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Randomized Placebo-Controlled Trial of Granulocyte-Macrophage Colony-Stimulating-Factor Support for Dose-Intensive Cyclophosphamide, Etoposide, and Cisplatin

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This is a double-blind randomized placebo-controlled trial to evaluate the efficacy and safety of granulocyte-macrophage colony-stimulating-factor (GM-CSF) after dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP). Fifty-six patients with lymphoma or breast carcinoma were randomized to receive GM-CSF 250 μg/m² or placebo subcutaneously (SC) every 12 hr after each course of DICEP until recovery of absolute neutrophil count (ANC) of 1.5 × 10⁹/L. Each patient was to receive three courses of DICEP. There were 28 patients in each group. The median duration of ANC below 0.5 × 10⁹/L was 10 versus 12 days for Course 1 ($P = 0.010$), 10 versus 12 days for Course 2 ($P = 0.248$), and 16.5 versus 15 days for Course 3 ($P = 0.126$); platelet counts below 20 × 10⁹/L was 4 versus 4 days for Course 1 ($P = 0.586$), 8.5 versus 7 days for Course 2 ($P = 0.013$), and 23.5 versus 10.5 days for Course 3 ($P = 0.104$); hospitalization for patients readmitted with cytopenic fever were 4 versus 8 days for Course 1 ($P = 0.035$); 7 versus 6 days for Course 2 ($P = 0.692$); and 8 versus 12 days for Course 3 ($P = 0.884$) in the GM-CSF and placebo group, respectively. GM-CSF significantly shortens the duration of neutropenia and readmission only during the first course of DICEP. There was a delay in platelet recovery and an increase in transfusion requirement during subsequent courses in the GM-CSF group. The result cautions the routine use of lineage specific hematopoietic growth factors in supporting repeated cycles of dose-intensive chemotherapy.

Key words: breast cancer, GM-CSF, high-dose chemotherapy, lymphoma

INTRODUCTION

Dose-intensified combination chemotherapy supported by progenitor cell support has produced improved response rates in patients with refractory malignancies although the duration of remission is usually brief [1–3]. More recent trials using this approach in patients with relapsed lymphoma or metastatic breast carcinoma who had no prior chemotherapy or who were responding to induction chemotherapy has consistently produced a proportion of long-term disease-free survivors [4–6].

A nonmyeloablative regimen of dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) has been developed at doses similar to those in transplantation regimens [7–9]. Marrow reinfusion had not been shown to alter the morbidity or mortality after DICEP [9]. Repeated courses of DICEP can provide a means to achieve a higher dose rate and intensity. This approach has achieved similar response rates and survival outcomes as those by a single course of myeloablative regimens with progenitor

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support in patients with metastatic breast cancer or refractory non-Hodgkin's lymphoma [6,10,11].

Granulocyte-macrophage and granulocyte colony-stimulating factors (GM-CSF, G-CSF) can support dose intensification preventing prolonged neutropenia from chemotherapy [12–14]. GM-CSF has been shown to accelerate neutrophil recovery after autologous marrow transplantation, resulting in reduced hospital stays [15,16]. In the Phase I trial of GM-CSF to support DICEP, GM-CSF at 500 and 750 $\mu g/m^2$/day given as divided subcutaneous (SC) injections were the optimal regimens for shortening duration of hospitalization and decreasing readmission for cytopenic fever [17]. This Phase III study is designed to evaluate the efficacy and safety of GM-CSF at 500 $\mu g/m^2$/day SC in divided doses versus placebo for the support of repeated courses of DICEP.

PATIENTS AND METHODS

Patient Selection

Patients with histologically confirmed advanced breast carcinoma or non-Hodgkin's lymphoma were eligible for this double-blind randomized trial. Advanced breast carcinoma was defined as stage IV disease with no prior systemic chemotherapy except for adjuvant therapy or high-risk primary breast carcinoma (resected disease with more than nine ipsilateral lymph nodes involved, unresectable regional disease, or inflammatory carcinoma) with no prior systemic therapy. Advanced non-Hodgkin's lymphoma was defined as intermediate- or high-grade lymphoma (Working Formulation for non-Hodgkin's Lymphoma [18]) in first or second relapse or refractory to first or second induction chemotherapy. Patients were accrued from six centers: University of New Mexico Cancer Center, Albuquerque, New Mexico; Ontario Cancer Foundation, Ottawa, Ontario; Ohio State University, Columbus, Ohio; Baylor University, Dallas, Texas; Scott and White Clinic, Temple, Texas; and Shadyside Hospital, Pittsburgh, Pennsylvania. All patients had a performance status <2 (Zubrod scale), adequate hematologic function (hemoglobin > 100 g/L, absolute neutrophil count (ANC) > 1.5×10^9/L, platelet count > 100×10^9/L), serum creatinine level <140μmol/L (1.6 mg/dl), total bilirubin <26 μmol/L (1.5 mg/dl), pulmonary diffusion capacity >60% of predicted value, normal multigated cardiac scan, and no previous treatment with dose-intensive chemotherapy or any hematopoietic growth factors.

Pretreatment Evaluation

All patients has a complete history and physical examination, complete blood counts (CBC), reticulocyte counts, biochemistry, urinalysis, electrocardiogram (ECG), chest radiograph, pulmonary function tests including diffusion capacity, and multigated cardiac scan and dental assessment. Physical examination, appropriate radiographs, or computed tomographic (CT) scans were obtained for measurement of disease sites.

Treatment Plan

As approved by each Institutional Review Board, written informed consent acknowledging the investigational nature of this study was obtained from all patients. Patients were randomly assigned to receive yeast-derived GM-CSF (Sargramostim, Immunex Corp, Seattle, WA) or a visually identical placebo in a double-blinded fashion. All patients had a central venous catheter placed and were admitted to the hospital for chemotherapy. Chemotherapy consisted of intravenous cyclophosphamide 2,500 mg/m^2/day daily on days 1 and 2, etoposide 500 mg/m^2/day daily on days 1–3, and cisplatin 50 mg/m^2/day on days 1–3. One day after completion of the chemotherapy (day 4), patients were started on GM-CSF 250 $\mu g/m^2$ or placebo subcutaneously twice a day. These patients were continued on this treatment until recovery of the ANC to 1.5×10^9/L for 2 consecutive days or for a maximum of 49 days. DICEP was repeated every 35–49 days in responding patients if the patient had hematopoietic recovery (ANC > 1.5×10^9/L, platelet > 100×10^9/L) and/or resolution of residual non-hematological toxicity. A maximum of three cycles of chemotherapy were administered.

Supportive Care

Patients were discharged one day after completion of the chemotherapy provided that emesis was under control. The oral prophylactic antibiotic regimen consisted of ciprofloxacin 500 mg twice a day, fluconazole 200 mg on day 1, then 100 mg/day. Acetaminophen as a dose of 650 mg every 6 hr was given starting on day 4. Acyclovir at a dose of 200 mg five times a day was started on day 4 for patients with a history of herpes infection or patients with stomatitis during the prior course of DICEP. Packed red blood cells were given to maintain the hematocrit above 24% and platelet transfusions were given for platelet counts of $<10 \times 10^9$/L. All blood products were irradiated with 25 Gy. Patients with an ANC of $<0.3 \times 10^9$/L and a fever of >38.4°C (e.g., persisting at least 4 hr after transfusion) were admitted to hospital. Broad-spectrum antibiotics were started after appropriate cultures were obtained. In the absence of microbiological or clinical documentation of infection, therapeutic or prophylactic antimicrobial treatment and acetaminophen were continued until ANC $>0.3 \times 10^9$/L for 2 consecutive days. Patients who developed dyspnea associated with granulocyte recovery were given prednisone 100 mg/day PO for 3 days.

Evaluation and Statistical Methods

The primary endpoints of this study were the durations of ANC $<0.5 \times 10^9$/L, ANC $<1.0 \times 10^9$/L, white blood

TABLE 1. Patient Characteristics

	GM-CSF	Placebo
No. of patients		
Course 1	28	28
Course 2	24	19
Course 3	12	10
Female/Male	23/5	26/2
Mean age (range)	45 (22–60)	49 (31–64)
Disease		
Breast	23	23
Lymphoma	5	5

cell (WBC) count $<1.0 \times 10^9$/L, and platelet count $<20 \times 10^9$/L for the first cycle of therapy. These durations were compared between the GM-CSF and placebo-treated groups with Cochran-Mantel-Haenszel row means tests on ranks controlling for site. Durations for, and numbers of, hospital readmissions following febrile neutropenia were similarly compared for each course. Transfusion requirements were compared by *t*-tests. Time to death were calculated using Kaplan–Meier techniques. Subjects who were alive were censored on the last day for which information was available on their status, as long as that day was ≤365. If day of death or last available date was >365, subjects were censored (status=alive) on day 365. An interim analysis was done for this study at 50 patients at the $\alpha = 0.025$ level for the primary endpoint (duration of ANC $< 0.5 \times 10^9$/L for Course 1). The result was statistically significant leading to the closing of the study. In the final analysis, significant was defined as $P < 0.034$. The statistical power to confirm differences in durations of cytopenia for Courses 2 and 3 or for many of the secondary endpoints is low.

RESULTS

Fifty-six patients were entered in the study from six centers between January 1992 and July 1993. Twenty-eight were entered in each group. Patient characteristics were well matched, as shown in Table I. All patients received 97–100% of the intended dosages during each course of DICEP.

Four of the 28 patients in the GM-CSF group did not receive Course 2, two because of no tumor response, one because of delay in therapy (>49 days), and one due to a lack of response to platelet transfusions. Nine of the 28 patients in the placebo-treated group did not receive Course 2, two because of no tumor response, one due to the delay in Course 2 of >49 days, four because of toxicities (one patient died of sepsis, one patient died from gastrointestinal bleeding and renal failure, one patient developed subdural hematomas, and one patient had metabolic acidosis). Two patients were withdrawn at either their own or their physicians' request. Twelve of the 24 patients in the GM-CSF group did not receive Course 3, two because of disease progression, one because of delay in therapy unrelated to toxicity, six because of toxicities (four with delayed hematopoietic recovery, one with decreased pulmonary functions, and one with deterioration in cardiac ejection fraction), and three because of a decision by the physician or patient. Nine of the 19 patients in the placebo group did not receive Course 3, one because of delay in therapy unrelated to toxicity, four because of toxicities (two with delayed hematopoietic recovery and two with decreased pulmonary function tests), three because of decision by physician or patients, and one due to progression of disease. Overall, 12 of 28 (43%) patients completed all three cycles on the GM-CSF arm and 10 of 28 (36%) completed three cycles on the placebo arm. Seventy-seven percent of patients received at least two cycles.

TABLE II. Duration of Neutropenia and Thrombocytopenia

	GM-CSF	Placebo (median days:range)	*P*
Neutrophil $<0.5 \times 10^9$/L			
Course 1	10 (7–28)	12 (7–58)	0.010
Course 2	10 (6–29)	12 (10–27)	0.248
Course 3	16.5 (10–64)	15 (10–42)	0.126
Neutrophil $<1.0 \times 10^9$/L			
Course 1	10 (8–28)	13 (10–59)	0.004
Course 2	12 (7–40)	14 (10–28)	0.964
Course 3	20.5 (11–64)	29 (17–94)	0.522
Platelet $<20 \times 10^9$/L			
Course 1	4 (0–14)	4 (0–29)	0.586
Course 2	8.5 (2–44)	7 (1–25)	0.013
Course 3	23.5 (7–63)	10.5 (0–93)	0.104

Durations of cytopenia are shown in Table II. The median durations of neutropenia were significantly reduced in the GM-CSF group during Course 1. The median durations of thrombocytopenia (platelet count $<20 \times 10^9$/L) were the same during Course 1 but 1.5 day longer in the GM-CSF group for Course 2 ($P = 0.013$) and 13 days longer in Course 3 ($P = 0.104$).

The incidence and duration of readmissions and transfusion requirements are shown in Table III. There were no differences in the incidence of readmission for febrile neutropenia or the incidence of bacteremia between the groups for all courses. There were 33 episodes of positive blood cultures, 17 with streptococci, 11 with staphylococci, one with *Pseudomonas aeroginosa,* and four with mixed organisms. The median duration of the hospital stay following readmission for cytopenic fever was four days shorter during Course 1 ($P = 0.035$) and Course 3 ($P = 0.884$) in the GM-CSF groups. The median numbers of transfusion for both red blood cells and platelets were the same for the groups during Course 1. Over the next

TABLE III. Incidence or Duration of Fever, Bacteremia, Hospitalization, and Transfusion Requirements

	GM-CSF	Placebo	*P*
Incidence of febrile neutropenia			
Course 1	15/28	14/28	NS
Course 2	11/24	11/19	NS
Course 3	6/12	7/10	NS
Incidence of bacteremia			
Course 1	8/28	8/28	NS
Course 2	6/24	6/19	NS
Course 3	2/12	3/10	NS
Duration of readmission			
Course 1	4 (0–14)	8 (0–55)	0.035
Course 2	7 (0–14)	6 (0–18)	0.692
Course 3	8 (0–26)	12 (0–18)	0.884
Units of red blood cell transfusion			
Course 1	2 (0–6)	2 (0–22)	0.328
Course 2	4 (0–18)	2 (0–16)	0.013
Course 3	5 (2–15)	4 (2–13)	0.328
No. of platelet transfusion			
Course 1	2 (0–9)	2 (1–21)	0.413
Course 2	4 (2–24)	3 (0–6)	0.002
Course 3	6 (4–16)	4 (1–16)	0.154

TABLE IV. Nonhematological Adverse Events (Grade 3 or 4 Toxicities)

	GM-CSF	Placebo
No. of courses	64	57
Vomiting	5	4
Weakness	4	5
Nausea	4	4
Diarrhea	5	2
Dyspnea	5	2
Peripheral edema	2	4
Hypotension	1	4
Pain	1	3
Chills	4	0
Stomatitis	0	3

two courses, patients receiving GM-CSF required a total of three more units of both red cells and platelet transfusions than did patients in the placebo group.

In Course 1, 16 of 28 patients (57%) receiving GM-CSF had at least one grade 3 or 4 nonhematologic toxicity, compared to 20 of 28 patients (71%) receiving placebo. The overall rate of grade 3 or 4 nonhematologic toxicities for all cycles was 1.47 for GM-CSF (64 cycles) and 1.65 for placebo (57 cycles). The incidence of specific grade 3 or 4 nonhematologic toxicities occurring in more than three patients in either group is shown in Table IV. Three patients on each arm developed pleural effusions, and one on each arm developed pericardial effusions. The incidence of these toxicities was similar in both arms and not statistically significant. There were four treatment-related deaths (within 30 days of last dose of study drug).

TABLE V. Tumor Responses to DICEP

	GM-CSF	Placebo	Overall
Breast cancer	23	23	46
Evaluable	19	22	41
Complete response	6	4	10 (24%)
Partial response	7	9	16 (39%)
Stable or progression	6	9	15 (37%)
Non-Hodgkin's lymphoma	5	5	10
Complete response	1	3	4 (40%)
Partial response	4	0	4 (40%)
Stable or progression	0	2	2 (20%)

All were in the placebo group. Three patients died during Course 1. One died from sepsis and renal failure on day 10, one with gastrointestinal bleeding and renal failure on day 11, and one with pneumonia and hyponatremia on day 43. One died during Course 2 from sepsis on day 20. Tumor responses to DICEP is shown in Table V.

DISCUSSION

The escalated doses of chemotherapeutic agents can produce improved response rates in malignancies that are refractory to standard dose chemotherapy regimens [1–3]. These regimens are most often given with hematopoietic progenitor cells obtained from either the bone marrow or peripheral blood stem cells. However, bone marrow or stem cells from patients with malignancies have been shown to contain tumor cells even when they are histologically normal [19–21]. In patients with acute leukemia or non-Hodgkin's lymphoma, these occult tumor cells may predict for poor long-term survival after autologous bone marrow transplantation [22,23]. With gene-marking techniques, it has been shown that reinfused occult tumor cells contribute to the relapse in patient with leukemia or neuroblastoma after autologous bone marrow transplantation [24,25]. The significance of reinfusing occult tumor cells after high-dose chemotherapy in patients with breast cancer is unclear. The safety advantages of hematopoietic progenitor cell support may therefore be compromised by a lower efficacy due to the reinfusion of tumor cells. The doubling time for human solid tumors is in the range of 4–14 weeks [26]. A single tumor cell grows to a clinically detectable tumor (1×10^9 cells) in 20–90 months with these growth rates. Therefore, long follow-up and randomized studies will be needed to detect the clinical relevance of reinfusion of occult tumor cells.

DICEP can be administered for two to three courses without hematopoietic progenitor cell support to achieve greater dose rate intensity and total dose intensity [7,9]. Hepatotoxicity and interstitial pneumonitis are rare with this combination and do not limit the administration of repeated cycles. This is in contrast to regimens based on

certain myeloablative agents (e.g., nitrosourea, total body irradiation) that have a high incidence of these toxicities and generally cannot be repeated. It is difficult to compare the efficacy of DICEP to myeloablative regimens because of different patient selection. Preliminary historical comparisons, however, suggest that the efficacy in terms of both complete remission rates and survival benefit are similar with up to 5 years follow-up of patients [6,27]. The complete response of patients with metastatic breast cancer to myeloablative regimens with autologous bone marrow support has ranged from 0 to 59% [28]. The complete response rate of 24% and partial response of 39% (total response 73%) in this study appear to be similar to other studies using DICEP and other myeloablative regimens [7,9,28]. The overall response rate in patients with non-Hodgkin's lymphoma to repetitive courses of DICEP in this study was 80% with a complete remission rate of 40%. The number of patients with non-Hodgkin's lymphoma in this study is small. In a larger series of non-Hodgkin's lymphoma patients with primary refractory or refractory relapses patients treated with DICEP, 52% achieved a complete response and 26% partial response with a 3-year survival of 45% [11,27]. Patients with bone marrow involvement were included in the DICEP treatment, while whey were usually excluded from autologous bone marrow transplantation. The response rates of metastatic breast carcinoma and relapsed or refractory non-Hodgkin's lymphoma to DICEP compare favorably with those using myeloablative regimens with autologous hematopoietic progenitor cell support [4,27]. Randomized trials of DICEP versus myeloablative regimens with hematopoietic progenitor cell support in metastatic breast carcinoma and intermediate grade non-Hodgkin's lymphoma in sensitive relapse may be appropriate.

The hematological toxicities of DICEP are significant with all patients developing absolute neutropenia of less than 0.1×10^9/L for a minimum of 5–6 days and platelet counts below 10×10^9/L requiring platelet transfusion support. Approximately 25% of patients have documented sepsis and slightly over half require antibiotic therapy for cytopenic fever. GM-CSF and G-CSF had been employed to modify the hematopoietic toxicities of this regimen [17,29]. This randomized trial confirms the beneficial effect of GM-CSF on the duration of neutropenia and the length of hospitalization for cytopenic fever during Course 1. More subjects on GM-CSF went on to receive two courses of DICEP. Similar benefit were observed after high-dose chemotherapy with autologous hematopoietic progenitor cell and growth factor support in randomized trials [30,31]. The cumulative difference in days of hospitalization for treatment of cytopenic fever over three cycles was a median of seven. The difference in death rate between the GM-CSF and placebo arm (0% vs. 14%) is difficult to ignore. There was very little, if any, difference in either incidence or severity of non-hematologic toxicities between the two arms.

In this study, GM-CSF demonstrated no benefit over placebo in stimulating platelet recovery. In fact, recovery was slower during Course 2 and 3 in patients receiving GM-CSF. The 1-day longer duration of thrombocytopenia (platelet count $<20 \times 10^9$/L) during Course 2 in the GM-CSF arm, while statistically significant, is of limited clinical importance. The fourteen day prolongation of thrombocytopenia in the GM-CSF arm during Course 3, while not statistically significant, may be more clinically relevant. No patient had bleeding related to thrombocytopenia. Since platelet transfusions were given only for a platelet count below 10×10^9/L, the slower platelet recovery resulted in a difference of only three additional platelet transfusion for patients receiving GM-CSF. GM-CSF has not been shown to accelerate platelet recovery after autologous stem cell support [30,32]. We can only speculate as to the mechanisms for delayed platelet recovery during Course 2, and particularly Course 3 in patients receiving GM-CSF in this study. In a previous study using two courses of DICEP, the recovery of platelets was delayed in Course 2 [9]. Reinfusion of autologous bone marrow cells without hematopoietic growth factors did not alter this pattern of recovery. When a combination of bone marrow, peripheral blood stem cells, and GM-CSF was administered after a second cycle of DICEP, recovery of platelets was accelerated by 4 days [33]. There are no data regarding use of autologous hematopoietic progenitor cell support following a third cycle of DICEP. While recovery of endogenous progenitor cells if vigorous as measured in the peripheral blood samples after one and sometimes two cycles of DICEP, there is a cumulative depletion after repeated cycles and a concomitant slowing of recovery [34]. The number of remaining progenitors may not be adequate or not sufficiently responsive to GM-CSF to affect recovery. It is also possible that GM-CSF may differentiate uncommitted progenitors into committed myeloid precursors thereby "stealing" the progenitors and compromising the recovery of platelet counts. Infusion of a large number of progenitors may overcome the problem [33]. However, the enhancement of recovery may not worth the risk of possible tumor cell reinfusion. The other method may be the use of platelet lineage-specific or multilineage colony-stimulating factors that can stimulate the self-renewal and proliferation of multipotential cells before the introduction of lineage-specific colony-stimulating factors.

This randomized placebo controlled trial confirms that administration of GM-CSF significantly shortens the duration of neutropenia and hospitalization for cytopenic fever following the first course of DICEP therapy. Treatment-related mortality was decreased but the differences did not achieve statistical significance. In the GM-CSF group there was a delay in platelet recovery and in in-

crease in the transfusion requirement during the later courses. The primary endpoints of this study were the durations of ANC $<0.5 \times 10^9$/L, ANC $<1.0 \times 10^9$/L, white blood cell (WBC) count $<1.0 \times 10^9$/L, and platelet count $<20 \times 10^9$/L during the first course of therapy. The study was stopped with a small number of patients; therefore, other endpoints may not achieve statistical significance. While this dose-intensive regimen, as described, can be given with relative safety for three cycles, a different approach is needed to accelerate the platelet recovery if multiple courses are planned. The result cautions the routine use of lineage specific hematopoietic growth factors in supporting repeated cycles of dose-intensive chemotherapy.

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