Sequential Interleukin-3 and Granulocyte-Colony Stimulating Factor prior to and following High-Dose Etoposide and Cyclophosphamide: A Phase I/II Trial

Steven H. Bernstein, Joseph P. Fay, Neal P. Christiansen, Luis Pinerio, Deven Shah, Margaret Stephan, and Geoffrey P. Herzog

Departments of Hematological Oncology and Bone Marrow Transplantation, Roswell Park Cancer Institute, Buffalo, New York 14263 [S. H. B., N. P. C., D. S., M. S., G. P. H.], and Baylor University/Sammons Cancer Center, Dallas, Texas 75246

J. P. F., L. P.]

ABSTRACT

Administration of growth factors prior to chemotherapy (priming) may reduce myelosuppression and provide an alternative to the use of stem cell support for the delivery of dose-intensive therapy. It is possible, however, that such priming may worsen aplasia, either by recruitment of progenitors into cell cycle and thereby increasing their sensitivity to chemotherapy or by depleting stem cell pools. We performed a Phase I/II trial of sequential interleukin 3 (IL-3)/granulocyte colony-stimulating factor (G-CSF) prior to and following high-dose etoposide and cyclophosphamide to determine the safety and efficacy of priming.

IL-3 was given for 7 days, and then G-CSF was given until the WBC count reached a level of 100,000/μl or stopped rising. Chemotherapy was started 48 h after the last dose of G-CSF. Sequential administration of IL-3/G-CSF was repeated beginning 36 h after the last dose of chemotherapy. Twenty-five eligible patients with Hodgkin's disease, non-Hodgkin's lymphoma, or breast cancer were enrolled.

Priming was generally well tolerated. The median maximum WBC count and absolute neutrophil count achieved was 66,400 and 57,600/μl, respectively. Significant decreases in platelet counts were seen during priming with 15 patients having a ≥40% decrease from prepriming values. Hematopoietic recovery of study patients was compared to that of an unprimed historical control group (n = 38) treated with the same chemotherapy followed by G-CSF alone. Neutrophil recovery to 500 and 1000/μl and platelet recovery to ≥50,000/μl was significantly faster in the study group compared to that of historical controls (P = 0.03, 0.05, and 0.01, respectively).

Sequential IL-3/G-CSF given prior to and following high-dose etoposide and cyclophosphamide is safe and is a feasible strategy to compare in prospective randomized trials to patients treated with only postchemotherapy IL-3 and G-CSF and to patients treated with peripheral blood stem cell support.

INTRODUCTION

Stem cell transplantation is widely used to facilitate dose-intensive therapy. Allogeneic stem cell transplants are limited by availability of compatible donors, age constraints, and the toxicity associated with graft versus host disease. In the autologous setting, limitations are related to the inability to collect adequate numbers of stem cells (for example, in heavily pretreated patients or patients with a history of pelvic radiation) and tumor cell contamination. The use of hematopoietic growth factors may reduce the need for stem cell support after dose-intensive therapy. However, our preliminary experience suggests that both G-CSF and GM-CSF have little ability to accelerate hematopoietic recovery when given after extremely intensive regimens, such as high-dose etoposide and cyclophosphamide (1).

The use of cytokines prior to chemotherapy, growth factor “priming,” represents a novel approach to deliver dose-intensive therapy without stem cell support. Priming may reduce myelosuppression directly, delaying the onset of cytopenias by expanding the mature cellular compartment, and shortening the duration of cytopenia by expanding progenitor cell mass. In addition, previous publications have demonstrated that priming may render committed progenitors mitotically quiescent after cytokines are withdrawn, thereby making them less sensitive to the cytotoxic effects of chemotherapy (2, 3).

GM-CSF priming has been shown to accelerate hematopoietic recovery when used with standard dose chemotherapy regimens (3, 4). In contrast, we have recently shown that it has no significant effect on recovery after a dose-intensive regimen of etoposide and cyclophosphamide (5). This may have been due to the modest stimulation of hematopoiesis achieved with GM-CSF or to expansion of a progenitor population sensitive to chemotherapy or by depleting stem cell pools. We have recently shown that both G-CSF and GM-CSF have little ability to accelerate hematopoietic recovery when given after extremely intensive regimens, such as high-dose etoposide and cyclophosphamide (1).

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Requests for reprints should be addressed, at Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. Phone: (716) 845-7611; Fax: (716) 845-8446.

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3 The abbreviations used are: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage CSF; ANC, absolute neutrophil count; IL, interleukin; PBSC, peripheral blood stem cell.
priming both with a cytokine (IL-3) that stimulates an earlier progenitor population than GM-CSF and with a cytokine (G-CSF) that has the potential for greater neutrophil expansion than was seen with GM-CSF. In addition, because of preclinical and clinical data suggesting that sequential cytokine therapy may have more pronounced effects on hematological recovery than single cytokine therapy, this sequential IL-3 and G-CSF combination was also given after chemotherapy (6). Here, we report our findings regarding the safety, feasibility, and hematopoietic effects of sequential IL-3 and G-CSF prior to and following high-dose etoposide and cyclophosphamide treatment.

**PATIENTS AND METHODS**

**Patients.** Patients with relapsed or refractory Hodgkin’s disease, non-Hodgkin’s lymphoma or breast cancer were eligible for this study. Patients who received any myeloid growth factor within 2 weeks prior to study entry or any investigational or biological agent within 4 weeks prior to entry were excluded. Patients were required to have adequate bone marrow function (WBC count ≥3000/μl and platelets greater than 100,000/μl). No cytotoxic therapy or radiation therapy to more than 50% of marrow-bearing areas within 4 weeks prior to entry onto the study was allowed. Adequate hepatic function (bilirubin and aspartate aminotransferase less than 3 times the upper limit of normal except if disease related), renal function (BUN ≤50 mg/dl and creatinine <2.0 mg/dl), cardiac function (ejection fraction >45%), and pulmonary function (FEV1 >1 liter and DLCO >50% of predicted) were required. Written consent was obtained from all patients before entry onto this study. This study was conducted at Roswell Park Cancer Institute and Baylor University/Sammons Cancer Center with high-dose etoposide and cyclophosphamide followed by G-CSF alone (no growth factor priming). The criteria used for the selection of historical control patients were as follows: (a) received etoposide at a dose of either 3.6 or 4.2 g/m² and cyclophosphamide at a dose of 200 mg/kg; (b) received G-CSF (dose not mandated) beginning within 48 h postcyclophosphamide; and (c) a diagnosis of non-Hodgkin’s lymphoma, Hodgkin’s disease, or breast cancer. The patient characteristics are described in Table 1.

**Study Design.** IL-3 (supplied by Sandoz Corporation, East Hanover, NJ) was administered as a single daily s.c. injection (5 µg/kg/day) for 7 days (days 0–6). G-CSF (Neupogen; Amgen, Thousand Oaks, CA) was begun on day 7 and was given as a s.c. injection (5 µg/kg) twice daily. A complete blood count was obtained daily prior to growth factor administration. The peripheral WBC count was used as a surrogate marker to determine when the progenitor pool was maximally expanded. G-CSF was continued until the WBC count reached a plateau for 3 days or reached a level of 100,000/μl, beyond which continued priming was felt not to be safe due to the potential for toxicity associated with hyperleukocytosis. In addition, patients were admitted to the hospital if the WBC count rapidly rose above a level of 50,000/μl to observe for such toxicity. Forty-eight h after the last dose of G-CSF patients received high-dose etoposide and cyclophosphamide as described previously (7). Briefly, 3.6 or 4.2 g/m² etoposide was given as a continuous i.v. infusion for 52 or 60 h, respectively. After the etoposide was completed, cyclophosphamide (50 mg/kg/day) was given as an IV infusion over 2 h for 4 consecutive days. Thirty-six h after the last dose of cyclophosphamide, when the active metabolites of cyclophosphamide had cleared, IL-3 was restarted and given as a single daily s.c. injection (5 µg/kg/day) for 7 days. Twenty-four h after the last dose of IL-3, G-CSF was started at a dose of 5 µg/kg given twice daily until an ANC ≥1500/μl was reached for 2 consecutive days, after which it was discontinued.

**Table 1** Patient characteristics

<table>
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<tr>
<td>WBC countb</td>
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<tr>
<td>ANCb</td>
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<tr>
<td>Plateletsb</td>
<td>240.0 (133-438)</td>
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<tr>
<td>a Median (range).</td>
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<td>b ×10⁹ cells/liter (prior to G-CSF priming for the study group and prior to chemotherapy for the control group).</td>
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Statistical Analysis. Pretreatment characteristics of the study group were compared to those of the control group using the Mann-Whitney test for continuous variables and the Fisher's exact or $\chi^2$ test for discrete variables. Pre- and postpriming WBC count, ANC, and platelet count were compared using the Wilcoxon sign-rank test for paired samples. The distribution of the probability of hematological recovery was determined using the method of Kaplan-Meier. Comparisons of recovery distributions were done using the log rank test. Specifically, starting from the first day of etoposide administration, the number of days to an ANC $\geq 500$ and $1000/\mu l$; the number of days with an ANC $\leq 500/\mu l$; and the number of days to an untransfused platelet count $\geq 50,000/\mu l$ were compared between the two groups. Differences in number of febrile days and days of antibiotic utilization were compared between the two groups using the Mann-Whitney test. Comparisons of the time to last RBC transfusion was done using the log rank test. All inferences were made using a significance level of 0.05. Finally, correlations between maximum WBC count and ANC achieved during priming and hematological recovery were determined using Cox proportional hazards. The reported $P$ values were adjusted for multiple comparisons.

RESULTS

Study Groups. The clinical and laboratory characteristics of the study patients evaluable for hematological recovery and those of the historical control patients are shown in Table 1. Whereas the median age of the patients were similar, there was a higher proportion of female patients in the study group. The distribution of diseases treated were similar in both groups, as were the number of prior chemotherapeutic regimens. These prior regimens were standard induction and salvage chemotherapy regimens. No patient had a prior regimen of a dose intensity that required stem cell support. Of the 21 control patients having a diagnosis of non-Hodgkin's lymphoma or Hodgkin's disease, 5 had had prior radiation therapy (none of them to a pelvic field). Of the nine study patients with these diseases, only one had had prior radiation (to the mediastinum). The distribution of the etoposide dose received (3.6 g/m$^2$) was not different in the study and control groups. Of note, previous studies showed no difference in hematological recovery between patients receiving 3.6 g/m$^2$ compared to those receiving 4.2 g/m$^2$ of etoposide (7). Finally marrow function, as assessed by peripheral blood counts, was normal in both groups.

Growth Factor Priming. IL-3 priming had a minimal but significant effect on WBC count ($P = 0.001$); median relative increase of 1.41-fold ($0.86-2.4$) compared to pre-IL-3 levels. Similarly, IL-3 also had a minimal but significant effect on ANC ($P = 0.01$); a median relative increase of 1.0 ($0.41-1.81$). In contrast, G-CSF administered after completion of IL-3 (median, 8 days; range, 7-11 days) resulted in a significant leukocytosis as shown in Fig. 1A; the median maximum WBC count was 66,400/\mu l (range, 31,500-97,000/\mu l) compared to a median prepriming WBC count of 5,300/\mu l (range, 3,300-18,200/\mu l; $P < 0.0002$), representing a median relative increase of 13.2-fold (6.2-33.1). The median number of priming days needed to achieve the maximum WBC count was 13. There was a rapid drop in WBC count 48 h after G-CSF was discontinued; the median WBC count and ANC on day 1 of chemotherapy were 11,800/\mu l (3,500-24,400/\mu l) and 9,800/\mu l (2,200-20,300/\mu l), respectively (Fig. 1, A and B).

The effect of growth factor priming on platelet count is shown in Fig. 2. IL-3 had no significant effect on platelet count. The median platelet count after IL-3 priming was 251,000/\mu l (121,000-459,000/\mu l), compared to a median count of 244,000/\mu l (133,000-438,000/\mu l) prior to growth factor priming ($P = 1.0$), representing a median relative increase of 1.1-fold (0.5-1.4). In contrast, a significant decrease in platelet count was seen after G-CSF was administered ($P = 0.01$). The median platelet count on the last day of G-CSF priming was 154,000/\mu l (55,000-401,000/\mu l), representing a median relative change of 0.73-fold (0.22-1.8) compared to the prepriming

Fig. 1 A, the prepriming WBC count (PP WBC), the maximum WBC count achieved with priming (Max WBC), and the WBC count on the first day of chemotherapy (D1 WBC). Each box plot is composed of five horizontal lines representing (from top to bottom) the 10th, 25th, 50th, 75th, and 90th percentiles of the WBC count. B, the prepriming ANC (PP ANC), the maximum ANC achieved with priming (Max ANC), and the ANC on the first day of chemotherapy (D1 ANC). Each box plot is composed of five horizontal lines representing (from top to bottom) the 10th, 25th, 50th, 75th, and 90th percentiles of the ANC.
platelet count. Eight patients had a $\geq 40\%$ decrease in counts after G-CSF priming compared to pre-growth factor priming counts. Platelets continued to drop after G-CSF was discontinued. Forty-eight h after G-CSF was stopped, immediately prior to starting etoposide, the median platelet count was 115,000/μl (59,000–274,000/μl), representing a median relative change of 0.73-fold (0.54–1.1) compared to the platelet count on the last day of G-CSF priming ($P = 0.0008$) and a 0.44-fold (0.18–1.1) change compared to the pre-growth factor priming count ($P = 0.0008$). Prior to the start of chemotherapy, 15 patients had a $\geq 40\%$ decrease in platelet count compared to the pre-growth factor priming count. There were no obvious clinical features that were predictive for a cytokine-induced decrease in platelet count.

**Toxicity.** No patient had a delay in hematological recovery that required use of their back-up stem cells or had toxicity attributable to hyperleukocytosis. Five patients who were initially enrolled in the study withdrew: two patients due to constitutional symptoms (headaches, myalgias, and arthralgias) and fever believed to be directly related to IL-3; one patient had progressive disease, and the patient’s physician felt that chemotherapy needed to be initiated immediately; one patient developed pulmonary infiltrates thought unrelated to IL-3; and one patient developed heparin-induced thrombocytopenia and thrombosis. Adverse events believed to be probably or definitely related to IL-3 and G-CSF are presented in Table 2. The only grade III toxic events due to IL-3 were fever (three patients) and chills (one patient). Only one patient had a grade III toxicity due to G-CSF, which was an injection site reaction. No patient had a cytokine-related grade IV toxicity. The most common grade I/II toxicities related to IL-3 included fever (occurring in 60% of evaluable patients), chills (44%), headaches (44%), myalgias (36%), injection site reactions (32%), arthralgias (20%), neck stiffness (20%), flushing (16%), and conjunctivitis (16%). The most common grade I/II toxicities related to G-CSF included bone pain (25%), myalgias (20%), fever (15%), and arthralgias (10%).

**Hematological Recovery.** The primary end points of this study were number of days to an ANC $\geq 500/\mu l$, number of days with an ANC $\leq 500/\mu l$, number of days to an ANC $\geq 1000/\mu l$, and number of days to an untransfused platelet count $\geq 50,000/\mu l$. The first day of etoposide administration was designated day 1.

The Kaplan-Meier plots comparing the time to an ANC $\geq 500/\mu l$ and an ANC $\geq 1000/\mu l$ for the study and control patients are shown in Figs. 3 and 4, respectively. Neutrophil recovery to 500 and 1000/μl was significantly faster for the study patients compared to the control patients ($P = 0.03$ and 0.05, respectively). The major difference in recovery between these two groups appeared to be related to fewer study patients having late recovery than control patients. For example, whereas no patient in the study group had neutrophil recovery beyond day 30, 21% of the control patients did. Although it did not reach statistical significance, the number of days with an ANC $\leq 500/\mu l$ was less for the study group than for the control group ($P = 0.06$; Fig. 5). No significant differences in the onset of neutopenia was seen between the two groups ($P = 0.4$; data not shown).

The Kaplan-Meier plot comparing the time to an untransfused platelet count $\geq 50,000/\mu l$ for the study and control patients is shown in Fig. 6. Platelet recovery to 50,000/μl was significantly faster for the study patients compared to that of the control patients ($P = 0.01$). As with neutrophil recovery, the major difference in recovery between these two groups appeared to be related to fewer study patients having late recovery than control patients. Whereas no patient in the study group achieved a platelet count $\geq 50,000/\mu l$ beyond day 36, 17% of the control patients did.

Correlations between the hematopoietic response to priming and hematological recovery were examined using a Cox proportional hazard test. There was no correlation between either maximum WBC count or ANC achieved by growth factor priming and hematological recovery.
Additional End Points. Differences in the number of febrile days or days of antibiotic utilization were not statistically different among the two groups. In addition, the time to last RBC transfusion was not significantly different among the study and control groups (Table 3).

DISCUSSION

Previous studies have demonstrated enhanced hematological recovery when cytokines are given prior to chemotherapy (3, 4). Such growth factor priming may be of benefit by (a) delaying the onset of cytopenia by expanding the mature cellular compartment; (b) shortening the duration of cytopenia by expanding progenitor cell mass such that a larger progenitor population remains after chemotherapy on which posttherapy cytokines can act; and (c) inducing a state of quiescence when cytokines are withdrawn, thereby decreasing the sensitivity of progenitor populations to cell cycle-sensitive agents (2, 3). Earlier clinical studies exploring the use of growth factor priming have used GM-CSF given prior to chemotherapy regimens of only modest dose intensity (3, 4). The rationale for the use of GM-CSF was based on work examining progenitor cell cycle kinetics in patients receiving GM-CSF. Whereas GM-CSF increased the cycling of committed progenitor populations, within 48–96 h of its discontinuation, the fraction of cycling progenitors dropped to values lower than pretreatment levels (2, 3).

We have previously reported the results of a Phase I/II trial of GM-CSF priming prior to high-dose etoposide and cyclophosphamide treatment (5). Although GM-CSF priming was safe, it had no significant effect on hematological recovery. There are several possible explanations for this. First, GM-CSF...
priming resulted in an only modest neutrophil expansion such that no significant delay in the onset of neutropenia occurred. Second, GM-CSF may have expanded a progenitor population exquisitely sensitive to this chemotherapeutic regimen. Finally, it is possible that the colony-forming unit, granulocyte-macrophage compartment was not quiescent 48 h after completion of priming, prior to the initiation of chemotherapy, as has previously been described by others (2, 3). A logical next step was to use a combination of cytokines, expanding both an early progenitor population and the mature neutrophil compartment. Therefore, we initiated this Phase I/II trial examining the safety and hematological efficacy of sequential IL-3 and G-CSF priming.

The hematopoietic effects of sequential IL-3 and G-CSF seen during the priming phase were more striking than has previously been reported for G-CSF alone (8, 9). For example, in a Phase I trial of G-CSF given for 14 days at a dose of 10 μg/kg/day by a 30-min i.v. infusion, the mean maximum increase in neutrophil count was 5.2-fold (8). Similarly, Gabrilove et al. (9) reported a 3.9–5.7-fold increase in neutrophil count over baseline in their Phase I trial of patients receiving 10 μg/kg of G-CSF given over 30 min for 6 days. In contrast, the mean maximum increase in neutrophil count in this study was 14.1-fold. Although differences in schedule, routes of administration, and duration of G-CSF treatment may account for some of these differences, it is possible that the enhanced neutrophil response seen in the present study is due to the sequential administration of IL-3 and G-CSF. The theoretical benefit of such sequential use of cytokines is that initial exposure to IL-3 may expand the G-CSF responsive progenitor pool. Indeed, several clinical studies exploring the hematological benefit of sequential cytokine therapy have recently been reported (6, 10, 11).
whereas IL-3 had no significant effect on platelets, platelet counts decreased a median of 27% from prepriming values on the last day of exposure to G-CSF and a median of 56% 48 h later, on the first day of chemotherapy. In contrast, Lindemann et al. (8) reported a transient decrease in platelet counts of up to 30% in his Phase I study of G-CSF alone, followed by spontaneous recovery despite continuation of treatment. The reasons for the cytokine-induced decrease in platelets seen in this study are not clear. It is possible that the sequential use of IL-3 and G-CSF results in a “lineage steal” phenomenon such that progenitors are driven toward myeloid and away from megakaryocyte differentiation. Alternatively, IL-3 and G-CSF may either directly or indirectly, through the induction of secondary cytokines, activate the monocyte/macrophage system such that there is an increased consumption of platelets.

The concern that priming may prolong marrow aplasia after dose-intensive therapy is based primarily on work by Broxmeyer et al. (12), who examined progenitor cell cycle kinetics in sarcoma patients who received G-CSF. Like GM-CSF, G-CSF enhanced the fraction of cycling progenitors. In contrast to GM-CSF, however, this enhanced cycling was maintained for at least 2–4 days after discontinuation of G-CSF (12). Despite these data, no patient in our study had prolonged hematological recovery as a result of sequential IL-3 and G-CSF priming. We did not, however, measure changes in cell cycle kinetics in this study. In addition, we did not examine progenitor subsets after chemotherapy to determine whether such populations were protected as a result of growth factor priming.

The recovery of platelets to ≥50,000/μl was significantly faster in the study group compared to the historical control group. In addition, recovery of neutrophils to ≥500 and 1000/μl was significantly faster in the study group. Finally, the number of days with an ANC ≤500/μl was less for the study patients, although this did not reach statistical significance. In all cases, the major difference in recovery for the patients who received IL-3/G-CSF before and after chemotherapy appeared to be that the number of patients having late recovery was reduced, rather than there being a significant enhancement of early hematological recovery. Limitations on comparisons of clinical outcome to that of historical control patients do exist. For example, although such variables as number of prior regimens and baseline blood counts were similar among the study and control groups, other variables that may affect marrow function, such as the type and dose intensity of prior treatment regimens, may differ. As such, differences in recovery between the two groups may in part be due to differences in clinical variables that were not controlled for in this study. Using these results, however, if hematological recovery is calculated in the same fashion as it is for stem cell transplants (designating day 1 as the first day after completion of chemotherapy rather than, as we did in this analysis, the first day of chemotherapy), the median day to an ANC of ≥500/μl (day 14) and to a platelet count of ≥50,000/μl (day 16) for the study patients is similar to the recovery times seen after PBSC transplants.

Because the patients used as historic controls received only postchemotherapy G-CSF, it cannot be determined from this study whether any recovery benefit seen for the study patients is due to priming or just to the sequential use of IL-3 and G-CSF after chemotherapy. In this regard, some studies have demonstrated a thrombopoietic effect of IL-3 when it is given after chemotherapy (13), although when it is given after myeloablative therapy and autologous marrow support it does not appear to accelerate platelet recovery compared to historical controls (14). Most IL-3 combination trials have been conducted using sequential IL-3 and GM-CSF and have had variable results. For example, sequential IL-3 and GM-CSF enhanced platelet recovery after 5-fluorouracil, leucovorin, doxorubicin, and cyclophosphamide for breast cancer when compared to those patients who received GM-CSF alone after this regimen (6). In contrast, Brugger et al. (10) found similar platelet recovery times for patients who received sequential IL-3 and GM-CSF after etoposide, ifosfamide, and cisplatin compared to those who received GM-CSF alone. A recently completed randomized Phase III trial, however, demonstrated no difference in platelet or neutrophil recovery for those patients undergoing autologous bone marrow transplantation for lymphoma that received sequential IL-3 and GM-CSF compared to those who received GM-CSF alone after transplant (11). Finally, studies of sequential IL-3 and G-CSF for PBSC mobilization suggest that such a regimen may have greater mobilizing effects than G-CSF or IL-3 alone (15–17).

In conclusion, use of sequential IL-3 and G-CSF priming is safe when used with a dose-intensive chemotherapy regimen, such as high-dose etoposide and cyclophosphamide. The true benefit of priming, however, can only be determined in prospective randomized studies. Such studies need to include a comparison of patients treated with sequential cytokine therapy before and after chemotherapy to those treated only posttherapy to determine the benefit of priming. In addition, if priming is to be used as an alternative to PBSC transplants, it must be compared to such patients. The end points of such studies should not only include an analysis of neutrophil and platelet recovery but of number of transfusions, febrile days, days of antibiotics, and hospitalization, end points that are clinically more relevant than recovery. In addition, differences in health care costs must be determined. Although priming does not encumber the costs of leukopheresis and stem cell processing as does PBSC transplants, it does use greater cytokine support. In addition, the use of IL-3 is associated with constitutional symptoms, which may necessitate additional medical interventions and encumber additional costs. Differences in patient quality of life also need to be compared. Finally, because a potential benefit of priming is that it would abrogate the need for stem cells and their inherent risk of being contaminated with tumor cells, differences in treatment outcome will also be of interest.

Table 3 Additional study endpointsa

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<tr>
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<td>6.0 (1–48)</td>
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<tr>
<td>Day of last RBC transfusion</td>
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<td>18.5 (12–60)</td>
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a Median (range).
b Febrile days are days with a temperature ≥38°C.
c NS, not significant (P > 0.5).
REFERENCES


Sequential interleukin-3 and granulocyte-colony stimulating factor prior to and following high-dose etoposide and cyclophosphamide: a phase I/II trial.

S H Bernstein, J P Fay, N P Christiansen, et al.