Factors Affecting Mobilization of Peripheral Blood Progenitor Cells in Patients with Lymphoma

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ABSTRACT

The objective of this study was to identify factors associated with poor mobilization of peripheral blood progenitor cells (PBPCs) or delayed platelet engraftment after high-dose therapy and autologous stem cell transplantation in patients with lymphoma.

Fifty-eight patients with Hodgkin's disease or non-Hodgkin's lymphoma underwent PBPC transplantation as the "best available therapy" at Memorial Sloan-Kettering Cancer Center (New York, NY) between 1993 and 1995. PBPCs were mobilized with either granulocyte colony-stimulating factor (G-CSF) alone (n = 19) or G-CSF following combination chemotherapy (n = 39). Forty-eight of these patients underwent a PBPC transplant, receiving a conditioning regimen containing cyclophosphamide, etoposide, and either total body irradiation, total lymphoid irradiation, or carmustine.

A median number of 4.6 × 10^6 CD34+ cells/kg were obtained with a median of three leukapheresis procedures. Mobilization of PBPCs using chemotherapy plus G-CSF was superior to G-CSF alone (6.7 × 10^6 versus 1.5 × 10^6 CD34+ cells/kg; P = 0.0002). Poorer mobilization of progenitor cells was observed in patients who had previously received stem cell-toxic chemotherapy, including (a) nitrogen mustard, procarbazine, melphalan, carmustine or >7.5 g of cytarabine chemotherapy pre-mobilization (2.0 × 10^6 versus 6.0 × 10^6 CD34+ cells/kg; P = 0.005), or (b) ≥11 cycles of any previous chemotherapy (2.6 × 10^6 versus 6.7 × 10^6 CD34+ cells/kg; P = 0.02). Platelet recovery to >20,000/μl was delayed in patients who received <2.0 × 10^6 CD34+ cells (median, 13 versus 22 days; P = 0.06). Patients who received ≥11 cycles of chemotherapy prior to PBPC mobilization tended to have delayed platelet recovery to >20,000/μl and to require more platelet transfusions than less extensively pretreated patients (median, 13.5 versus 23.5 days; P = 0.15; median number of platelet transfusion episodes, 13 versus 9; P = 0.17).

These data suggest that current strategies to mobilize PBPCs may be suboptimal in patients who have received either stem cell-toxic chemotherapy or ≥11 cycles of chemotherapy prior to PBPC mobilization. Alternative approaches, such as ex vivo expansion or the use of other growth factors in addition to G-CSF, may improve mobilization of progenitor cells for PBPC transplantation.

INTRODUCTION

The use of high-dose chemoradiotherapy supported by cryopreserved autologous hematopoietic progenitor cells is effective in treating relapsed HD and NHL; a high complete response rate is seen and a significant fraction of patients appear to be cured by this approach (1, 2). The preferred source of progenitor cells has shifted from bone marrow to peripheral blood over the last several years, because of logistical and other advantages of collecting PBPCs. PBPCs provide more rapid hematopoietic recovery than bone marrow-derived progenitors, if the PBPCs are collected following a strategy to mobilize or increase the number of circulating progenitor cells (3). In contrast, the rapidity of hematopoietic recovery using unmobilized PBPCs is not significantly different from that using bone marrow cells (4). Since the initial demonstration that high-dose cyclophosphamide, with or without GM-CSF, can mobilize large numbers of progenitor cells into the peripheral blood (5, 6), various combinations of chemotherapy, with or without cytokines, have been used to obtain sufficient numbers of progenitor cells for autologous transplant. The use of CSFs following combination chemotherapy appropriate for the patient’s underlying disorder is currently the most common approach to stem cell mobilization.

Prior to the shift from bone marrow transplants to PBPC transplant for patients with lymphoma, some patients received both bone marrow progenitor cells and PBPCs because of concerns about the long-term engraftment potential of PBPCs. The amount or type of prior chemotherapy received has been reported to affect the mobilization of PBPCs as well as the long-term survival rate.

The abbreviations used are: HD, Hodgkin’s disease; PBPC, peripheral blood progenitor cell; PBPC transplant; CSF, colony-stimulating factor; GM-CSF, granulocyte-macrophage CSF; NHL, non-Hodgkin’s lymphoma; IGL, intermediate-grade NHL; MNC, mononuclear cell; TBI, total body irradiation; TLI, total lymphoid irradiation; ASCT, autologous stem cell transplantation.
Table 1  Distribution of patient characteristics

| All (%) | LGL<sup>a</sup> | IGL<sup>b</sup> | HD<sup>c</sup>
|---------|-----------------|-----------------|-------------
| Total   | 58              | 8               | 39          | 11          |
| No. that received SCTC<sup>c</sup> | 23 (40) | 4 | 10 | 9 |
| No. that received previous XRT | 16 (28) | 0 | 8 | 8 |
| Male    | 35 (60)         | 16              | 26          | 6           |
| Female  | 23 (40)         | 5               | 13          | 5           |
| No. with bone marrow + | 15 (26) | 7 | 7 | 1 |
| No. that received boost<sup>f</sup> | 18 (31) | 1 | 16 | 1 |
| No. that received HDCYTX | 15 (26) | 2 | 12 | 1 |
| G-CSF mobilization | 19 (33) | 4 | 9 | 6 |
| Chemotherapy/G-CSF mobilization | 39 (67) | 4 | 30 | 5 |
| BM infused | 16 (33) | 6 | 5 | 5 |
| No. that received TBI/TLI | 30 (63) | 8 | 21 | 1 |
| Chemotherapy only | 18 (37) | 0 | 9 | 9 |

<sup>a</sup>LGL, low-grade lymphoma; SCTC, stem cell-toxic chemotherapy; XRT, radiotherapy; HDCYTX, high dose cyclophosphamide.

<sup>b</sup>Seven patients with follicular small cleaved cell and one patient with follicular mixed small- and large-cell lymphoma.

<sup>c</sup>Thirty-one patients with diffuse large-cell lymphoma, 5 patients with diffuse mixed lymphoma, and 3 patients with immunoblastic lymphoma.

<sup>d</sup>Nine patients with nodular sclerosis, one patient with mixed cellularity, and one patient with lymphocyte-predominant HD.

<sup>e</sup>Two or more cycles of procarbazine, nitrogen mustard, melphalan, nitrosoureas, or >7.5 g cytarabine prior to PBPC mobilization.

<sup%f</sup>Hyperfractionated radiotherapy given to 1–2 sites in BID fractions over a 1–2-week period (total dose, 1800–3600 cGy).

of patients with several different hematological malignancies. Therefore, we analyzed the efficacy of progenitor cell collection and hematological recovery posttransplantation in patients with lymphoma who received either a chemotherapy-only or a chemotherapy- and radiotherapy-containing transplant conditioning regimen. Using univariate and multivariate analyses, we identified several factors that were associated with successful PBPC mobilization and rapid hematological recovery. We identified both patient-related and treatment-related factors that may aid in optimizing patient management and the design of clinical trials.

**PATIENTS AND METHODS**

**Patient Information.** Fifty-eight patients with HD or NHL that was histologically confirmed at Memorial Hospital underwent PBPC mobilization between 1993 and 1995. This group represented all patients transplanted between 1993 and 1995 who were not eligible for cytokine trials or had not received initial salvage chemotherapy at Memorial Hospital. Eleven patients had HD, and 47 patients had NHL. Forty-eight of these patients ultimately received a PBPCCT, of which 46 were evaluable for engraftment. Patients <65 years old with relapsed HD or NHL were offered PBPCCT if their disease was responsive to salvage chemotherapy and they were HIV negative, had adequate pulmonary and cardiac function, and had a serum creatinine <2.0 mg/dl and a serum bilirubin <2.0 mg/dl. The autologous transplant was given as standard of care for the treatment of chemosensitive relapsed or primary refractory lymphoma, and the conditioning regimen consisted of either cyclophosphamide, carmustine, etoposide (CBV); TBI, cyclophosphamide, etoposide (TBI/Cy/Etop); or TLI, cyclophosphamide, etoposide (TLI/Cy/Etop) conditioning regimens, as described previously by us (7, 8) and other centers (9, 10). The distribution of patient characteristics, including the number of cycles of prior chemotherapy, the presence or absence of bone marrow involvement, and the type of prior chemotherapy and radiotherapy received by the patients, is listed in Table 1. The median age for all patients was 45; the median ages for patients with low-grade NHL, IGL, and HD were 46, 50, and 31, respectively.

**Transplant Regimens Used.** Twenty-nine patients with NHL received TBI (1200–1375 cGy), 60 mg/kg/day cyclophosphamide for 2 days, and 250 or 350 mg/m<sup>2</sup> etoposide for 3 days, and 9 patients received 6000 mg/m<sup>2</sup> cyclophosphamide, 1600 mg/m<sup>2</sup> etoposide, and 450 mg/m<sup>2</sup> carmustine. One patient with HD who had not received extensive irradiation received TLI, 4500 mg/m<sup>2</sup> cyclophosphamide, and 1000 mg/m<sup>2</sup> etoposide. Nine patients with HD who had received extensive radiotherapy in the past were treated with 6000 mg/m<sup>2</sup> cyclophosphamide, 1600 mg/m<sup>2</sup> etoposide, and 300 mg/m<sup>2</sup> carmustine. Seventeen patients with NHL and 1 patient with HD had bulky disease prior to transplant and received hyperfractionated boost radiotherapy (1800–3600 cGy) to the sites of bulky disease.

**PBPC Mobilization.** Patients underwent between one and eight leukapheresis procedures in an attempt to obtain at least 2 × 10<sup>6</sup> CD34<sup>+</sup> cells/kg or 4 × 10<sup>7</sup> MNCs/kg. For each apheresis, 10 liters of blood were processed over a 2.5–3-h time period (representing a median number of blood volumes processed per collection of 1.9; range, 1.4–3.4). Bone marrow harvests were performed for all patients, but the bone marrow was kept as a back-up (i.e., should the patient not engraft) for all patients except the first six patients, who received bone marrow plus PBPCs regardless of the number of PBPCs obtained. A minimum of 1 × 10<sup>8</sup> MNCs/kg of bone marrow was collected. If <2 × 10<sup>6</sup> CD34<sup>+</sup> cell/kg were obtained, both PBPCs and bone marrow cells were reinfused. Sixteen patients received bone marrow and PBPCs; 11 patients with NHL and 5 with HD.

Patients with chemosensitive disease received disease-specific chemotherapy and 10 μg/kg/day G-CSF to mobilize PBPCs. Thirty patients received ifosfamide, carboplatin, and etoposide; 5 patients received cyclophosphamide (3 g/m<sup>2</sup>); 2 patients received cyclophosphamide, doxorubicin, vincristine, and prednisone; 1 patient received etoposide, vinblastine, and doxorubicin; and 1 patient received methotrexate and cytarabine. Patients whose disease was in second (or greater) remission received 10 μg/kg/day G-CSF alone for mobilization. Leukapheresis was initiated when the white blood count was ≥1000 WBCs/μl and continued on a daily basis (except on Sunday) for...
a median of 3 days in patients receiving chemotherapy and G-CSF. In patients who had PBPCs mobilized with G-CSF alone, G-CSF was given for 7–9 days and PBPC collection was initiated on day 5 and continued on a daily basis (except on Saturday) for a median of 3 days.

Prior to cryopreservation, MNCs in each leukapheresis collection were analyzed for CD34 expression using flow cytometry. Briefly, 250 μl of the apheresis sample were incubated with a FITC-conjugated CD34 monoclonal antibody (HPCA1, Becton Dickinson, Mountainview, CA) and a phycoerythrin-conjugated CD33 monoclonal antibody (MY9, Coulter, Hialeah, FL) for 30 min at 4°C. Erythrocytes were then lysed using a commercially available lysing solution (Immunoprep Leukocyte FL) for 30 mm at 4°C. Erythrocytes were then lysed using a 1.5% SDS solution for 1 min at room temperature. After washing, the samples were resuspended in 1 ml of a 4% serum albumin (Albuminar-25, Armour Pharmaceutical Co., Kankakee, IL) and 4% hydroxyethyl starch (Penn catastrophe Corp., Salt Lake City, UT), 6% hydroxyethyl starch (Pentastarch, McGaw Inc., Irvine, CA) and 4% serum albumin (Albuminar-25, Armour Pharmaceutical Co., Kankakee, IL) as the cryopreservation solution (final concentrations). Components were placed in a −80°C electrical freezer overnight and then transferred to a −15°C electrical freezer for storage.

**In-Hospital Management.** All patients were cared for in single rooms once the absolute neutrophil count was <500/μl. Fever in the neutropenic patient was usually managed with Timentin and Gentamicin, with the addition of Vancomycin and/or Amphotericin B when necessary for continuing or recurrent fever. All patients received 5–10 μg/kg/day G-CSF s.c. posttransplantation. RBC transfusions were administered for a hemoglobin concentration ≤7 g/dl. Platelet transfusions were administered prophylactically for a platelet count <20,000/μl within 10 days of transplant, or a platelet count <10,000/μl beyond that day, if the patient had no other risk factors for bleeding. All blood products were leukocyte depleted and irradiated prior to administration.

**Statistical Analysis.** This was a retrospective study to identify prognostic factors that predict for adequate PBPC mobilization and rapid hematological recovery. Univariate analyses were performed on 8 previously identified variables that might affect CD34+ PBPC mobilization and on 10 variables that might affect the speed of platelet recovery. For both analyses, a Wilcoxon rank test was used in stage one of the analysis to screen the possible prognostic factors. (The t test results were similar but are not reported because median values were the preferred parameter for describing the results.) Subsequently, multiple regression analyses were performed following log transformation of the values for these same variables to identify those variables that were most predictive of PBPC mobilization and platelet recovery.

**RESULTS**

**PBPC Mobilization.** Forty-eight of the 58 patients who underwent leukapheresis procedures underwent transplantation. Four patients did not undergo immediate transplantation because of either disease progression (n = 2) or marked deterioration in their performance status (n = 2). Six patients had PBPCs collected prior to therapeutic whole-pelvis radiation as a precaution, in case they needed cryopreserved stem cells to support a future autologous transplant for relapsed disease.

Although the quantity of CD34+ cells is now used to define the adequacy of PBPC collection, initially the number of MNCs/kg was more reliable, and we used that number to define what constituted an adequate collection. Nonetheless, CD34+ cell counts were analyzed on all patients, and univariate Wilcoxon rank tests were performed to determine what factors affected the collection of CD34+ cells (Table 2). A median of $5.1 \times 10^6$ CD34+ cells/kg were obtained from patients with NHL, and $1.6 \times 10^6$ CD34+ cells/kg were obtained from patients with HD ($P = 0.06$). Sixteen patients received bone marrow in addition to PBPCs. The median number of MNCs/kg infused in patients who received both bone marrow and peripheral blood was $4.2 \times 10^6$ (range, 0.7–14.0 $\times 10^6$). Patients with NHL received a median of $4.7 \times 10^6$ MNCs/kg, and those with HD received $3.4 \times 10^6$ MNCs/kg. In addition, the median number of CD34+ cells/kg infused in these 16 patients was 0.6 $\times 10^6$ (range, 0–6.0). Patients who received G-CSF alone mobilized significantly fewer PBPCs than those who received G-CSF + chemotherapy (median CD34+ cells collected/kg = $1.5 \times 10^6$ versus $6.7 \times 10^6; P = 0.0002$). Patients who received previous treatment with nitrogen mustard, procarbazine, melphalan, or nitrosoureas or >7.5 g of cytarabine chemotherapy (referred to as stem cell-toxic chemotherapy; see Tables 1 and 2) had significantly poorer mobilization (median, $2.0 \times 10^6$ versus $6.0 \times 10^6$ CD34+ cells/kg; $P = 0.005$). In addition, patients who received ≥11 cycles of chemotherapy prior to PBPC mo-

| Table 2 | Prognostic factors for CD34+ cells/kg collection |
|---|---|---|---|---|
| Factor | n | CD34+ cells/kg (median) | P |
| NHL | 47 | 5.1 | 0.06 |
| HD | 11 | 1.6 | 0.25 |
| <11 cycles | 39 | 6.7 | 0.02 |
| ≥11 cycles | 19 | 2.6 | 0.0002 |
| No SCTC | 35 | 6.0 | 0.005 |
| SCTC | 23 | 2.0 | 0.25 |
| Chemotherapy/G-CSF mobilization | 39 | 6.7 | |
| G-CSF mobilization | 19 | 1.5 | |
| No previous XRT | 42 | 5.5 | |
| Previous XRT | 16 | 3.7 | |

* SCTC, stem cell-toxic chemotherapy; XRT, radiotherapy.
Factors Affecting PBPC Mobilization in Lymphoma

**Table 3** Correlation of days to platelet count of 20,000/μl versus the number of CD34+ cells/kg infused in patients who received a TBI/TLI- versus non-TBI/TLI-containing transplant-conditioning regimen

<table>
<thead>
<tr>
<th>No of CD34+ cells/kg</th>
<th>Days to platelet count &gt;20,000/μl</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TBI/TLI</td>
<td>&gt;2 million</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&lt;2 million</td>
<td>22</td>
</tr>
<tr>
<td>TBI/TLI</td>
<td>&gt;2 million</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>&lt;2 million</td>
<td>24</td>
</tr>
<tr>
<td>All</td>
<td>&gt;2 million</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&lt;2 million</td>
<td>22</td>
</tr>
</tbody>
</table>

"P = 0.06 by Wilcoxon test (when all patients were analyzed).

Transfusions. The 48 patients undergoing PBPCCT received a median of 5 units of packed RBCs posttransplantation and had received nine platelet transfusion episodes before sufficient endogenous hematopoietic recovery occurred to obviate the need for transfusions.

Length of Hospital Stay. The median length of stay was 29 days, which included the 7–11 days needed to administer the conditioning regimen. Patients who received TBI required 7 days longer hospitalization than patients who received a chemotherapy-only regimen (median, 31 versus 24 days; \( P = 0.008 \)).

**DISCUSSION**

The efficacy of PBPCCT versus autologous bone marrow transplantation for patients with lymphoma remains unclear, but a randomized trial comparing G-CSF-mobilized PBPCCT with autologous bone marrow transplantation in lymphoma patients determined that PBPCCTs significantly reduce the number of platelet transfusions, the time to platelet and neutrophil recovery, and the length of hospital stay (11). Tumor cell contamination of PBPCCT appears to be less than bone marrow, but the reduction may not be clinically relevant. A survival benefit for PBPCCT was suggested by a retrospective analysis from the University of Nebraska; "good prognosis" patients with relapsed IGL (defined by the following: a tumor mass ≤10 cm, ≤2 prior chemotherapy treatment programs prior to PBPCCT mobilization, and chemotherapy-sensitive disease) who received PBPCCTs as the stem cell source had a superior event-free survival compared to patients who received bone marrow (12). However, other retrospective studies have not suggested a benefit. A prospective randomized trial is under way to determine whether PBPCCT provides a therapeutic advantage over autologous bone marrow transplantation for patients with IGL.

The mobilization of PBPCCT using chemotherapy and/or hematopoietic growth factors is generally successful; however, the optimal scheme for procuring progenitor cells, especially in patients who have been heavily pretreated, has not been defined. Several studies have delineated parameters that may be associated with poor mobilization of PBPCCTs, including slow recovery of monocytes and platelets at the time of PBPCCT collection, poor performance status, the use of <4 g/m² of cyclophosphamide for mobilization, prior radiation therapy, receiving ≥6 cycles of chemotherapy prior to PBPCCT mobilization, cytotoxic chemotherapy within 2 months of PBPCCT mobilization, and increasing age and bone marrow involvement (13–16). In addition, it was difficult to mobilize PBPCCTs in patients who had previously received MOPP, Dexa-BEAM, or melphalan chemotherapy, and significant delays in platelet recovery were seen in these patients after high-dose therapy and ASCT (17, 18, 19).

We recently reported that in patients with IGL who received hematopoietic growth factors as the sole mobilization strategy (20), prior therapy with specific stem cell-toxic chemotherapeutic agents (either ≥2 cycles of nitrogen mustard, procarbazine, nitrosoureas, or melphalan or ≥7.5 g of cytarabine) predicted for the collection of statistically fewer CD34+ cells, burst-forming unit erythroid, MNCs, and granulocyte-macrophage colony-forming units per kg by repeated leukaphereses. This definition of stem cell-toxic chemotherapy also
predicted for delayed platelet count recovery to 20,000/μl when compared to patients who were not similarly treated.

In the current study, we examined PBPC mobilization and hematological recovery in patients with relapsed and primary refractory HD or NHL. G-CSF plus combination chemotherapy was more effective at mobilizing PBPCs than G-CSF alone, using both univariate and multivariate analysis, and the use of combination chemotherapy plus G-CSF provided the added benefit of further cytodestruction of the lymphoma prior to myeloablative therapy. After evaluating all of the variables that have previously been reported to adversely affect the collection of CD34+ cells, we determined that patients who had received either stem cell-toxic chemotherapy (as defined above and in Ref. 20) or ≥11 cycles of chemotherapy prior to PBPC mobilization had a statistically significant poorer yield of CD34+ cells, using univariate analysis. Multiple regression analysis determined that only a prior history of receiving stem cell-toxic chemotherapy (i.e., being “extensively pretreated”) but not receiving ≥11 cycles of prior chemotherapy, and receiving G-CSF alone to mobilize PBPCs, predicted for a poor yield of CD34+ cells.

Despite differences in the efficacy of PBPC mobilization, rapid hematopoietic recovery was seen in nearly all patients infused with >2.0 × 10^6 CD34+ cells/kg, independent of whether they had received prior irradiation or stem cell-toxic chemotherapy. Although several studies have shown the limited proliferative capacity of hematopoietic progenitors from patients who have received extensive prior chemotherapy (21), neutrophil and platelet recovery was not delayed in these patients post-stem cell infusion. The lack of correlation between the number of CD34+ cells infused and blood count recovery may be the result of the oligoclonal hematopoietic recovery seen post-ASCT. Although a large fraction of the stem cells or progenitor cells may be damaged by prior therapy a sufficient number of relatively normal progenitor cells may proliferate to provide hematopoietic function early post transplant.

We observed an effect of the conditioning regimen on the rate of platelet recovery that was not quite statistically significant. Patients who received TBI had a slightly delayed time to attain an untransfused platelet count >20,000/μl compared to patients who received a chemotherapy-only transplant regimen. Additionally, patients who received a TBI-containing conditioning regimen had a more prolonged post-stem cell infusion hospitalization independent of the time to neutrophil and platelet count recovery, due to a greater incidence of grade III and IV mucositis and anorexia and the greater need for intravenous narcotics and total parenteral nutrition.

Our data suggest that current strategies to mobilize PBPCs may be suboptimal in patients who are given hematopoietic growth factors alone. Although the use of chemotherapy and G-CSF was superior to G-CSF alone, it is still suboptimal for patients who have received stem cell-toxic chemotherapy prior to PBPC mobilization. One approach to insure an adequate PBPC collection is to define, as early as possible in the course of treatment, which patients with lymphoma will likely require either stem cell-toxic chemotherapeutic agents or a substantial amount of chemotherapy (i.e., >11 cycles of chemotherapy) to achieve a cure. It would be prudent to collect PBPCs early in the course of therapy for these patients. Such a treatment strategy can easily be applied to patients with advanced-stage HD. Chemotherapy programs, such as ABVD (the combination of doxorubicin, vinblastine, bleomycin, and dacarabazine), have been shown in randomized clinical trials to have efficacy equivalent to the more toxic and leukemogenic nitrogen mustard-based chemotherapy programs for the initial treatment of advanced-stage HD (22). Prognostic models have been developed (23) that can reliably predict which patients with advanced-stage HD have less than a 50% chance of long-term event-free survival; perhaps the use of doxorubicin, vinblastine, bleomycin, and dacarabazine as initial treatment in these patients who may later require an ASCT for relapsed or primary refractory disease would be especially prudent.

Although earlier PBPC collection could result in more lymphoma cell contamination of the apheresis product, this speculation cannot be answered by available data. Various purging strategies are being developed that may ultimately be useful when more effective treatment regimens have been developed. Such approaches may be combined with ex vivo expansion or the use of other growth factors in addition to G-CSF (such as stem cell factor or flt-3 ligand), which may increase the number of PBPCs available for transplantation.

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