

# CD34<sup>+</sup>-Enriched Peripheral Blood Progenitor Cell Collections in Lymphoma Autotransplants Are Associated With Increased Morbidity

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## ABSTRACT

**Background.** CD34<sup>+</sup> enrichment of peripheral blood progenitor cells (PBPCs) may reduce tumor burden but could compromise immunologic reconstitution and increase infectious risk in the autologous PBPC transplant patient.

**Design.** We compared infectious complications in lymphoma autotransplant patients treated with a single high-dose chemotherapy regimen and supported either with CD34<sup>+</sup>-enriched PBPCs ( $n = 19$ ) or unmanipulated PBPCs ( $n = 24$ ). Analysis was limited to patients followed for a minimum of 1 year after discharge from initial hospitalization and free of lymphoma recurrence.

**Results.** We observed a statistically significant increase in the number of patients with 1 or more infectious events in the CD34<sup>+</sup>-enriched group (14 of 19) compared with the unmanipulated PBPCs group (9 of 24,  $P < .01$ ). Greater numbers of patients with 2 or more infectious events were observed in the CD34<sup>+</sup>-enriched population (7 of 19 vs. 2 of 24,  $P < .03$ ) as well as an increased incidence of bacterial infections (10 of 19 vs. 5 of 24,  $P < .05$ ). Two deaths due to infectious complications were observed in the CD34<sup>+</sup>-enriched subjects. There was no significant difference in blood lymphocyte or monocyte recovery between groups.

**Conclusions.** Lymphoma patients undergoing autotransplant using CD34<sup>+</sup>-enriched rather than unmanipulated PBPC collections have a significant increase in long-term incidence of infectious events. Patients who undergo CD34<sup>+</sup> selection of PBPC transplantation should be followed closely for infectious complications, and prolonged infectious prophylaxis should be considered.

## INTRODUCTION

High-dose chemotherapy followed by autologous peripheral blood progenitor cell transplantation can provide prolonged disease-free survival for refractory and

relapsed Hodgkin's disease and non-Hodgkin's lymphoma patients.<sup>1-7</sup> A number of investigators have provided evidence in leukemia, lymphoma, breast cancer, and neuroblastoma that contaminating tumor cells in the harvested PBPC collections may be responsible for relapse after transplantation.<sup>8-17</sup> Positive selection of PBPC collections for CD34<sup>+</sup> progenitors may reduce the number of contaminating tumor cells while preserving hematopoietic engraftment.<sup>18-20</sup> Along with reducing tumor burden, the CD34<sup>+</sup> cell enrichment procedure may also compromise immunologic reconstitution by depleting the grafts of mature T and B lymphocytes<sup>20-22</sup>; an increase in the number of opportunistic infections may result. Severe viral infections, including cytomegalovirus (CMV) retinitis, adenovirus-associated hemorrhagic cystitis, fatal herpes pneumonitis, and severe cryptosporidiosis, have been reported after autologous CD34<sup>+</sup>-enriched PBPC transplants.<sup>21,22</sup> One study found a higher frequency of CMV disease in patients transplanted with the CD34<sup>+</sup>-enriched PBPCs compared with patients transplanted with unselected PBPCs.<sup>23</sup> We therefore compared infectious morbidity associated with CD34<sup>+</sup>-enriched PBPC transplantation in lymphoma patients with that in patients treated with an identical high-dose chemotherapy regimen but who received unmanipulated PBPCs. In this single-institution study, we determined that patients supported with autologous CD34<sup>+</sup>-enriched PBPCs had a higher 1-year infectious morbidity after transplantation.

## PATIENTS AND METHODS

We reviewed the records of all lymphoma patients undergoing autologous PBPC transplantation at the Ireland Cancer Center, University Hospitals of Cleveland, Case Western Reserve University. Patients with relapsed, primary refractory (induction failure), or high-risk non-Hodgkin's lymphoma or Hodgkin's disease were treated with high-dose carmustine (BCNU), etoposide, and cisplatin<sup>7</sup> and were supported using either CD34<sup>+</sup>-enriched autologous PBPCs (1996-1998) or unmanipulated autologous PBPCs (1993-1998). A total of 19 CD34<sup>+</sup>-enriched and 24 unmanipulated PBPC transplant patients who had a minimum of 1 year of follow-up and were free of malignant disease recurrence were included in this analysis. All patients achieved myeloid engraftment before discharge from the hospital.<sup>19,24</sup> The total leukocyte, absolute lymphocyte, and monocyte counts were recorded from patient charts at approximate intervals of 3 weeks, 6 weeks, 6 months, and 1 year after autotransplant. The records were reviewed for complications after transplant, commencing at discharge from the initial hospitalization and limited to 1 year after transplantation. Complications incurred during the inpatient autotransplant hospitalization are not part of this report. The demographic and clinical characteristics of the study patients are included in Table 1.

### **Eligibility for Autotransplant**

Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and have adequate visceral organ function, including left ventricular ejection fraction at least 45% of predicted, no uncontrolled congestive heart failure or hypertension, no myocardial infarction in the previous 6 months, 1-second forced expiratory volume and pulmonary carbon monoxide diffusing capacity >50% of predicted, actual or calculated creatinine clearance >60 mL/min, alanine transaminase and aspartate transaminase <3 times normal, and no active infections or severe endocrine or neurologic disorders. Patients were excluded if they had cumulative exposure to BCNU >200 mg/m<sup>2</sup>, cumulative exposure to bleomycin >100 U/m<sup>2</sup>, cumulative exposure to doxorubicin >550 mg/m<sup>2</sup>, evidence of active infection, or a history of another malignant disease within the past 5 years. Patients were not excluded for evidence of tumor on routine histologic staining of bilateral paraffin-embedded posterior iliac crest bone marrow biopsies.

### **Mobilization and Collection of PBPCs**

The PBPC mobilization regimen consisted of cyclophosphamide 4.0 g/m<sup>2</sup> intravenously over 3–6 hours on the first day of mobilization; mesna 3.0 g/m<sup>2</sup> was contained within the cyclophosphamide dosing bag, followed by 500 mg every 3 hours by mouth or by vein for 8 doses.<sup>19,24</sup> Prednisone 2 mg/kg per day was given orally for the first 4 days of mobilization. Granulocyte colony-stimulating factor (Amgen, Thousand Oaks, CA) 10 µg/kg per day was given subcutaneously beginning between 36 and 48 hours after the completion of cyclophosphamide until combined PBPC collections provided at least  $2.0 \times 10^6$  CD34<sup>+</sup> cells/kg patient weight.

### **Positive Selection of CD34<sup>+</sup> Cells From Mobilized PBPCs**

Mononuclear cells from each leukapheresis collection were prepared and passed over the immunoaffinity column device (Ceprate, SC System) as directed by the manufacturer (CellPro, Bothell, WA).<sup>19,24</sup> Absorbed CD34<sup>+</sup> cells were resuspended at  $2 \times 10^7$  cells/mL and frozen using a controlled-rate liquid nitrogen freezer in the presence of 7.5% (final concentration) dimethylsulfoxide (Sigma, St. Louis, MO).<sup>19,24</sup>

### **Evaluation**

This study included only patients who were followed frequently at the Ireland Cancer Center, ie, who returned for follow-up approximately every 2 months. Patients were given antimicrobial prophylaxis with trimethoprim-sulfamethoxazole

for up to 3–4 months after discharge from the initial transplant hospitalization. Acyclovir and ciprofloxacin were not given routinely as prophylaxis. Furthermore, vaccination with pneumococcus and Hemophilus influenza b vaccines and diphtheria/tetanus toxoid was not begun until 1 year after transplant.

Complications and infections occurring during the initial hospitalization while patients were neutropenic are not reported herein. Patients lacking documentation of follow-up visits and those with documented disease relapse in the year after transplantation also were excluded from analysis, as were patients who received rituximab (Genentech, South San Francisco, CA), anti-B-cell monoclonal antibody therapy. Bacterial, viral, and fungal infections were defined either by clinical symptoms and response to treatment or by confirmation with laboratory culture. Infections leading to sepsis and multiorgan failure, adult respiratory distress syndrome (ARDS), and death were considered as one infectious event. Infections occurring in different anatomical sites concurrently were recorded as separate infections. Presumed infectious complications that had an unproven or unknown etiology were included in a “presumed infectious complications” category. Such events included upper respiratory infections, flu-like illnesses, and unexplained fevers unrelated to malignancy.

### **Statistical Methods**

The Fisher exact test was used to compare the frequency of infectious and noninfectious complications between the CD34<sup>+</sup>-enriched transplant patients and the unmanipulated PBPC transplant patients.

## **RESULTS**

### **Demographics**

Study patients' clinical characteristics are summarized in Table 1. Median age at transplant was similar in the 2 groups, as was the number of prior chemotherapy regimens. Patients transplanted using unmanipulated PBPCs included a greater number of women, and more patients had received localized radiation therapy, either in conjunction with transplant or earlier in the treatment course.

### **Infectious Complications**

The CD34<sup>+</sup>-enriched population had a significantly increased number of patients with 1 or more infectious events compared with the unmanipulated PBPCs group (14 of 19 vs. 9 of 24,  $P < .01$ ) (Table 2). Additionally, there were increased numbers of patients with 2 or more infectious events in the CD34<sup>+</sup>-enriched group

**Table 1.** Characteristics of Lymphoma Patients Undergoing Autotransplants\*

	<i>CD34<sup>+</sup>-Enriched PBPCs</i>	<i>Unmanipulated PBPCs</i>
Patients	19	24
Age, y	39 (22–58)	44 (22–59)
Sex, M/F	9/10	15/9
Diagnosis		
Hodgkin's disease	7	6
Non-Hodgkin's lymphoma	12	18
Number of prior chemotherapy regimens	2 (1–3)	2 (1–4)
Prior radiation†	7 (37)	13 (54)

\*Data are *n*, median (range), or *n* (%). PBPC, peripheral blood progenitor cell. †Includes any previous exposure to local radiation therapy, either in conjunction with transplantation or earlier in the treatment course.

(7 of 19 vs. 2 of 24,  $P < .03$ ). This difference reflected an increased incidence of bacterial infections observed in the CD34<sup>+</sup>-enriched group (10 of 19 in the CD34<sup>+</sup>-enriched group vs. 5 of 24 in the unmanipulated PBPCs group,  $P < .05$ ). The greater numbers of viral infections and the presumed infections found in the CD34<sup>+</sup>-enriched group was not significantly different from those in the unmanipulated PBPCs group. Only 1 fungal infection (hepatosplenic candidiasis) was noted; it occurred in the unmanipulated PBPC transplant population. A detailed documentation of the infectious complications in individual patients, including the type and timing of bacterial, viral, and fungal infections, appears in Table 3. Infectious events occurred at a median of 4 months in the CD34<sup>+</sup>-enriched patients and

**Table 2.** Comparison of Infectious Complications Within 1–12 Months in Patients Given Unmanipulated vs. CD34<sup>+</sup>-Enriched Peripheral Blood Progenitor Cells

<i>Complication</i>	<i>Unmanipulated</i>	<i>CD34<sup>+</sup>-Enriched</i>	<i>P</i> *
<i>n</i>	24	19	—
No infections	15	5	.01†
>1 infectious complication	9	14	—
>2 infectious complications	2	7	—
One or more bacterial infections	5	10	.05
One or more viral infections	2	5	.21
One or more fungal infections	1	0	NS
One or more presumed infections	3	5	NS
Infectious deaths	0	2	NS

\*Fisher exact test; †ordered columns, 2×3 table.

**Table 3.** Infectious Complications and Time to Occurrence After Transplant in Patients Receiving CD34<sup>+</sup>-Enriched and Unmanipulated PBPC Collections\*

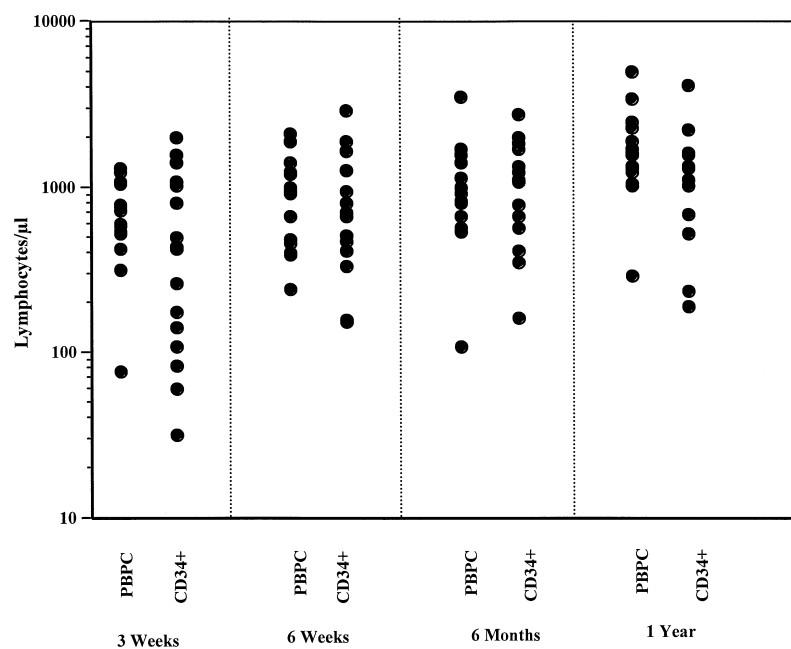
<i>Patient</i>	<i>Infectious Complication</i>
CD34 <sup>+</sup> -enriched PBPCs	
1	Flu-like illness, 1 mo
2	Sinusitis/mastoiditis, 7 mo
3	Sinusitis, 3 mo and 10 mo
4	URI, 1 mo and 9 mo
5	<i>Streptococcal sp</i> pharyngitis, 11 mo
6	<i>S. aureus</i> sepsis, 1 mo Flu-like illness, 12 mo
7	pericolonic <i>Pseudomonas sp</i> abscess, 1 mo
8	Sinusitis, 1 mo
9	Flu-like illness and Guillain-Barré syndrome, 5 mo Sepsis, ARDS, death, 5 mo
10	Varicella zoster, 4 mo Viral thyroiditis, 4 mo Perianal HSV-II, 4 mo Pneumonia, 7 mo
11	Bronchitis ( <i>Pseudomonas sp</i> ), 1 mo UTI, 2 mo and 3 mo Pneumonia, ARDS, death, 4 mo
12	FUO, 1 mo
13	URI, 2 mo and 7 mo Pneumonia, 4 mo Varicella zoster, 7 mo
14	Varicella zoster, 10 mo
Unmanipulated PBPCs	
1	FUO, 3 mo Hepatosplenic candidiasis, 5 mo Varicella zoster, 11 mo
2	Sinusitis, 12 mo
3	Polymicrobial sepsis, 1 mo
4	Vestibulitis, 1 mo
5	Varicella zoster, 4 mo
6	Varicella zoster, 5 mo
7	Bacterial conjunctivitis, 5 mo URI, 5 mo
8	Flu-like illness, 1 mo
9	Sinusitis, 10 mo

\*ARDS, adult respiratory distress syndrome; FUO, fever of unknown origin; HSV, herpes-simplex virus; URI, upper respiratory infection; UTI, urinary tract infection.

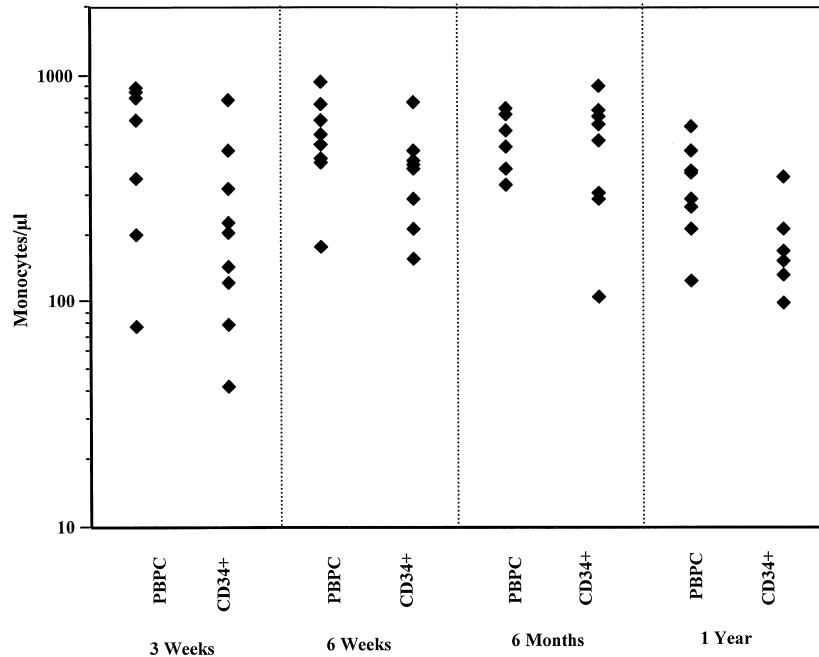
5 months in the unmanipulated PBPC recipients. Sixty-nine percent of the infections in the CD34<sup>+</sup>-selected patients occurred before 6 months, and 75% in the unmanipulated PBPC transplant patients. There were 2 infectious deaths in the CD34<sup>+</sup>-selected group and none in the unmanipulated PBPC patients. This low event rate precludes a statistically significant conclusion; infectious deaths in lymphoma patients undergoing autologous PBPC transplantation, however, is uncommon at our center and thus has clinical significance.

### Lymphocyte and Monocyte Counts

Peripheral blood lymphocyte and monocyte counts at 3 weeks, 6 weeks, 6 months, and 1 year after transplant are shown in Figures 1 and 2. There was no significant difference in mean lymphocyte and monocyte counts between study groups during the 12-month posttransplant follow-up period. There appeared to be a greater variability in blood lymphocyte and monocyte counts obtained from patients transplanted using CD34<sup>+</sup>-enriched cells.



**Figure 1.** Peripheral blood lymphocyte counts obtained from patients undergoing autotransplant using autologous unmanipulated peripheral blood progenitor cells (PBPC) or CD34<sup>+</sup>-enriched PBPCs. Scattergram of lymphocyte counts after transplant at indicated time points.



**Figure 2.** Peripheral blood monocyte counts obtained from patients undergoing auto-transplant using autologous unmodified peripheral blood progenitor cells (PBPC) or CD34<sup>+</sup>-enriched PBPC. Scattergram of monocyte counts after transplant at indicated time points.

## DISCUSSION

We report a significant increase in the incidence of 1 or more late infectious complications in lymphoma patients transplanted using autologous CD34<sup>+</sup>-enriched PBPCs compared with unmanipulated PBPCs within the first year after transplantation. The two patient groups had comparable demographics, and both populations were monitored frequently after autograft. Interestingly, there was an increased incidence of bacterial infections but neither fungal nor viral infections in the CD34<sup>+</sup>-enriched patients. This finding may be due to a low detection rate of viral infections, because viral cultures are not routinely performed in these patients. Only 1 documented fungal infection occurred in the entire study population, and the low event rate precludes meaningful comparison between cohorts for fungal infections.

The increased morbidity in the CD34<sup>+</sup>-enriched transplant patients may be attributed to either qualitative or quantitative differences in the reconstituted immune systems of the patients. The absolute lymphocyte and monocyte counts do not appear to differ between groups, and it is more likely that qualitative and

quantitative differences in CD4<sup>+</sup> or CD8<sup>+</sup> lymphocyte subsets may be responsible for the increased infection rate in this group. Others investigating the lymphoid reconstitution of patients given CD34<sup>+</sup>-selected PBPC collections found fewer circulating B-cells and CD4<sup>+</sup> T-cells after autotransplant compared with subjects who received unmanipulated PBPC grafts.<sup>25</sup> According to reverse transcription–polymerase chain reaction amplification of the T-cell receptor antigen binding region (VDJ regions), T cells in the CD34<sup>+</sup>-enriched transplant patients had decreased diversity of VDJ regions compared with those in the unmanipulated PBPC transplant group. These studies suggest that the CD34<sup>+</sup> enrichment process may result in both quantitative and qualitative deficiencies in a reconstituted immune system compared with the immune system of patients reconstituted with the unmodified PBPC graft. A lower CD4<sup>+</sup>/CD8<sup>+</sup> ratio and/or fewer B lymphocytes could result in a clinically significant defect in immunity of the patients transplanted with CD34<sup>+</sup>-enriched cells. Two studies found that chemotherapy exposure alters blood lymphocyte subsets, ie, PBPC collections obtained from patients have a decreased CD4<sup>+</sup>/CD8<sup>+</sup> ratio compared with the peripheral blood of normal volunteers.<sup>26,27</sup> Furthermore, the autotransplant patients had increased suppressor T-cell activity.<sup>22</sup> The use of an additional step in the processing of PBPCs for transplantation, such as the CD34<sup>+</sup> enrichment process, may further alter the lymphoid reconstitution of autologous PBPC recipients.

We did not focus on infectious events that occurred during the initial hospitalization but chose to address those episodes that occurred during posttransplant months 1–12. Patients transplanted with CD34<sup>+</sup>-enriched cells may require increased infectious prophylaxis and closer monitoring than patients receiving unmanipulated PBPC grafts. To address the mechanism responsible for our observation, it may be necessary to prospectively examine B-cell and CD4<sup>+</sup>CD8<sup>+</sup> T-lymphocyte engraftment and function after autotransplant. The problem of an increased infectious diathesis may be magnified with the increased use of the newly developed anti-B-cell or anti-T-cell targeted therapies designed to decrease tumor recurrence. Such agents may further decrease tumor burden, but also could delay immune reconstitution and increase infections when used in the autotransplant setting.

#### ACKNOWLEDGMENTS

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