Phase III randomized study comparing 5 or 10 μg per kg per day of filgrastim for mobilization of peripheral blood progenitor cells with chemotherapy, followed by intensification and autologous transplantation in patients with nonmyeloid malignancies

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BACKGROUND: It is not known whether increasing the dose of filgrastim after mobilizing chemotherapy improves collection of peripheral blood progenitor cells (PBPC) and leads to faster hematopoietic engraftment after autologous transplantation.

STUDY DESIGN AND METHODS: A randomized, open-label, multicenter trial was carried out in patients with breast cancer, multiple myeloma, and lymphoma, in which patients were randomized to receive 5 or 10 μg per kg per day of filgrastim after standard chemotherapy to mobilize PBPCs. After high-dose chemotherapy, the components from the first two leukapheresis procedures were returned, and all patients received 5 μg per kg day of filgrastim after transplantation.

RESULTS: A total of 131 patients were randomized, of whom 128 were mobilized (Group A, 5 μg/kg, n = 66; Group B, 10 μg/kg, n = 62) and 112 were transplanted. Only six patients were not transplanted because of insufficient CD34+ cell numbers. The median number of CD34+ cells collected in the first two leukapheresis procedures tended to be higher in Group B than in Group A (12.0 vs. 7.2 × 10^6/kg, NS), but after transplantation there was no significant difference in median times to platelet (9 days in both groups) or neutrophil (8 days in both groups) engraftment or the number of platelet transfusions (three in both groups). A subsequent subgroup analysis separating patients transplanted after first- or second-line chemotherapy also showed no measurable impact of filgrastim dose on the median CD34+ cell yield or on platelet engraftment in either subgroup.

CONCLUSION: PBPC mobilization with chemotherapy and 5 μg per kg of filgrastim is very efficient, and 10 μg per kg of filgrastim does not provide additional clinical benefit.

There is experimental and clinical evidence that the total dose and/or dose intensity of chemotherapy may be important determinants of treatment outcome.[1-3] Dose intensification is, however, limited by hematologic toxicity, but transplantation of HPCs after high-dose chemotherapy (HDCT) allows timely recovery of hematopoiesis. The use of peripheral blood progenitor cells (PBPCs) instead of marrow is associated with faster engraftment,[4] but there is still a period of severe neutropenia and thrombocytopenia. Retrospective studies have demonstrated that there is a relationship between the dose of PBPCs infused and the speed of hematopoietic recovery after transplantation.[5,6] PBPCs may be mobilized using hematopoietic growth factors alone or a combination of chemotherapy and hematopoietic growth factors. While a clear dose-response relationship exists for PBPC mobilization with filgrastim

ABBREVIATIONS: FEC = 5-Fluorouracil-epirubicin-cyclophosphamide; HDCT = high-dose chemotherapy; PBPC = peripheral blood progenitor cell.

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alone,[7,8] it is not known whether a higher dose of filgrastim after mobilizing chemotherapy may improve the collection of PBPCs and lead to faster hematopoietic engraftment.

Therefore, we undertook a study to investigate whether an increase in the mobilizing dose of filgrastim from 5 to 10 μg per kg per day after chemotherapy could lead to a higher CD34+ cell yield and faster hematopoietic (and, in particular, platelet) recovery after HDCT and PBPC reinfusion.

MATERIALS AND METHODS

Patients

Patients were eligible for the study if they were aged 18 to 65 years; had a diagnosis of breast cancer, multiple myeloma, or lymphoma; and were planned to undergo HDCT with PBPC support for the following clinical indications. Breast cancer patients were either primary high risk (seven or more positive lymph nodes), inflammatory or metastatic (with or without previous adjuvant chemotherapy). Multiple myeloma patients were Stage II or III patients treated at diagnosis or at first relapse. Patients with Hodgkin's or intermediate- to high-grade non-Hodgkin's lymphoma were treated at first relapse. All patients gave written informed consent. The study was approved by the Ethics Committee of each participating center and conducted according to good clinical practice.

Treatment plan

The design of the study is summarized in Fig. 1. Before inclusion into the protocol, patients with measurable disease received tumor-specific chemotherapy to test their sensitivity to chemotherapy. Patients with inflammatory or metastatic breast cancer received a maximum of three cycles of chemotherapy not containing carboplatin, nitrosoureas, or mitomycin C. Patients with multiple myeloma, non-Hodgkin's lymphoma, or Hodgkin's disease received one line of chemotherapy (one to three cycles). Only patients with an objective tumor response were further screened for eligibility. This was not applicable to patients with primary high-risk breast cancer who received, after breast surgery, an optional cycle of FEC (500 mg/m^2 5-fluorouracil, 75 mg/m^2 epirubicin, 600 mg/m^2 cyclophosphamide) and were then screened for eligibility.

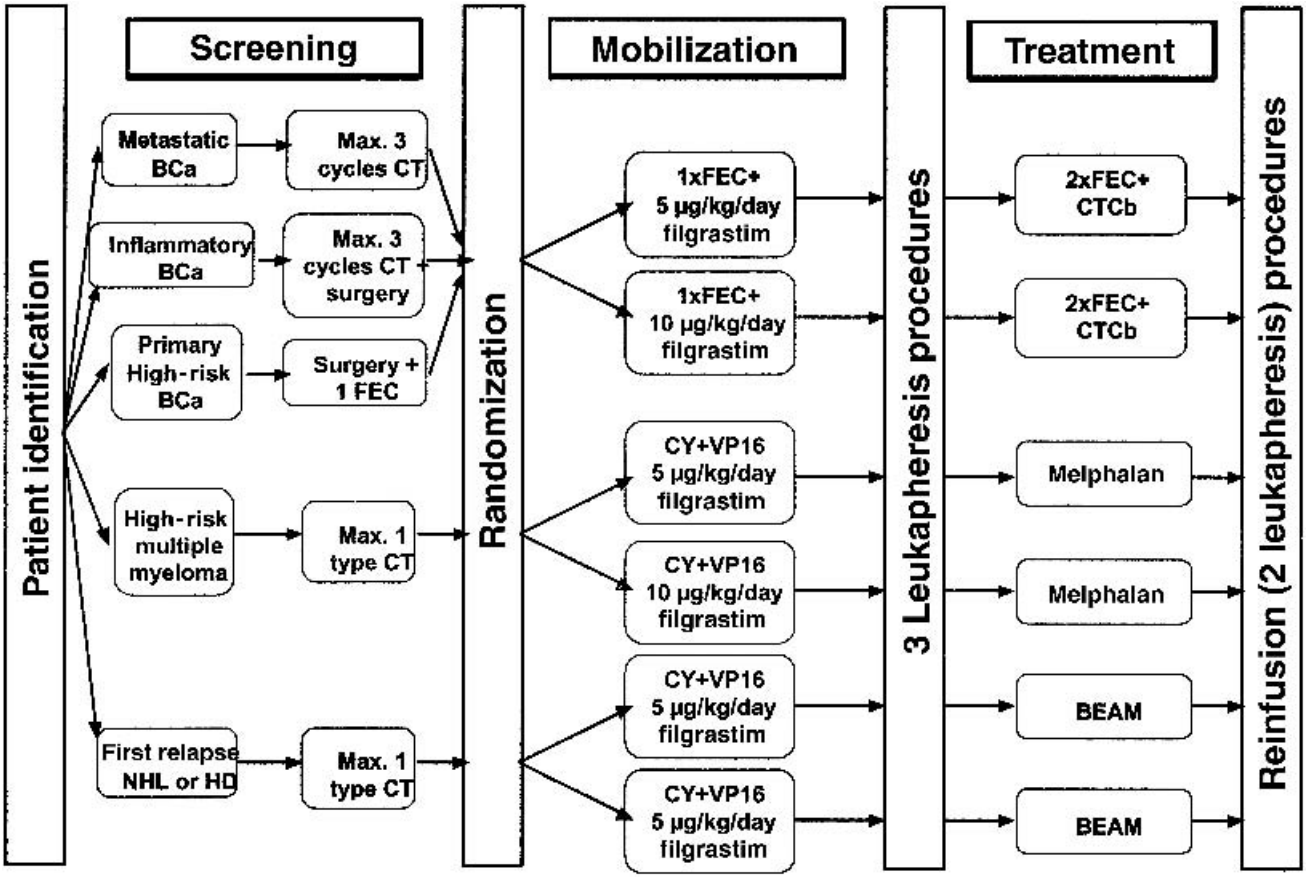

Fig. 1. Schematic representation of the study design. BCa = breast cancer; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; CT = chemotherapy; CY = cyclophosphamide; VP = etoposide; CTCb = cyclophosphamide, thiotepa, carboplatinum.

If eligible, patients were randomized between the two doses of filgrastim within 4 days of the mobilizing chemotherapy. Chemotherapy for PBPC mobilization consisted of an intensified FEC (500 mg/m^2 5-fluorouracil, 100 mg/m^2 epirubicin; 1200 mg/m^2 cyclophosphamide) for breast cancer patients or in a combination of 4500 mg per m^2 of cyclophosphamide and 450 mg per m^2 of etoposide for myeloma and lymphoma patients. Filgrastim (5 or 10 μg/kg/day) was given subcutaneously, starting on the third day after chemotherapy until the second day of leukapheresis. Exact dosing based on body weight was always performed. Leukapheresis procedures had to start within 24 hours of WBC recovery to 1.0 $\times$ 10^9 per L and peripheral CD34+ blood count was not evaluated. Three leukapheresis procedures were performed for each patient. If the yield of the first two leukapheresis procedure was lower than 0.5 $\times$ 10^6 CD34+ cells per kg, the patient was removed from the study.

Patients with myeloma or lymphoma received the HDCT regimen as soon as possible after mobilizing chemotherapy and PBPC collection. Patients with breast cancer first received two (adjuvant) or three (inflammatory or metastatic) additional cycles of standard FEC. The HDCT regimen for myeloma patients was 200 mg per m^2 of melphalan, for lymphoma patients BEAM (300 mg/m^2 of BCNU, 800 mg/m^2 of etoposide, 800 mg/m^2 of cytarabine, and 140 mg/m^2 of melphalan), and for breast cancer patients CTCb (6.0 g/m^2 of cyclophosphamide, 500 mg/m^2 of thiotepa, and 800 mg/m^2 of carboplatinum).[9] The HDCT regimen was supported by reinfusion of components from the two first leukapheresis procedures if the number of CD34+ cells was at least 0.5 $\times$ 10^6 per kg.

Supportive care

Platelet transfusions were given if the platelet count was less than 15 $\times$ 10^9 per L or in case of bleeding. RBC transfusions were given if the Hb level was less than 8 g per dL or if clinically required. Filgrastim (5 μg/kg/day) was administered from the day after the PBPC infusion until ANC recovery (>1 $\times$ 10^9/L for 3 consecutive days or >10 $\times$ 10^9/L for 1 day).

Statistical methods

The study was designed as an open, randomized, multicenter, parallel-group Phase III trial comparing two doses of filgrastim to mobilize PBPC in combination with chemotherapy. Patients were stratified by center and by disease group and allocated randomly to the two treatment groups in a 1-to-1 ratio within center and disease group. The primary endpoint of the study was the time to transfusion-independent platelet recovery to greater than or equal to 20 $\times$ 10^9 per L after PBPC reinfusion. To detect a difference of 3 days in time to platelet recovery with a significance level of 5 percent and a power of 80 percent, and assuming a dropout rate of 20 percent, a total of 65 patients were required in each arm. Secondary endpoints were times to greater than or equal to 50 $\times$ 10^9 per L platelets or to greater than or equal to 0.5 and 1.0 $\times$ 10^9 per L ANC, number of platelet transfusions and yield of CD34+ cells in the first two leukapheresis procedures. Times to greater than or equal to 100 or 150 $\times$ 10^9 per L platelets were not considered because they usually occur after discharge from the hospital and return of the patients to their referring physician. Safety endpoints included withdrawal due to adverse events and death.

All analyses were performed in an intent-to-treat manner (i.e., including all randomized patients). The "time to" endpoints were subject to Kaplan-Meier analysis with comparisons using the stratified log-rank test. The number of platelet transfusions was compared by calculating the Cochran-Mantel-Haenzel statistic and the difference between the two groups estimated by calculating the Hodges-Lehman estimator and its 95-percent CI.

Retrospectively, it was also decided to divide the patients in two groups according to their risk of being poor mobilizers and to compare their leukapheresis CD34+ cell yield and their time to platelet recovery to greater than or equal to 20 $\times$ 10^9 per L. Patients who had already received chemotherapy before their current treatment plan (the later including standard chemotherapy for debulking, mobilizing chemotherapy, and HDCT) were considered to be "poor risk," and those who had not were considered to be "good risk" mobilizers. The "poor risk" group included 33 patients (21 in Group A and 12 in Group B) with either metastatic breast cancer having received prior adjuvant chemotherapy, or with myeloma or lymphoma in first relapse, while the "good risk" group included 93 patients (44 in Group A and 49 in Group B) with either de novo multiple myeloma or with primary high-risk or inflammatory or metastatic breast cancer without prior adjuvant chemotherapy. Two patients could not be classified.

RESULTS

Patients

A total of 131 patients were randomized between January 1995 and December 1998, but three patients were removed from the study shortly after randomization: one patient withdrew informed consent, one patient moved to another hospital, and for one patient, the treating physician decided after randomization not to participate in the study. Among the remaining 128 patients, there were 86 patients with breast cancer (primary high risk, 48; inflammatory, 16; metastatic, 22), 24 with myeloma, 10 with non-Hodgkin's lymphoma, and 8 with Hodgkin's disease. All these patients underwent PBPC mobilization. Sixty-six patients received 5 μg per kg per day of filgrastim (Group

A) and 62 received 10 μg per kg per day (Group B). The main characteristics of the two groups were well balanced (Table 1). A total of 112 patients received HDCT and PBPC support. Sixteen patients did not receive HDCT due to a CD34+ cell yield lower than 0.5×10^6 per kg (n = 6), progressive disease (n = 4), toxicity after mobilization or debulking chemotherapy (n = 2), or investigator's decision (n = 4).

Leukapheresis cell yield

The CD34+ cell yield of the first two leukapheresis procedures tended to increase with the higher filgrastim dose, but this did not reach significance (Fig. 2). In the first two apheresis procedures, the median yield of CD34+ cells was 7.2×10^6 per kg (95% CI, 5.2-13.3; range, 0.1-106.3) in Group A versus 12.0×10^6per kg (95% CI, 6.8-19.2; range, 0.1-145.6) in Group B. The mean CD34+ cell yield was 14.2×10^6 per kg (95% CI, 9.5-18.8) in Group A versus 22.9×10^6 per kg (95% CI, 15.1-30.7) in Group B. In both groups, 93 percent of the patients achieved the minimal target of 0.5×10^6 per kg CD34+ cells in two apheresis procedures (Fig. 2). The proportions of patients achieving cell yields greater than or equal to 5×10^6 per kg CD34+ cells were 63 percent in Group A and 65 percent in Group B (NS). The median and mean values of the second and third leukapheresis procedures were very similar and neither of them were different between Groups A and B.

The CD34+ cell yield was 4.1×10^6 per kg (95% CI, 1.4-6.7) in the "poor risk" group versus 12.2×10^6 per kg (95% CI, 7.6-15.3) in the "good risk" group. The proportions of patients achieving less than 2×10^6 per kg CD34+ cells were 39 versus 10 percent in the "poor risk" and "good risk" groups, respectively (p = 0.0001). In neither group was there a significant difference in median CD34+ cell yield according to the dose of filgrastim (Fig. 2). In "poor risk" patients, the figures were 4.3×10^6 per kg (95% CI, 1.4-6.8) with 5 μg per kg versus 3.4×10^6 per kg (95% CI, 0.6-13.6) with 10 μg per kg. In the "good risk" group, the figures were 10.6×10^6 per kg (95% CI, 6.0-15.0) with 5 μg per kg versus 12.8×10^6 per kg (95% CI, 9.8-20.6) with 10 μg per kg of filgrastim.

TABLE 1. Characteristics of the 128 patients included in the study

	5 μg filgrastim	10 μg filgrastim	Total
Number of patients	66	62	128
Median age (years)	46	49	47
Median Eastern Cooperative Oncology Group	1	1	1
Gender			
Female	55	47	102
Male	11	15	26
Breast cancer	45	41	86
Primary high risk	25	23	48
Inflammatory	7	9	16
Metastatic	13	9	22
Non-Hodgkin's lymphoma	4	6	10
Hodgkin's disease	5	3	8
Multiple myeloma	12	12	24

Hematopoietic recovery after transplantation

There was no significant difference in the median time to transfusion-independent platelet recovery to greater than or equal to 20×10^9 per L between the two groups: 9 days (95% CI, 9-10) in Group A and 9 days (95% CI, 8-10) in Group B (Fig. 3). Analysis of the results within the various disease groups did not show any significant difference, but the number of patients within each group was rather small. Similarly, there was no significant difference in the median time to platelet recovery to greater than or equal to 50×10^9 per L: 13 days (95% CI, 12-15) in Group A versus 13 days (95% CI, 12-15) in Group B. In addition, neutrophil recovery was similar. The median time to ANC recovery to greater than or equal to 0.5×10^9 per L was 8 days (95% CI, 8-9) in Group A versus 8 days (95% CI, 8-9) in Group B (Fig. 4) and median time to ANC recovery to greater than or equal to 1.0×10^9 per L was 9 days in Group A (95% CI, 9-10) versus 8 days (95% CI, 8-9) in Group B. Finally, there was no significant difference in the median number of platelet transfusions (three in both groups).

There was no significant difference in platelet recovery between the two risk groups. In "poor risk" patients, the median time to transfusion-independent platelet recovery to greater than or equal to 20×10^9 per L was 10 days (95% CI, 9-11) with 5 μg per kg versus 10 days (95% CI, 8-17) with 10 μg per kg of filgrastim. In the "good risk" group, the figures were 9 days (95% CI, 9-10) with 5 μg per kg and 9 days (95% CI, 8-10) with 10 μg per kg of filgrastim.

Safety

There were no deaths during the study. Only one patient was withdrawn from the study after randomization due to adverse events (abnormal renal function). During the mobilization phase, three patients (4.5%) in Group A versus 10 patients (16.1%) in Group B (p = 0.03) had adverse events considered to be related or possibly related to filgrastim. The reasons were back pain in one case and bone pain in two cases in Group A, and headache in one, nausea in one, pruritus in one, back pain in two, and bone pain in five cases in Group B. Morphine-like analgesics were required in one patient in Group A and 6 in Group B (NCI Grade II). The proportion of patients with any serious adverse event (Grade II-IV NCI) during the mobilization phase was 10.6 percent in Group A versus 11.3 percent in Group B (NS), but none was considered to be related or possibly related to filgrastim. During the HDCT phase, five patients (8.8%) in Group A and seven

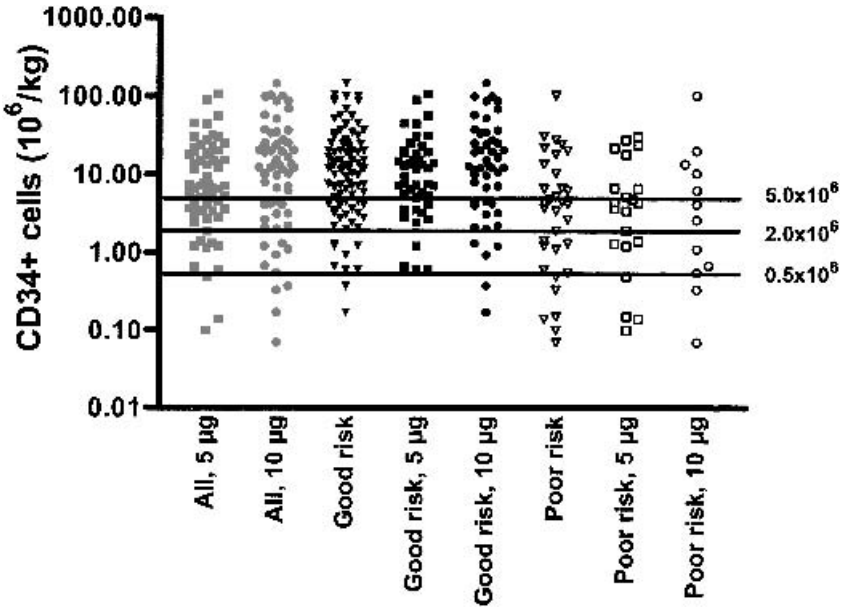

Fig. 2. PBPC collection yields in the two first leukapheresis procedures in all patients (triangles) and in patients receiving 5 (squares) or 10 (circles) μg per kg of filgrastim. "Good risk" (black labels), "poor risk" (white labels), and the two combined (gray labels) are shown separately. The three horizontal lines denote cut-points of 0.5, 2, and 5 × 10^6 CD34+ cells per kg.

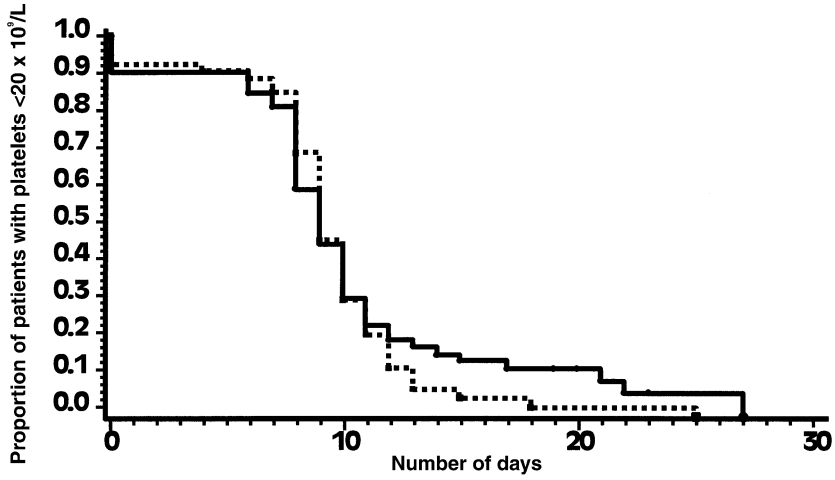

Fig. 3. Kaplan-Meier plot of time to sustained unsupported platelet recovery to greater than or equal to 20 × 10^9 per L after infusion of PBPCs mobilized with 5 (broken line) or 10 (continuous line) μg per kg of filgrastim.

patients (12.7%) in Group B (NS) had adverse events (NCI Grade I-II) considered to be related or possibly related to filgrastim. These events were hematoma at the injection site in one, vomiting in one, back pain in one, and bone pain in two cases in Group A, and pain at the injection site in one, bronchospasm in one, back pain in two, and bone pain in three cases in Group B. In the first 30 days post-transplant, 10 patients in Group A and 15 in Group B experienced documented infections. The proportion of patients with any nonhematologic serious adverse event (Grade II-IV NCI) during the HDCT phase was 4.5 percent in Group A versus 4.8 percent in Group B, but none was considered to be related or possibly related to filgrastim.

DISCUSSION

The introduction of growth factors into clinical practice has allowed HDCT with PBPC support in poor-risk patients with malignancies. The dose of CD34+ cells per kg infused is highly correlated with hematologic recovery.[10,11] In addition, optimized cell doses are associated with shorter hospital stay, lower platelet and RBC transfusion requirements, and reduced usage of antibiotic and antifungal therapy, resulting in clinical benefit for the patient as well as economic advantage.[12,13] It thus appears important to ensure adequate yields of CD34+ cells during apheresis. A dose-response effect has been demonstrated for G-CSF when used alone for PBPC mobilization.[6] However, most patients are mobilized with a combination of G-CSF and chemotherapy that might blunt the dose-response relationship. Although most centers use G-CSF at the dose of 5 μg per kg in this setting, some administer higher doses with the presumption that this would result in improved collections. However, no comparative trial has been published to date.

Our study is the first prospective randomized study comparing two doses of filgrastim for PBPC mobilization in combination with chemotherapy. Although there was a trend favoring the higher filgrastim dose in median and mean CD34+ cell yield in the first two apheresis procedures, the range of the results was very wide so that the 95-percent CIs were overlapping and the detected differences were not significant (Fig. 2). The proportions of patients achieving the minimal (0.5 × 10^6/kg) or optimal (5 × 10^6/kg) CD34+ cell yields were similar in the two groups. In addition, we were not able to detect a clinically significant difference of 3 days in the time to transfusion-independent platelet recovery to greater than or equal to 20 × 10^9 per L between patients receiving 5 or 10 μg per kg of filgrastim. Indeed, platelet and neutrophil

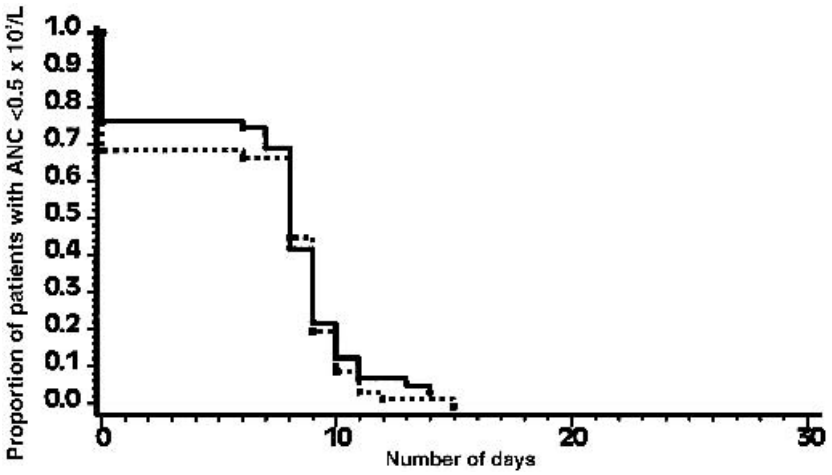

Fig. 4. Kaplan-Meier plot of time to sustained neutrophil recovery to greater than or equal to 0.5 × 10^9 per L after infusion of PBPCs mobilized with 5 (broken line) or 10 (continuous line) μg per kg of filgrastim.

recoveries after transplantation as well as the number of platelet transfusions were almost identical with the two doses of filgrastim.

A smaller randomized clinical trial has been presented only in abstract form.[14] In a patient population also including previously treated patients with myeloma or lymphoma but not breast cancer, no difference in the number of CD34+ cells collected, in the first apheresis or in total, could be demonstrated between mobilizing doses of 3.6 and 10.5 μg per kg of lenograstim. Although it cannot be ruled out that even higher doses could provide some advantage, this study confirms on a wider dose range that it is not useful to double the dose of G-CSF over the current standard of 5 μg per kg.

Our study included patients with three different diseases (myeloma, lymphoma, and breast cancer), some in first-line and others in second-line therapy. In addition, the mobilizing chemotherapy and the high-dose intensification regimens were disease-specific. One could argue that this heterogeneity could hamper our ability to detect a difference between the two groups. However, patients were stratified for disease group and the treatment plan was constant within each disease group. Indeed, disease and disease status were well balanced between the two dose groups. In addition, patients were stratified by center to avoid imbalances in the techniques of collection, freezing, and thawing, as well as in cell counting. The study was designed to be able to detect a difference of 3 days in time to platelet recovery to greater than or equal to 20,000 per μL with a significance level of 5 percent and a power of 80 percent. Given the almost identical median values and CIs for this and other parameters of engraftment, it is very unlikely that larger numbers of patients would result in a meaningful difference of 3 days between the two groups. One could argue that higher targets such as time to platelets greater than or equal to 100,000 or ANC greater than or equal to 2000 might show differences. However, this is very unlikely because times to various ANC or platelet levels are usually correlated with each other. In addition, this would require daily follow-up in the outpatient setting, a highly impractical endeavor when patients have returned to their referring physician. Furthermore, such high targets represent only cosmetic figures with little clinical impact, whereas lower targets determine such critical medical endpoints as duration of hospitalization, antibiotic use, and number of transfusions, not to mention costs of medical treatment.[12,13]

The protocol started in 1995, and it is was decided to start leukapheresis procedures when the WBC count was greater than or equal to 1000 per μL, but it is now recognized that WBC counts higher than 2000 per μL or CD34+ cell counts higher that 20 per μL are better triggers.[15] However, in our study, the yields of the second or third leukapheresis procedures that were carried out at more current peripheral WBC and CD34 cutoff values were quite similar and did not differ between the two treatment arms. On the other hand, the minimal cell dose for transplantation was only 0.5 × 10^6 per kg, which is now generally considered inadequate, whereas doses greater than 5.0 × 10^6 per kg have been associated with rapid platelet recovery. However, the proportion of patients achieving our minimal dose as well as the more optimal dose of 5.0 × 10^6 per kg were identical in the two treatment arms. Therefore, in our opinion the conclusions of our study should apply to current practice as well.

It could be argued that the benefit of higher doses would be less blunted in patients with better marrow function (i.e., patients mobilized during first-line therapy as opposed to more heavily pretreated patients). Alternatively, one could hypothesize that higher doses of G-CSF would rather show their potential in patients with poor marrow function. Hence, we carried out a subgroup analysis, which confirmed that previous chemotherapy negatively influences the efficiency of CD34+ cell collection. This is now widely recognized,[12,16] but it was not that evident when the protocol was developed in 1995 and, therefore, patients were not additionally stratified according to their risk status. The "poor risk" group had indeed significantly lower CD34+ cell yields and a smaller proportion of patients achieving an optimal cell dose. However, neither in the "good risk" nor in the "poor risk" groups were there any significant differences in CD34+ cell yield or platelet engraftment between pa-

tients who were mobilized with 5 or 10 μg per kg of filgrastim.

Whereas mobilization with chemotherapy and 5 μg per kg of filgrastim will enable collection of more than 2 × 10^6 per kg CD34+ cells in two leukapheresis procedures in over 90 percent of the patients during first-line chemotherapy, in nearly 40 percent of patients in second-line chemotherapy, this collection threshold is not reached. Although in most of these patients additional apheresis precedures may allow collection of sufficient CD34+ cells, some patients may need more-efficient mobilizing regimens. This may involve the use of more-effective chemotherapy regimens (e.g., higher doses of cyclophosphamide, the combination of cyclophosphamide and etoposide [as used in this study for patients with hematologic malignancies], or novel combinations of various agents).[12,16] This could also be achieved with other growth factors that may provide more potent tools to further increase or qualitatively modify mobilized progenitor cells.[12] These factors may include pegylated G-CSF[17] used alone or a combination of G-CSF with GM-CSF,[18] erythropoietin,[19] or SCF,[20,21] as well as newer growth factors such as thrombopoietin[22] or Flt-3 ligand.[12] In particular, SCF after mobilizing chemotherapy has been shown to increase CD34+ and progenitor cell yields and to offer a greater window of opportunity in which to perform the apheresis,[18] thus allowing a reduction in the number of apheresis procedures required for collecting an optimal harvest.[21] Alternatively, ex vivo expansion of mobilized PBPCs may be an interesting approach for the poor mobilizers.[23,24]

In conclusion, mobilization with chemotherapy plus 5 μg per kg of filgrastim is very efficient, particularly in patients mobilized during first-line chemotherapy. Mobilization with 10 μg per kg of filgrastim does not provide any additional clinical benefit in an unselected population of moderately treated patients with lymphoma, myeloma, or breast cancer. Other strategies should be pursued to improve outcome of PBPC collections and post-transplant engraftment in patients predicted to be poor mobilizers on the basis of heavy previous chemotherapy or other prognostic factors.

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