Breast Cancer: High-Dose Therapy

SMITHA SUBRAMANYAN, M. JOHN KENNEDY
Johns Hopkins Oncology Center, Baltimore, Maryland, USA

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ABSTRACT

Breast cancer has become the leading indication for high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR) in North America. The rapid increase in HDC/ASCR for breast cancer has been driven by belief in the response rates and survival times demonstrated in phase II studies, which have been higher than that of historical controls. However, there is a growing body of data to suggest that selection bias has had a significant impact on the outcome of non-randomized studies of HDC. Few randomized comparisons of HDC to standard-dose chemotherapy exist.

Early studies of dose-intensification and phase II studies of HDC/ASCR for patients with metastatic and high-risk disease are reviewed here, with emphasis on those studies with long-term follow-up. Studies demonstrating the selection bias present in phase II studies of HDC are also discussed. Finally, randomized studies of HDC/ASCR are reviewed, including the National Cancer Institute high-priority trials. Currently, HDC/ASCR for the treatment of breast cancer can only be recommended in the context of a clinical trial. Results of several large randomized trials are awaited to determine the future of HDC/ASCR for breast cancer. The Oncologist 1998;3:289-299

INTRODUCTION

This article will provide an overview and interpretation of the literature regarding high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR) for the treatment of breast cancer, with emphasis on key publications.

DOSE RESPONSE

Among tumors that are sensitive to chemotherapy, a linear increase in chemotherapeutic dose generally results in a logarithmic reduction in tumor cells in in vitro models [1]. Tumors that are more sensitive than others to chemotherapy display steeper dose-response curves. Heterogeneous tumors may deviate from this rule, and other conditions may apply in vivo. For example, large tumors may have regions with relative hypoxia and less cell cycle activity and therefore less sensitivity to chemotherapy. This hypothesis is based on the Gompertzian model of tumor kinetics, in which the rate of tumor doubling decreases with tumor size. Based upon these experimental findings, HDC, which allows a 5- to 10-fold increase in chemotherapeutic agents with myelosuppression as their major toxicity, became an attractive therapeutic option for evaluation in chemotherapy-sensitive malignancies such as breast cancer, especially in the setting of cytoreduction with induction chemotherapy.

In 1981, Bonnadonna and Valagussa published a report of the dose-response effect of chemotherapy on breast cancer [2]. Theirs was a retrospective study in which patients from a trial of cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU) (CMF) versus no adjuvant therapy and another trial of six months of CMF versus 12 months of CMF, were divided into three groups based upon the cumulative dose of CMF received. This cumulative dose was then expressed as a percentage of the optimal dose (the originally intended dose without any reduction) for each patient. Patients receiving 85% or more of the optimal dose had a significantly improved relapse-free survival versus patients in the other groups. This and similar retrospective studies have been criticized, however, because confounding factors such as differences in performance status and age were not taken into account [3].

DOSE INTENSITY NOT REQUIRING ASCR

Hryniuk and Bush noted that published response rates to CMF-based chemotherapy for patients with stage IV breast

Correspondence: Smitha Subramanyan, M.D., Oncology 126, Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, Maryland 21287, USA. Telephone: 410-283-4420; Fax: 410-955-0125; e-mail: ssubrama@welchlink.welch.jhu.edu
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cancer were on average 47%, significantly lower than that reported by Cooper (88%) for the CMFVP (CMF, vincristine, prednisone) regimen [4]. Recognizing that doses were modified in each study, they converted the dosages of CMF to a standard form of mg/m²/week, representing dose intensity. They then reported each study’s CMF dose intensity as a fraction of the dose intensities of Cooper’s modification of his original regimen. A positive correlation was found between response rate and dose intensity. The same relationships were found in their review of cyclophosphamide, doxorubicin, and 5-FU regimens (CAF). Of further interest is that a small but significant increase in median survival time was found with increasing dose intensity of CMF and CAF regimens.

A randomized trial of CAF versus high-dose CAF (although not to the extent of requiring ASCR) found no statistically significant differences in survival or complete response (CR) rate between the high- and low-dose arms [5]. Another randomized study of CMF (600/40/600) versus half-dose CMF (300/20/300) had similar results, although there was an increase in overall response (OR) rate in the high-dose arm versus the low-dose arm (30% versus 11%, p = 0.03) [6].

Bastholt and colleagues examined the efficacy and toxicity of epirubicin when given at 40, 60, 90, and 135 mg/m² every three weeks to women with metastatic breast cancer [7]. An increase in response rate and time to disease progression were observed with the increase of epirubicin from 40 mg/m² to 90 mg/m², but not thereafter. Survival was not affected by epirubicin dose. Toxicity, however, increased with increasing epirubicin levels. This study established 90 mg/m² to be the recommended three-weekly dose of epirubicin. It was not evident that doses higher than 90 mg/m² improved outcome in any way.

The importance of dose and dose intensity in the range of conventional chemotherapies was addressed by a large randomized study conducted by the Cancer and Leukemia Group B (CALGB) [8]. In this study, 1,572 women with stage II breast cancer were randomized to receive adjuvant CAF on one of three treatment arms. Group 1 received cyclophosphamide at 600 mg/m², doxorubicin at 60 mg/m², and fluorouracil at 600 mg/m² every 28 days for four cycles. Group 2 received CAF at 50% lower doses (C400/A40/F400) every 28 days for a total of six cycles, i.e., at an equivalent dose but lower intensity than Group 1. Group 3 received CAF at half the total dose of the other groups (C300/A30/F300) every 28 days for six cycles, i.e., half the dose and half the intensity of Group 1. Over 95% of the patients received at least 90% of their assigned dose. At three years of follow-up, the disease-free survival (DFS) was significantly higher in Group 1 versus Group 3 (74% versus 63%, p < 0.001) and Group 2 versus Group 3 (70% versus 63%, p = 0.002) but not between Groups 1 and 2. The overall survival (OS) was also significantly higher in Groups 1 and 2 versus Group 3 but not between Groups 1 and 2. These findings suggest that there may be a dose-response effect or at least a threshold dose below which clinical outcomes are significantly worse. There appeared to be a trend of improving DFS and OS with increasing dose intensity, but the differences observed between Group 1 and Group 2 were not statistically significant.

Of significant interest is a companion study to CALGB 8541 in which tumors from a subgroup of participants were analyzed for any relationship between HER-2/neu overexpression and response to chemotherapy by dose [9]. Among women whose tumors overexpressed HER-2/neu, there was a significant positive interaction between higher dose of chemotherapy and DFS and OS. This interaction was not observed in the HER-2/neu-negative women. An updated study, with a median follow-up of eight years, in which another large subset of women was analyzed by HER-2/neu status confirmed the persistence of an important relationship between dose and outcome in patients with HER-2/neu-positive tumors [10].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-22 randomized patients with primary operable breast cancer to adjuvant therapy with either four cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² (AC, Group 1) or dose-intense therapy with doxorubicin 60 mg/m² for four courses and cyclophosphamide 1,200 mg/m² during two of those courses (Group 2), or dose-increased and dose-intensive therapy with doxorubicin 60 mg/m² and cyclophosphamide 1,200 mg/m² for four courses (Group 3) [11]. No significant differences were observed in DFS and OS among the three groups. Toxicity, however, increased, with grade 4 toxicity experienced by 6.5% of patients in Group 1, 16.4% of patients in Group 2, and 20.6% of patients in Group 3. The authors concluded that increased cyclophosphamide beyond standard doses in an AC combination is inappropriate adjuvant therapy.

All of these studies suggest that patients should not receive less than standard doses of chemotherapy. Elevations in dose beyond what is adequate was associated with increased toxicity without clear evidence of a significant improvement in outcome in these studies. The effects of increasing dose and dose-intensity to the HDC range necessitating ASCR, however, remain undetermined.

**Choice of Chemotherapeutic Agents**

Key requirements for high-dose chemotherapeutic regimens are that the drugs used should be markedly more toxic to tumor cells than normal cells, should exhibit non-cross-resistance, and possibly even synergy, and have dose-limiting toxicity with stem cell support which is higher than without.
Drugs with differing toxicity profiles are preferable for combination studies. Alkylating agents form the cornerstone of high-dose chemotherapy for the treatment of breast cancer. Schabel et al. used variants of the L1210 leukemia cell line, each resistant to a specific alkylating agent, to demonstrate that resistance to one alkylating agent does not preclude sensitivity to another [12]. These authors also demonstrated that toxicity to normal cells from two alkylating agents used in combination is generally not more than additive, and in many cases is less than additive.

Teicher et al. demonstrated synergistic killing of tumor cells by the combination of thiopeta and cyclophosphamide in vitro using the MCF-7 breast cancer cell line and in vivo using EMT6 murine mammary carcinoma cells [13]. Toxicity to bone marrow with this combination regimen was sub-additive or additive. The overall reduction of tumor cells was one log greater than the reduction of bone marrow cells [14].

Chemotherapeutic agents commonly used in high-dose chemotherapy for breast cancer are the alkylating agents cyclophosphamide, thiopeta, carmustine, and ifosfamide as well as cisplatin, carboplatin, mitoxantrone, etoposide, and hydroxyurea. A review of results from the Autologous Bone Marrow Transplant Registry of North America (ABMTR) lists cyclophosphamide, thiopeta, and carboplatin as the most common preparative regimen used from January to June of 1995. Cyclophosphamide and thiopeta was the next most commonly used regimen [15].

### SUMMARY OF RESULTS OF HDC/ASCR REPORTED TO THE ABMTR

Despite the widespread use of autologous bone marrow transplantation for the treatment of breast cancer, there is a paucity of reports on the long-term outcome of such therapy. As prolonged DFS is a more meaningful outcome to practicing oncologists than short-term responses to treatment, we will focus on publications that provide long-term results of HDC/ASCR.

In May, 1997 Antman et al. published summary statistics of data from the ABMTR regarding consecutive autologous transplants for breast cancer recorded between January 1, 1989 and June 30, 1995 [15] (Tables 1 and 2). By 1993-1994, breast cancer had become the leading indication for autologous transplants. Two trends observed were a shift from treating patients with metastatic disease to treating those with high-risk disease in the adjuvant setting, and a dramatic use in peripheral blood as a source of stem cells. One-hundred-day mortality has significantly decreased from 22% in 1989 to 5% in 1995. This likely reflects the change in patient population from patients with refractory metastatic disease to those with high-risk primary disease. In addition, factors such as the use of G-CSF, peripheral blood progenitor cells, and improved use of antibiotics and antifungal agents are also likely contributors to this decrease in mortality.

Among women with metastatic breast cancer, response to pretransplant chemotherapy is an important predictor of survival after HDC/ASCR. Those women with unresponsive

<table>
<thead>
<tr>
<th>All stages</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>44 years</td>
<td>72</td>
<td>3</td>
</tr>
<tr>
<td>% ≥10 LN +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-day mortality (%)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS at 3 years (% 95% CI)</td>
<td>65 (59-71)</td>
<td>60 (53-67)</td>
<td>42 (31-53)</td>
</tr>
<tr>
<td>OS at 3 years (% 95% CI)</td>
<td>74 (68-80)</td>
<td>70 (63-77)</td>
<td>52 (40-64)</td>
</tr>
</tbody>
</table>

LN = lymph node; + = positive; CI = confidence interval.

<table>
<thead>
<tr>
<th>All patients</th>
<th>CR to induction Rx</th>
<th>PR to induction Rx</th>
<th>No response to induction Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>3,451</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>44 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR %</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-day mortality (%)</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS at 3 years (% 95% CI)</td>
<td>18 (16-20)</td>
<td>32 (27-37)</td>
<td>13 (9-17)</td>
</tr>
<tr>
<td>OS at 3 years (% 95% CI)</td>
<td>30 (28-32)</td>
<td>46 (40-52)</td>
<td>29 (25-33)</td>
</tr>
</tbody>
</table>

Rx = treatment.
disease have a <10% chance of long-term DFS. It should be noted that the women from the ABMTR registry data were in general younger than the average patient with breast cancer. Those women with limited-stage disease had more involved lymph nodes than most patients with limited-stage disease. The authors emphasized the need to compare outcomes of patients treated with HDC/ASCR with comparable patients treated otherwise.

**Phase II Trials of HDC/ASCR for Metastatic Disease**

A listing of representative phase II trials, which is not meant to be comprehensive, evaluating HDC/ASCR in patients with metastatic breast cancer is provided in Table 3. As an example, Ayash et al. reported results of two studies, with a median observation period of 50 months post-transplant, in which 62 women with metastatic breast cancer were treated with induction chemotherapy, consisting of doxorubicin, 5-FU, and methotrexate (AFM) in most cases, followed by a single high-dose consolidation course with cyclophosphamide, thiopeta, and carboplatin [20]. In a multivariate analysis, the most significant predictors of progression-free survival (PFS) were having a single metastatic site \( (p = 0.0015) \) and achieving a CR to induction chemotherapy \( (p = 0.04) \). A trend of increasing PFS with increasing interval from primary diagnosis to metastatic disease was also observed \( (p = 0.066) \). Studies such as this suggest that HDC may provide long-term benefit to some women with metastatic breast cancer who have a relatively small burden of disease when entering transplant and whose disease is sensitive to chemotherapy.

**Phase II Trials of HDC/ASCR as Adjuvant Treatment of High-Risk Disease**

Trials of HDC for use in the adjuvant setting initially focused on high-risk patients with ten or more positive lymph nodes (Table 4). Peters and colleagues reported results for patients who received high-dose cyclophosphamide, cisplatin,

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**Table 3. Representative early phase II trials of HDC/ASCR in metastatic breast cancer. Adapted from [43], with permission.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Patients</th>
<th>HDC Agents</th>
<th>Induction/ Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters [16]</td>
<td>1988</td>
<td>22</td>
<td>CPB</td>
<td>—</td>
</tr>
<tr>
<td>Kennedy [17]</td>
<td>1991</td>
<td>30</td>
<td>CT</td>
<td>27%</td>
</tr>
<tr>
<td>Antman [18]</td>
<td>1992</td>
<td>29</td>
<td>CTCb</td>
<td>34%</td>
</tr>
<tr>
<td>Williams [19]</td>
<td>1992</td>
<td>27</td>
<td>CT</td>
<td>15%</td>
</tr>
<tr>
<td>Ayash [20]</td>
<td>1995</td>
<td>62</td>
<td>CTCb</td>
<td>19%</td>
</tr>
<tr>
<td>Gisselbrecht [21]</td>
<td>1996</td>
<td>61</td>
<td>CMMe</td>
<td>51%</td>
</tr>
</tbody>
</table>

C = cyclophosphamide; P = cisplatin; B = carmustine, T = thiopeta; Cb = carboplatin; M = mitoxantrone; Me = melphalan; mo = months.

**Table 4. Representative phase II trials of HDC/ASCR as adjuvant treatment**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Patients</th>
<th># Positive LN</th>
<th>Induction/ HDC</th>
<th>DFS (at median follow-up in mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters [22]</td>
<td>1993</td>
<td>85</td>
<td>≥10</td>
<td>CAF/CPB</td>
<td>86% (30)</td>
</tr>
<tr>
<td>Gianni [23]</td>
<td>1997</td>
<td>67</td>
<td>≥10</td>
<td>-/CMMe plus std dose VP</td>
<td>60% (48) from day of surgery</td>
</tr>
<tr>
<td>Tomas [24]</td>
<td>1997</td>
<td>40</td>
<td>≥10</td>
<td>CTCb</td>
<td>72% (35)* from induction</td>
</tr>
</tbody>
</table>

LN = lymph nodes; C = cyclophosphamide; A = doxorubicin; F = 5-fluorouracil; P = cisplatin; B = carmustine; BM = bone marrow; PB = peripheral blood; mo = month; M = methotrexate; Me = melphalan; V = vincristine; std = standard; T = thiopeta; Cb = carboplatin. * = actuarial event-free survival at three years.
and carmustine following four courses of standard CAF chemotherapy [22]. The DFS at five years was 71%, which was considered favorable compared to the 30% seen in historical age and stage-matched controls. The OS at five years also appeared to be substantially improved for the patients treated with HDC (78% versus 38%–48%).

Gianni et al. recently published five-year results of their high-dose sequential chemotherapy program with ASCR as adjuvant therapy for women with stage II or III breast cancer with \( \geq 10 \) positive lymph nodes [23]. Sixty-seven eligible women were enrolled following modified radical mastectomy or breast-conserving surgery. The HDC regimen consisted of cyclophosphamide at 7 g/m\(^2\) on day 0, followed by cytokine infusion on days 1-13, followed by peripheral blood progenitor cell harvest on days 13-17 and/or bone marrow harvest on day 17, followed by standard-dose vincristine at 1.4 mg/m\(^2\) and high-dose methotrexate at 8 g/m\(^2\) on day 22, followed by standard-dose cisplatin at 120 mg/m\(^2\) on days 29 and 36, followed by high-dose melphalan at 200 mg/m\(^2\) on day 53, and finally marrow and/or stem cell reinfusion on day 54 plus cytokines until day 70. Radiation therapy was subsequently administered to the remaining breast or chest wall. By administering high-dose chemotherapeutic agents at separate intervals, the authors hoped to maximize the doses of these drugs. In addition, the administration of methotrexate after cyclophosphamide allowed this drug, an S-phase specific agent, to be given at a time of possible tumor-cell recruitment.

Patients treated with HDC therapy were compared with controls who were breast cancer patients of the same stage, treated at the same institution, until the time immediately preceding this study, with four courses of doxorubicin followed by eight courses of CMF. The two groups of women were similar in terms of median age, menopausal status, and receptor status but differed in the number of positive lymph nodes. A significantly higher percentage of women in the HDC group had \( \geq 20 \) positive lymph nodes, compared with only 7% in the doxorubicin-CMF group (\( p = 0.014 \)). Another important feature of this study is that both groups of women underwent a similar staging process. Specifically, computed tomography (CT) and bone marrow biopsies were not performed in the HDC group. Thus the two groups may be considered more comparable than is usually the case when historical controls are used.

DFS and OS were analyzed on an intent-to-treat basis. The median follow-up was 48 months. For those women receiving HDC therapy, the five-year probability of remaining relapse-free was 57% (95% confidence interval [CI], 44% to 70%) and the OS was 70% (95% CI, 57% to 83%). In comparison, the control group had a five-year probability of relapse-free survival of 41% (95% CI, 28% to 54%) and a five-year probability of being alive of 60% (95% CI, 48% to 72%). The difference in relapse-free survival between the two groups was statistically significant (\( p = 0.04 \)), while the difference in OS was not statistically significant.

A subgroup analysis comparing only women with \( 10-20 \) positive lymph nodes found the five-year relapse-free survival for the control subgroup to be 42% versus 65% for the HDC patients (\( p = 0.01 \)). The five-year OS rate was 61% for the control subgroup versus 77% for the HDC subgroup, a difference of borderline statistical significance (\( p = 0.05 \)). A major therapeutic difference between the HDC and control group was the administration of breast or chest wall radiation to all patients given HDC, which may account, at least in part, for some of the differences observed.

Recently, Bearman et al. published their experience with HDC/ASCR as adjuvant therapy for women with four to nine positive lymph nodes [25]. All patients received induction therapy, initially with doxorubicin and 5-FU in the first four patients, then doxorubicin and cyclophosphamide in subsequent patients. All but two patients went on to receive HDC consisting of cyclophosphamide, cisplatin, and carmustine, with peripheral blood stem cell support. The carmustine dose used in this study was a 25% reduction of the BCNU dose used by Peters et al. [21]. All patients received radiation therapy and tamoxifen as well. After a median of 947 days, 43 of the original 54 patients enrolled were disease-free. While the DFS is promising, longer follow-up is needed in order to compare survival of these patients with patients historically treated with standard-dose chemotherapy.

While these studies suggest that HDC may improve DFS and OS when used in the adjuvant setting, it must be emphasized that the use of historical controls or no controls makes these studies extremely susceptible to selection biases. Available data from randomized trials will be presented below.

**Selection Bias and the Need for Randomized Studies**

The rapidly increasing use of HDC for the treatment of breast cancer has been driven by belief in the response rates and survival times from phase II studies for the treatment of high-risk and metastatic breast cancer, which have been higher than those of historical controls. Major limitations of such phase II studies are the inability to generalize due to restrictive patient selection criteria, extensive evaluation for metastatic disease among high-risk patients, and improvement in the use of chemotherapy, antibiotics, and parenteral nutrition, for example, which invalidates the use of historical controls.

Greenberg and colleagues described the natural history of patients who enter CR following standard-dose chemotherapy (SDC) for metastatic breast cancer [26]. Of 1,581 patients who received consecutive doxorubicin-alkylating combination regimens at the MD Anderson Cancer Center between
1973 and 1982, 16.6% achieved a CR in response to treatment. Of those 16.6%, 49 patients (3.1% of the original 1,581) remained in CR for over five years. The median length of CR was 191 months. This study confirmed that a small percentage of women with metastatic breast cancer can achieve a long-term remission in response to SDC.

Mick and colleagues examined the survival of women with metastatic breast cancer who received their initial chemotherapy for metastatic disease on CALGB protocols between February, 1980 and January, 1987 [27]. In addition to including all usual study entry criteria, all patients over age 55 were excluded from analysis to make the patients more comparable to HDC/ASCR candidates. The median OS for the 432 women was 1.6 years. The estimated three-year survival was 26%. Negative ER status, prior adjuvant chemotherapy, and the presence of liver metastases were found to have a significantly negative effect on survival. Those patients with ER-positive tumors who had not received adjuvant chemotherapy and who had no liver metastases had a median survival of three years. In contrast, patients with all three negative prognostic factors had a median survival of 0.5 years. Thus it appears that patient selection factors could potentially be of paramount importance in the outcome of HDC trials.

Crump and colleagues examined the importance of the pre-HDC/ASCR evaluation of women with stage II disease with regard to the detection of metastatic disease. Study subjects were women with stage II breast cancer referred to the Toronto Hospital for participation in a randomized trial of the addition of HDC/ASCR to four cycles of adjuvantCAF [28]. These women had completed surgery within eight weeks and had negative margins, as well as normal physical examination, abdominal ultrasound, bone scan, and chest x-ray. Thirty women were identified who met these criteria and agreed to participate in the trial. These patients then underwent bilateral bone marrow biopsies as well as CT of the head, chest, abdomen, and pelvis. Of these 30 patients, seven (23%; 95% CI, 12% to 41%) were found to have metastatic disease. Three of these women had metastatic disease detected by chest CT, one by abdominal CT, and three by bone marrow biopsy. The bone marrow biopsies were evaluated by routine methods, not immunohistochemistry or flow cytometry. All three women with micrometastatic disease found on bone marrow biopsy had normal alkaline phosphatase levels and normal bone scans. This study exemplifies the stage migration that can occur with an extensive pre-HDC/ASCR evaluation and illustrates the inherent disadvantage in using historical controls.

Two recently published studies explored the impact of patient selection on outcome in women with breast cancer. Rahman and colleagues reviewed records from 18 successive trials from MD Anderson Cancer Center of doxorubicin-containing regimens for treatment of metastatic breast cancer [29]. A total of 1,581 women were enrolled into these studies between 1973 and 1982, and the median follow-up was 14 years. Patients who would have been candidates for HDC were identified by the following criteria: age <60 years, PS of 2 or less on the Zubrod scale, a CR or partial response (PR) to chemotherapy, as well as bilirubin level ≤ 2 mg/dl, WBC of ≤ 2000/µl, platelet count of > 100,000/µl and no symptomatic cardiac dysfunction. Pulmonary function, cardiac function and bone marrow involvement were major criteria not used because information was not available for all patients. Thus, many women classified as HDC candidates may have been considered ineligible had they undergone an actual extensive pre-HDC/ASCR evaluation.

The median PFS was 16 months for HDC candidates and eight months for non-candidates (p < 0.0001). The median OS was 30 months for HDC candidates and 17 months for non-candidates (p < 0.0001). To remove the effect of response to SDC, the authors analyzed the non-candidates who responded to chemotherapy. When HDC candidates were compared to non-candidates with response to SDC, the median PFS was, respectively, 16 months versus 14 months (p = 0.002), and the median OS was 30 months versus 26 months (p = 0.0001), both small but statistically significant differences. Therefore, performance status and organ function were also significant predictors of outcome.

It is evident from this study that among women with breast cancer, those who do not receive HDC but are simply eligible for HDC may have higher response rates and survival times than those women who are not eligible to receive HDC. This study demonstrates the importance of patient selection factors with regard to outcome with HDC as treatment of metastatic breast cancer.

Garcia-Carbonero et al. reviewed records in a similar manner to ascertain the importance of patient selection factors with regard to outcome for women with stage II breast cancer [30]. From records from 1975 to 1995, 171 women were identified who had 10 or more positive lymph nodes and had received SDC but not HDC. The following criteria were then applied to classify these patients as HDC candidates or non-candidates: < 60 years of age, no significant concomitant medical or psychiatric diseases, and no recurrence during adjuvant SDC. Of these 171 patients, 128 met criteria for HDC and 43 did not. After a median follow-up of 53.1 months, the median DFS was 35.9 months for HDC candidates and 26.4 months for non-candidates. The median OS was 86.2 months for HDC candidates and 42.7 months for non-candidates (p < 0.01).

To determine the effect of HDC on short-term prognosis, a separate group of 39 patients who had received HDC was assessed. After a median follow-up of 23.6 months, the median DFS and OS had been reached. The actuarial 2.5-year DFS and OS were 70.9% and 84.5%, respectively. These
results were no different from survival rates of women who were HDC candidates but treated with SDC. The women in this study who did not receive HDC were evaluated by laboratory tests, liver ultrasonography, and bone scan, initially as indicated by laboratory abnormalities and later routinely. Had these women undergone CT scanning and bone marrow biopsy, it is likely that some of them would have been found to harbor metastatic disease. One would therefore expect the true differences in survival between recipients of HDC and those who were simply candidates for HDC, but who had undergone equivalent pretreatment evaluations, to be even less distinguishable.

The findings of this study indicated that patient selection criteria are significant predictors of outcome among women with high-risk stage II disease. Treatment with HDC does not appear to prevent early relapse better than SDC among patients who qualify for HDC. The long-term effects of HDC remain unknown.

**Randomized Studies of HDC for Metastatic Disease**

The first published randomized trial comparing HDC/ASCR with SDC as a treatment for breast cancer was conducted by Bezwoda, Seymour, and Dansey in 1995 [31]. In that study, 90 women with metastatic breast cancer who had received no prior chemotherapy for metastatic disease were randomized to treatment with six courses of cyclophosphamide 600 mg/m², mitoxantrone 12 mg/m², and vincristine 1.4 mg/m² (CNV), or one or two courses of high-dose cyclophosphamide 2.4 g/m², mitoxantrone 35-45 mg/m², and VP-16 2.5 g/m² (HD-CNV) with marrow or stem cell rescue. The CNV regimen had previously been studied by the authors in a pilot study in 17 women with metastatic breast cancer who had received two to four prior chemotherapy regimens. In that pilot study, a response rate of 81% was obtained (including a 23% CR rate), making CNV a reasonable choice as the SDC in the randomized trial [32]. The authors stated that although VP-16 is not an active drug against breast cancer at standard doses, activity has been demonstrated at high doses, which justified its use in the high-dose treatment arm. Dose intensities for the two chemotherapeutic agents shared by each treatment arm were examined by the authors. In the standard CNV regimen, the actual dose intensity of cyclophosphamide achieved was 0.17 g/m²/week and of mitoxantrone 3.1 mg/m²/week. In the HD-CNV regimen, the dose intensity of cyclophosphamide achieved was 0.65 g/m²/week (3.8-fold higher) and of mitoxantrone was 6.8 mg/m²/week (2.2-fold higher).

Forty-five women were randomized to each arm. Patients in each arm were similar in age, performance status, menopausal status, estrogen receptor status, prior adjuvant chemotherapy, and hormonal therapy for metastatic disease. The response rates of the two treatment arms were significantly different. In the HD-CNV arm, 23 of 45 patients had a CR (51%), and 20 of 45 patients had a PR (44%). Of the 45 women treated with standard-dose CNV, only two experienced a CR (4%, p-value <0.01), and 22 had a PR (49%). The median survival time was 45 weeks for conventional CNV versus 90 weeks for HD-CNV. Toxicities occurred more frequently in the HD-CNV arm and consisted mainly of hematologic toxicity, nausea and vomiting, alopecia, neutropenic fever (69% versus 13% in the standard CNV arm), and hemorrhage. There were no treatment-related deaths. In a recent update of these results, all nine patients alive and in CR at the time of initial publication remain in CR, now for over five years [33].

Although this is a randomized study suggesting that the use of higher dose and higher dose intensity in the treatment of metastatic breast cancer may improve response rates and survival, the findings must be interpreted with caution. One issue of concern is that the CR rate noted in women who received standard-dose CNV is lower than expected. In the authors’ own previous study with the CNV regimen given for up to 12 cycles to patients with recurrent or metastatic breast cancer, an OR rate of 81%, including a 23% CR rate, was noted [31]. Another point of concern is that only women who responded to chemotherapy received tamoxifen as continuation therapy. There were far more responses in the HD-CNV arm, so a larger percentage of these women received tamoxifen compared with the standard CNV arm. This discrepancy may have contributed in part to the improved results seen with the HD-CNV treatment. Finally, one must consider that small studies such as this one may over-emphasize treatment benefits.

A second prospective, randomized trial of HDC/ASCR for women with metastatic breast cancer has been published in abstract form [34]. In this study, 423 women with metastatic breast cancer received two to four cycles of AFM chemotherapy consisting of doxorubicin (25 mg/m²/d × 3 days), 5-FU (500 or 750 mg/m²/d × 5 days) and methotrexate (250 mg/m²). The 98 patients who achieved a CR were then randomized to receive immediate consolidation with HDC consisting of cyclophosphamide (5,625 mg/m²), cisplatin (165 mg/m²), and Carmustine (600 mg/m²) and ASCR versus observation, with the same HDC/ASCR given at the time of first relapse.

DFS was significantly improved in the group receiving immediate HDC (0.9 years versus 0.3 years, p = 0.008). OS, however, was significantly higher for those patients randomized to observation with HDC at relapse (3.2 years versus 1.9 years, p = 0.04). The discrepancy in survival rates for women receiving immediate versus delayed HDC is unexplained but suggests that the timing of HDC may be of importance. The superior survival with delayed HDC may
be the result of improved patient immunity after recovery from SDC or may reflect favorable tumor kinetics following recovery from SDC [35].

**Randomized Trials of HDC as Adjuvant Treatment**

Two further randomized trials, both in early-stage disease, have recently been presented. Rodenhuis et al. presented an update of their randomized trial in which women with breast cancer who had a positive infraclavicular lymph node biopsy received three courses of cyclophosphamide 500 mg/m², epirubicin 120 mg/m², and fluorouracil 500 mg/m² (FEC) followed by surgery [36]. Those patients who were stable or responding were then randomized to receive either a fourth course of FEC, followed by radiation therapy and two years of tamoxifen, or the same treatment with HDC/ASCR administered after the fourth course of FEC. The HDC consisted of cyclophosphamide 6 g/m², thiotepa 480 mg/m², and carboplatin 1,600 mg/m². Among the 92 patients who began the study, 81 were randomized to one of the two treatment arms following surgery. With a median follow-up of 49 months, there were no significant differences between the HDC and standard-dose treatment arms in OS (79% versus 72% at four years) and DFS (45% versus 56%). Although this is a small study with a reported 80% power to detect a 30% difference in outcome between the two arms, its findings suggest that when selection bias is minimized, HDC may be no better than SDC, at least within the first four years of follow-up.

The second randomized trial of HDC recently presented had similar conclusions. This study, conducted at the MD Anderson Cancer Center beginning in 1989, recruited 78 women with 10 or more positive lymph nodes after surgery or four or more positive lymph nodes following four courses of neoadjuvant chemotherapy [37]. All participants received a total of eight courses of FAC chemotherapy (cyclophosphamide 500 mg/m², doxorubicin 50 mg/m² as a 72-h infusion, and 5-FU 500 mg/m² on days 1 and 4). Half were randomized to receive two additional courses of HDC consisting of cyclophosphamide 5,250 mg/m², etoposide 1,200 mg/m², and cisplatin 165 mg/m². All patients were to receive radiation therapy and tamoxifen if the estrogen receptor status was positive. The patients were well-matched with regard to age, estrogen receptor status, and stage of disease. The authors accounted for three patients in the standard-dose arm who received HDC off-protocol elsewhere and six patients randomized to HDC who did not receive it by analyzing the data by intention to treat and by treatment actually received. The four-year DFS was 55% and 48% for the HDC versus the standard-dose arm, respectively, by intention to treat (p = 0.45) and was 52% versus 51% by treatment received (p = 0.84). The OS at four years was also not significantly different between the HDC and standard-dose arms, respectively (60% and 68%, p = 0.27) by intention to treat and by treatment received (63% and 64%, p = 0.66). Significant toxicity (two patients with congestive heart failure, one with acute leukemia, and one with fatal sepsis) was limited to the HDC arm. This is a small trial which was actually closed ahead of schedule in January, 1997 due to slow accrual, but its findings speak to the possibility of increased morbidity without increased survival with HDC as adjuvant treatment of breast cancer.

The results from the above two studies are remarkably similar. If the results were combined, the hazard ratio for HDC would actually be 1.02 (95% CI, 0.6-1.7). The large CI reflects the small number of patients in each trial and demonstrates the need for increased power. In order to reduce the CI by half, an additional 500-600 patients would be required.

These well-designed studies are illustrative of the difficulty in studying the issue of HDC. More definitive conclusions can only result from large randomized trials. The NCI has designated four randomized trials of HDC/ASCR as high-priority (Table 5). The Philadelphia Bone Marrow Transplant group (PBMT)-sponsored trial of CMF or CAF followed by 24 months of maintenance CMF versus CMF plus HDC/ASCR with cyclophosphamide, thiotepa, and carboplatin for patients with metastatic breast cancer completed its accrual with over 550 patients in December of 1997. An Intergroup-sponsored trial of adjuvant CAF for patients with ≥10 positive lymph nodes, followed by low- or high-dose cyclophosphamide, cisplatin and carmustine completed its enrollment of over 850 patients in May, 1998. In addition, the Intergroup-sponsored trial of adjuvant CAF, in patients with ≥10 positive lymph nodes, followed by HDC/ASCR versus observation, represents what would typically occur in clinical practice. This trial has recently met its proposed accrual of 536 patients and is expected to close. The remaining trial is a study of sequential doxorubicin, paclitaxel, and cyclophosphamide versus four courses of AC followed by high-dose cyclophosphamide, thiotepa, and carboplatin with ASCR, in women with four to nine positive lymph nodes. As of May 1998, 300 of a proposed 1,000 patients have been enrolled over 18 months.

**Quality of Life**

Although patients’ quality of life (QOL) is difficult to quantitate, it is of primary importance in considering the efficacy of any therapy. Patients undergoing HDC/ASCR for breast cancer were assessed by interview and questionnaire pre- and post-treatment with regard to QOL [38]. Concerns following HDC/ASCR included physical health (51%),...
finances (42%), planning for the future (38%), and health or life insurance status (37%). Many of these concerns arose from the significant financial cost of HDC/ASCR. Another group explored QOL in women after HDC/ASCR as compared to healthy women [39]. Patients who had undergone HDC not surprisingly reported impaired physical functioning, physical role functioning, social functioning, emotional role functioning, and general health. Of note is that diminished QOL was significantly associated with lower income, longer hospital stay, poor performance status, and greater symptom severity.

A recently published study assessed cognitive function, in women with high-risk breast cancer randomly assigned to HDC/ASCR or SDC with adjuvant tamoxifen, and in patients with early-stage breast cancer who had not received chemotherapy (controls) [40]. After an average time from last chemotherapy for all patients of two years, cognitive impairment was found in 32% of the HDC group, 17% of the SDC group, and 9% of the controls. The odds ratio for cognitive impairment after treatment with HDC versus SDC was 3.5 (95% CI, 1.0-12.8), and for HDC versus no chemotherapy 8.2 (95% CI, 1.8-37.7). Thus, central nervous system toxicity may be a dose-limiting toxicity of HDC and may result in decreased QOL following HDC. Several randomized phase III trials of HDC/ASCR include QOL or psychosocial functioning as an outcome, and results of these studies should further clarify this issue (Table 5).

NEW DIRECTIONS

Some investigators are examining allogeneic peripheral blood progenitor cell transplantation in ten women with metastatic breast cancer at the MD Anderson Cancer Center [42]. The preparative regimen consisted of cyclophosphamide, thiotepa, and BCNU. Methotrexate or methotrexate and cyclosporine or Tacrolimus and methotrexate were used for GVHD prophylaxis. The patients were of relatively poor prognosis for transplant patients, as six of the ten patients had three or more sites of disease and all patients had disease in either the liver or bone marrow. Following transplantation, there was one CR, five PR, and four cases of stable disease. Three patients developed GVHD ≥grade 2 and four patients developed chronic GVHD. In two patients, the development of skin GVHD when immunosuppression was withdrawn was associated with regression of liver lesions. The median PFS was 238 days. The studies have shown that allogeneic stem cell transplantation for metastatic breast cancer is feasible. It remains to be shown that a GVT response can be demonstrated.

CONCLUSIONS

After nearly two decades of HDC/ASCR trials in patients with breast cancer, the utility of this treatment remains uncertain. There is a growing body of evidence to suggest that

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Table 5. NCI high-priority randomized trials of HDC/ASCR for the treatment of breast cancer. Used with permission from [43].

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Stage</th>
<th>HDC/ASCR arm</th>
<th>Standard arm</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td>II/III, 4-9 LN +</td>
<td>AC × 4, then HDC/ASCR: CTCb or CPB</td>
<td>Sequential ATxC</td>
<td>DFS, OS, toxicity</td>
</tr>
<tr>
<td>Intergroup</td>
<td>II/IIIA, ≥ 10 LN +</td>
<td>Adjuvant CAF, then HDC/ASCR: CPB</td>
<td>Adjuvant CAF, then lower dose CPB</td>
<td>DFS, OS, toxicity, QOL companion study</td>
</tr>
<tr>
<td>Intergroup</td>
<td>II/III, ≥10 LN +</td>
<td>Adjuvant CAF, then HDC/ASCR: CT</td>
<td>Adjuvant CAF</td>
<td>DFS, OS, toxicity, occult marrow involvement, psychosocial functioning, establish tissue bank</td>
</tr>
<tr>
<td>PBT</td>
<td>IV, responsive disease</td>
<td>HDC/ASCR: CTCb</td>
<td>CMF maintenance × 24 months</td>
<td>Toxicity, cost, QOL</td>
</tr>
</tbody>
</table>

SWOG = Southwest Oncology Group; PBT = Philadelphia Bone Marrow Transplant Group; LN = lymph node; + = positive; C = cyclophosphamide; T = thiotepa; Cb = carboplatin; A = doxorubicin; Tx = paclitaxel; P = cisplatin; B = carmustine; F = 5-fluorouracil; M = methotrexate.
higher response rates and OS observed in HDC trials compared with historical results with SDC may be due in large part to patient selection. The outcome of HDC in an individual patient may be influenced by the biology of the patient’s tumor, such as HER-2/neu expression status. Definitive answers are urgently needed given the large number of patients with breast cancer who are treated with HDC and the poor outcomes in women with high-risk or metastatic disease treated with SDC. At this time, HDC can only be recommended in the setting of a clinical trial. The analyses of the three NCI high-priority randomized trials which have completed accrual are awaited. These and other large randomized studies should answer the question of whether there is a future for HDC/ASCt as a treatment of breast cancer.

REFERENCES


