Low Infectious Morbidity after Intensive Chemotherapy and Autologous Peripheral Blood Progenitor Cell Transplantation in the Outpatient Setting for Women with Breast Cancer

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Autologous peripheral blood progenitor cell (PBPC) transplantation is increasingly employed in the outpatient setting, yet data on early complications following PBPC transplantation are scant. We evaluated 105 women with high-risk primary or metastatic breast cancer who were treated at a single institution during 1996–1997. The mean duration of neutropenia (absolute neutrophil count, <500 cells/mm³) was 7.5 days. Twenty-nine percent of women remained afebrile throughout the neutropenic period. Of the remaining 71%, most (64 of 75) had fever of unknown origin. Infections, mostly of mild severity, occurred in 34% of women; these infections included bacteremia due to gram-positive organisms, catheter site infection, cellulitis, pneumonia, oral candidiasis, herpes simplex virus infection, and vaginitis. Fifty percent of PBPC transplant recipients required hospital admission, usually because of persistent fever; the mean duration of hospitalization was 3 days. No deaths or serious adverse events occurred. Such reduced infectious morbidity may be a consequence of minimal oral and/or gastrointestinal mucositis associated with the conditioning regimen and broad-spectrum antimicrobial prophylaxis used for this patient population.

Hematopoietic progenitor cell transplantation is commonly used to treat hematologic and nonhematologic malignancies. In recent years, peripheral blood has become the main source for hematopoietic progenitor cells. Data suggest that the duration of neutropenia is shorter and there are fewer associated complications with mild to moderate severity after a patient undergoes peripheral blood progenitor cell (PBPC) transplantation than after a patient undergoes marrow transplantation [1–3]. Furthermore, the administration of granulocyte colony-stimulating factor after autologous PBPC transplantation accelerates the rate of neutrophil engraftment [4, 5]. Hence, PBPC transplantation and subsequent care may be feasible in the outpatient setting. Most institutions, however, perform transplantation in hospital settings; consequently, data on early complications following PBPC transplantation in the outpatient environment are scant [6–10].

At our institution, women with high-risk primary or metastatic breast cancer receive intensive chemotherapy in an inpatient setting and are then discharged to the outpatient transplantation clinic for PBPC transplantation and close, daily follow-up care. Early complications that followed PBPC transplantation in women with breast cancer are not adequately documented. The
PATIENTS AND METHODS

Patients. One hundred twenty women with breast cancer who were consecutively treated from January 1996 through December 1997 comprise the entire study group. Complete medical records were available and comprehensively reviewed for 105 of the 120 patients. The study period was the first 14 days after transplantation.

All the women had high-risk primary or metastatic breast cancer. Before high-dose chemotherapy, PBPCs were mobilized with filgrastim or filgrastim plus chemotherapy, washed, frozen, and stored until use.

Chemotherapy. High-dose chemotherapy consisted of iv cyclophosphamide (1875 mg/m²/d) as a 1-h infusion on days −6, −5, and −4; iv cisplatin (55 mg/m²/d) as a continuous infusion on days −6, −5, and −4; and iv carmustine (600 mg/m²) as a 2-h infusion on day −3. Chemotherapy was administered along with fluids via an indwelling central venous catheter. Most patients (96 of 105) had Arrowgard catheters (Arrow International) placed in the subclavian vein. Groshong and Hickman catheters were used less frequently.

After high-dose chemotherapy, the patients were discharged from the hospital and were seen daily in the outpatient transplantation clinic. On day 0, PBPCs were iv infused into patients via the central vascular catheter. Filgrastim was iv administered at a dosage of 5 μg/kg/d from day 0 until the absolute neutrophil count was ≥5 × 10⁹ cells/L for at least 3 days. Nine of the 105 patients received CD34⁺ selected cells. CD34⁺ cells were isolated from PBPCs by use of the Isolect 300i system (Nexell Therapeutics).

Antimicrobial prophylaxis and therapy. The prophylactic antimicrobial regimen was identical to that used in a previously reported study [6]. The regimen consisted of oral ciprofloxacin (500 mg t.i.d.) and oral rifampin (300 mg b.i.d.); treatment was begun 2 days before transplantation. Patients with severe gastrointestinal intolerance received iv vancomycin (30 mg/kg once daily) and iv ciprofloxacin (400 mg every 12 h). Prophylaxis was continued until fever occurred, infection was documented, or the absolute neutrophil count was ≥500 cells/mm³.

When fever occurred during neutropenia, patients underwent physical examination, chest radiography, and blood and urine cultures and additional tests were performed when indicated. Empirical antibiotic therapy for fever consisted of once-daily iv tobramycin or iv ceftriaxone and once-daily vancomycin. Intravenous vancomycin (30 mg/kg/d) was given in 500 mL of water (with 3% dextrose) over 2–4 h. Trough (not peak) levels were usually measured before administration of the second dose; when levels were <2 or ≥10 μg/mL, the dose was changed, depending on the clinical situation. If a gram-positive bacterial infection was confirmed, then vancomycin treatment was given at conventional dosages. Ciprofloxacin therapy was continued either orally or iv.

This empirical regimen was modified on the basis of results of clinical examination or culture findings. Management was continued in the outpatient setting unless fever persisted or other complications occurred, such as hypotension, fluid over-load, and severe mucositis. Those patients who were hospitalized were promptly discharged upon resolution of the acute problem; they continued to be seen daily in the outpatient transplantation clinic. Patients with clinically and/or microbiologically documented infection were treated for several days until complete resolution of signs and symptoms of infection.

All patients also received clotrimazole troches (10 mg 5 times per day) as antifungal prophylaxis. The protocol allowed the use of empirical systemic antifungal therapy if patients remained febrile after 5 days of iv antibiotic treatment. Intravenous or oral acyclovir was added to treatment for probable or proven infection caused by herpes simplex virus (HSV).

Definitions. Neutropenia was defined as an absolute neutrophil count of <500 cells/mm³. Fever was defined as 2 oral temperature recordings of ≥38°C (100.4°F) 4 h apart or a single temperature spike of ≥38.3°C (101°F). Infection was defined clinically (symptoms and physical signs compatible with an infectious process) and microbiologically (positive result on culture of a specimen from an infected site along with clinical evidence of infection). Bacteremia was defined as the recovery of bacteria from a blood culture in the presence of fever with or without other symptoms and/or signs of infection. Pneumonia (clinical) was defined as a new infiltrate on a chest radiogram along with clinical evidence of lower respiratory tract infection. Cellulitis was defined as symptoms and signs of inflammation at the suspected site with or without positive results on microbiological cultures. Catheter site infection was defined as the presence of erythema and/or tenderness with or without drainage; the presence of a positive bacterial culture of a specimen from the exit site of the intravascular catheter was not needed to define the infection.

RESULTS

The main characteristics of the 105 women who underwent PBPC transplantation are shown in Table 1. The mean age of the women was 45 years. Nine of 105 women received CD34⁺ selected progenitor cells, while the remainder received unse-
lected cells. The duration of neutropenia was 5 days in 2 patients, 6–8 days in 86 patients, 9–10 days in 16 patients, and 11 days in 1 patient. Most patients (78%) tolerated oral antimicrobial prophylaxis well. Other patients required iv antimicrobial prophylaxis.

Fever developed in 75 (71%) of 105 patients while they had neutropenia; 71 patients had a single episode of fever, while 4 had 2 episodes. The cause of fever was not identified in 64 of 75 patients. Twenty-eight patients developed fever of unknown origin around the time of engraftment.

Thirty-six patients (34%) had clinical and/or microbiological documentation of infection; there were 40 infectious episodes. The types and frequency of infections encountered are shown in table 2. Bacteremia occurred in 6 patients; 5 cases of bacteremia were due to methicillin-resistant coagulase-negative staphylococcus, and 1 case was due to viridans streptococcus. Bacteria were recovered from only 1 set of blood cultures from all 6 patients. Of note, there were no gram-negative bacillary or systemic fungal infections. The most commonly encountered infection was due to HSV. All infections promptly responded to appropriate antimicrobial therapy. Vascular catheters were removed from 8 women; infection was the suspected reason for removal for 6 of these patients. In 2 of 5 patients with catheter site infection, Staphylococcus aureus was recovered from the exit site.

Of the 9 patients who received CD34+ selected cells, 3 developed fever. Bacteremia was seen in 2 patients; 1 case was due to viridans streptococcus, and 1 case was due to coagulase-negative staphylococcus. One patient developed orolabial herpetic infection.

Of the 105 patients, 52 (50%) were cared for in the outpatient setting during the entire study period. For the remaining 53 patients, the cause of hospitalization was persistent fever for 41 patients (39%), nausea and/or vomiting for 4 (4%), and miscellaneous reasons, such as fluid overload, congestive heart failure, and renal insufficiency, for 7 (7%). The hospital stays were brief, with a mean duration of 3 days (range, 1–12 days; figure 1). Most patients were discharged promptly. No deaths or serious adverse events occurred during the entire study period.

Antimicrobial use was common. Besides the prophylactic regimen, 72 patients received antibacterial therapy, 5 received antifungal therapy, and 24 received antiviral therapy. Ceftriaxone, ceftazidime, vancomycin, tobramycin, and acyclovir were commonly administered.

**DISCUSSION**

PBPC transplantation after intensive chemotherapy for breast cancer in women may be safely performed in the outpatient setting, as demonstrated in the present study. There were no deaths and no serious or life-threatening events during the 2 weeks immediately after transplantation in our study. It must be underscored that all of our patients stayed close to the hospital, medical personnel were readily available, and the patients were rigorously monitored daily in the outpatient clinic. Several previous studies have described the outpatient setting for autologous PBPC transplantation for patients with a variety of underlying disorders, including multiple myeloma, breast cancer, ovarian cancer, and lymphoma [6–10].

In this study, the rate of infectious morbidity during the neutropenic period before engraftment (mean duration, 7.5 days) was remarkably low. Slightly more than one-third (35) of the women developed infections, all of which were mild to moderate in severity. There were no systemic gram-negative bacterial or fungal infections. The incidence of bacteremia was low (6 women), compared to the 39% (26 of 66 patients) incidence that was reported in a study by Kolbe et al. [11] in which no antimicrobial prophylaxis was used. In the present study, relatively few virulent coagulase-negative staphylococci accounted for 5 of 6 bacteremic episodes. Furthermore, these staphylococci may have been contaminants and not pathogens, because even a single set of positive blood culture results was interpreted as representative of true bacteremia in the present study. Bacteremia due to viridans streptococcus occurred in only 1 patient. Other researchers have reported viridans streptococci as a major cause of bacteremia after transplantation, having accounted for 15% to 44% of pathogens [2, 12, 13]. The infrequency of infection due to viridans streptococcus in our patients may be explained by the absence of previously

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>CMV-seropositive women, %</td>
<td>41</td>
</tr>
<tr>
<td>HSV-seropositive women, %</td>
<td>61</td>
</tr>
<tr>
<td>CD34+ cell dose, ×10^6 cells/kg</td>
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<tr>
<td>Mean</td>
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</tr>
<tr>
<td>No. of women who received</td>
<td></td>
</tr>
<tr>
<td>Unselected cells</td>
<td>96</td>
</tr>
<tr>
<td>CD34+ selected cells</td>
<td>9</td>
</tr>
<tr>
<td>Duration of neutropenia, d</td>
<td>5–11</td>
</tr>
<tr>
<td>Mean</td>
<td>7.5</td>
</tr>
</tbody>
</table>

NOTE. CMV, cytomegalovirus; HSV, herpes simplex virus.
Infections during Outpatient Transplantation

Table 2. Infectious complications in women with breast cancer who underwent peripheral blood progenitor cell transplantation in an outpatient setting.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Documentation</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Microbiological</td>
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<tr>
<td>Bacteremia</td>
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<tr>
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<td>0</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
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</tr>
<tr>
<td>Viridans streptococcus</td>
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<td>0</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Catheter site infection</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>HSV infection</td>
<td>Perianal</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Genital</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vaginitis (cause unknown?)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. HSV, herpes simplex virus. 

a No microbiological confirmation.

recognized risk factors, such as cytosine arabinoside use and gut epithelial damage [14].

The conditioning regimen used in this study did not lead to severe mucositis or diarrhea; there were no documented cases of Clostridium difficile colitis. Overall, the very low rate of infectious morbidity seen in our study may be because none of the drugs that were used in the conditioning regimen are associated with significant oral or gastrointestinal mucositis. In contrast, PBPC transplant patients in other studies with an increased frequency of bacteremia received mucositis-producing chemotherapeutic agents [11]. In addition, our antibacterial prophylactic regimen (oral ciprofloxacin and rifampin), used successfully in the past [6–8], may explain the very low frequency of gram-negative as well as gram-positive bacterial infections. A unique combination of a mucositis-sparing conditioning regimen and aggressive antimicrobial prophylaxis probably accounts for such a low frequency of infection among our patient population.

In contrast, Salazar et al. [15] noted that 31% of PBPC transplant recipients developed bacteremia due to gram-positive and/or gram-negative organisms while they were receiving ciprofloxacin alone as antibacterial prophylaxis. Previous animal and clinical studies showed that rifampin, when added to quinolone treatment, significantly reduced both gram-negative and gram-positive bacterial infections [16, 17]. However, because oral rifampin produced gastrointestinal intolerance in some of our patients, the newer fluoroquinolones with augmented activity against gram-positive bacteria may replace rifampin in future prophylaxis regimens. Such a change, if proven to be useful in this setting, may enhance the tolerability of the regimen.

HSV reactivation was common in oral, genital, and perianal sites. Twenty-three of the 40 infectious episodes were due to HSV. Results of direct fluorescent antibody testing and viral culture documented the presence of virus. All HSV infections responded to acyclovir therapy, and no antiviral resistance was encountered. Because nearly two-thirds of the women were HSV-seropositive, we have now included routine prophylaxis with acyclovir during the pre-engraftment period for all carriers of the virus.

Systemic fungal infection or candidemia was notably absent, although it frequently occurs in patients who undergo allogeneic marrow transplantation [18]. Fungal infections, albeit rarely, have been reported in other studies involving PBPC transplantation [3, 8]. No evidence exists to support the use of systemic antifungal prophylaxis during PBPC transplantation. Although antifungal prophylaxis with itraconazole was given to PBPC transplant recipients in a recently reported study [15], we believe that prophylaxis with systemic antifungal agents is unwarranted in our setting for autologous PBPC transplantation. In addition, use of empirical therapy with systemic antifungal agents for persistent fever in our patients was rare; in no instance was there any use of conventional or the lipid formulation of amphotericin B. Because serious fungal infections are rare, empirical therapy with antifungal agents need not be instituted on a routine basis; when deemed necessary (as was the case with 5 of our patients), fluconazole may be a useful alternative to potentially toxic amphotericin B. Nosanchuk et al. [1], however, noted that empirical amphotericin B therapy for persistent fever was administered to 15 (68%) of 22 PBPC transplant patients with underlying refractory leukemia or lymphoma.

One-half of our patients avoided hospitalization during the 2-week posttransplantation period. Meisenberg et al. [8] re-

Figure 1. No. of hospital days during the 2-week period after peripheral blood progenitor cell transplantation in an outpatient setting for women with breast cancer. Duration of hospitalization ranged from 1 to 12 days (mean, 3 days).
ported a 25% rate of hospitalization for their patients who underwent outpatient PBPC transplantation. In our study, fever was the main reason that 41 of 52 patients were hospitalized; less common reasons were nausea and/or vomiting, fluid overload, and congestive heart failure. No significant morbidity was encountered. The mean duration of hospitalization for our patients was 3 days (range, 1–12 days). None of the women required a second hospitalization. Successful outpatient management has also been documented for neutropenia with fever in “low-risk” cancer patients after they undergo chemotherapy [19–21]. Most such patients had nonhematologic neoplasms, and the duration of chemotherapy-related neutropenia was relatively short.

Fever during neutropenia was common among the patients in our study, despite broad-spectrum antibacterial chemoprophylaxis. Unexplained fever and the need for empirical antimicrobial therapy have not been reduced in most antibacterial prophylaxis studies [22]. It is noteworthy that 29% of our patients did not develop fever despite profound neutropenia. Most temperature spikes were unexplained and they were perhaps due to noninfectious causes, such as the conditioning regimen. It is interesting that 28 patients developed fever at or around (≤48 h after) the time of engraftment. Fever around the time of engraftment was not associated with clinically or microbiologically identifiable infection and had no major sequela. We now recognize this noninfectious febrile syndrome around the time of engraftment as a distinct entity and we withhold antibacterial or antifungal therapy while closely observing such patients. Engraftment syndrome that consists of noninfectious fever along with fluid retention, pulmonary infiltrates, and skin rashes has been described elsewhere in patients who undergo autologous marrow and peripheral blood transplantation [23, 24].

Although most patients received CD34+ unselected cells, 9 women received CD34+ selected cells. Six of these 9 women did not develop fever, and 3 infections occurred in this small group of patients. No serious adverse events were seen. Thus, we did not observe any excess morbidity in the immediate posttransplantation period in our women who received CD34+ selected cells. In a large study, Vescio et al. [25] reported encouraging data: although use of CD34+ selected cells significantly reduced tumor cell contamination, the infection rate and the types of infections were similar from day 0 to day 100 or after day 100 among CD34+ selected and unselected cell recipients with multiple myeloma.

In conclusion, the present study demonstrates that young women with breast cancer can safely undergo intensive chemotherapy followed by progenitor cell transplantation in the outpatient setting. The use of a mucositis-sparing conditioning regimen and broad-spectrum antimicrobial prophylaxis is unique to this study population; therefore, the findings cannot be generalized to other types of patients who undergo autologous or allogeneic transplantation. It cannot be overemphasized that intensive monitoring and the ready, round-the-clock availability of medical personnel are of crucial importance for successful outpatient management.

References

eral blood stem cell transplantation. Bone Marrow Transplant 1999; 23:27–33.


