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Role of granulocyte-macrophage colony stimulating factor (GM-CSF) after autologous bone marrow transplantation for Hodgkin's disease

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Use of growth factors to augment hematopoietic recovery after cytotoxic therapy is a useful method for dose intensification. We wanted to evaluate the clinical and cost-effectiveness of granulocyte-macrophage colony stimulating factor (GM-CSF; Leucomax™) in patients undergoing autologous bone marrow transplantation (ABMT) for Hodgkin's disease. Twenty-four patients with Hodgkin's disease were treated with high-dose chemotherapy and ABMT. Patients were then randomized in a double-blind manner to receive GM-CSF intravenously (10 μg/kg) over 6 h or placebo until the absolute neutrophil count (ANC) was greater than 1000/mm³ for 3 days. The study medication was stopped after 30 days. Patients treated with GM-CSF ($n = 12$) had shorter periods of neutropenia (median duration of an ANC of less than 1000 cells/mm³, 16 versus 27 days on placebo; $p = 0.23$), shorter periods of platelet-transfusion dependency (median duration, 13.5 versus 21 days on placebo; $p = 0.03$), shorter hospitalizations (median hospital stay, 32 versus 40.5 days on placebo; $p = 0.0004$). Other clinical outcomes, such as frequency and severity of toxicities, development of pneumonia or infection, in-hospital death, and response rate were similar in the two groups. Actuarial long-term disease free survival was 58% for patients treated with GM-CSF and 50% for patients who received placebo after 38 months of follow up ($p = 0.6$). The group treated with GM-CSF had lower total charges after infusion of autologous marrow than the placebo group (median in-hospital charges of $39 800 compared with $62 500; $p = 0.005$) because of lower post-infusion charges for room and supportive therapy. Administration of GM-CSF enhances myeloid and platelet recovery and is cost effective in the treatment of patients with relapsed Hodgkin's disease who received intensive chemotherapy and ABMT. Further work is needed in improving route and duration of GM-CSF infusion.

Key words: Autologous bone marrow transplantation, granulocyte-macrophage colony stimulating factor, high-dose chemotherapy, Hodgkin's disease, in-hospital charges, myeloid cell recovery, platelet recovery.

Leucomax™ is the trade name for Molgramostim.

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Introduction

High-dose chemotherapy followed by the re-infusion of bone marrow or peripheral blood stem cells has been shown to be an effective salvage therapy for patients with Hodgkin's disease, lymphoma and acute myeloblastic leukemia.[1–5] The major limits to high-dose treatments are the severity and duration of drug-induced myelosuppression during the peritransplant period.[2–5] Hematopoietic growth factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) have been included in recent trials of cytotoxic therapy in patients with relapsed lymphomas and solid tumors. These factors decrease the duration of neutropenia and associated morbidity, and increase the safety of intensive chemotherapeutic regimens.[6–9] In a recent study of patients with relapsed lymphoma and leukemia who received high-dose chemotherapy, patients who received GM-CSF had a reduced duration of severe neutropenia and shorter hospitalizations compared with patients who received placebo.[9] Because both clinical effectiveness and cost effectiveness are important in calculating new therapies, both were evaluated aspects during a randomized double-blind, placebo-controlled study of GM-CSF in patients with relapsed Hodgkin's disease.[2]

Materials and Methods

Twenty-four patients with relapsed Hodgkin's disease who received care at Memorial Sloan Kettering Cancer Center participated in a trial designed to evaluate the role of GM-CSF as an adjunct to autologous bone marrow transplantation (ABMT). Patients were eligible for the study if they

were between 15 and 65 years of age, and were eligible to undergo ABMT. All patients gave their informed consent to participate in the study and all patients had received previous chemotherapy or chemoradiotherapy as detailed. In brief, patients were treated with one of two similar schedules consisting of etoposide (VP-16), cyclophosphamide, and radiation therapy or carmustine. Patients who had no previous radiotherapy were given total nodal irradiation, 500 rad in three fractions daily for 4 days; VP-16, 750 mg/m^2 body surface area intravenously; and cyclophosphamide, 60 mg/kg body weight intravenously over 2 days. Patients who had previous radiotherapy were given carmustine, 250 mg/m^2 intravenously; VP-16 350 mg/m^2 intravenously per day for 3 days and cyclophosphamide, 150 mg/kg over 3 days intravenously was used. On day 0, all patients received re-infusion of unpurged autologous bone marrow cells. All care was given in either a bone marrow transplant unit or an intensive care unit.[2,3]

GM-CSF or placebo

Recombinant *Escherichia coli* derived GM-CSF (Leucomax, Schering-Plough Corporation, Kenilworth, NJ, and Sandoz Corporation, East Hanover, NJ) or placebo were provided as lyophilized powder and infused intravenously daily over 6 h at 10 μg of protein/kg body weight/day. The study drug was given within 24 h of re-infusion of autologous bone marrow cells and continued for 30 days or until 3 days after the absolute neutrophil count reached and remained at a level of at least 1000/mm^3 whichever came first. Clinical guidelines about the use of in-hospital resources were derived before initiating the study to ensure that decisions influencing important study end points were made consistently from patient to patient.

Measurement of resources and estimation of costs

Resource use was determined for each patient by reviewing medical records and hospital bills. The following eight broad categories of services were considered when assessing resource use: hospital accommodation; laboratory tests; radiology and diagnostic tests; antimicrobial therapy; physician consultations; blood products; respiratory, physical and occupational therapy; and surgical and invasive procedures as medically indicated. The procedure followed has been previously detailed.[2,10–12]

Data acquisition and analysis

Data acquisition began at the time of autologous bone marrow infusion and ended with the last day of hospitalization. Re-hospitalization within 96 h of discharge was considered to be part of the original hospitalization. Because the purpose of these analyses was to estimate differences in clinical utility and resource use between the GM-CSF and placebo groups, resources in the early part of the hospitalization before the re-infusion of bone marrow cells were not included in the analyses.

Results

Twenty-four patients with Hodgkin's disease were enroled in the clinical trial. The baseline characteristics and clinical outcomes of the 12 patients who received GM-CSF and the 12 patients who received placebo have been previously detailed.[2] The two groups were similar with respect to age, sex distribution, duration of disease and number of bone marrow cells transfused. However, more patients in the GM-CSF group had received previous radiation therapy (83% compared with 42%) and had also received previous chemotherapy with carmustine, melphalan, mitoxantrone or busulfan—agents that have the potential to damage stem cells (83% compared with 33%). Compared with the placebo group patients who received GM-CSF had a shorter duration on the study drug (median, 17.5 days compared with 27.5 days; $p = 0.003$) and a shorter period before the ANC returned to 1000 cells/mm^3 (median, 16 days compared with 27 days; $p = 0.02$).[2]

Actuarial disease-free survival was 58% for patients receiving GM-CSF and 50% for the placebo group after 38 months of follow up ($p = 0.6$; Figure 1). All 24 patients had neutropenic fevers and required systemic antibiotic therapy. The GM-CSF group and the placebo group had similar rates of laboratory-confirmed bacteria (17% compared with 8%), fungemia (8% compared with 0%), pulmonary infection (0% in both groups), and radiographic evidence of pneumonia without laboratory confirmation of any pathogen (42% compared with 50%). Herpes simplex infections occurred in 17% of the patients in both groups, whereas Herpes zoster infection was noted in only one patient (who

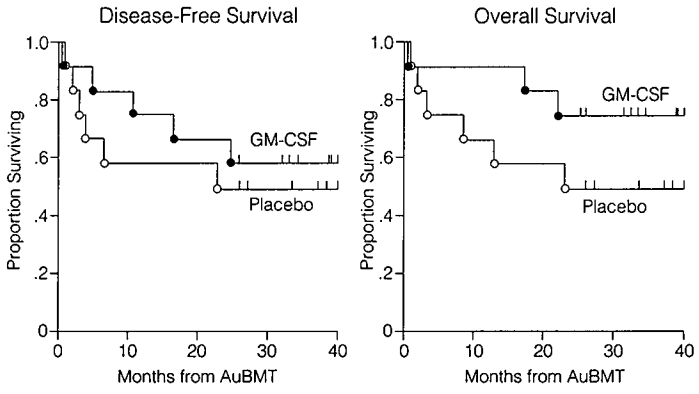

Figure 1. Survival of patients with resistant refractory Hodgkin's disease undergoing ABMT.

was receiving GM-CSF). A positive urine, stool or sputum culture was noted in 42% of the patients who received GM-CSF and in 83% of the placebo patients ($p = 0.10$).

GM-CSF was generally well tolerated; recipients showed few major toxicities. Generalized edema and erythema occurred in three patients: two patients discontinued the study drug and the other had a dose reduction of 50%. In both cases, the erythema and edema resolved rapidly after the alteration in drug dosing was made.

The two groups were compared regarding resource use.[13,14] The patients receiving GM-CSF were hospitalized for a shorter period of time relative with the placebo group (median, 32 days compared with 40.5 days; $p = 0.004$) which reflected a trend towards fewer platelet transfusions, fewer visits by physical therapist, fewer radiographs and fewer laboratory tests. The number of red blood cell transfusions, medical consultations and days of hyperalimentation were similar in the two groups.

Resource-based charge analyses for the two groups for the period after infusion of autologous marrow were then evaluated (Table 1). Using estimates based on individual resource use, the mean ($\pm$SD) and median total charges were \$43 600 $\pm$ 15 050 and \$39 800, respectively, for those receiving GM-CSF and \$61 900 $\pm$ \$17 550 and \$62 500, respectively, for those receiving placebo ($p = 0.01$). The difference in in-hospital charges reflected lower post-infusion charges for accommodations, physical therapy visits, laboratory test charges and antibiotics, and trends towards lower transfusion charges.

Table 1. Cost analysis of GM-CSF in bone marrow transplants

Resource	Imputed cost (\$)		Savings (\$)
	GM-CSF	Placebo	
Room costs	24100	34400	10300
Drugs[a]	6200	10500	4300
Laboratory studies	3100	4300	1200
Transfusions (RBC, platelets)	4100	6250	2150
Other	2300	7050	4750
Total resource costs	39800	62500	22799

[a] Does not include cost of GM-CSF.

Discussion

In our study, clinical analyses indicated that GM-CSF had a shorter duration of neutropenia, a shorter duration of platelet transfusion dependency and a shorter duration of hospitalization; used fewer resources; and had lower in-hospital charges relative to patients who received the placebo. A saving of 8 days of hospitalization, more than 1 week in platelet-transfusion dependency and \$22 700 (exclusive of costs for GM-CSF) was seen when median values for patients receiving GM-CSF were compared with those for placebo patients. Although these analyses from a phase III clinical trial did not include any estimate of the cost of GM-CSF, the magnitude of the differences in resource use suggest that savings would have been observed even if the drug cost as much as \$1200 per day for a 70 kg patient. Using current prices associated with yeast-derived recombinant

GM-CSF, therapy would have cost approximately $300/day and a saving of almost $16 00/ patient would have been noted.

Limitations of our study must also be considered.[15] Firstly, the data is only for patients with Hodgkin's disease treated at one established center. Care in university settings may differ from care in centers with less experienced personnel or in non-university centres. Secondly, the results observed in this trial with high-dose chemotherapeutic regimens do not provide any insight into the more common clinical setting in which lower doses of chemotherapy without hematopoietic support are given. We encourage future trials to address this important issue. The role of intermediate dose cytotoxic therapy with growth factors but without hematopoietic rescue also needs to be developed. Thirdly, the optimal schedule for GM-CSF therapy has not been determined. Clinical and economic benefits were noted in our study in which the drug was infused intravenously over 6 h and in a previous study in which the drug was infused over 2 h.[9] An optimum schedule for GM-CSF administration needs to be developed. Also GM-CSF may result in quicker return of ANC to arbitrary levels such as 1000 cells/mm^3, without improving patient outcome in terms of infectious complications. Availability and proper use of GM-CSF and other growth factors will improve the proper use of intensive cytotoxic therapy. Finally the small sample size in our study resulted in subgroups that differed in baseline characteristics relative to the previous use of stem cell damaging chemotherapeutic agents and previous history of radiation therapy. However, the resultant bias was in the direction of more unfavorable baseline characteristics in the group that received GM-CSF.[15]

In our phase III study, we found that treatment with GM-CSF was significantly better than placebo in terms of duration of neutropenia, duration of platelet transfusion dependency, costs of care, and resource use. These issues are especially relevant for patients with cancer who are undergoing intensive and costly therapy.

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