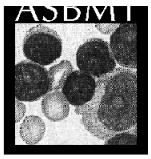

Matched-pair analysis of hematopoietic progenitor cell mobilization using G-CSF vs. cyclophosphamide, etoposide, and G-CSF: enhanced CD34$^+$ cell collections are not necessarily cost-effective

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ABSTRACT

Using matched-pair analysis, we compared two popular methods of stem cell mobilization in 24 advanced-stage breast cancer patients who underwent two consecutive mobilizing procedures as part of a tandem transplant protocol. For the first cycle, 10 μg/kg/day granulocyte colony-stimulating factor (G-CSF) was given and apheresis commenced on day 4 and continued for ≤5 days (median 3 days). One week after the first cycle of apheresis, 4000 mg/m^2 cyclophosphamide, 400 mg/m^2 etoposide, and 10 μg/kg G-CSF were administered for ≤16 days (cycle 2). Apheresis was initiated when the white blood cell (WBC) count exceeded 5000 cells/μL and continued for ≤5 days (median 3 days). Mean values of peripheral blood WBC (31,700 ± 3200 vs. 30,700 ± 3300/μL) were not significantly different between cycles 1 and 2. Mean number of mononuclear cells (MNC) collected per day was slightly greater with G-CSF mobilization than with the combination of chemotherapy and G-CSF (2.5 ± 0.21×10^8 vs. 1.8 ± 0.19×10^8 cells/kg). Mean daily CD34$^+$ cell yield, however, was nearly six times higher (12.9 ± 4.4 vs. 2.2 ± 0.5×10^6/kg; p = 0.01) with chemotherapy plus G-CSF. With G-CSF alone, 13% of aphereses reached the target dose of 5×10^6 CD34$^+$ cells/kg in one collection vs. 57% with chemotherapy plus G-CSF. Transfusions of red blood cells or platelets were necessary in 18 of 24 patients in cycle 2. Three patients were hospitalized with fever for a median of 3 days after cycle 2. No patients received transfusions or required hospitalization during mobilization with G-CSF alone. Resource utilization (cost of drugs, aphereses, cryopreservation, transfusions, hospitalization) was calculated comparing the median number of collections to obtain a target CD34$^+$ cell dose of 5×10^6 cells/kg: four using G-CSF vs. one using the combination in this data set. Resources for G-CSF mobilization cost $7326 vs. $8693 for the combination, even though more apheresis procedures were performed using G-CSF mobilization. The cost of chemotherapy administration, more doses of G-CSF, transfusions, and hospitalizations caused cyclophosphamide, etoposide, and G-CSF to be more expensive than G-CSF alone. A less toxic and less expensive treatment than cyclophosphamide, etoposide, and G-CSF is needed to be more cost-effective than G-CSF alone for peripheral blood progenitor cell mobilization.

KEY WORDS

Cost analysis • Hematopoietic stem cell mobilization • Resource utilization

INTRODUCTION

Peripheral blood progenitor cells (PBPC) have replaced bone marrow as the preferred source of stem cells because of more rapid engraftment and possible improvement in malignant contamination [1–3]. Current medical practice is to use hematopoietic growth factors either alone or in combination with chemotherapy to mobilize PBPC. The primary purpose of this study was to determine if the combination of chemotherapy plus colony-stimulating factors—in this case, cyclophosphamide, etoposide, and G-CSF—was better than

G-CSF alone to mobilize PBPC. A second purpose was to compare resource utilization associated with these two methods.

Our group has been evaluating models of consecutive or tandem stem cell harvests and transplants for a number of years [4–6]. We previously published a matched-pair analysis for a series of stage IV breast cancer patients who underwent two separate mobilizing treatments using combinations of chemotherapy and hematopoietic growth factors. In that study, we demonstrated that two consecutive courses of cyclophosphamide, etoposide, and G-CSF led to progenitor cell depletion following the second cycle of mobilizing treatment and that insufficient numbers of cells were collected to support a second transplant using only the cells collected from the second harvest [6]. In the current study, we again performed matched-pair analysis of consecutive breast cancer patients who were treated with two sequential mobilizing treatments. The first treatment used G-CSF alone beginning after full recovery from any prior chemotherapy, and the second used cyclophosphamide, etoposide, and G-CSF after return of the white blood cell (WBC) count to baseline after the first collection. Leukapheresis was performed beginning on the 4th day of G-CSF treatment and continued for up to 5 days during the first cycle. During the second cycle, leukapheresis commenced when WBC reached 5000/mm^3 and continued for up to 5 days. Each patient therefore served as a matched control for comparison of the two mobilizing methods. This study clearly shows the superiority of the combination of chemotherapy and G-CSF compared with G-CSF alone, with statistical validity comparable to a prospective randomized study. This superiority, however, did not translate into improved resource utilization during the mobilization procedure.

MATERIALS AND METHODS

Patient population

We studied 24 consecutive patients with stage III or IV breast cancer who were not eligible for intergroup breast cancer transplant protocols. Table 1 shows patient characteristics. All met criteria for stem cell transplantation based on hormone-insensitive disease; first chemotherapy treatment for stage III or metastatic disease; and normal heart, lung, and renal function. Patients were enrolled from three different treatment sites, and all patients gave written informed consent for the protocol approved by the Institutional Review Boards of Methodist, St. Vincent, and Community Hospitals in Indianapolis. Twenty of the 22 patients with stage IV disease had prior adjuvant chemotherapy for an initial stage II breast cancer and enrolled in this treatment at the time of first relapse. All but one patient received four to six cycles of standard chemotherapy for metastatic breast cancer before beginning the mobilizing treatment below. That one patient had locally recurrent disease that was treated using irradiation and was not treated with additional chemotherapy at the time of relapse.

Table 1. *Patient characteristics*

n	24
Age (years)	
Median	43
Range	33–58
Stage III disease	2
Stage IV disease	22
Prior chemotherapy	20
Known marrow involvement	0

Mobilizing tr eatment

Before stem cell mobilization was attempted, patients received several different chemotherapy regimens as induction therapy (patients with stage III disease) and to establish chemosensitivity (patients with stage IV disease). Each regimen was chosen by the referring oncologist. All patients then received two cycles of mobilizing treatment and leukapheresis after completing the initial phase of chemotherapy. Cycle 1 of mobilizing treatment used 10 μg/kg G-CSF administered subcutaneously once a day. G-CSF was started 21–31 days from the previous cycle of chemotherapy to ensure that any mobilizing effect of the prior chemotherapy was not a factor. Leukapheresis commenced on day 4 of treatment and continued for up to 5 days (median 3). Cycle 2 of mobilizing treatment was given as previously described using 4000 mg/m^2 cyclophosphamide over a 2-hour infusion on day 1, 200 mg/m^2 etoposide over a 2-hour infusion on days 1 and 2, and 10 μg/kg G-CSF subcutaneously once a day beginning on day 3 and continuing until the final day of leukapheresis [6]. This second cycle began no sooner than 7 days after the last day of leukapheresis of cycle 1. Supportive care consisted of mesna for uroprophylaxis and dexamethasone with intravenous ondansetron or granisetron for emesis prevention. Leukapheresis was carried out daily, starting when the peripheral blood count had risen to at least 5000 per mm^3, for up to 5 days. No routine monitoring of peripheral blood $CD34^+$ cells was done.

Leukapheresis

Leukapheresis and cryopreservation were performed daily as previously described [6] using the Cobe Spectra (Lakewood, CO). All patients had 2.5 to 3 blood volumes processed per day with flow rates between 60 and 120 mL/hour through central venous access (Quinton or Permcath dialysis catheter). The collection procedure during the first mobilization started on the 4th day of G-CSF. After the second mobilizing procedure, the collection began when the peripheral WBC exceeded 5000 cells/mm^3. Cryopreservation was performed using a Cryomed controlled rate freezer with 10% dimethylsulfoxide. Each product was stored in the liquid phase of N_2 until use.

Quantification of progenitor cells

A sample of each day's product was taken for the analyses described, and the rest was cryopreserved. The samples were routinely analyzed for leukocyte counts, white cell differential, colony-forming units-granulocyte-macrophage (CFU-GM), and $CD34^+$ cell assays. The total mononuclear cells (MNC) were determined by excluding neutrophils, bands, and eosinophils.

CFU-GM content was determined by plating total leukocytes at a concentration of 10^5–10^6/mL in methylcellulose and complete medium as previously described [6].

Colonies were enumerated on day 14 from duplicate plates; mean values were reported.

The $CD34^+$ cells were enumerated using a directly conjugated anti-CD34 antibody labeled with phycoerythrin (Becton Dickinson) and analyzed on a FACStar^{plus} flow cytometer (Becton Dickinson). Gating was performed either according to ISHAGE standards [7] or (prior to the 1997 publication of those standards) by previously described methods [6].

Resource utilization

Outpatient and inpatient resource utilization was determined based on the services performed and the complications of treatment. Mobilizing therapy was performed on an outpatient basis, so the total charges assessed for the outpatient services were collected and assigned the cost of the services as 50% of charges. Blood products were treated separately and assigned the costs of $300 per red cell unit transfused and $800 per platelet product transfused. Inpatient hospitalization for complications of treatment was assigned the cost of $1500 per day based on published data from MEDPAR [8]. Using these costs, it was possible to determine the resource utilization for each patient individually and for group as a whole.

Resource utilization by the 24 patients was separately modeled to determine a cost for the mobilization treatment. We developed three different models based on two different methods of determining costs and two different endpoints for apheresis. In models 1 and 3, we made cost calculations based on discount of current outpatient charges as above. Model 2 used costs as reported by Meisenberg et al. [9]. In models 1 and 2, the costs associated with obtaining 5×10^6 $CD34^+$ cells/kg using the mean daily $CD34^+$ cells collected for each patient were calculated with no limit to the number of aphereses. Model 3 limited the total number of aphereses to five procedures per cycle. In these models, we purposely omitted oral medications and routine laboratory tests such as complete blood counts since these costs were small and varied little between the two courses of mobilization. We also did not include an accounting of indirect costs, which were greater during the second cycle, which was administered over 13–16 days (the first cycle lasted 5–8 days). Model 2 calculations were made based on average wholesale price and the costs of apheresis as reported [9].

Statistical methods

Sample size was determined by analysis for dependent *t* testing using a power of 0.9, a standard deviation of 10, and a difference in means of three times or more for CD34 results. The paired *t* test was used to compare parameters between the first and second cycle of mobilization for data with a normal distribution. The two-tailed Mann-Whitney test was used to compare parameters when the data did not have normal distribution. There was no randomization regarding which mobilizing treatment was administered first, chemotherapy plus G-CSF or G-CSF alone, because our previous data showed that chemotherapy plus G-CSF can diminish the number of PBPC collected during a second cycle of the same treatment [6], and we wanted to avoid the likely possibility that the combination would negatively affect the collection using G-CSF alone.

RESULTS

Patients and treatments

Twenty-four patients, median age 45 (range 33–58), underwent two cycles of mobilizing therapy. All had a minimum of 2 days of collections with each cycle of treatment. The median number of days between the end of the first collection after cycle 1 and the start of cycle 2 chemotherapy was 9 (range 8–21). A median of 3 days of leukapheresis took place during cycle 1 (range 2–5) and 4 days during cycle 2 (range 2–5). Cycle 2 leukapheresis commenced a median of 13 days (range 9–15) after starting cyclophosphamide. Four of the 24 patients had a WBC count <5000 at the start of cycle 2 leukapheresis. The mean peripheral blood WBC during cycle 1 was $31{,}700 \pm 3200$ cells/μL, and during cycle 2, $30{,}700 \pm 3500$ cells/μL ($p = 0.4$). According to a predetermined goal, the second collection was completed when there were sufficient numbers of cells collected during both harvests to support two transplants. If patients mobilized poorly during cycle 1, they were more likely to undergo 5 days of leukapheresis during cycle 2 to ensure that sufficient PBPC were collected to perform two transplants. To ensure prompt engraftment, at least 5×10^6 $CD34^+$ cells were collected per transplant (10×10^6 total); six patients failed to meet this goal after both cycles of collections. Four of the six underwent procedures to collect additional progenitors: three had bone marrow harvests and one had an additional leukapheresis cycle using the combination of G-CSF and granulocyte-macrophage (GM)-CSF. All patients had prompt engraftment following subsequent tandem transplants, and there was no treatment-related mortality (data not shown).

When we began this study, we had anticipated performing two transplant procedures for all patients, the first using PBPC from the first mobilization with G-CSF alone and the second using stem cells derived from the combination. This strategy was anticipated to decrease the number of potential contaminating malignant cells in the final product infused during the second transplant. We knew from our prior studies using the identical combination of chemotherapy and growth factors that the average daily collection contained $>5\times10^6$ $CD34^+$ cells/kg [6]. We reasoned that if G-CSF alone resulted in a similar product, we would be able to collect sufficient stem cells for two transplants in a reasonably small number of collections, since another goal of this study was to perform as few apheresis procedures as possible. We therefore limited the total number of collections during the first cycle to five or fewer, assuming that, on average, the second collection cycle could meet the total collection goal after 2 days. Any patient who failed to have sufficient cells collected using G-CSF alone would thus have needed to meet the goal for both transplants by having the deficit collected during the second cycle. While the study was ongoing, it was clear that many patients were failing to reach the goal of 5×10^6 $CD34^+$ cells/kg during the first cycle of mobilizing treatment with G-CSF alone. Therefore, we abandoned the plan to infuse only those cells obtained during the first collection during the first transplant. Hence, it is not possible to compare the engraftment kinetics following the two different transplants.

Leukapheresis products

Table 2 shows the content of leukapheresis products obtained using the two mobilizing regimens. The number of

Table 2. *Compositions of collected leukapheresis products*

Mean daily value	Cycle 1	Cycle 2	*p* value
MNC $\times 10^8$/kg	2.5 ± 0.21	1.8 ± 0.19	0.0045
CFU-GM $\times 10^4$/kg	22.0 ± 4.4	48.5 ± 2.3	0.012
$CD34^+$ cells $\times 10^6$/kg	2.2 ± 0.50	12.9 ± 4.41	0.016

Table 3. *Resource utilization*

	Number of patients	
	Cycle 1	Cycle 2
Red cell transfusions	0	13 (34 units)
Platelet transfusions	0	10 (21 units)
Fever >101°	0	3
Hospitalization	0	3

MNC per kilogram of patient weight was greater following cycle 1, but the number of progenitor cells as measured by either CFU-GM or $CD34^+$ cells was significantly higher with cycle 2. The daily median number of $CD34^+$ cells/kg was 1.23×10^6 (range $0.2–7.66\times10^6$) for cycle 1 and 5.62×10^6 (range $0.48–88.8\times10^6$) for cycle 2. Four of the 24 patients had poorer PBPC yields during the second cycle than the first; all four had lower mean $CD34^+$ values than the group as a whole, and three of the four had lower median $CD34^+$ values, suggesting that these patients had intrinsic factors causing poor mobilization. Ten patients had a mean of $\leq1.0\times10^6$ $CD34^+$ cells/kg for the cycle 1 daily collection; six of the 10 had $CD34^+$ cell yields during cycle 2 in excess of 2.5×10^6 per day. Thus, even when fewer than average progenitors were collected during cycle 1, the combination of chemotherapy and G-CSF still was able to generate very good PBPC products in most patients. For the group as a whole, there was a 5.8-fold higher yield using the combination of chemotherapy and G-CSF compared with G-CSF alone.

Most transplant programs have adopted minimum acceptable criteria for PBPC collections, usually based on the total number of $CD34^+$ cells collected. Only seven of the patients (29%) obtained a target of 2×10^6 $CD34^+$ cells/kg with the first day of leukapheresis using G-CSF alone, while 16 (67%) achieved this level using the combination of chemotherapy and G-CSF. For a target of 5×10^6 $CD34^+$ cells/kg, the success rates of a single apheresis were 13 and 57%, respectively. Eight patients failed to meet the target dose of 5×10^6 $CD34^+$ cells/kg with the first cycle and three failed with the second.

Resour ce utilization

Resource utilization for both mobilization methods is recorded in Table 3. The initial mobilizing treatment using G-CSF was generally well tolerated and did not require any blood products, intravenous medications, or hospitalization. Specific use of oral analgesics or oral antibiotics was not separately evaluated during either mobilization cycle. The chemotherapy plus G-CSF mobilization cycle was associated with a frequent need for red cell or platelet transfusions. Eighteen of the 24 patients (75%) required red cells, platelets, or both. The indication for red cell transfusion was the presence of symptomatic anemia with a hemoglobin level <8. The indication for platelet transfusion was a value <20,000 on a day of apheresis or <10,000 if no apheresis was planned. Episodes of neutropenic fever occurred in three patients, all of whom were hospitalized and given intravenous antibiotics. No documented infections were identified. No patient failed to have leukapheresis performed after the second mobilization treatment.

Cost comparison

From the above data, we calculated the costs of mobilizing treatment during cycles 1 and 2. Since no patient needed blood products or hospitalization during cycle 1, the costs of the G-CSF administration, apheresis, and cryopreservation represented the expenditures during that cycle. The costs of cycle 2 included the chemotherapy administration, G-CSF administration, hospitalization for neutropenic fever, blood products, apheresis, and cryopreservation. To generate a mean value for cycle 2, the costs for blood products and hospitalization were totaled and divided by 24. From the data above, the average number of collections to reach the target goal of 5×10^6 $CD34^+$ cells/kg was four for cycle one and one for cycle two. The cost assigned to cycle 1 was $7326 and cycle 2, $8693.

We further explored this data set by evaluating three different cost models. Table 4 shows cost modeling to obtain a target goal of 5×10^6 $CD34^+$ cells/kg. The cost calculations were performed on each patient during both cycles of treatment and used the individual's mean daily $CD34^+$ cell number for that cycle to determine how many collections that patient would need to obtain the target goal. The median number of collections was four (range one to 25) for cycle 1 and two (range one to 10) for cycle 2. Method 1 in this table calculated costs as described above, which used 50% of outpatient charges as being typical for expenditures for this procedure. Model 2 followed the method and costs

Table 4. *Cost comparisons to achieve 5×10^6 $CD34^+$ cells/kg*

	Cycle 1	Cycle 2	*p* value
Method 1	$9504 ± 1613	$11,135 ± 982	0.20
Method 2	$14,079 ± 2403	$13,635 ± 1188	0.71
Method 3	$6864 ± 500	$10,475 ± 741	<0.01

Method 1: Charges for cyclophosphamide ($102.85/1000 mg), VP-16 ($273/100 mg), G-CSF ($573.80/480 µg), ondansetron ($384/32 mg), IV fluids ($28/liter), nursing administration ($150), leukapheresis ($1100), and cryopreservation ($1100), all multiplied by 50%. Costs of transfusions and hospitalizations as described in the text.

Method 2: Chemotherapy charges based on 1998 average wholesale prices. Nursing time, apheresis, cryopreservation as published [9].

Method 3: Costs assigned as in method 1 but no more than five aphereses performed during either cycle. Seven patients during cycle 1 and three during cycle 2 would have failed to meet the goal of $CD34^+$ cells during that collection. Median number of collections to meet the goal was four (range one to five) for cycle 1 and two (range one to five) for cycle 2.

in Meisenberg's analysis [9]. Since it is usually not feasible to ask patients to undergo more than about five apheresis procedures during any planned collection, we also determined the costs for each patient to obtain the goal of 5×10^6 $CD34^+$ cells/kg during a maximum of five collections (method 3). With this final method, seven patients would have failed to meet the goal using G-CSF mobilization and three would have failed to meet the goal during the combination. In these three models, the cost for cycle 1 ranged from $6864 to $14,079 and for cycle 2, $10,475 to $13,635. Only model 3 appeared to have a significant cost difference between cycle 1 and 2 (favoring cycle 1). There was no cost advantage to using the combination of cyclophosphamide, etoposide, and G-CSF in this group of patients in any of the models.

DISCUSSION

Our data show a nearly sixfold average increase in the number of $CD34^+$ PBPC that can be mobilized from treatment with 4000 mg/m^2 cyclophosphamide, 400 mg/m^2 etoposide, and 10 μg/kg/day G-CSF compared with G-CSF alone. The optimal method to mobilize and collect PBPC remains to be defined. This report is one of very few that have directly compared one method of mobilization with another and demonstrates improved $CD34^+$ cell mobilization using chemotherapy plus a cytokine vs. using a cytokine alone. Available data strongly support the conclusion that PBPC infusions containing $>5\times10^6$ $CD34^+$ cells/kg are associated with more rapid engraftment and less graft failure [13–17]. Table 5 summarizes recently published data for the quantity of $CD34^+$ cells collected per day using several different methods of PBPC mobilization. These publications were chosen because one method was compared with at least one other method, mostly using consecutive groups of patients rather than randomized groups. No definite conclusions can be drawn from this compilation of results, but important trends might guide current clinical practice. First, most methods appear adequate to reach a target goal of 5×10^6 $CD34^+$ cells/kg for patients who have not been heavily pretreated, but five collections may be required in some patients. Second, the highest numbers of $CD34^+$ cells are found using combinations of more than one cytokine or chemotherapy plus cytokines. How important chemotherapy is to eliminate potential contaminating tumor cells in the stem cell product cannot be answered by the referenced

Table 5. *Comparison of PBPC mobilization methods*

Patient population	Mobilization method* (number of patients)	Daily number $CD34^+$ cells ($\times10^6$/kg) †	% of patients who did not meet goal ‡	% of patients who met goal in one collection ‡	Reference
Breast cancer	Cytoxan 1.5 g/m^2 + GM-CSF 5 μg/kg × 5d + G-CSF 10 μg/kg (35)	4.5	0§	66§	[9]
	G-CSF 10 μg/kg (21)	1.8	10§	14§	
Myeloma	Cytoxan 4 g/m^2 + GM-CSF 8 μg/kg (18)	1.98	NA	NA	[10]
	G-CSF 10 mg/kg (22)	1.05	NA	NA	
Myeloma	Cytoxan 6g/m^2 + G-CSF 5 μg/kg (22)	4.8	18§	NA	[11]
	G-CSF 16 μg/kg (22)	1.2	24§	NA	
Breast cancer	Cytoxan 4 g/m^2 + VP-16 600 mg/m^2 + G-CSF 6 μg/kg (156)	11.1	6	70	[12]
	Cytoxan 2 g/m^2 + VP-16 600 mg/m^2 + G-CSF 6 μg/kg (162)	9.9	4	72	
Breast cancer	Cytoxan 4 g/m^2 + paclitaxel 170 mg/m^2 + G-CSF 10 μg/kg (58)	12.9	0	NA	[18]
	Cytoxan 4 g/m^2 + VP-16 600 mg/m^2 + G-CSF 10 μg/kg (13)	11.0	0	NA	
	Cytoxan 4 g/m^2 + G-CSF 16 μg/kg (10)	2.0	30	NA	
Breast cancer	G-CSF 10 μg/kg + SCF 250 μg/m^2 (59)	2.6	40	NA	[19]
	G-CSF 10 μg/kg (41)	1.1	67	NA	
Breast cancer (untreated)	G-CSF 10 μg/kg continuous SQ + SCF 10 μg/kg (11)	8.2	NA	NA	[20]
	G-CSF 12 μg/kg continuous SQ (18)	3.8	NA	NA	
Breast cancer	G-CSF 30 μg/kg (14)	2.4	29	29	[21]
	G-CSF 10 μg/kg (14)	0.6	86	0	
Breast cancer	Daniplestim 2.5 μg/kg + G-CSF 10 μg/kg (6)	3.6	50§	NA	[22]
	G-CSF 10 μg/kg (16)	2.1	83§	NA	
Breast cancer	Cytoxan 4 g/m^2 + VP-16 400 mg/m^2 + G-CSF 10 μg/kg (24)	12.9	13	57	Current study
	G-CSF 10 μg/kg (24)	2.2	33	13	

**G-CSF, GM-CSF, and SCF given daily subcutaneously until the completion of apheresis unless otherwise specified.*

†Median values.

‡Goal of 5×10^6 CD 34$^+$ cells/kg unless marked by §4×10^6 CD 34$^+$ cells/kg.

NA, not assessed in report.

studies. Third, it is possible to obtain the target goal of $>5\times10^6$ $CD34^+$ cells/kg in most breast cancer patients with just one leukapheresis procedure using the combination of chemotherapy and cytokines. Fourth, a small group of patients cannot be adequately mobilized with any of the methods listed; second-line strategies for these patients continue to be needed.

The data are surprisingly consistent from one group to another as to the quantity of $CD34^+$ cells mobilized using the daily single-dose administration of 10 μg/kg G-CSF alone (0.6–2.2 $CD34^+$ cells $\times10^6$/kg). For most patients receiving only 10 μg/kg/day G-CSF subcutaneously, two or more apheresis procedures will be necessary to reach the target goal as described. To improve on these results, it will be necessary to find better combinations of chemotherapy, better combinations of the currently available cytokines, better dosing schedules such as two or three administrations per day, or more effective agents to mobilize stem cells.

Cost considerations cannot be disregarded when comparing one method of PBPC mobilization with another. We had anticipated that the increased resources used during the administration of chemotherapy would be more than offset by the decreased use of resources during apheresis and cryopreservation. However, the increased number of transfusions and need for hospitalizations for neutropenic fever offset the potential cost savings for this strategy. The benefit of fewer numbers of apheresis during the combination of chemotherapy and G-CSF was at the cost of added toxicity and resource utilization.

Three recent studies reach different conclusions when comparing mobilization with cyclophosphamide and G-CSF (or GM-CSF) vs. G-CSF alone [9–11]. Both a nonrandomized study [10] and a randomized study [11] in multiple myeloma patients showed enhancement of the number of $CD34^+$ cells collected by the combination compared with the cytokine alone. Both also concluded that the increased toxicity with the combination was not offset by chemotherapy-induced enhancement of progenitors, since most patients were able to meet preestablished goals for harvesting using G-CSF alone. Neither study looked at costs specifically, but both evaluated certain categories of resource utilization. The two studies demonstrated that engraftment following transplantation was the same regardless of the method used to mobilize stem cells. Our data draw similar conclusions in a different patient population (advanced breast cancer) but offer more detailed cost analysis. In both of the myeloma studies, 100% of the patients required hospitalization during chemotherapy plus G-CSF mobilization, shifting the cost advantage considerably in favor of G-CSF alone. In our study, however, even when only 13% of patients were hospitalized for a total of 9 days, there still was no clear cost advantage for the treatment that produced higher numbers of circulating progenitor cells.

Meisenberg came to different conclusions in a cohort study of 56 stage II–IV breast cancer patients receiving 1500 mg/m^2 cyclophosphamide combined with 250 $\mu g/m^2$ GM-CSF on days 3–5 and 10 μg/kg G-CSF on days 6–11 compared with the same dose of G-CSF alone [9]. The number of patients who developed toxicity or required hospitalization during the cycle of chemotherapy and cytokines appeared to be significantly less than in our report. Only one patient required hospitalization, and no patient required red cell or platelet transfusions. The combination of cyclophosphamide and cytokines was cost-effective when compared with G-CSF alone in Meisenberg's study.

The most effective cyclophosphamide dose for stem cell mobilization was addressed by a recent study that compared 2000 and 4000 mg/m^2 cyclophosphamide in combination with 600 mg/m^2 etoposide and 6 μg/kg/day G-CSF [12]. The number of $CD34^+$ cells collected was the same for both doses, as was engraftment following transplant, but the frequency of complications including hospitalization, mucositis, nausea, vomiting, and red cell and platelet transfusions was greater at the higher dose. While our study differed from these two studies in the dose of either cyclophosphamide or etoposide, a clear conclusion is that a decreased dose of cyclophosphamide is associated with less toxicity.

Our results in a breast cancer population are similar to the results in two myeloma populations [10,11], in which doses of cyclophosphamide were at least 4000 mg/m^2. Our results differ from Meisenberg [9] who used a lower dose of cyclophosphamide (1500 mg/m^2) but had a slightly lower goal of harvested $CD34^+$ cells (4×10^6 cells/kg). Our data suggest that the cost of mobilization using combination chemotherapy and G-CSF in the dose of 10 μg/kg/d has a minimum expense of about $8500, including ~$7000 for the administration of the chemotherapy, antiemetics, G-CSF, and management of complications, plus a cost of ~$1500 per extra day of leukapheresis. Indirect costs and patient expenses are additional considerations. The complications that occurred during the combination treatment resulted in ~$2000 per patient when averaged over the entire patient group, a figure dramatically different from Meisenberg's data, which showed complications averaging $224. The minimum expense of administering just G-CSF and performing a single apheresis is about $2750, $1250 for the G-CSF administration and monitoring and $1500 for leukapheresis.

Potential opportunities to obtain cost savings from our methods include decreasing the dose of cyclophosphamide, eliminating VP-16 from the program, omitting the use of mesna as a urothelial protectant, and using less G-CSF by either giving a lower daily dose or starting it later. Data from Table 5 suggest that decreasing the dose of cyclophosphamide would provide similar numbers of $CD34^+$ cells as well as decrease associated toxicity. The elimination of etoposide would likely decrease the number of progenitors collected, resulting in an increase in the number of collections required to obtain the target goal. This may or may not be a cost-effective strategy. Decreasing the toxicity would allow the combination of chemotherapy and G-CSF to be more cost-effective than G-CSF alone.

As newer agents become available that enhance PBPC mobilization compared with G-CSF or GM-CSF alone, simple cost calculations can guide whether the expense of the new agent is balanced by the elimination of the expense of the apheresis procedure, which costs about $1500 per day. If the newer agent has a cost similar to G-CSF or GM-CSF and is used in combination with one of those drugs at similar doses, the expense of using the cytokine combination is

doubled compared with either G-CSF or GM-CSF alone. The above cost data would suggest that this improvement will be cost-effective only if it decreases the number of apheresis procedures by more than half. The initial reports using either stem cell factor or daniplestim [19,20,22] suggest that doubling the number of PBPC mobilized (and thereby halving the number of apheresis procedures) may not be accomplished with these agents, but further studies are needed.

In summary, the combination of cyclophosphamide, VP-16, and G-CSF enhances the number of PBPC mobilized by more than fivefold compared with G-CSF alone, but this enhancement was offset by increased toxicity, resulting in considerable costs for the combination.

REFERENCES

1 *To LB, Haylock DN, Simmons PJ, Juttner CA:* The biology and clinical use of blood stem cells. Blood 89:2333, 1997.

2 *Gillespie TW, Hillyer CD:* Peripheral blood progenitor cells for marrow reconstitution: mobilization and collection strategies. Transfusion 36:611, 1996.

3 *Ross AA:* Minimal residual disease in solid tumor malignancies: a review. J Hematother 7:9, 1998.

4 *Nichols CR, Tricot G, Williams SD, Van Besien K, Loehrer PJ, Roth BJ, Akard L, Hoffman R, Goulet R, Wolff SN, Giannone L, Greer J, Einhorn L, Jansen J:* Dose intensive chemotherapy in refractory germ cell cancer: a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol 7:932, 1989.

5 *Van Besien K, Nichols CR, Tricot G, Langefeld C, Miller ME, Akard LP, English DK, Graves VL, Cheerva A, McCarthy LJ, Jansen J:* Characteristics of engraftment after repeated autologous bone marrow transplantation. Exp Hematol 18:785, 1990.

6 *Akard LP, Wiemann M, Thompson JM, Swinney M, Lynn K, Hanks S, Jansen J:* Impaired stem cell collection by consecutive courses of high-dose mobilizing chemotherapy using cyclophosphamide, etoposide, and G-CSF. J Hematother 5:271, 1996.

7 *Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I:* The ISHAGE guidelines for $CD34^+$ cell determination by flow cytometry. J Hematother 5:213, 1996.

8 *Department of Health and Human Services Health Care Financing Administration:* Medicare Provider Analysis and Review (MEDPAR), 1996.

9 *Meisenberg B, Brehm T, Schmeckel A, Miller W, McMillan R:* A combination of low-dose cyclophosphamide and colony-stimulating factors is more cost effective than granulocyte-colony-stimulating factors alone in mobilizing peripheral blood stem and progenitor cells. Transfusion 38:209, 1998.

10 *Alegre A, Tomas JF, Martinez-Chamorro C, Gil-Fernandez JJ, Fernandez-Villalta MJ, Arranz R, Diaz MA, Granda A, Bernardo MR, Escudero A, Lopez-Lorenzo JL:* Comparison of peripheral blood progenitor cell mobilization in patients with multiple myeloma: high dose cyclophosphamide plus GM-CSF vs G-CSF alone. Bone Marrow Transplant 20:211, 1997.

11 *Desikan KR, Barlogie B, Jagannath S, Vesole DH, Siegel D, Fassas A, Munshi N, Singhal S, Mehta J, Tindle S, Nelson J, Bracy D, Mattox S, Tricot G:* Comparable engraftment kinetics following peripheral-blood stem-cell infusion mobilized with granulocyte colony stimulating factor with or without cyclophosphamide in multiple myeloma. J Clin Oncol 16:1547, 1998.

12 *Schwartzberg LS, Weaver CH, Birch R, Manner C, Tauer K, Beeker T, Morgan-Ihrig C, MacAneny B, Leff R, Smith R, Hainsworth J, Greco T, Schwerkoske J, Murphy MN, Buckner CD:* A randomized trial of two doses of cyclophosphamide with etoposide and G-CSF for mobilization of peripheral blood stem cells in 318 patients with stage II-III breast cancer. J Hematother 7:141, 1998.

13 *Van der Wall E, Richel DJ, Holtkamp MJ, Baars JW, Schornagel JH, Peterse JL, Beijnen JH, Rodenhuis S:* Bone marrow reconstitution after high-dose chemotherapy and autologous peripheral blood progenitor cell transplantation: effect of graft size. Ann Oncol 5:795, 1994.

14 *Weaver, CH, Hazelton B, Birch R, Palmer P, Allen C, Schwartzberg L, West W:* An analysis of engraftment kinetics as a function of the CD34 content of peripheral blood progenitor cell collections in 692 patients after the administration of myeloablative chemotherapy. Blood 86:3961, 1995.

15 *Dercksen MW, Rodenhuis S, Dirkson MK, Schaasberg WP, Baars JW, Van der Wall E, Slapper-Cortenbach IC, Pinedo HM, Von dem Borne AE, Van der Schoot CE:* Subsets of $CD34^+$ cells and rapid hematopoietic recovery after peripheral-blood stem-cell transplantation. J Clin Oncol 13:1922, 1995.

16 *Kiss JE, Rybka WB, Winkelstein A, deMagalhaes-Silverman M, Lister J, D'Andrea P, Ball ED:* Relationship of $CD34^+$ cell dose to early and late hematopoiesis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 19:303, 1997.

17 *Shpall EJ, Champlin R, Glaspy JA:* Effect of $CD34^+$ peripheral blood progenitor cell dose on hematopoietic recovery. Biol Blood Marrow Transplant 4:84, 1998.

18 *Demirer T, Buckner CD, Storer B, Lilleby K, Rowley S, Clift R, Appelbaum FR, Storb R, Bensinger WI:* Effect of different chemotherapy regimens on peripheral-blood stem-cell collections in patients with breast cancer receiving granulocyte colony-stimulating factor. J Clin Oncol 15:684, 1997.

19 *Glaspy JA, Shpall EJ, LeMaistre CF, Briddell RA, Menchaca DM, Turner SA, Lill M, Chap L, Jones R, Wiers MD, Sheridan WP, McNiece IK:* Peripheral blood progenitor cell mobilization using stem cell factor in combination with filgrastim in breast cancer patients. Blood 90:2939, 1997.

20 *Basser RL, To LB, Begley CG, Maher D, Juttner C, Ceborn J, Mansfield R, Olver I, Duggan G, Szer J, Collins J, Schwartz B, Marty J, Menchaca D, Sheridan WP, Fox RM, Green MD:* Rapid hematopoietic recovery after multicycle high-dose chemotherapy: enhancement of filgrastim-induced progenitor-cell mobilization by recombinant human stem-cell factor. J Clin Oncol 16:1899, 1998.

21 *Weaver CH, Birch R, Greco FA, Schwartzberg L, McAneny B, Moore M, Oviatt D, Redmond J, George C, Alberico T, Johnson P, Buckner CD:* Mobilization and harvesting of peripheral blood stem cells: randomized evaluations of different doses of filgrastim. Br J Haematol 100:338, 1998.

22 *DiPersio JF, Abboud CN, Schuster MW, Winter JN, Collins DM, Santos VR, Baum CM:* Phase II study of mobilization of PBSC by administration of daniplestim (SC-55494) and G-CSF in patients with breast cancer or lymphoma. Proc Annu Meet Am Soc Clin Oncol 16:A306, 1997.