Phase II Trial of High-Dose Chemotherapy with Autologous Stem Cell Transplant for Stage IV Breast Cancer with Minimal Metastatic Disease

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ABSTRACT

The purpose of this study was to assess the efficacy of high-dose chemotherapy (HDC) with autologous stem cell transplant in stage IV breast cancer patients with minimal metastases. Eligible patients had (a) a disease that could be resected en bloc and/or irradiated with curative intent using a single field and could, thus, be rendered as having no evidence of disease (NED); and/or (b) <5% bone marrow involvement. From September 1991 to August 1997, 40 consecutive patients were prospectively entered on the study. Pre-HDC local treatment consisted of surgery (n = 31) and radiotherapy (XRT; n = 3). All patients received HDC with cyclophosphamide, cisplatin, and 1,3-bis(2-chloroethyl)-1-nitrosourea and autologous stem cell transplant, with or without CD34 selection. Following HDC, 22 patients received XRT. Four patients died of treatment-related complications. Eighteen patients developed grade 3 nonhematological toxicities (15 lung, 2 cardiomypathy, and 1 optic neuritis), which resolved with therapy. Within a median follow-up of 49 (15–91) months, 14 patients had relapsed. Twenty-five patients (62.5%) were alive, and 22 patients (55%) were alive and free of disease. Median event-free and overall survivals were 43 and 77 months, respectively. In the subset of patients with one metastatic site, 17 of 24 (68%) remained relapse free. Grade 2 tumors, a single metastatic site, and delivery of XRT were favorable predictors of relapse-free survival in univariate but not multivariate analyses. Inclusion of HDC, as described, in the multimodal treatment of stage IV breast cancer patients with minimal metastases is promising. These results warrant prospective randomized trials with a HDC-containing arm in this patient population.

INTRODUCTION

It is widely accepted that the vast majority of MBC2 patients are not cured with conventional-dose CT (1). In a large series of MBC patients treated at the M.D. Anderson Cancer Center with doxorubicin-containing CT, 28 of 1581 (1.7%) patients remained alive and in complete remission with long-term follow-up (2). HDC with autologous stem cell transplant achieves a higher tumor cell kill than does conventional-dose CT (3, 4). In several Phase II studies, 15–20% of MBC patients treated with HDC remain free of relapse at 5 years (5–8). Whether these results are due to patient selection bias, as has been suggested (9), or to an increased efficacy is presently being addressed in randomized Phase III studies.

Low tumor burden has been retrospectively identified as a favorable prognostic factor for outcome after both conventional-dose CT (2, 10) and HDC (11–14) for MBC. In addition, some selected MBC patients with low tumor burden can have all macroscopic tumor sites resected or irradiated, thus achieving a clinical status known as NED.

CD34 selection targets the CD34 antigen, expressed on early hematopoietic progenitors, but not on BC cells (15). CD34-positive cells, isolated by a biotin-avidin immunoadsorption device, are capable of reconstituting hematopoiesis and immune function in BC patients receiving HDC (16, 17). This procedure achieves a median 2-log (range, 1 to > 4) tumor cell depletion in the stem cell product (16). Therefore, patients with limited BM involvement can potentially be rendered NED by the use of a CD34-selected cell product for the support of HDC. Involvement of the BM by BC is patchy and focal by nature, and therefore, sampling is a major factor determining its detection by histology. Aware of this important caveat, for the purpose of this trial, we arbitrarily defined “limited BM involvement” as <5% involvement in bilateral biopsies.

We present here the results of a prospective study of stage IV BC patients with minimal metastatic tumor treated at our program with HDC, using CCB.

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2 The abbreviations used are: MBC, metastatic breast cancer; CT, chemotherapy; HDC, high-dose CT; NED, no evidence of disease; BC, breast cancer; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; cDDP, cisplatin; CPA, cyclophosphamide; XRT, radiotherapy; PK, pharmacokinetic; DFS, disease-free survival; OS, overall survival; DFI, disease-free interval; ER, estrogen receptor; PR, progesterone receptor; AUC, area under the curve; ADR, Adriamycin; FU, fluorouracil; MTX, methotrexate; PBPC, peripheral blood progenitor cell; CI, confidence interval; IP, interstitial pneumonitis; LRR, locoregional relapse; CCB, CPA-cDDP-BCNU; CMF, CPA-MTX-FU.
PATIENTS AND METHODS

Patient Population. Patients who were prospectively enrolled onto this study had histologically proven MBC and met one or both of the following criteria: (a) metastatic disease that could either be surgically excised en bloc prior to HDC or encompassed within a single XRT field with curative intent; and (b) limited BM involvement, defined as <5% tumor by microscopic examination of bilateral biopsies, with either no other known metastases or metastases meeting the criteria outlined in point 1. Patients who had relapsed within a prior XRT field, with liver or brain metastases, or who had received prior CT for metastatic disease were not eligible. Patient evaluation included: computed tomographic scans of the head, chest, abdomen, and pelvis; bone scan; bilateral iliac crest BM biopsies; and visceral organ function testing, with pulmonary function tests, radionuclide ventriculogram, and measurement of serum creatinine, bilirubin, aspartate aminotransferase, and alanine aminotransferase. The protocol was approved by the Institutional Review Board of the University of Colorado Health Sciences Center. Written informed consent was obtained from all patients.

After study entry, patients could receive induction CT at standard doses, for a maximum of four cycles, prior to the delivery of HDC. Any nodal region involved with tumor was considered a single site of disease, regardless of the actual number of individual nodes involved.

HDC. Enrolled patients were treated with HDC if they had adequate visceral organ function, defined as follows: forced expiratory volume in 1 s of >60% of predicted; CO diffusion capacity of >60% of predicted; left ventricular ejection fraction (measured by radionuclide ventriculogram) of >45% at rest, with at least 5% augmentation upon exercise; creatinine clearance (measured or estimated using the Cockcroft-Gault formula) of ≥60 mL/min; and bilirubin/aspartate aminotransferase/alanine aminotransferase levels of <1.5 times the upper limit of normal values.

Patients were admitted to the University of Colorado BMT Unit on day −7, at which time i.v. hyperhydration, sufficient to ensure a urinary output of >200 mL/h, and continuous bladder irrigation were initiated. All CT drug doses were calculated based on the actual patient body surface area, unless the actual weight was ≥20% over the ideal body weight, in which case the average of the actual and the ideal weight was used to calculate the body surface area. cDDP was administered at 165 mg/m² as a 72-h i.v. continuous infusion, starting on day −6. CPA was delivered at 1875 mg/m²/day as a 1-h i.v. infusion, on days −6, −5, and −4. On day −3, immediately after completion of the cDDP infusion, 600 mg/m² BCNU was given i.v. over 2 h.

Uniform supportive care measures were used. Prochlorperazine, diphenhydramine, and lorazepam were used as antiemetic therapy. Ciprofloxacin and rifampin were administered beginning on day −2, for infection prophylaxis. Patients with febrile neutropenia were switched to piperacillin, gentamicin, and vancomycin. Antifungal treatment was added for patients who remained febrile 48–96 h after starting empiric antibiotics. Patients received packed RBC transfusions for hematocrits of <28% and single donor apheresed platelets for platelet counts of <10,000/µL. All blood products were irradiated. Patients in stable condition were discharged on day −1 to be followed daily as outpatients until engraftment.

Time to engraftment was defined as the number of days following transplant to achieve an absolute neutrophil count of ≥500/mm³ and an unsupported platelet count of ≥20,000/mm³.

PK Studies. Patients had PK analysis of the three drugs included in the HDC regimen. Blood sampling, assay methodology, and analysis were performed as described previously (18).

Statistical Methods. DFS was defined as the time from study entry to a documented relapse or death without relapse. OS was defined as the time from study entry to death from any cause. Both DFS and OS were analyzed using the method of Kaplan and Meier (19). The log-rank test (20) was used to study the correlation of the following variables with DFS and OS: age, primary nodal status, length of prior DFI, prior adjuvant CT, previous exposure to doxorubicin, ER and PR status, tumor grade, LRR versus distant metastases, number of tumor sites, BM involvement, involvement of other organs (soft tissue, chest wall, or bone), the reinfection of a CD34-selected or an unmanipulated graft, and the delivery or omission of the standard induction CT or XRT. A stepwise Cox proportional hazard model was developed with the predictive variables (21).

The nonparametric Wilcoxon two-sample test was used to analyze the correlation of the AUC of CPA, cDDP, and BCNU with the following variables: toxic death, post-HDC relapse, and grade 3–4 nonhematological toxicities. The engraftment times in patients who received CD34-selected grafts or unmanipulated grafts were compared using the Student’s t test. All statistical calculations were performed using the SAS software package, Version 6.12 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Enrollment. From September 1991 to August 1997, 40 consecutive patients were prospectively entered on study. Patient demographics are listed in Table 1. Twenty-nine patients had recurrent MBC, after a median DFI of 35 months (range, 7–144 months). Of those patients, 24 (83%) received prior adjuvant CT, with CMF (11 patients) or ADR-CPA/CPA-ADR-FU (13 patients). Adjuvant hormonal therapy was prescribed to 23 patients. Eleven patients had metastatic disease at the time of the initial diagnosis.

Local Treatment. Local treatment is summarized in Table 2. Prior to HDC, 31 of 40 patients were rendered NED by surgery. Following HDC, 19 of those patients received consolidation XRT to the prior sites of macroscopic disease. Solitary bone lesions that were judged irresectable were included in a single irradiation port in six patients, either before (n = 3) or after (n = 3) HDC. CD34 selection of the stem cell product was performed in nine cases of limited BM involvement, either as the only local therapy for patients with BM-only disease (n = 3) or combined with surgery (n = 3), XRT (n = 2), or both (n = 1) in patients with BM and extramedullary disease.

Conventional-Dose Induction CT. Thirty-four patients received a median of four cycles (range, three to four cycles) of induction standard CT, with ADR-FU-MTX (n = 27), ADR-CPA/CPA-ADR-FU (n = 4), or paclitaxel (n = 3). There were no toxic deaths, and none of the patients experienced tumor progression before HDC.
Stem Cell Collection. Ten patients underwent a BM harvest under general anesthesia. PBPCs were mobilized in 30 patients with granulocyte colony-stimulating factor (Amgen, Thousand Oaks, CA) 10 μg/kg/day s.c. for 7 consecutive days and collected with sequential leukapheresis starting on day 5 of granulocyte colony-stimulating factor treatment, using a Cobe Spectra apheresis machine (Cobe BCT, Lakewood, CO). Eleven patients with and 5 patients without BM involvement underwent CD34-positive selection of PBPCs (n = 8) or BM (n = 6) or both (n = 2). CD34 selection was performed using an anti-CD34 antibody and an immunoadsorption column (CellPro Inc., Bothell, WA), as described previously (11). The unmanipulated (n = 24) or CD34-selected (n = 16) stem cell graft was cryopreserved and subsequently used to reconstitute hematopoiesis after HDC.

High-Dose Chemotherapy. All 40 patients enrolled onto the study received HDC with CCB, as described above.

Post-HDC Hormonal Therapy. Five patients with ER-/PR-positive tumors who had not been previously treated with hormonal therapy received tamoxifen for 5 years.

Survival and Relapse. At a median follow-up from study entry of 45 months (range, 12–91 months), 14 of 36 (39%) patients have relapsed. Posttransplant relapses were systemic in 12 patients and locoregional in 2 patients. In an intent-to-treat analysis, 22 of 40 patients (55%) were alive and free of disease, 8 of them 5 years after HDC. Twenty-five patients (62.5%) were alive. Median DFS and OS were 43 and 77 months, respectively. Fig. 1 shows the Kaplan-Meier DFS and OS curves of the overall population.

At the latest follow-up, 46% of patients with a LRR, confined to the chest wall, ipsilateral axillary, and supraclavicular nodal regions, remained free of recurrence. In the subset of patients with an isolated relapse, either locoregional or at a distant site, the relapse rate was 15%, and 68% of patients were alive and free of disease.

HDC-related Toxicity. There were four HDC-related deaths (10%; 95% CI, 0.7–19.3%). These four patients were analyzed for DFS and OS but were nonassessable for the study of prognostic factors. Causes of death were hemorrhagic colitis with sepsis, capillary leak syndrome, multimodal toxicity, and septic shock. Eighteen patients had grade 3 nonhematological toxicities: IP (n = 15), cardiomyopathy (n = 2), and optic neuritis (n = 1). The observed 37.5% rate of IP is within the range reported previously with CCB (22). Both IP and optic neuritis resolved clinically in all patients after a 10-week course of prednisone. The two patients who experienced cardiomyop-
athy were treated with captopril for 3 months and recovered a normal cardiac function.

**Engraftment.** In the whole group, the median times to neutrophil and platelet engraftment were 9 days (range, 7–26) and 10 days (range, 7–42), respectively. There were no cases of engraftment failure. Comparing patients who received a CD34-selected graft and an unselected graft, the median engraftment times of both neutrophils (8 and 9 days, respectively) and platelets (11 and 10 days, respectively) were not significantly different.

**Predictive Factors for DFS and OS.** By univariate analyses, DFS was superior in patients with grade 1–2 tumors (P = 0.01), a single metastatic site (P = 0.02) and with XRT (P = 0.02). Figs. 2, 3, and 4 illustrate the DFS by number of sites, tumor grade, and delivery of XRT, respectively. OS was favorably affected by grade 2 (P = 0.03) and the delivery of XRT (P = 0.02). None of the following variables were significantly associated with DFS or OS: age, nodal status of the original tumor, prior adjuvant CT, prior exposure to doxorubicin, length of the DFI, ER or PR status, locoregional or distant disease, BM involvement, specific type of organ involved (soft tissue versus lymph nodes versus chest wall versus bone versus BM), delivery of induction CT or timing of XRT (pre- versus post-HDC), and reinfection of a CD34-selected versus an unmanipulated graft.

In a multivariate Cox proportional hazard analysis, there was no independent association of tumor grade (P = 0.12) and XRT (P = 0.13) were not independent predictors of OS.

**PK/Pharmacodynamic Analysis.** The average AUCs for cDDP (n = 34), BCNU (n = 34), and CPA (n = 37) in the whole group were 522, 452, and 69,900 µg/ml/min\(^{-1}\), respectively. These values were not different from those from control patients with BC treated with the same HDC (data not shown). Post-HDC relapse was not associated with the AUC of cDDP (P = 0.7), BCNU (P = 0.8), or CPA (P = 0.5).

The AUC of cDDP in the patients who had a toxic death was significantly higher than that in those who survived HDC: 1019 versus 522 µg/ml/min\(^{-1}\), respectively (P < 0.005). Those groups had respective AUCs of BCNU of 700 and 450 µg/ml/min\(^{-1}\) (P = 0.08) and of CPA of 69,900 and 84,000 µg/ml/min\(^{-1}\) (P = 0.16).

The AUC of CPA was significantly lower in patients who developed grade 3 or greater nonhematological toxicities than it was in those who did not present them: 62,600 and 76,000 µg/ml/min\(^{-1}\), respectively (P = 0.02). The AUCs of cDDP and BCNU were not significantly different in either group.

**DISCUSSION**

Stage IV BC patients with minimal metastases are characterized by a low tumor burden and are amenable to being rendered NED by local therapy. They are different from those MBC patients in complete remission after CT, who are primarily defined by their chemosensitivity and not necessarily by a low tumor burden before treatment.

To our knowledge, this is the first prospective study of HDC in this group of patients reported to date. In an intent-to-treat analysis at a median follow-up of 49 months, the DFS of the whole group was 55%. The relapse rate in patients who survived treatment and were assessable for relapse was 39%. The DFS in the subset of patients with a single metastatic site was 68%. These encouraging results seem superior to the outcome of the overall MBC population treated with HDC and closer to the results of Phase II trials of HDC in high-risk primary BC (23–27). Although a single metastatic site has been previously identified as a favorable prognostic factor for MBC treated with HDC (11–14), our results seem superior to those of previous studies in this subset of patients. The addition of local therapy, capable of rendering MBC patients NED, seems a major contributor in this multimodal approach.
Patients with metastatic relapse after a prolonged DFI are known to have better outcome after HDC (11–14), possibly reflecting a slower growth of their tumor. In our series, 11 patients had MBC at diagnosis and 29 patients had recurrent disease after a median DFI of 35 months. Thus, a word of caution on our results seems necessary until longer follow-up is seen, considering the prolonged DFI of recurrent MBC patients in our series.

In addition, the possibility that minimal tumor can cause late relapses after HDC cannot be excluded, and DFS might decrease with longer follow-up. In the group of patients with ≥10 positive nodes treated with HDC at our program, only 12% of the relapses occur after the first 36 months posttransplant. Retrospective analyses of large series of patients treated in different Eastern Cooperative Oncology Group and Cancer and Leukemia Group B adjuvant CT trials show that the hazard ratio of recurrence depends on the length of follow-up and peaks in the first few years after therapy (28, 29). This effect is more striking in patients with more extensive nodal involvement (23). Our study involves patients who, despite their with minimal metastatic disease, with all probability have larger tumor burden than primary BC patients after surgery, including those with extensive nodal involvement. Therefore, it is reasonable to hypothesize that the time-dependent hazard ratio principle might also apply here, and the likelihood of post-HDC relapses may decrease substantially after the first several years of follow-up.

There were four toxic deaths (10%) in this study. This rate is higher than the overall 4.1% toxic death rate (95% CI, 2.2–6.3%) in more than 450 patients treated with different ADR-containing combinations followed by maintenance CT. Total duration of treatment was not specified. In a second study conducted at the M. D. Anderson Cancer Center, Holmes et al. (36) reported 59 patients with an isolated relapse (n = 136) or multiple (n = 20) relapses with CPA-ADR-FU followed by CMF over a total of 2 years. At a median follow-up of 73 months, DFSs in patients with one and more than one metastatic sites was 34 and 45%, respectively. In a second study conducted at the M. D. Anderson Cancer Center, Holmes et al. (36) treated 86 patients with isolated relapses over 2 years with vincristine-ADR-CPA-prednisone followed by MTX-FU-leucovorin. At 46 months, 39% of the patients remained relapse-free. Blumenschein et al. (37) reported 59 patients with an isolated relapse treated with different ADR-containing combinations followed by maintenance CT. Total duration of treatment was not specified. At a median follow-up of 44 months, DFS was 55%.

In our study, tumor grade, number of tumor sites (but not the multivariate analyses. In the trial by Blumenschein et al., chest wall recurrences, surgical resectability of the lesions and no prior adjuvant CT favorably correlated with DFS (37). In the pooled results from the two M. D. Anderson studies, bone disease and nodal involvement at the original diagnosis negatively influenced outcome (30, 31).

LRRs after mastectomy virtually always represent a component of widespread disease (38, 39). Therefore, our study, as well as those mentioned above, included LRR in their definition of stage IV NED. The question on the effectiveness of systemic therapy for patients with LRR remains unsettled. Janjan et al. (40) retrospectively compared XRT alone to XRT combined with CT, using CPA-ADR-FU followed by CMF, in 164 patients, 98% of whom were CT naive. Patients who received the toxic metabolite, 4-hydroxy-CPA, may account for this last observation, consistent with prior pharmacodynamic data of CPA in a different HDC regimen (32). Whether real-time dose adjustment of these drugs might result in less severe toxicity will be the subject of further study.

Table 3 summarizes the few prospective studies that have used conventional-dose CT in MBC with minimal tumor burden. Most patients included in these trials had isolated soft-tissue relapses after extensive staging work-up and were rendered NED by surgery and/or XRT. Patients with BM involvement or metastases at the time of the initial diagnosis were excluded. Prior exposure to adjuvant CT, an adverse prognostic factor for subsequent response to CT and survival in MBC (33, 34), was substantially lower in those studies than in ours. Buzdar et al. (35) treated NED patients with isolated (n = 136) or multiple (n = 20) relapses with CPA-ADR-FU followed by CMF over a total of 2 years. At a median follow-up of 73 months, DFSs in patients with one and more than one metastatic sites was 34 and 45%, respectively. In a second study conducted at the M. D. Anderson Cancer Center, Holmes et al. (36) treated 86 patients with isolated relapses over 2 years with vincristine-ADR-CPA-prednisone followed by MTX-FU-leucovorin. At 46 months, 39% of the patients remained relapse-free. Blumenschein et al. (37) reported 59 patients with an isolated relapse treated with different ADR-containing combinations followed by maintenance CT. Total duration of treatment was not specified. At a median follow-up of 44 months, DFS was 55%.

In our study, tumor grade, number of tumor sites (but not whether the recurrence was locoregional or distant) and consolidation with XRT had prognostic significance in the univariate but not the multivariate analyses. In the trial by Blumenschein et al., chest wall recurrences, surgical resectability of the lesions and no prior adjuvant CT favorably correlated with DFS (37). In the pooled results from the two M. D. Anderson studies, bone disease and nodal involvement at the original diagnosis negatively influenced outcome (30, 31).

Table 3  Prospective studies of conventional-dose CT in stage IV NED breast cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Inclusion criteria</th>
<th>% patients with no prior adjuvant CT</th>
<th>CT regimen</th>
<th>Median follow-up (months)</th>
<th>Median OS (months)</th>
<th>% EFS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buzdar et al. (35)</td>
<td>Isolated relapse</td>
<td>136</td>
<td>100</td>
<td>FAC→CMF</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>Holmes et al. (36)</td>
<td>Isolated relapse</td>
<td>86</td>
<td>100</td>
<td>VACP→MFL</td>
<td>46</td>
<td>N/R</td>
</tr>
<tr>
<td>Blumenschein et al. (37)</td>
<td>Isolated relapse</td>
<td>59</td>
<td>37</td>
<td>Several</td>
<td>44</td>
<td>132</td>
</tr>
<tr>
<td>Buzdar et al. (35)</td>
<td>Multiple relapses</td>
<td>20</td>
<td>100</td>
<td>FAC→CMF</td>
<td>54</td>
<td>N/S</td>
</tr>
<tr>
<td>This study</td>
<td>Isolated/multiple relapses and/or limited BM involvement</td>
<td>40</td>
<td>12.5</td>
<td>High-dose CCB</td>
<td>45</td>
<td>77</td>
</tr>
</tbody>
</table>

* EFS, event-free survival; FAC, CPA-ADR-FU; VACP, vincristine-ADR-CPA-prednisone; MFL, MTX-FU-leucovorin; N/R, not reached; N/S, not stated.

Unpublished observations.
combined treatment had a 33% 5-year DFS, significantly superior to the 22% from the XRT-treated group, although the OS was similar in both groups. Other retrospective analyses of smaller series of patients treated with XRT with or without different CT combinations offer varying results (41–44). Borner et al. (45) prospectively randomized 167 tamoxifen- and anthracycline-naive patients, with a “good-risk” LRR (defined by ER positivity or DFI of >12 months and three or fewer nodules of ≤3 cm each) to tamoxifen or observation, following local treatment of the recurrent disease. Fifty-nine % of the patients had not received any prior adjuvant CT. The tamoxifen group had better 5-year DFS than the control group (49 versus 36%), in relationship to fewer local but not systemic second relapses. Both arms had similar OS (74 and 76%, respectively).

In conclusion, the results of our study suggest that MBC patients with minimal metastatic disease constitute a unique population that may benefit from HDC, as described. Taken together, the results from the prospective studies with conventional CT and our own HDC trial strongly suggest that a significant fraction of these patients may achieve survival benefit from systemic treatment. If this promising conclusion is further validated in prospective randomized trials, a compelling case could be made for a closer follow-up of selected primary BC patients after mastectomy and adjuvant treatment. Early detection of recurrences may allow systemic treatment to be delivered at a time when the probability of cure might exceed the outcome of patients with more widespread metastatic disease.

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REFERENCES


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