Adjuvant Treatment of High-Risk Breast Cancer Using Multicycle High-Dose Chemotherapy and Filgrastim-mobilized Peripheral Blood Progenitor Cells


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ABSTRACT

Women with primary breast cancer associated with extensive axillary node involvement or large primary tumors have a very poor prognosis despite treatment with standard-dose adjuvant chemotherapy. In an attempt to improve the outlook of these patients, we investigated the safety and feasibility of delivering three cycles of high-dose epirubicin and cyclophosphamide supported with filgrastim-mobilized peripheral blood progenitor cells (PBPC). Fifteen previously untreated women, median age 50 years (range, 30–58) years, with poor prognosis early stage breast cancer received filgrastim (12 µg/kg daily for 6 days) prior to chemotherapy to mobilize progenitor cells. Patients were then given three cycles of epirubicin (200 mg/m²) and cyclophosphamide (4 g/m²) at planned 28-day intervals, each followed by infusion of one third of the PBPC collected and daily administration of filgrastim (5 µg/kg s.c.). Three leukophereses collected a median of 114.9 (range, 22.7–273.5) × 10⁹ granulocyte-macrophage-colony-forming cells/kg body weight. Hemopoietic recovery was rapid after each cycle, and there was no correlation between the rate of recovery and the number of granulocyte-macrophage-colony-forming cells infused. There was a small but significant progressive delay in recovery from hematological and nonhematological toxicities across the three cycles. Left ventricular ejection fraction fell to below 50% in eight (53%) patients, but none developed congestive cardiac failure. Two patients did not complete three cycles because of insufficient PBPC for a third cycle (n = 1) and 2-mercaptoethane sodium sulfonate-related drug reaction during the second cycle (n = 1). There were no deaths during the study or during the follow-up period (median, 70 weeks; range, 50–85 weeks), and no late toxicities occurred. Therefore, we concluded that the delivery of multiple cycles of nonmyeloablative, dose-intensive chemotherapy supported by PBPC and filgrastim is safe, and may be widely applicable to a variety of common chemosensitive cancers with a poor prognosis. The efficacy of three cycles of high-dose epirubicin and cyclophosphamide is to be compared with standard-dose chemotherapy in a randomized trial in patients with high-risk, operable stage II and III breast cancer.

INTRODUCTION

More effective treatment is required for patients with primary breast cancer and extensive axillary node involvement or large primary tumors. Many patients in this group are young and have a very poor prognosis, even when treated with standard-dose adjuvant chemotherapy (1, 2). High doses of chemotherapy may be of benefit by exploiting the dose-response effect observed in patients with metastatic breast cancer (3, 4). High response rates can be achieved in patients with metastatic disease with a single course of myeloablative chemotherapy with autologous stem cell support, but without improvement in long-term survival (5). In vitro and clinical data suggest that administration of multiple cycles of chemotherapy given at the maximum safe dose intensity (dose/unit time; Ref. 6) is likely to be more effective than a single cycle of chemotherapy (7, 8). Furthermore, it is believed the drugs that should be dose intensified are those that are most active in breast cancer (9).

Until recently, the administration of multiple courses of high-dose chemotherapy was not possible because of profound toxicity issues.

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5 The abbreviations used are: PBPC, peripheral blood progenitor cells; GM-CFC, granulocyte-macrophage-colony-forming cells; MESNA, 2-mercaptoethane sodium sulfonate.
The duration of severe neutropenia and thrombocytopenia after high-dose chemotherapy can now be significantly shortened by administration of PBPC\(^5\) and granulocyte-colony-stimulating factor (filgrastim; Refs. 10 and 11). Furthermore, granulocyte-colony-stimulating factor is effective at mobilizing PBPC into the circulation and enabling large numbers of PBPC to be collected (12). We sought to determine the feasibility of delivering three cycles of high-dose epirubicin and cyclophosphamide to women with untreated early stage, poor prognosis breast cancer by supporting each cycle with filgrastim-mobilized PBPC and filgrastim. We also examined whether sufficient PBPC to support this regimen could be collected from these patients by three leukaphereses during administration of filgrastim.

**PATIENTS AND METHODS**

**Eligibility and Evaluation.** Eligible patients were ages between 16 and 60 years with histologically confirmed poor prognosis breast cancer, defined as stage II disease with 10 or more positive axillary nodes or an estrogen-receptor-negative tumor with at least four positive axillary nodes, or stage III disease. Staging procedures included complete blood count, liver function tests, chest X-ray, bone scan, and bone marrow aspirate and trephine. Patients were required to have a resting left ventricular ejection fraction greater than 50% as measured by radionuclide scan. Women receiving adjuvant therapy commenced treatment on protocol within 8 weeks of surgery. Prior hormonal or radiation therapy for breast cancer was allowed, but not chemotherapy. This study was approved by the relevant Institutional Ethics Committees, and conformed with the ethical guidelines of the National Health and Medical Research Council of Australia and the Food and Drug Administration of the United States. All patients gave written informed consent.

**Treatment.** Progenitor cells were collected from peripheral blood after mobilization by filgrastim prior to chemotherapy, as described previously (11). Briefly, filgrastim (Amgen, Thousand Oaks, CA) was given as a continuous s.c. infusion (12 \(\mu\)g/kg daily) for 6 days, and leukaphereses were performed on the fifth, sixth, and seventh days using a modified mononuclear cell collection program with the RBC interface set at 0.2 units on the Fenwal CS-3000 cell separator (Baxter, Deerfield, IL). One patient had an additional leukapheresis on the eighth day due to leakage of apheresis product from a faulty collection bag. The product from each apheresis specimen was concentrated as described previously (10), and either divided into three equal fractions (\(n = 9\)) or stored in a single bag (\(n = 6\)), then cryopreserved. All patients had back-up bone marrow harvested after the leukapheresis phase for use if hematopoietic recovery failed.

High-dose chemotherapy consisted of epirubicin (Farmitalia Carlo Erba, Milan, Italy), 200 mg/m\(^2\) i.v. over 12 h on day \(t - 4\), and cyclophosphamide (Farmitalia Carlo Erba), 4 g/m\(^2\) on day \(t - 3\), given as 1 g/m\(^2\) i.v. over 30 min in four divided doses. The uroprotective agent MESNA was given as an i.v. bolus prior to the first dose of cyclophosphamide (0.8 g/m\(^2\)), then as a continuous infusion on days \(t - 3\) (4 g/m\(^2\)) and \(t - 2\) (2.4 g/m\(^2\)). All patients received antiemetic therapy consisting of ondansetron and dexamethasone. One third of the total cryopreserved PBPC obtained by leukapheresis was infused on day 0. Reinfusion of PBPC was timed to allow for the long terminal half-life of epirubicin. Filgrastim (5 \(\mu\)g/kg daily by bolus s.c. injection) was administered from day \(t + 1\) until the WBC count was \(>10 \times 10^9/liter\). Broad spectrum i.v. antibiotics were commenced when the WBC count fell below 1 \(\times 10^9/liter\), and continued until the absolute neutrophil count was \(\geq 0.5 \times 10^9/liter\) on 2 consecutive days. Three cycles of chemotherapy were delivered at planned 28-day intervals. Chemotherapy could only commence if the absolute neutrophil count was \(\geq 1.5 \times 10^9/liter\) and platelet count was \(\geq 100 \times 10^9/liter\). Two patients did not complete three cycles because of an inadequate number of remaining cryopreserved PBPC in one (two cycles completed), and MESNA-related toxicity in the other (one cycle completed). Eight patients received radiotherapy to the chest wall (seven to the left side) after completion of chemotherapy.

Hospitalization policy was flexible. If toxicities permitted, patients were discharged after delivery of chemotherapy, and the progenitor cell infusion and filgrastim were administered in the outpatient clinic. Patients were admitted to the hospital when i.v. antibiotics commenced, and discharged once the antibiotics were ceased.

Clinical assessment and complete blood count were performed daily during and after high-dose chemotherapy until recovery, and then three times weekly until the next cycle. Platelet and RBC transfusions were given when the platelet count fell below 20 \(\times 10^9/liter\), and the hemoglobin to <90 g/liter, respectively. Following completion of three cycles of chemotherapy, patients were reviewed for 3 months for ongoing assessment of hematopoiesis, recovery from toxicities, and disease status. Measurement of resting left ventricular ejection fraction was performed before treatment, and at completion of the third cycle of chemotherapy or after radiotherapy.

The number of GM-CFC was determined in the peripheral blood and leukapheresis product by enumerating colony numbers after 14 days of incubation, as previously described (12, 13). Patients could only proceed with each cycle of chemotherapy if more than 10 \(\times 10^9/kg\) body weight of GM-CFC were available for infusion.

All statistical tests were performed with the computer statistics program SAS Version 6 (First Edition; SAS, Cary, NC). Comparisons between cycles were made with the Friedman two-way ANOVA by the rank test for hematopoietic end points and with the \(\chi^2\) test for mucositis. Associations between GM-CFC and hematopoietic end points were assessed with Pearson’s correlation coefficients. Results are given as median (range) unless otherwise stated.

**RESULTS**

**Leukapheresis.** All 15 patients (Table 1) completed the leukapheresis phase of the study. The WBC count during the 6 days of filgrastim treatment rose from a baseline of 6.8 \(\times 10^9/liter\) (range, 4.2–12.1) to 63.6 \(\times 10^9/liter\) (range, 40.2–98.8), and consisted of predominantly band forms and mature neutrophils. The number of peripheral blood GM-CFC prior to filgrastim was 93/ml (range, 46–1459) and rose to 10,600/ml (range,
cycles 1, 2, and 3, respectively (P < 0.01 for trend over successive cycles). Thirteen of the 15 patients lost weight, with an average loss of 3.6 kg, or 5.1% of pretreatment body weight. Delivery of filgrastim administration. No patient required parenteral nutrition. Mucositis was the major nonhematological toxicity of chemotherapy. There were 1 of 15, 5 of 14, and 7 of 13 episodes of either grade 3 or 4 mucositis in cycles 1, 2, and 3, respectively (P = 0.02, Table 2). These severe episodes lasted a median of 6 (range, 3–10) days, and all mucositis resolved rapidly at the time of neutrophil recovery. No mucosal toxicity was observed in 13 (31%) of the 42 cycles, including in three patients after the third course of chemotherapy. Despite the prolongation of hematological recovery with successive cycles, the duration of the hospital stay did not vary significantly (Table 2).

Packed RBC transfusions were required in 41 of the 42 cycles of chemotherapy delivered, and the number of units given to each patient during the study was 10 (range, 4–19). The number of units transfused did not vary with successive cycles (P = 0.14, Table 2).

Nonhematological Toxicity. Patients with estrogen receptor-negative tumors.

Hematological Recovery. Hematological recovery was rapid after each cycle of chemotherapy, although there was a 1–2-day increase in the time taken for recovery following successive cycles. No patient required back-up bone marrow infusion for prolonged cytopenia. The times after PBPC infusion to neutrophil recovery ≥0.5 × 10⁹/liter for cycles 1, 2, and 3 were 9, 9.5, and 11 days, respectively (P = 0.01 for trend over successive cycles; Fig. 2A and Table 2). Neutrophils recovered to normal (≥2.5 × 10⁹/liter) by day 13 in all cycles. The number of episodes of either grade 3 or 4 mucositis in cycles 1, 2, and 3, respectively (P = 0.02, Table 2). These severe episodes lasted a median of 6 (range, 3–10) days, and all mucositis resolved rapidly at the time of neutrophil recovery. No mucosal toxicity was observed in 13 (31%) of the 42 cycles, including in three patients after the third course of chemotherapy. No patient required parenteral nutrition.

Other nonhematological toxicities were generally mild (Table 3). Thirteen of the 15 patients lost weight, with an average loss of 3.6 kg, or 5.1% of pretreatment body weight. Delivery of the second and third cycles of chemotherapy was delayed beyond the planned 28 days in 13 of (45%) 28 cycles for 6 (range, 4–14) days. In four instances this was due to unresolved infec-

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>No. of study patients</td>
<td>15</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>50 yr (30–58)</td>
</tr>
<tr>
<td>No. of involved axillary nodes</td>
<td></td>
</tr>
<tr>
<td>&lt;10⁹</td>
<td>3</td>
</tr>
<tr>
<td>10–14</td>
<td>6</td>
</tr>
<tr>
<td>15–20</td>
<td>3</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2</td>
</tr>
<tr>
<td>Primary tumor T₁ or T₄</td>
<td>4</td>
</tr>
<tr>
<td>Prior mastectomy</td>
<td>12</td>
</tr>
<tr>
<td>Prior conservative surgery</td>
<td>2</td>
</tr>
<tr>
<td>No prior surgery</td>
<td>1</td>
</tr>
</tbody>
</table>

* Patients with estrogen receptor-negative tumors.

* Lumpectomy or segmental mastectomy.
Cardiac function was assessed at baseline and after recovery from acute toxicities following the third cycle of chemotherapy. At the completion of treatment the resting left ventricular ejection fraction fell by a median of 9% (range, 0–18%) from baseline. The ejection fraction fell to below 50% in 8 (53%) patients, including the 2 patients who did not complete three cycles (who received cumulative doses of epirubicin of 475 mg/m² and 400 mg/m²). Seven of these patients had a fall in the ejection fraction from baseline of >10% (absolute value), and four had received chest wall irradiation (three to the left side). One patient developed an asymptomatic sinus tachycardia following adjuvant radiotherapy to the left chest wall given after chemotherapy, but no patient developed clinical or radiological evidence of congestive cardiac failure.

There were no treatment-related deaths. No late hematological failure occurred at a median follow-up of 70 (range, 50–85) weeks, and there were no late onset nonhematological toxicities. Assessment of disease-free and overall survival is ongoing.

### DISCUSSION

Our main finding was that three cycles of high-dose epirubicin and cyclophosphamide were well tolerated when supported by PBPC and filgrastim. Furthermore, sufficient PBPC to ensure rapid hematopoietic recovery after each cycle could be obtained by three leukaphereses after mobilization by filgrastim in the majority of previously untreated patients. This regimen offers an alternative approach to the treatment of women with high-risk stage II (as previously defined) and stage III breast cancer. These women are often young and between 55 and 85% will suffer relapse of breast cancer by 5 years, even when treated with conventional dose adjuvant or primary chemotherapy (1, 2). Other strategies aimed at improving these results use standard-dose induction chemotherapy followed by a single myeloablative treatment (14), or dose-intensive sequential therapy supported by growth factors and progenitor cells (15). Both of these approaches involve drugs not generally used at standard doses to treat breast cancer. The regimen used in the current study was developed based on the hypothesis that improved disease-free and overall survival would be achieved using the most active agents at the maximum dose intensity that is safe (6, 9). Furthermore, the cell kinetics of breast cancer (16) and the cytotoxicity of chemotherapy drugs in vitro (8) suggest that enhanced cell kill is likely with multiple courses of chemotherapy compared to a single course. The potential superiority of multiple cycles is supported by the clinical observation that treatment with six cycles of conventional dose adjuvant treatment in patients with node-positive breast cancer result in more long-term survivors than one cycle of perioperative chemotherapy (7). The present study demonstrates the safety of delivering three cycles of high-dose epirubicin and cyclophosphamide, and a randomized clinical trial is warranted to determine the efficacy of this regimen.

### Table 2 Hematological recovery and hospital morbidity for each of the three cycles of chemotherapy

| Toxicity | Cycle 1 (n = 15) | Cycle 2 (n = 14) | Cycle 3 (n = 13) | P
|
|----------|-----------------|-----------------|-----------------|---|
| Platelet transfusions | 1 (0–6) | 2 (0–6) | 3 (1–10) | 0.01 |
| Units RBCs transfused | 3 (0–10) | 4 (2–6) | 4 (2–8) | 0.14 |
| Median (range) no. of days | | | | |
| to neutrophils > 5 x 10⁹/liter | 9 (8–11) | 9.5 (8–12) | 11 (8–11) | <0.01 |
| with neutrophils < 0.5 x 10⁹/liter | 5 (4–8) | 6 (4–10) | 7 (5–9) | <0.01 |
| to platelets > 20 x 10⁹/liter | 8 (7–12) | 9 (8–13) | 10 (7–14) | <0.01 |
| with platelets < 20 x 10⁹/liter | 1 (0–7) | 3.5 (0–9) | 6 (1–14) | <0.01 |
| of parental antibiotics | 7 (5–20) | 8 (5–14) | 9 (6–15) | 0.16 |
| of hospitalization | 15 (11–22) | 17 (10–25) | 15 (11–32) | 0.23 |
| of filgrastim | 10 (8–12) | 10 (8–13) | 11 (8–18) | 0.06 |
| Episodes of grade 3/4 mucositis | 1 | 5 | 7 | 0.02 |

P values for trends across the three cycles of chemotherapy in individual patients were determined using the Friedman two-way ANOVA by the rank test.

### Table 3 Nonhematological toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenic fever (T &gt; 38°C) + ANC &lt; 1 x 10⁹/liter</td>
<td>25/42 (60%) cycles</td>
</tr>
<tr>
<td>median duration (range)</td>
<td>3 days (1–10)</td>
</tr>
<tr>
<td>Grade 3 vomiting</td>
<td>5/42 (12%) cycles</td>
</tr>
<tr>
<td>Grade 3 diarrhea</td>
<td>3/42 (9%) cycles</td>
</tr>
<tr>
<td>Epirubicin-related fever &gt; 38°C</td>
<td>16/42 (38%) cycles</td>
</tr>
<tr>
<td>Nasopharyngeal herpes simplex</td>
<td>8/15 (53%) patients</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>6/15 (40%) patients</td>
</tr>
<tr>
<td>Fatigue (grade 2)</td>
<td>8/15 (53%) patients</td>
</tr>
<tr>
<td>Reinsertion of central venous catheter</td>
<td>7/15 (47%) patients</td>
</tr>
</tbody>
</table>

T, temperature; ANC, absolute neutrophil count.

These are nonhematological toxicities.

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The basis of this approach was suggested by the observation that sufficient progenitor cells could be collected from previously treated patients with lymphoid cancers after mobilization by filgrastim to support a single cycle of high-dose chemotherapy. We hypothesized that a greater yield of progenitor cells would be achieved in untreated patients whose hemopoietic stem cell reserve had not been damaged by prior therapy. Indeed, yields were approximately 5-fold higher than in previously treated patients undergoing the same mobilization regimen. We were able to collect enough progenitor cells from three leukapheresis to be confident of rapid recovery (18) following the three cycles of chemotherapy in all but one patient, and from a single apheresis in eight of the 15 (53%) patients. However, it was not possible prospectively to identify patients in whom one apheresis would have been sufficient. The use of combinations of cytokines that exhibit in vitro and in vivo synergy, such as interleukin 3 with granulocyte-macrophage-colony-stimulating factor (19) or filgrastim with stem cell factor (20), or the combined use of standard-dose chemotherapy and filgrastim (21), might improve the mobilization of progenitor cells so that the need for multiple aphereses can be consistently and predictably reduced.

Variation in granulocyte-macrophage progenitor cell yield during filgrastim administration of up to 200-fold has been reported in previously treated patients, and attributed to differences in the extent of prior treatment (17). Although patients in the current study were untreated, and all had documented nor-mocellular bone marrows with no evidence of malignant infiltration, substantial variation (12-fold) in the yield of progenitors also occurred. Interestingly, response heterogeneity of about 10-fold is observed in syngeneic mice given granulocyte-macrophage-colony-stimulating factor (22). The variability observed in progenitor cell yield in the current study therefore most likely reflects unexplained, inherent biological differences between individuals.

Infusion of PBPC after myeloablative chemotherapy has been demonstrated to result in faster platelet and neutrophil recovery than autologous bone marrow supported by posttransplant filgrastim (11). Although the role of PBPC in accelerating hemopoietic recovery in nonmyeloablative high-dose chemotherapy regimens is not clearly defined, the women in this study appeared to experience substantially shorter periods of severe neutropenia and thrombocytopenia than patients with breast cancer receiving similar but less intensive chemotherapy supported with filgrastim alone (23). Indeed, the maximum tolerated doses of epirubicin and cyclophosphamide when supported with filgrastim alone are 150 mg/m² and 1500 mg/m², respectively. In the current study, no correlation was found between the rate of hemopoietic recovery after each cycle of chemotherapy and the number of GM-CFC infused. This is not surprising because most cycles were supported by more GM-CFC than the apparent threshold necessary for rapid hemopoietic recovery, above which no further reduction in the period of neutropenia or thrombocytopenia is observed (18). The small but statistically significant progressive delay in hematological recovery across the three cycles of chemotherapy suggests that factors other than infusion of large numbers of progenitor cells and filgrastim administration are responsible for rapid hemopoietic reconstitution. The integrity of the marrow microenvironment (24), endogenous cytokine responses (25), and endogenous hematological recovery may also play a part in this process. Irrespective of the mechanism(s) of delayed recovery, the consequences were not clinically important in this study.

This study was designed to determine the feasibility of delivering multiple cycles of dose-intensive chemotherapy. Supportive care was therefore conservative to ensure patient safety, and this cautious approach was responsible for the long overall median duration of hospitalization. However, the rapid hematological recovery and small number of life-threatening infections suggest that modifications to the protocol should be possible. We are currently assessing the toxicity of treatment every 3 weeks. Further reduction is unlikely to be feasible in view of the marked epithelial morbidity encountered with delivery of dose-intensive doxorubicin at 2-week intervals (26). Patients will also receive p.o. rather than i.v. antibiotics at the onset of neutropenia to try to minimize the length of in-patient care.

The increase in frequency of severe mucositis with successive cycles of chemotherapy demonstrates that cumulative damage occurs to epithelium as well as bone marrow. Attempts to further increase the dose intensity or number of cycles of epirubicin are likely to be associated with increasingly severe, and potentially unacceptable, epithelial toxicity. Filgrastim has been reported to reduce mucositis (27), possibly by enhancing oral mucosal neutrophil migration (28), but it is not fully protective following high-dose chemotherapy. Other measures currently used to ameliorate drug-induced mucositis are only partly effective (29) or are impractical with prolonged cytotoxic drug infusion (30), and new approaches are needed (31).

Concerns regarding anthracycline-induced cardiotoxicity have limited attempts to increase the dose intensity of these drugs. We chose to use high doses of epirubicin because of its activity and steep dose-response curve in breast cancer, and its more favorable toxicity profile compared with doxorubicin (32). Furthermore, clinical data suggest that cardiotoxicity is related to the cumulative dose of drug received rather than the individual dose delivered (33). The observations in this study are consistent with other reports of administration of high-dose epirubicin, in which falls in left ventricular ejection fraction are common but congestive heart failure rare (34). The follow-up in the current study is short, but anthracycline-induced cardiac failure usually becomes apparent 4–8 weeks after the last dose or during treatment. However, it occasionally occurs some years later (33). Reduction of epirubicin-induced cardiac damage would reduce the risk of clinical sequelae, and allow greater cumulative doses to be delivered safely. The most promising prospect for achieving this is with concurrent administration of dextrazoxane, which prevents anthracycline cardiotoxicity without influencing antitumor efficacy (35).

The ability to deliver multiple cycles of dose-intensive chemotherapy safely allows the investigation of similar strategies in the treatment of patients with other common chemosensitive cancers, including lymphomas, small cell lung cancer, and ovarian and testicular tumors. As with metastatic breast cancer,
a single course of myeloablative therapy in these diseases has produced high response rates, but improvement in long-term survival has not been confirmed. The early use of nonmyeloablative, multicyle regimens with highly active agents supported with growth factor-mobilized PBPC may provide more effective therapeutic alternatives to patients at high risk of death from their disease.

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