A Feasibility Study of Multiple Cycle Therapy with Melphalan, Thiotepa, and Paclitaxel followed by Mitoxantrone, Thiotepa, and Paclitaxel with Autologous Hematopoietic Cell Support for Metastatic Breast Cancer


Division of Bone Marrow Transplantation, Department of Medicine, Stanford University Medical Center, Stanford, California 94305

ABSTRACT

Dose-intensive chemotherapy appears to be important in the treatment of patients with recurrent solid tumors. Expanding upon our prior experience, we report the results of our most recent approach to administering dose-intensive therapy using four cycles of moderately high-dose chemotherapy with hematopoietic cell support for patients with metastatic breast cancer. This outpatient therapy includes high-dose melphalan, thiotepa, and paclitaxel for two cycles followed by mitoxantrone, thiotepa, and paclitaxel for two cycles, with each cycle supported with autologous peripheral blood progenitor cells (PBPCs).

Between December 1994 and June 1996, 16 patients with recurrent or refractory breast cancer were enrolled in this prospective study. They had received a median of two previous chemotherapy regimens, with a median of nine prior cycles of chemotherapy. For mobilization of autologous PBPCs, patients received cyclophosphamide, 4 g/m², followed by granulocyte colony-stimulating factor (G-CSF). PBPCs were collected by apheresis. Each day’s collection followed by granulocyte colony-stimulating factor (G-CSF).

PBPCs were performed on an outpatient basis. The first seven patients were randomized to receive alternate cycle G-CSF or placebo on day +1 of each cycle.

Including the initial pulse of cyclophosphamide, 67 (84%) of a planned 80 total courses of chemotherapy were delivered. Of the planned 64 cycles of high-dose combination chemotherapy, 52 cycles (81%) were delivered. Treatment was discontinued for progressive disease (one patient) or morbidity (five patients). Twelve of 16 patients completed at least three cycles of therapy. Nine patients completed all four cycles. One death resulted from fungal sepsis. In 20 cycles delivered to the first seven patients, day +1 G-CSF versus placebo was administered, with a median WBC recovery of 10 versus 13 days, respectively (P = 0.048 in cycle 1). The median duration of response was almost 9 months, and the median survival was 18 months after therapy. With a median follow-up of 1.5 years and longest follow-up of 4.2 years, two patients continue to be without evidence of disease. The 3-year event-free survival, freedom from progression, and overall survival are 19%, 20%, and 31%, respectively.

This four-cycle regimen of high-dose combination therapy supported with hematopoietic progenitor cells is feasible, but it is associated with a range of posttransplant complications. The efficacy of such a treatment would have to be substantially superior to that of other currently available therapies, including single autologous transplant procedures, to justify the prolonged period of treatment, multiple episodes of pancytopenia, and associated toxicities, including infectious risks. G-CSF administration after each PBPC infusion appears to accelerate time to neutrophil recovery but does not affect red cell or platelet engraftment.

INTRODUCTION

Much experience has been gleaned throughout decades of research into tumor growth kinetics and cytotoxic therapy. The observation of a specific log-kill curve for an individual chemotherapeutic drug led to the development of treatment schemes using combinations of agents, with each one potentially adding to the overall cell kill. Subsequently, the timing and sequence of chemotherapy, the method of drug delivery, dose escalation, and dose intensity have become important concepts in the treatment of cancer.

Substantial data exist to support the importance of dose intensity (the amount of drug delivered per unit of time) in the treatment of solid tumors (1–3). However, increasing dose intensity to levels that require cytokine support has not been unequivocally established as more efficacious than standard dose therapy in prolonging overall survival in the treatment of
metastatic breast cancer (4–9). Proposed reasons for these results include variable reporting of actual doses received and insufficient dose escalation to achieve statistically significant improvements in survival. Bezwoda and colleagues (10) attempted to administer dose-intensive therapy in their randomized study demonstrating improvement in survival outcomes for patients with newly diagnosed metastatic breast cancer. However, this somewhat controversial study was criticized for its lack of high-dose cyclophosphamide in the standard dose arm, the use of an unusual combination chemotherapy regimen in the standard dose arm, the unbalanced dispensing of tamoxifen therapy, and the resulting surprisingly poor survivals therein. Although this study suggested that the second course of high-dose therapy may have been necessary to achieve the superior results, the impact of this was not ascertained sufficiently. The phase III studies that have demonstrated improvement in outcome from high-dose therapy for patients with lymphoma (11) and multiple myeloma (12) have administered a peak dose of single myeloablative therapy as consolidation after response to standard dose therapies. The role of sufficiently dose-intensive multiple-cycle therapy made possible by hematopoietic progenitor cell support has not yet been fully addressed (13–19), and the development of future clinical studies for this question may depend upon the results of current randomized studies using single courses of high-dose therapy.

We have previously reported a pilot study that described administration of dose-intensive four-cycle therapy with hematopoietic cell support (20). Patients received repetitive cycles of high-dose mitoxantrone, thiotepa, and cyclophosphamide. Each cycle was supported with PBPCs that had been collected after recovery from high-dose etoposide and G-CSF. We subsequently modified the regimen by escalating the doses of MTC and adding paclitaxel to the regimen (MTTC). However, 10 of 18 patients treated with MTTC experienced cyclophosphamide-related toxicity, including hemorrhagic cystitis, interstitial pneumonia, and cardiac dysfunction.

We attempted to ameliorate the toxicity of MTTC by further modification of the regimen. Cyclophosphamide was eliminated from the repetitive cycle regimen, and melphalan (Alkeran) was substituted for mitoxantrone (ATT) in the first two treatment cycles (ATT ×2/MTT ×2). An initial pulse of cyclophosphamide followed by G-CSF was used to mobilize autologous PBPCs. Our present report describes this four-cycle regimen and treatment outcomes for women with metastatic breast cancer.

MATERIALS AND METHODS

Patient Eligibility. Sixteen patients with recurrent breast cancer were enrolled in this study between January 1995 and June 1996. Patient eligibility criteria included the following: age <65 years, Karnofsky performance status ≥80%, the absence of central nervous system metastasis, and demonstration of adequate organ function and HIV seronegativity. Chemotherapy-responsive disease or minimal tumor volume was not criteria for eligibility. The risks and benefits of the therapy were explained to patients at the initial clinic visit and again at enrollment when written consent was obtained. The clinical protocol was approved by the Administrative Panel on Human Subjects in Medical Research at Stanford University. The study schema is depicted in Fig. 1. Patient characteristics are listed in Table 1. Patients were assessed for toxicity and response after each cycle of high-dose therapy. A patient could be taken off the study if she did not demonstrate continued improvement of disease status with each cycle of therapy based upon investigator discretion and assessment of clinical status.

Collection of PBPCs. All patients underwent placement of a double-lumen tunnelled catheter (12 French Cook, Bloomington, IN) before the administration of high-dose cyclophosphamide. Patients received cyclophosphamide at 4 g/m² i.v. over 2 h. They were discharged the following day and treated with G-CSF (Amgen, Thousand Oaks, CA) at ~10 µg/kg beginning 24 h after the completion of cyclophosphamide infusion. G-CSF was continued daily until the target number of CD34+ cells or alternate target of mononuclear cells was collected by apheresis. Prophylactic oral rifampin and ciprofloxacin were begun at the time of discharge and continued until recovery from neutropenia. The collection of autologous PBPCs by apheresis was initiated after recovery from cyclophosphamide the day after the leukocyte count was >1,000/µl and was continued daily until the target goal of 10 × 10⁶ CD34+ cells/kg or an alternate goal of 1 × 10⁹ mononuclear cells/kg was collected. Cells expressing the surface marker CD34 were identified by indirect immunofluorescence with the monoclonal antibody HPCA-2 (Becton Dickinson, Mountain View, CA) conjugated to phycoerythrin using a FAC-STAR cell sorter (Becton Dickinson). Bone marrow was not collected from any patient. Platelet counts were maintained >10,000/µl with irradiated (2500 cGy) platelet concentrates. The PBPCs were processed and cryopreserved as described previously (20).

3 The abbreviations used are: PBPC, peripheral blood progenitor cell; G-CSF, granulocyte colony-stimulating factor; ANC, absolute neutrophil count; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; SPN, Stanford patient number; PCP, Pneumocystis carinii pneumonia; ATT, melphalan (Alkeran), thiotepa, paclitaxel (Taxol); MTT, mitoxantrone, thiotepa, paclitaxel (Taxol).

4 Unpublished data.
Chemotherapy Regimen and PBPC Infusion. This schema called for administration of four cycles of high-dose therapy every 21 days on an outpatient basis. After the adequate collection of PBPCs, melphalan at 80 mg/m² was infused i.v. over 20 min on day 24. Thiotepa, 200 mg/m², was then delivered by continuous infusion pump over 48 h from day 4 to day 6. After completion of thiotepa, patients received paclitaxel, 200 mg/m², over 3 h on day 2. On day 0, one quarter of the cryopreserved autologous PBPCs were thawed and infused. This therapy was repeated in cycle 2. In cycles 3 and 4, mitoxantrone, 30 mg/m², and thiotepa were delivered by continuous infusion over 48 h from day 4 to day 6. Paclitaxel and PBPCs were administered as in the first two cycles.

Supportive Care. Patients were evaluated twice daily on an outpatient basis. Each morning, patients presented to the Day Hospital for physician evaluation and infusions of medications or blood products, if necessary, as determined by the previous evening’s laboratories. In the evening, patients received home care nursing assessment, blood sampling for laboratory analysis, and infusion of medications. Continuous infusion of i.v. fluid containing low-dose heparin (10 units/kg/day) was administered by Cadd pump (Sims Deltech, St. Paul, MN) at the start of each chemotherapy and continued until recovery from neutropenia. With the first cycle of therapy, all patients received prophylactic trimethoprim-sulfamethoxazole (160 mg/800 mg IV bid) for 3 days on day 4 to day 2. Inhaled pentamidine (300 mg) was substituted if patients were allergic to sulfa antibiotics. Except for the initial patient, all patients received either prophylactic trimethoprim-sulfamethoxazole or pentamidine at the beginning of each cycle. At the time of neutropenia, patients received prophylactic i.v. antibiotics starting with vancomycin (1 g bid). Ceftriaxone (2 g daily) was added for low-grade febrile episodes. Patients were admitted to the hospital when fever was >38.5°C. Antibiotics were continued until the ANC was >500/µl. All patients received transfusions of irradiated packed RBCs or platelet concentrates to maintain a hematocrit >30% and platelet count >10,000/µl. The first seven patients enrolled were also randomized to start day +1 G-CSF in cycles 1 and 3 and placebo in cycles 2 and 4 versus placebo in cycles 1 and 3 and G-CSF in cycles 2 and 4. All subsequent patients received G-CSF after each cycle starting day +4. G-CSF was discontinued the day after the ANC was >1500/µl.

Engraftment Evaluation. The number of days to WBC and platelet engraftment was defined as the number of days after hematopoietic cell reinfusion (day 0) to ANC >500/µl and platelets >20,000/µl. The number of transfusion products (packed red cells or platelets) transfused was monitored after each cycle of chemotherapy.

Toxicity Monitoring. Toxicity monitoring was graded using the Southwest Oncology Group common toxicity criteria. Patients were removed from the trial for any grade III-IV nonhematological toxicity or for PD.

Assessment of Response. Breast cancer lesions were assessed by physical examination and imaging studies at the start of high-dose therapy. Patients were evaluated before each cycle of therapy with physical examination and chest X-ray. Computed tomographic reassessment, if applicable, was performed after two cycles of therapy, CR, VGPR, and PR were defined by standard criteria: disappearance of all measurable...
tumor; a ≥90% reduction in measurable lesions; and ≥50% reduction in the product of the bidimensional measurements, respectively, for 4 weeks duration. Definitions for minimal response, SD, and PD included: <50% reduction in disease; no change in tumor size; and a ≥25% increase in tumor size or the appearance of new lesions, respectively.

**Treatment Following Recovery From High Dose Therapy.** Hormonal therapy for patients with receptor-positive tumors and/or radiation therapy to sites of prior disease were administered after recovery from high-dose therapy.

**RESULTS**

**Patient Data.** Patient characteristics and outcome data are listed in Table 1. The median age was 43 years (range, 33–58 years). All but one patient had premenopausal primary breast cancer. Prior primary treatment included the following: all but two patients had received primary adjuvant chemotherapy; seven patients had been initially treated with a doxorubicin-containing regimen; seven patients had previously undergone primary treatment with radiotherapy; and four patients had received hormonal therapy. In the development of recurrent disease, eight patients demonstrated visceral metastases, and eight patients manifested bony disease, with none of them associated with bone-only disease. Salvage chemotherapy was administered to 13 patients for a median of one regimen (range, 0–3). Four patients received radiotherapy, and five patients had hormonal manipulation for relapsed disease. Before enrollment, all patients had received a doxorubicin-containing regimen. Seven patients also had treatment with a paclitaxel-containing salvage regimen. The median number of prior chemotherapy regimens at the time of high-dose therapy was two (range, 1–4), with the number of prior cycles of therapy being nine (range, 4–15).

**Mobilization Data.** Fifteen of sixteen patients received cyclophosphamide and G-CSF for the mobilization of PBPCs. The median time to WBC recovery and initiation of apheresis was 10 days (range, 9–13). All patients achieved the apheresis goal of $10 \times 10^9$ CD34+ cells/kg patient weight or the alternate goal of $100 \times 10^9$ mononuclear cells/kg. The median number of aphereses was 3 (range, 1–7). A median of 2 units of packed red cells (range, 0–3) and zero platelet products (range, 0–3) were transfused around the time of cell collection. The median number of days from high-dose cyclophosphamide to commencement of the multicycle therapy was 27 (range, 24–56).

One patient did not receive cyclophosphamide because her PBPCs had been collected with G-CSF, as specified in another protocol from which she became ineligible when her disease progressed through standard dose chemotherapy.

**Hematological Recovery (with or without G-CSF).** To infuse equivalent numbers of PBPCs at each cycle, each day’s apheresis collection was split into four equal fractions. Each cycle’s quarter fraction was subsequently thawed and reinfused on day 0 of each cycle. The median number of mononuclear cells infused per cycle was $2.8 \times 10^8$/kg (range, 0.64–11.47 $\times 10^8$). Of 10 patients for whom numbers of CD34+ cells are available, the median number of CD34+ cells infused per cycle was $3.15 \times 10^8$/kg (2.2–5.0 $\times 10^8$).

In our previous report on multiple cycle therapy supported with PBPCs, time to neutrophil and platelet recovery remained constant throughout the four courses of therapy when G-CSF was initiated on day +1 of each cycle (20). At the time this present study was proposed, the impact of G-CSF after autologous PBPC transplant was unclear. Therefore, a secondary aim was to determine whether G-CSF was necessary to accelerate time to neutrophil or platelet recovery following infusion of “primed” PBPCs collected after recovery from chemotherapy and G-CSF. Patients received either G-CSF or placebo in alternate cycles starting day +1. To avoid an effect from initial cycle or prior cycle G-CSF, patients were randomized to G-CSF in cycles 1 and 3 and placebo in cycles 2 and 4 versus G-CSF in cycles 2 and 4 and placebo in cycles 1 and 3. The first seven patients agreed to randomization. However, because the sixth and seventh patients both refused postinfusion blinded treatment after cycle 2, they received G-CSF in cycles 3 and 4. Because of patient preference and reports of the utility of postransplant G-CSF (21), this aspect of the protocol was suspended, and the nine subsequent patients enrolled received G-CSF in each cycle.

The median number of days to WBC recovery (with and without G-CSF) and platelet recovery after each cycle of therapy are listed in Table 2. As listed in Table 3, 20 cycles of G-CSF or placebo were administered to seven patients on day +1. The median time to WBC recovery using G-CSF was 10 days compared to placebo at a median of 13 days. Because there were so few patients evaluable for this part of the study, only cycle 1 demonstrated a statistically significant WBC recovery time with the use of G-CSF after autograft infusion ($P = 0.048$). The median time to platelet recovery and the median number of transfusions of packed RBCs and platelets were not statistically significant between the groups who received G-CSF versus placebo. The median number of transfusions administered at each cycle are listed in Table 4.

**Toxicities.** The toxicities associated with this treatment (Table 5) were primarily related to infections rather than organ toxicity. There were no cases of hemorrhagic cystitis, veno-occlusive disease of the liver, nor documented cardiac dysfunction. There was one mortality secondary to fungemia.

**Infections.** Despite prophylaxis with i.v. sulfamethoxazole/trimethoprim, the first study patient developed PCP and diffuse alveolar hemorrhage on day +13 of cycle 3. She recovered fully; nonetheless, a fourth cycle of therapy was not administered. Patient SPN 1254 developed *Candida tropicalis* sepsis in cycle 2. She experienced multiorgan failure and ex-

**Table 2** Time to recovery of absolute neutrophil count $>500/\mu$l and platelet count $>20,000/\mu$l following each cycle of therapy

<table>
<thead>
<tr>
<th>Cycle #</th>
<th>Days to ANC $&gt; 500$ (range)</th>
<th>Days to PLTs $&gt; 20$ K (range)</th>
<th>Interval to next cycle (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>10 (9–15)</td>
<td>11 (8–23)</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>10 (8–13)</td>
<td>10 (6–19)</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>11 (9–17)</td>
<td>10 (9–17)</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>10 (8–17)</td>
<td>11 (8–16)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

# number of patients; PLT, platelet.
pired. Patient SPN 1094 developed cytomegalovirus pneumonia after completion of therapy. Three patients experienced reactivation of dermatomal zoster. Overall, there were 10 episodes of bacteremia in eight patients and 1 episode of fungemia after completion of therapy. Thirteen patients had at least one positive culture of blood, urine, stool, or bronchoalveolar lavage specimens for any infectious organism and/or developed dermatomal zoster (three patients) before completion of therapy.

**Hospitalizations.** All patients were hospitalized at least once during treatment, which included the initial high-dose cyclophosphamide. There were 29 hospitalizations (range, 1–4 per patient), including four episodes of overnight (23 h) observation during 67 courses (78%) of administered therapy. Duration of hospitalizations ranged from overnight to 42 days (20 days in the intensive care unit). The diagnosis requiring hospitalization in 25 cases was febrile neutropenia.

**Treatment Outcome.** Twelve patients completed at least three cycles of therapy (as shown in Table 1). Three patients did not receive cycle 4: one developed PCP; one developed interstitial pneumonitis (treated with corticosteroids) and shingles; and a third was taken off the study for achievement of only SD after cycle 3. Four patients completed only one or two cycles of therapy as follows: one expired after cycle 2; one patient was removed from the study due to kinetically failing disease; one developed refractoriness to platelet transfusion support in cycle 1; and one had pneumonia and prolonged bacteremia associated with venous thrombosis. Nine of 16 patients completed all four cycles of therapy.

Including the initial course of cyclophosphamide, 67 (84%) of a planned total of 80 courses of chemotherapy and 52 (81%) of a planned 64 cycles of high-dose combination therapy were delivered. As of March 31, 1999, the median follow-up was 18 months. Freedom from progression at 2 years was 27% and at 3 years was 20%. Overall survival at 3 years was 31%.

**DISCUSSION**

Tumor response in the setting of recurrent disease may differ from that seen in the treatment of primary disease. Although the strategy of “high-dose sequential” or “dose-dense” serial monotherapy over short intervals appears promising in the treatment of patients with newly diagnosed high-risk lymphoma (22) and breast cancer (23, 24), its role in the treatment of recurrent disease is unclear. Given the greater degree of tumor heterogeneity, administration of a single drug, even at a maximal dose, may kill only a small population of susceptible cells while allowing the remaining population of resistant cells to proliferate. For patients with recurrent breast cancer, reports of single-agent high-dose cyclophosphamide (60 mg/kg × 2; Ref. 25) or melphalan (140–180 mg/m²; Ref. 26) used for cytoreduction before myeloablative chemotherapy and autografting have not demonstrated improvement in survival outcomes. Because dose intensity and total dose appear to be important factors in achieving CR and in the duration of response (27), multiple-cycle high-dose combination therapy administered in relatively short intervals and supported with hematopoietic cells may be the optimal treatment strategy for recurrent disease.

In our previous report on four-cycle therapy supported with PBPCs (20), we described the feasibility of repetitive cycles of high-dose mitoxantrone, 18 mg/m², thiotepa, 150–200 mg/m², and cyclophosphamide, 4500–5000 mg/m². We subsequently modified this regimen by adding paclitaxel at 150 mg/m² and escalating the thiotepa dose from 200 mg/m² to 300 mg/m² per cycle. However, 10 of 18 patients experienced one or more toxicities related to the cumulative dose of cyclophosphamide at 18 g/m². These included: hemorrhagic cystitis (four episodes), interstitial pneumonitis (five episodes), and cardiac dysfunction (four episodes). Our present report resulted from the last modification of multicyle treatment, which eliminated cyclophosphamide from the repetitive cycle regimen, increased the mitoxantrone dose, increased the paclitaxel dose, and substituted melphalan (Alkeran) into the first two cycles (ATT). The drugs included in our protocol have been used alone or in various combinations in the setting of high-dose therapy for stage IV or metastatic breast cancer. Melphalan and thiotepa are alkylators with steep dose-response curves in breast cancer cell lines. In Antman’s initial review of intensive therapy with stem cell support for breast cancer (28), a survey of clinical trials for advanced or refractory breast cancer using single agents yielded

### Table 3

The effect of G-CSF versus placebo on recovery of ANC > 500 by cycle on the seven patients randomized to posttransplant therapy

<table>
<thead>
<tr>
<th>Cycle</th>
<th>No. pts</th>
<th>+ G-CSF</th>
<th>No. pts</th>
<th>+ Placebo</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>0.048</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>8.5</td>
<td>4</td>
<td>12</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>14</td>
<td>2</td>
<td>14.5</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>11.5</td>
<td>3</td>
<td>17</td>
<td>0.54</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

*No. pts, number of patients who received G-CSF or placebo by cycle.

**Analysis performed by rank sum test.**

### Table 4

Number of transfusions of packed RBCs and platelets with each cycle of therapy

<table>
<thead>
<tr>
<th>Cycle</th>
<th>PRBCs</th>
<th>PLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (2–11)</td>
<td>3 (1–13)</td>
</tr>
<tr>
<td>2</td>
<td>5 (2–8)</td>
<td>3 (1–5)</td>
</tr>
<tr>
<td>3</td>
<td>4.5 (3–10)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>4</td>
<td>6 (3–9)</td>
<td>2 (1–4)</td>
</tr>
</tbody>
</table>

PRBC, packed RBC; PLT, platelet.
Multiple Cycle Therapy for Metastatic Breast Cancer

CRs only in patients treated with either high-dose melphalan (dose range, 120–180 mg/m²) or thiotepe (dose range, 180–1575 mg/m²). In a dose-escalation study, melphalan, 100 mg/m², and thiotepe, 500 mg/m², were combined with busulfan at 12 mg/kg in a single course of myeloablative therapy (29). Thiotepe (900 mg/m²) has been combined with mitoxantrone in dose escalation to 50 mg/m² (30, 31). Melphalan (180 mg/m²) with mitoxantrone (60 mg/m²) constituted a myeloablative regimen that yielded promising results in patients treated to CR before high-dose therapy. Of these patients, only one with chest wall recurrence remains free of disease. All six other patients have since relapsed, with five having developed PD between this study, seven patients had also received paclitaxel treatment from regimen-related toxicity, and the third progressed at 839 days after high-dose therapy. Two other patients have done well; one continues without evidence of disease progression, and the third progressed at 839 days. Both patients had limited cycles of prior chemotherapy (one regimen each).

In conclusion, we have reported the results of a novel four-cycle regimen of high-dose melphalan, thiotepe, and paclitaxel for two cycles followed by mitoxantrone, thiotepe, and paclitaxel for two cycles, with each cycle supported with hema-

<table>
<thead>
<tr>
<th>Toxocities</th>
<th>ATT/MTT (No. of episodes)</th>
<th>CY* (15 courses)</th>
<th>HDT (52 courses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (no source)</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>TPN</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Overnight Observation</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease of liver</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micrococcus</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacillus</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter infection: Staph epi</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary candidiasis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoxomgalovirus</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CY, cyclophosphamide; HDT, high-dose therapy; TPN, total parenteral nutrition.

CRs only in patients treated with either high-dose melphalan (dose range, 120–180 mg/m²) or thiotepe (dose range, 180–1575 mg/m²). In a dose-escalation study, melphalan, 100 mg/m², and thiotepe, 500 mg/m², were combined with busulfan at 12 mg/kg in a single course of myeloablative therapy (29). Thiotepe (900 mg/m²) has been combined with mitoxantrone in dose escalation to 50 mg/m² (30, 31). Melphalan (180 mg/m²) with mitoxantrone (60 mg/m²) constituted a myeloablative regimen that yielded promising results in patients treated to CR before high-dose therapy (32). Paclitaxel has been escalated to 825 mg/m² as a single myeloablative dose (33) or in combination to 775 mg/m² with cyclophosphamide, 5625 mg/m², and cisplatin, 165 mg/m² (34). Although the present study administered multidrug therapy over a 10-week span, the cumulative doses in this regimen (melphalan, 160 mg/m², thiotepe, 1200 mg/m², mitoxantrone, 60 mg/m², and paclitaxel 800 mg/m²) exceed those reported in studies of single-course high-dose therapies.

Although the protocol aim was to administer chemotherapy every 21 days, patients actually received treatment at a median of 24-day intervals. Delays in therapy were usually due to slow WBC recovery or infectious complications. Cycles of therapy during which patients received placebo rather than G-CSF resulted in a delay in WBC recovery (median, 13 days versus 10 days, respectively) and not in red cell or platelet transfusion requirements.

Regimen-related toxicity was moderate, with febrile neutropenia requiring hospitalization for all patients at some point during their treatment course. Otherwise, grade 1–2 diarrhea and neuropathy were the most frequently noted side effects. However, two patients developed infections (PCP and cytomegalovirus pneumonitis) characteristic of T-cell immunodeficiency. Although serious pulmonary infections may be found in T-cell-depleted autograft recipients (35), children undergoing autografting (36, 37), and those treated with immunosuppressive pretransplant therapies (38), we have not observed this morbidity with single-cycle autotransplants for breast cancer nor with our prior multicyle regimens. Other centers have reported this rare complication in standard or high-dose chemotherapy, however (39, 40). Review of both patients’ prior history and treatment did not yield information that would predict the development of these complications. Lymphocyte analysis was not performed at the time of these diagnoses; however, subsequent management included prolonged antimicrobial prophylaxis of PCP. Because our prior regimens had included cyclophosphamide, thiotepe, mitoxantrone, and later paclitaxel, perhaps the addition of melphalan to this high-dose combination regimen may have contributed to this type of immunocompromise.

The patients enrolled in this study generally had poor risk features of disease. In our multivariate analysis of prognostic variables associated with outcome after high-dose therapy for patients with metastatic breast cancer (41), factors associated with poor outcome were identified and were similar to those for women with breast cancer treated with standard therapies. These included hormone receptor-negative disease, the presence of visceral metastasis, two or more prior regimens, refractory disease, and less than VGPR to high-dose therapy. Other groups have identified prior history of anthracycline exposure (42) as an additional adverse risk factor. In contrast, the achievement of CR to induction therapy and presence of metastasis to a single site (43) are predictors of better outcome. In our study population, all patients had received prior anthracycline therapy, with a median of two prior regimens. Eight patients demonstrated visceral metastases, and 13 patients had disease metastatic to two or more sites. Only three patients had achieved minimal disease status before the time of high-dose therapy, all of whom had metastasis to the chest wall that was resected. One of these patients remains without evidence of disease, one patient died from regimen-related toxicity, and the third progressed at 839 days after high-dose therapy. Two other patients have done well; one continues without evidence of disease progression, and the other developed PD at 1358 days. Both patients had limited cycles of prior chemotherapy (one regimen each.)

Another possible adverse determinant of outcome may be prior paclitaxel therapy. The development of drug resistance mediated through the multidrug resistance model has been well-documented for several drugs, including anthracyclines and taxanes, which are substrates for the p-glycoprotein receptor. In this study, seven patients had also received paclitaxel treatment before high-dose therapy. Of these patients, only one with chest wall recurrence remains free of disease. All six other patients have since relapsed, with five having developed PD between 147 and 270 days after high-dose therapy. The sixth patient developed PD at 489 days after therapy.

In conclusion, we have reported the results of a novel four-cycle regimen of high-dose melphalan, thiotepe, and paclitaxel for two cycles followed by mitoxantrone, thiotepe, and paclitaxel for two cycles, with each cycle supported with hema-
topoietic progenitor cells. This therapy is feasible, but it is associated with a range of toxicities, including infectious complications. G-CSF administration after each PBPC infusion accelerates time to neutrophil recovery but appears to have no effect on red cell or platelet engraftment. The outcomes of this approach appear comparable to those reported to the North American Bone Marrow Transplant Registry for single courses of high-dose therapy in the treatment of recurrent breast cancer (44); however, they may represent treatment efficacy given that this study population has multiple poor prognostic features. The survival results of autotransplantation are best for patients who achieve CR with standard-dose salvage therapy. Another strategy to improve outcome would be to apply novel chemotherapy regimens such as this at standard doses to achieve minimal disease before single-course high-dose therapy. Administration of dose-intensive multiple-cycle therapy with hematopoietic cell support is possible; however, the efficacy of such a treatment would have to be substantially superior to that of currently available therapies, including single autotransplants, to justify the prolonged period of treatment, multiple episodes of pancytopenia, and associated toxicities, including infectious risks.

ACKNOWLEDGMENTS

We thank the medical house staff, the clinical hematology, oncology, and bone marrow transplantation fellows, and the Day Hospital nurses for their outstanding patient care efforts. Also, special thanks to Ruby Wong for statistical support.

REFERENCES

Multiple Cycle Therapy for Metastatic Breast Cancer


A Feasibility Study of Multiple Cycle Therapy with Melphalan, Thiotepa, and Paclitaxel followed by Mitoxantrone, Thiotepa, and Paclitaxel with Autologous Hematopoietic Cell Support for Metastatic Breast Cancer

Wendy W. Hu, Gwynn D. Long, Keith E. Stockerl-Goldstein, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/5/11/3411

Cited articles
This article cites 36 articles, 18 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/5/11/3411.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.