and CFU-GM concentrations in the BM immediately after withdrawal of GM-CSF therapy. This decline was particularly severe in those patients with low treatment because the early phase of BM recovery in these three patients in terms of BM CFU-GM and blood neutrophil counts was similar to those who had good evidence of late hematopoietic recovery. Of note, these three patients had the lowest levels of BM BFU-E during the period on GM-CSF therapy (Table 2). Thus, those patients with the best late recovery in neutrophil counts had the highest levels of CFU-GM and BFU-E in the BM, whereas those with the least recovery of neutrophil counts had the lowest levels of BFU-E in the BM and tended to have the lowest levels of BM CFU-GM as well.
neutrophil counts 60 to 90 days after transplant. During GM-CSF treatment there were often circulating BFU-E and CFU-GM stem cells at levels that were 30% to 50% of those seen before treatment (Fig 1). However, most patients recovered less than 50% of the numbers of BFU-E or CFU-GM cells in the peripheral blood 60 to 90 days after transplant. In no instance was the GM-CSF withdrawal-related decrease in blood counts or the later evidence of inadequate BM reserve associated with evidence of infection.

**Antitumor effect.** Eight of the 16 patients undergoing marrow transplantation and rhGM-CSF therapy achieved complete remission, the duration ranging from 4 to 21+ (median, 12+) months. Five patients remain in continued complete remission. These data are similar to our previously published experiences using this regimen in the absence of rhGM-CSF therapy.4

**DISCUSSION**

Infusion of hematopoietic stem cells (eg, BM or peripheral stem cell transplantation) after high-dose chemotherapy and radiation therapy is an effective therapeutic modality for a variety of malignant and non-malignant conditions.12-17 Despite the use of intensive supportive care, the morbidity and mortality of transplantation still remain high. For example, one group reported that in 143 consecutive autologous marrow transplants, 83 bacteremias (in 72 patients) occurred.18 Hematopoietic growth factor infusions have been administered to a number of patients undergoing transplantation, and, in the course of these phase I and II trials, morbidity appears to be less in some patients.19-27 All trials used rG-CSF or rGM-CSF therapy, except one21 in which human urinary colony-stimulating factor was infused.

Our study involved a number of unique aspects compared with other published trials. First, our patients received involved-field radiation, which can cause additional significant damage to the micro-environment and retard engraftment. All patients except one received at the least mediastinal irradiation, paraaortic irradiation, or both. Second, we documented both the number of patients undergoing transplantation, and, in the course of these phase I and II trials, morbidity appears to be less in some patients.19-27 All trials used rG-CSF or rGM-CSF therapy, except one21 in which human urinary colony-stimulating factor was infused.

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As in other trials, no discernable effects could be observed on recovery of platelet count in our patients. However, Nemunaitis et al27 did observe that their study group became independent of platelet transfusions about 19 days (mean) after transplant, compared with 38 days in the historic control group. It is unclear why these effects on platelet recovery occurred.

This study shows that decreased levels of CFU-GM and BFU-E are present in the BM 60 to 90 days after marrow transplant and that circulating levels of BFU-E are markedly lower than the pretransplant values. GM-CSF infusions allow earlier recovery of neutrophil counts and generation of both circulating and BM-derived CFU-GM and BFU-E. Most importantly, GM-CSF appears to enable patients with profound hematopoietic defects to regenerate neutrophils even though these patients later have evidence of poor hematopoietic recovery. However, in no instance was this level of hematopoiesis life-threatening or associated with late morbidity. The duration of GM-CSF in this study did not seem to influence the course of later hematopoietic recovery. Furthermore, the recovery of CFU-GM was better than BFU-E both early and late after transplant.

It is possible, of course, that pharmacologic doses of rhGM-CSF administered during the BM regeneration period may have forced premature differentiation of progenitors, depleting this pool and causing a persistent deficit in both CFU-GM and BFU-E at 60 to 90 days after BM infusion. This postulate could explain why a number of patients had a profound reduction in the concentration of stem cells at times remote to the transplant. Detailed accounting of stem cell concentrations are not available from the historic controls and, thus, a direct comparison is not possible. While the issue of stem cell depletion by growth factors remains of theoretical concern, there is no direct clinical evidence to indicate that it is a therapeutic issue.

Our progenitor data are in contrast to those reported by Kurtzberg et al,9 who reported in preliminary fashion that continuous infusion rhGM-CSF resulted in increases in CFU-GM that were not sustained, and BFU-E levels were depressed throughout the transplant period. These investigators did not report peripheral blood progenitor data. These differing results could be explained by technical differences in performing the assays, as well as the fact that our study used total body irradiation, and we infused the rhGM-CSF 4 hours daily, but for a longer duration after the transplant.

GM-CSF has been shown to stimulate myeloid leukemic blast cell proliferation in vitro.31,32 No obvious stimulation of lymphoma was noted, although one patient (no. 48810) developed a secondary neoplasm (T-cell non-Hodgkin's lymphoma 3 months after transplant for a B-cell lymphoma). In a prospective randomized, placebo-Hodgkin's lymphoma 3 months after transplant for a B-cell lymphoma). In a prospective randomized, placebo-controlled trial of 60 patients, Vose et al33 did not observe that GM-CSF promoted lymphoma progression when administered after high-dose chemotherapy and autologous stem cell transplantation. The anticancer effectiveness of the involved-field radiotherapy, cyclophosphamide, and fraction-
ated total body irradiation regimen plus rhGM-CSF therapy in this trial was similar to our previously published report.\textsuperscript{8}

Discontinuing growth factor infusions in 13 of 16 of our patients was associated with a marked decrease (median 42\%) in granulocyte count. Nemunaitis et al\textsuperscript{7} similarly reported that discontinuing growth factor infusions was associated in four of eight patients with a mean decrease in neutrophil count of 35\% (range, 4\% to 63\%) within 24 to 72 hours after stopping GM-CSF therapy (range, 4\% to 63\%). Brandt et al\textsuperscript{26} (using GM-CSF) and Taylor et al\textsuperscript{24} (using G-CSF) noted the same effect. While our data indicate that rhGM-CSF infusions have little or no effect on marrow stem cells and early progenitors, our in vitro marrow progenitor assays suggest that the growth factors are forcing stem cells to produce mature elements at an enhanced rate, hence a drop in granulocyte count when the recombinant colony-stimulating factor is withdrawn. Similarly, Lord et al\textsuperscript{27} showed that another hematopoietic growth factor, rG-CSF, temporarily accelerated early marrow progenitor maturation into neutrophils from a time period of 5 days to 1 day. rhGM-CSF is able to stimulate early neutrophil recovery even in those patients who exhibit defects in later tests of in vitro hematopoiesis. Our data also support the results of Blazar et al,\textsuperscript{25} who examined GM-CSF therapy after reinfusion of autologous BM purged in vitro. They noted efficacy of GM-CSF only when at least $1.2 \times 10^4$ CFU-GM progenitors/kg were infused. Their patients who received infusions containing lower numbers did not appear to benefit from GM-CSF therapy. Our data showed a relatively uniform number of CFU-GM per kilogram infused (median, $11.4 \times 10^4$; range, $4.4 \times 20.2 \times 10^4$), in part due to the fact that ex vivo purging was not used and most patients experienced prompt marrow recovery.

Previous phase I and II trials reported that most patients developed mild to moderate, self-limited toxicities attributable to recombinant hematopoietic growth factors. We observed a similar toxicity profile, and most patients experienced mild to moderate side effects such as fever, myalgias, and diarrhea. Effects previously reported at low or intermediate dose such as bone pain\textsuperscript{19} or adverse effects noted at high doses, such as pleural or pericardial effusions, were not observed during this trial.\textsuperscript{24} On the other hand, we observed synovial effusions in two patients, a previously unreported toxicity.

Recently, two randomized, placebo-controlled trials prospectively evaluating the efficacy of rhGM-CSF in autologous BM transplantation were presented in preliminary fashion.\textsuperscript{25,27} Both trials showed reduction in transplant-related morbidity and earlier hospital discharge. Additional studies using recombinant hematopoietic growth factors after autologous BM transplantation are warranted to define the optimum dose and schedule of these therapeutic agents.

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Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for relapsed non-Hodgkin's lymphoma: blood and bone marrow progenitor growth studies. A phase II Eastern Cooperative Oncology Group Trial

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