Much Ado About Not . . . Enough Data: High-Dose Chemotherapy With Autologous Stem Cell Rescue for Breast Cancer

JoAnne Zujewski, Anita Nelson, Jeffrey Abrams*

High-dose chemotherapy with autologous bone marrow or stem cell rescue (HDC/ASCR) has been proposed as a promising treatment strategy for breast cancer. Despite the frequency with which this procedure is performed, the role of HDC/ASCR in the treatment of breast cancer remains undefined. The purpose of this review is to examine the rationale for the procedure, the research progress to date, and the limitations of available data. A literature search of Medline from January 1966 through May 1997, CancerLit from January 1983 through May 1997, and Current Contents through May 1997 identified more than 600 English language papers or abstracts on this topic. Our review focuses on the preclinical and clinical data that explore the concept of chemotherapy dose intensity and the role of dose intensity in treating breast cancer. HDC/ASCR is based on the hypothesis that high-dose chemotherapy will overcome drug resistance, eradicate metastatic disease, and increase the proportion of women with breast cancer who are ‘cured.’

To date, results from only one phase 3 trial of HDC/ASCR compared with more conventional therapy have been published. Phase 2 and some phase 3 data on HDC/ASCR in the treatment of high-risk primary breast cancer and metastatic breast cancer are discussed. However, the results are inconclusive. The completion of national and international randomized trials is urgently needed to establish definitively the role of HDC/ASCR in the treatment of breast cancer. [J Natl Cancer Inst 1998;90:200–9]

For the year 1997, it was estimated that breast cancer would be diagnosed in more than 180,000 women in the United States and that more than 43,000 women would die of the disease (1). For many years, the rate of breast cancer mortality remained unchanged. However, from 1989 through 1993, the age-adjusted mortality from breast cancer declined by 6.8%. This decrease in mortality has been attributed to early detection (screening mammography) and to improved therapies (2). However, only 40%–60% of women with lymph node-positive breast cancer remain disease free at 5 years (3), and, for women with metastatic breast cancer, less than 5% remain disease free at 5 years (4). Clearly, more effective therapies are needed. High-dose chemotherapy with autologous bone marrow or stem cell rescue (HDC/ASCR) has been proposed as a promising treatment strategy for breast cancer. In fact, almost 6000 women have been reported to the Autologous Blood and Bone Marrow Transplant Registry of North America as having undergone bone marrow transplantation for breast cancer from 1989 through 1995 (5), and it is estimated that this number represents approximately one half of all breast cancer-related transplants in the United States (Horowitz M: personal communication).

Despite the frequency with which this procedure is performed, the role of HDC/ASCR in the treatment of breast cancer remains undefined. Given the limitations of available data, it is somewhat surprising that thousands of women have undergone HDC/ASCR for the treatment of breast cancer. Perhaps physicians are not as familiar with the limitations of the data as one might presume. The purpose of this review is to examine both the rationale for HDC/ASCR and the research progress to date with the aim of placing this treatment approach in an appropriate clinical context.

Methods

A literature search in Medline from January 1966 through May 1997, CancerLit from January 1983 through May 1997, and Current Contents through May 1997 was conducted. To be selected, a paper must have been in the English language, have a major focus on breast neoplasms, and have at least a major or minor focus on bone marrow transplantation or stem cell transplantation. The search strategy for Current Contents was based on the following key terms: ‘breast’ and either ‘bone marrow transplant’ or ‘stem cell.’ This search strategy identified 321 articles in Medline, 284 abstracts in CancerLit, and 103 abstracts in Current Contents. High-dose chemotherapy regimens are designated as HDC (high-dose chemotherapy), and sources of hematopoietic rescue, including bone marrow, peripheral blood stem cells, or bone marrow plus peripheral blood stem cells, are designated as ASCR (autologous stem cell rescue).

The first English language paper on this topic in the Medline database was published in 1981 (6). During the past 15 years, the number of papers published on HDC/ASCR for breast cancer has increased markedly (Fig. 1). Fig. 2 categorizes the papers published from January 1993 through May 1997 according to major topic. Although many papers include data relating to more than one topic, each paper was assigned to only one category on the basis of a review of the paper’s abstract. Phase 1 and phase 1/2 trials were grouped, as were pilot and phase 2 trials. Other categories include the following: 1) phase 3 trials; 2)

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sensitivity to other alkylating agents resistant to one alkylating treatment may retain chemotherapy regimens is that cancer cells them attractive candidates for high-dose combina-

tion of, bone marrow or stem cells were excluded. primarily discuss the procurement of, or tumor cell contamination associated with dose-intensive chemotherapy. Papers that pri-

mary trials on treatment outcome or significant toxic effects addressed in single-cell-monolayer experimental sys-

tems, an in vitro excision assay has been developed. Mice bearing transplanted tumor cells are given a single dose of the alkylating agents being studied. Twenty-four hours later, the tumors are excised, single-cell suspensions are made, and the tumors are quantitatively bioassayed in vivo using syngeneic mice or in vitro using a clonogenic as-

say. By use of this approach with EMT6 mammary carcinoma cells and alkylating agents (cyclophosphamide and thiotapec), a similar linear dose–response curve on semilog plots has been demonstrated.

In general, these preclinical studies support the concept of a steep dose–response curve for alkylating agents in the few breast or mammary tumor cell lines that have been studied. However, some work has been published providing evidence for a form of acquired drug resistance that is expressed only at the multicellular level. In these studies, mouse EMT6 mammary tumor cells selected for resistance to various alkylating agents in vivo manifested their resistance only when cultured as three-

dimensional multicellular aggregates or spheroids. A single ex-

Number of articles

Fig. 1. Number of English language articles on high-dose chemotherapy/autologous stem cell rescue for breast cancer published per year in Medline from 1981 through 1996 (n = 321 articles).

articles dealing with stem cell mobilization, stem cell selection, or tumor con-

tamination of bone marrow or stem cell products (designated ASCR); 3) review articles; 4) articles focusing primarily on the toxic effects of high-dose therapies; 5) prognostic factors; 6) articles focusing on selected novel approaches involving HDC/ASCR (discussed below); and 7) other articles (including editorials or commentaries, articles on economics, news items, letters, and case reports). Notably, there are more publications involving the stem cell "product" (mobil-

ization techniques, purging, CD34 selection, and tumor contamination) than trials involving treatment outcomes (phase 1, phase 2, or phase 3) and almost as many review articles (a body of literature to which we are contributing). Among the articles and abstracts identified, there has been only one published paper of a small, single-institution, phase 3 trial of HDC/ASCR in comparison with more conventional therapy (discussed below) (7). Our review focuses primarily on published papers that provide information on treatment outcomes. Data from abstracts are included only if they contain results from random-

ized trials on treatment outcome or significant toxic effects associated with dose-intensive chemotherapy. Papers that pri-

arily discuss the procurement of, or tumor cell contamination of, bone marrow or stem cells were excluded.

High-Dose Chemotherapy/Autologous Stem Cell Rescue

Preclinical Rationale

HDC/ASCR is based on the hypothesis that high doses of chemotherapy will overcome drug resistance, eradicate metastatic disease, and increase the proportion of women with breast cancer who are ‘‘cured.’’ In vitro studies (8–10) have demonstrated a steep dose–response curve for al-

kylation agents in a variety of tumor cell types. Small increases in drug dose in these systems lead to disproportionate increases in tumor cell kill. Another property of alkylating agents that makes them attractive candidates for high-dose combina-

tion chemotherapy regimens is that cancer cells resistant to one alkylating treatment may retain sensitivity to other alkylating agents (8,10). Although the majority of this work was done initially in murine leukemia cells and in other non-breast tumor cell types (11,12), some experiments have

Number of articles

Fig. 2. Number of English language articles on high-dose chemotherapy/autologous stem cell rescue (HDC/ASCR) published in Medline during the period from January 1993 through May 1997 according to major topic (n = 236 articles). Topic categories are as follows: 1 or 1/2 = phase 1 or phase 1/2 clinical trials; 2/pilot = phase 2 or pilot clinical trials (includes tandem HDC/ASCR regimens); other = editorials, economics, news, letters, or case reports; ASCR = stem cell mobilization, stem cell selection, purging, or tumor contamination of peripheral blood or bone marrow; review = review articles; toxicity = major topic of toxicity; novel = new approaches involving HDC/ASCR; and prognostic = major topic identifies prognostic factors.
posure to cisplatin or to 4-hydroperoxycyclophosphamide was sufficient to induce this resistance, as determined by clonogenic assays (14). These preclinical models illustrate the complexity of studying dose–response, even under experimental conditions where variables can be controlled. The heterogeneity of human tumors and variations in human pharmacology provide additional complexities that further limit the ability of in vitro assays to predict clinical responses.

Clinical Trials of Dose Intensity

Retrospective analysis of adjuvant cyclophosphamide, methotrexate, and fluorouracil (5-FU) (CMF) chemotherapy (15) demonstrated that patients who received the highest cumulative dose of chemotherapy had significantly better disease-free survival. Other retrospective analyses (16,17) have emphasized dose intensity (dose per unit time) as a potentially important variable for outcome. The retrospective analyses of dose intensity have been criticized because of a treatment bias effect resulting from the variable durations of therapy in the trials evaluated, which influenced toxicity and, in turn, dose intensity (9). Extrapolations from preclinical data and uncontrolled phase 2 trials are potentially misleading. Even for a very chemo-sensitive tumor, such as intermediate or high-grade lymphoma, randomized phase 3 trials have not confirmed that dose-intensive chemotherapy is superior to standard regimens, despite very promising phase 2 data (18).

Several prospective breast cancer studies of dose intensity in both the metastatic and adjuvant settings have been published. Investigators at The University of Texas M. D. Anderson Cancer Center studied standard-dose FAC (5-FU, doxorubicin [Adria-mycin], and cyclophosphamide) in comparison with high-dose FAC in 59 patients with untreated metastatic breast cancer (19). Survival rates were similar; however, dose reductions were more frequently necessary for toxic effects in the high-dose arm, reducing the dose intensity actually administered. More recently, the dose–response relationship of epirubicin in the treatment of 263 postmenopausal patients with metastatic breast cancer was reported (20). An increase in response rate and time to disease progression was found with an increase in dose from 40 to 90 mg/m², while no increase in efficacy was found by increasing the dose from 90 to 135 mg/m².

In the adjuvant setting, the Cancer and Leukemia Group B performed a randomized study of dose intensity and cumulative doses of cyclophosphamide, doxorubicin, and 5-FU (CAF) chemotherapy in 1572 women with lymph node-positive breast cancer (21). One group of patients received 400 mg/m² cyclophosphamide and 40 mg/m² doxorubicin once every 28 days and 400 mg/m² 5-FU twice every 28 days for six cycles. A second group received 50% more drug (600 mg/m² cyclophosphamide, 60 mg/m² doxorubicin, and 600 mg/m² 5-FU) for four cycles, so that the total dose in this group was identical to the dose in the first group, but the dose intensity was greater. (Note that the high-dose arm of this trial, which was initiated in 1985, would be considered standard chemotherapy today.) A third group of patients received half the total dose at half the dose intensity of the second group. Patients in both the moderate-dose and the high-dose arms exhibited increased disease-free survival and overall survival when compared with patients in the low-dose arm. These results are consistent with either a threshold effect or a modest effect of dose intensity. The equivalent outcomes for the patients in the moderate-dose and high-dose arms in this study make it difficult to decipher whether dose intensity or total cumulative dose is the critical factor within the standard-dose range.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has reported the results of their B-22 study in which standard doses of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) were compared with the same dose of doxorubicin and twice the dose of cyclophosphamide (1200 mg/m²) (22). The results of this trial have shown that neither dose intensity nor a dose-intense, higher cumulative dose has improved disease-free survival or overall survival. Critics of this study have suggested that a twofold escalation may be insufficient. The availability of growth factors (e.g., granulocyte colony-stimulating factor) has made further escalation feasible, and NSABP B-25 is comparing standard-dose doxorubicin (60 mg/m²) plus cyclophosphamide (1200 mg/m²) for four cycles with standard-dose doxorubicin and higher-dose cyclophosphamide (2400 mg/m²) for two or four cycles. The results of this trial should be available soon. It can be predicted, however, that, even if the findings of this trial are negative, the proponents of dose escalation are not likely to be dissuaded because higher doses of multiple alkylators, possible only with stem cell support, may be necessary to overcome drug resistance. Although proof of an increased dose effect for cyclophosphamide is lacking, there is evidence that increased doses are more mutagenic. The 4-year cumulative incidence of acute myelogenous leukemia or myelodysplasia in NSABP B-25 was 0.87%, approximately two to three times the incidence observed with standard-dose cyclophosphamide (23). The Intergroup adjuvant trial (INT-0148) took a different approach; rather than escalate cyclophosphamide, patients with positive lymph nodes are randomly assigned to doxorubicin at 60, 75, or 90 mg/m², with a constant dose of cyclophosphamide (600 mg/m²). The accrual of 3000 patients to this trial has been completed, but results are not yet available.

Taken together, the currently available results of these trials testing dose intensity indicate that every effort should be made to deliver full doses of standard adjuvant chemotherapy (regimens containing doxorubicin at 60 mg/m² plus cyclophosphamide at 600 mg/m² for four cycles). However, the role of increased dose or increased dose intensity beyond these levels, such as is achievable in a transplant setting, or the role of dose intensity of nonalkylating agents remains undetermined.

HDC/ASCR in Metastatic Breast Cancer

A report of HDC/ASCR for the treatment of breast cancer was published in Presse Med in 1966 (24), the first year of the Medline database. In this study, 10 patients with breast cancer (among 20 total patients) were treated with HDC (5-FU, thiotepa, or others) and ‘‘rescued’’ with autologous bone marrow that had been previously harvested and banked. There was an overall response rate of 80% in the patients with breast cancer (two complete responses and six partial responses). The authors concluded presciently that, ‘‘this method, yet in its first steps, has procured positive and promising results. The obtention and banking of bone marrow in view of autografting at the end of treatment has appeared efficient and allows for considerable increase in the total doses of the chemotherapeutic agent.’’

Early trials of autologous bone marrow transplantation for the treatment of solid tumors involved patients with multiple tumor types. The dose–response effect, the lack of cross-resistance, the synergism in vitro, and the differing nonhematologic toxic effects provided the rationale for combining multiple alkylating agents at or near full doses (8). Administered with hematologic bone marrow or stem cell rescue, these combined HDC regimens could achieve a dose intensity 5 to 30 times that obtained in standard chemotherapy regimens (10). Multiple phase 1/2, phase 2, or pilot studies of HDC with ASCR for the treatment of breast cancer have been published. The majority of these studies investigated the use of combinations of alkylating agents either in the same course (25–45) or in tandem courses (46–51). A few studies (52–54) have incorporated the use of agents such as paclitaxel or anthracyclines. Others have studied the feasibility of immune modulation (55), radioimmunotherapy (56), or gene transfer in conjunction with HDC/ASCR (57).

The three most common HDC regimens used in conjunction with autologous transplantation for breast cancer, as reported to the North American Transplant Registry, include cyclophosphamide and thiotepa; cyclophosphamide, thiotepa, and carboplatin (CTCb); and cyclophosphamide, BCNU (i.e., carmustine or 1,3-bis[2-chloroethyl]-1-nitrosourea), and cisplatin (5). These regimens employ alkylating agents administered at 5 to 30 times the conventional dosages. Given the combination of agents and the potential synergy between alkylating agents, the effective dose intensity of these regimens may be even higher. Selected phase 2 studies of HDC/ASCR for the treatment of metastatic breast cancer, including some of the studies that used the above-mentioned regimens, studies involving larger series of patients, and some studies that used tandem cycles of HDC, are included in Table 1. The HDC/ASCR arms of the two randomized trials (discussed below) are also included.

What can we learn from these phase 2 trials? First, the response rates are impressive, with higher overall and complete response rates than would be expected given historic controls. Second, toxicity is also higher, including a mortality of between 0% and 23%. Severe toxic effects may include infection (58), hepatic veno-occlusive disease (59–61), pulmonary drug toxicity (27), renal dysfunction (31,62), hemorrhagic cystitis (32), and secondary cancers (5). The degree of toxicity does appear to be improved in recent years, which may reflect better supportive care or patient selection. The Autologous Blood and Bone Marrow Transplant Registry of North America reports a decrease in 100-day mortality from 22% in 1989 to 5% in 1995. However, during this same period, the percentage of women reported to the transplant registry who underwent HDC/ASCR for metastatic breast cancer decreased from 93% to 50%, with a corresponding increase from 7% to 50% in the percentage of women with locoregional disease (5). Third, the median survival is similar to that of historic controls, and a small percentage of persons remain disease free 3–5 years after therapy. It is this small percentage of persons (the “tail on the curve”) who remain disease free that has led to the enthusiasm for this procedure. However, great caution is necessary in interpreting these phase 2 data because of the heterogeneous nature of breast cancer, the small sample sizes, selection bias, and publication or reporting biases. Finally, no single HDC regimen appears to be clearly superior in these phase 2 trials.

Unfortunately, there has been only one published report of a randomized phase 3 trial comparing HDC/ASCR with more conventional therapy in the treatment of metastatic breast cancer (7). A second randomized phase 3 trial, described in an abstract and involving patients who had obtained a complete response to induction chemotherapy, compared immediate HDC/ASCR with HDC/ASCR at relapse (63). The fully published trial (7) com-

Table 1. Selected trials of HDC/ASCR in metastatic breast cancer*

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Investigator(s)</th>
<th>Year</th>
<th>No. of patients</th>
<th>HDC agents</th>
<th>Complete response, %</th>
<th>Median overall survival, mo</th>
<th>Alive and disease free, %</th>
<th>Median follow-up, mo</th>
<th>Toxic deaths, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(29)</td>
<td>Williams et al.</td>
<td>1992</td>
<td>27</td>
<td>CT</td>
<td>55</td>
<td>15.1</td>
<td>7</td>
<td>50.4</td>
<td>14</td>
</tr>
<tr>
<td>(32)</td>
<td>Kennedy et al.</td>
<td>1991</td>
<td>30</td>
<td>CT</td>
<td>46</td>
<td>100</td>
<td>22</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>(25)</td>
<td>Peters et al.</td>
<td>1988</td>
<td>22</td>
<td>CBP</td>
<td>54</td>
<td>73</td>
<td>14</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>(63)</td>
<td>Peters et al.‡</td>
<td>1996</td>
<td>98</td>
<td>CBP</td>
<td>100§</td>
<td>22.8</td>
<td>25 (actuarial)</td>
<td>60 (actuarial)</td>
<td></td>
</tr>
<tr>
<td>(28)</td>
<td>Ayash et al.</td>
<td>1995</td>
<td>62</td>
<td>CTCb</td>
<td>29</td>
<td>88</td>
<td>24</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>(27)</td>
<td>Antman et al.</td>
<td>1992</td>
<td>29</td>
<td>CTCb</td>
<td>45</td>
<td>100</td>
<td>&gt;20</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>(34)</td>
<td>Shah et al.</td>
<td>1995</td>
<td>46</td>
<td>CTCb</td>
<td>15</td>
<td>7</td>
<td>53</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>(33)</td>
<td>Gisselbrecht et al.</td>
<td>1996</td>
<td>61</td>
<td>CNMe</td>
<td>59</td>
<td>85</td>
<td>26</td>
<td>18</td>
<td>51</td>
</tr>
<tr>
<td>(35)</td>
<td>Perkins et al.</td>
<td>1996</td>
<td>77</td>
<td>ICE</td>
<td></td>
<td></td>
<td>108 (actuarial)</td>
<td>36 (actuarial)</td>
<td></td>
</tr>
<tr>
<td>(47)</td>
<td>Ayash et al.‡</td>
<td>1996</td>
<td>67</td>
<td>Me-CTCb</td>
<td>33</td>
<td>83</td>
<td>20</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>(46)</td>
<td>Dunphy et al.</td>
<td>1994</td>
<td>80</td>
<td>CVP × 2</td>
<td>55</td>
<td>79</td>
<td>15</td>
<td>16‡</td>
<td>17–65 (range)</td>
</tr>
<tr>
<td>(7)</td>
<td>Bezwooda et al.‡</td>
<td>1995</td>
<td>45</td>
<td>CNV × 2</td>
<td>51</td>
<td>96</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*HDC/ASCR = high-dose chemotherapy/autologous stem cell rescue; CT = cyclophosphamide and thiotepa; CBP = cyclophosphamide, BCNU (carmustine or 1,3-bis[2-chloroethyl]-1-nitrosourea), and cisplatin; CTCb = cyclophosphamide, thiotepa, and carboplatin; CNMe = cyclophosphamide, mitoxantrone, and melphalan; ICE = ifosfamide, carboplatin, and etoposide; MeN = melphalan and mitoxantrone; Me-CTCb = melphalan, followed by cyclophosphamide, thiotepa, and carboplatin; CVP = cyclophosphamide, etoposide, and cisplatin; and CNV = cyclophosphamide, mitoxantrone, and etoposide. See text or references for dose information.

†Response rate includes complete and partial responses.
‡Phase 3 trials that include patients undergoing HDC/ASCR.
§Patients in complete response prior to HDC/ASCR.
¶May include patients alive with disease who are progression free.
pared two cycles of high-dose cyclophosphamide (2400 mg/m²), mitoxantrone (35–45 mg/m²), and etoposide (i.e., VP-16) (2500 mg/m²) (HD–CNV) administered in tandem with more conventional doses of cyclophosphamide (600 mg/m²), mitoxantrone (12 mg/m²), and vincristine (1.4 mg/m²) (CNV) in 90 patients with metastatic breast cancer who had not received chemotherapy for metastatic disease. Both the response rate and overall survival were significantly better with HD–CNV. In the HD–CNV arm, 43 (96%) of 45 patients responded with 51% complete responses. In the conventional-dose arm, only 24 (53%) of 45 patients responded, and only two patients (4%) obtained a complete response. The median response duration and overall survival were also longer in the HD–CNV arm (80 and 90 weeks, respectively) compared with the CNV arm (34 and 45 weeks, respectively). Although this study was positive, several concerns have been raised (64). The first concern is that the trial was relatively small. Thus, the results may not be representative of those obtainable in large, multi-institutional trials. A second concern is whether the standard-therapy arm was adequate. A complete response rate of only 4% is lower than would be expected. The investigators’ previous experience with the same regimen demonstrated an overall response rate of 81% and a complete response rate of 23% (65). A third concern is the imbalance in hormonal therapy administered. Tamoxifen was administered only to responding patients. Since the response rate was significantly higher in the HDC/ASCR arm (96% versus 53%), a significantly higher proportion of patients received combined chemotherapy and endocrine therapy. Finally, the median survival (21 months in the HD–CNV arm) is very similar to, or shorter than, the median survival of patients with metastatic breast cancer treated with other anthracycline-containing regimens (66–68). In both arms, the overall survival was only 10 weeks longer than the median survival, raising the question of the adequacy of second-line therapies in these patients. Despite these limitations, this study does raise the important issue of the value of induction with standard chemotherapy. Most U.S. studies use induction therapy with standard regimens to select chemosensitive patients for transplantation. However, this approach might actually induce drug resistance and make the eventual high-dose therapy less effective.

The results of the second randomized trial are also of interest (63). In this study, patients who obtained a complete response to induction chemotherapy (doxorubicin, 25 mg/m² per day × 3 days; 5-FU, 500 or 750 mg/m² per day × 5 days; and methotrexate, 250 mg/m²) were randomly assigned to either HDC/ASCR immediately following induction therapy or at the time of relapse. The disease-free survival was greater in the immediate HDC/ASCR group (0.9 versus 0.3 years). However, surprisingly, and of greater concern, the overall survival was significantly longer in the group assigned to observation, i.e., with HDC/ASCR given at the time of relapse (3.2 versus 1.9 years). The absence of a standard control arm in this trial makes interpretation of the study difficult. It is possible that an improvement in survival may also have resulted if standard-dose treatments were administered at the time of relapse. Nonetheless, this study does raise the issue of the appropriate timing of HDC/ASCR. Prior to this study, extrapolation from the adjuvant setting (in which treatment of micrometastases has improved survival) suggested that treatment at the time of lowest tumor burden (complete response) would be superior to waiting until the appearance of macroscopic disease. However, if the role of HDC is primarily cytoreduction, rather than overcoming drug-resistant micrometastatic disease, the optimal treatment approach may be to sequence each treatment maneuver to yield the greatest clinical benefit.

How do these results compare with the best available standard care in historic controls? As mentioned earlier, comparisons with historic controls are fraught with multiple biases. Furthermore, breast cancer relapses can occur many years after diagnosis, making long-term follow-up essential. Such follow-up is not yet available for HDC/ASCR. Investigators at the M. D. Anderson Cancer Center have recently reported long-term survival data for more than 1500 patients with metastatic breast cancer who were treated with more conventional doxorubicin-based therapy, usually FAC (4). This report included only patients treated before 1982, so at least a 10-year follow-up was obtained. Among a total of 1581 patients, 263 achieved a complete response. Among these 263 patients, 49 (18.6%) remained in complete response at 5 years. The investigators also noted that the patients in long-term, complete response were more likely to be younger (median age, 50 years), have fewer metastatic sites, and have a better performance status than the overall group of patients.

These investigators have used this same database of more than 1500 patients with metastatic breast cancer to compare the prognosis of patients who may have met the strict eligibility criteria for HDC/ASCR with those who did not (69). In a very informative analysis, almost 60% of patients who were eligible for trials of doxorubicin-based chemotherapy at a more conventional dose were eliminated for consideration of high-dose therapy. Another fraction of patients would be excluded on the basis of additional testing requirements for studies of HDC/ASCR (bone marrow biopsies, cardiac MUGA [multiple gated acquisition] testing [i.e., equilibrium radionuclide angiography], pulmonary function tests, and infectious disease serologies). The authors estimated that 65%–75% of patients eligible for conventional-dose chemotherapy programs would not be candidates for HDC/ASCR programs. This rigorous selection process would be expected to identify a subgroup of patients with a better prognosis. Indeed, in this analysis, patients potentially eligible for HDC/ASCR did have higher overall response rates, higher complete response rates, and a median response rate that was 65% longer than patients treated with the same doxorubicin-containing regimen in conventional doses.

Several phase 2 trials of HDC/ASCR have also evaluated prognostic factors for their ability to predict prolonged progression-free survival after HDC/ASCR (28,29,46). Williams et al. (29) reported improved median survival in 24 (41%) of 59 patients who did not receive previous adjuvant therapy compared with 34 (58%) of 59 patients who did (24 versus 9 months). Ayash et al. (28) determined that a single metastatic site and achievement of a complete response to induction therapy were the most important predictors for progression-free survival in a multivariate analysis of 62 patients. Dunphy et al. (46) determined that liver involvement by tumor, soft tissue disease, and previous adjuvant chemotherapy were negative predictors of overall survival in 80 patients. These analyses identify a subset...
of patients who would also be expected to have a better prognosis following more conventional therapies.

**HDC/ASCR in Locoregional Breast Cancer**

Patients with primary breast cancer and positive axillary lymph nodes are at increased risk for relapse and death from breast cancer. Fig. 3 illustrates, on the basis of the number of positive lymph nodes, the numbers of patients with stage I, stage II, or stage III breast cancer reported to the Surveillance, Epidemiology, and End Results registry of the National Cancer Institute (NCI) in 1994, the most recent year for which data are available. Given the particularly poor prognosis of patients with 10 or more positive lymph nodes—a relapse-free survival of 35%–47% and an overall survival of 55%–63% at 5 years following combination chemotherapy (70)—these patients were considered candidates for HDC/ASCR. Peters et al. (71) reported the results of HDC (cyclophosphamide, 1875 mg/m² per day × 3 days; BCNU, 600 mg/m²; and cisplatin, 55 mg/m² per day × 3 days) with ASCR in 102 patients with primary breast cancer and 10 or more positive lymph nodes. Actuarial event-free survival was approximately 72% (95% confidence interval = 56%–82%) at 5 years (72). These promising results have prompted the use of this treatment in patients with four to nine, or even fewer, positive lymph nodes. The data from the North American Transplant Registry illustrates this trend (5). In 1989, only 7% of patients undergoing HDC/ASCR had locoregional breast cancer; by 1995, approximately 50% had locoregional disease. Although the majority of patients undergoing HDC/ASCR had greater than 10 positive lymph nodes, 28% had fewer than 10 involved lymph nodes.

As in the case of metastatic breast cancer, the promising results of HDC/ASCR in primary breast cancer are difficult to interpret in relation to historic controls. Two recent reports are of interest when considering the potential implications of selection bias in this setting. Diel et al. (73) reported tumor cell contamination of bone marrow in 727 patients with primary breast cancer. By use of a monoclonal antibody technique, tumor cells were detected in 55% of 367 patients with lymph node-positive breast cancer. Evidence of tumor cell contamination of the bone marrow was associated with a reduction in disease-free survival and overall survival. Notably, patients with tumor cell contamination of the bone marrow, when detected on initial staging, would be excluded from trials of HDC/ASCR for patients with primary breast cancer. Similarly, Crump et al. (74) reported that 23% (95% confidence interval = 12%–41%) of patients considered for HDC/ASCR were excluded for metastatic disease found on extensive staging evaluations not originally detected with routine screening.

Results are available from only one randomized trial, a phase 2 trial, of HDC/ASCR in the treatment of primary breast cancer (75). Reported in abstract form, investigators in The Netherlands randomly assigned 95 patients with stage II or stage III breast cancer to dose-intensive FEC (5-FU, 500 mg/m²; epirubicin, 120 mg/m²; and cyclophosphamide, 500 mg/m²) or FEC induction followed by HDC/ASCR with CTCb (cyclophosphamide, 6 g/m²; thiotepa, 480 mg/m²; and carboplatin, 1600 mg/m²). With a median follow-up of 36 months, progression-free survival was clearly superior to that of historic controls, but results for the two treatment arms were superimposable. The detection of a small but statistically significant survival difference awaits the results of phase 3 randomized trials.

**Necessity for Randomized Trials of HDC/ASCR for Breast Cancer**

Although initial reports of HDC/ASCR are promising, the high probability that these results are biased make the completion of large, multicenter, randomized trials a necessity. Furthermore, the costs of HDC/ASCR are substantial. By use of a decision-analysis model and a Markov process, Hillner et al. (76) estimated the cost-effectiveness of standard chemotherapy and HDC/ASCR in the treatment of metastatic breast cancer. With the use of a variety of assumptions, HDC/ASCR (bone marrow) provided a survival benefit of 6.0 months at an incremental cost of $115,800 per year of life extension. If patients who were disease free after 5 years had normal survival, the benefit was 18.1 months at an incremental cost of $28,600 per year of life extension. The authors concluded that, “Decision analysis highlights the limitations in the currently available data and the assumptions made for the emotional question of using (HDC/ASCR) in metastatic breast cancer. The model supports the need for randomized clinical trials.” During the past several years, numerous other investigators have also indicated the need for randomized trials (33,77–79,80). However, data reported to the Autologous Blood and Bone Marrow Transplant Registry of North America indicate that less than 1% of the patients with metastatic breast cancer and only 11% of the patients with locoregional breast cancer underwent this procedure as part of randomized trials involving more than 1300 patients in 1994.

Currently, there are several ongoing randomized trials of HDC/ASCR internationally (Tables 2 and 3). Unfortunately, two of the NCI’s high priority trials (INT-0121 and INT-0163), begun in 1991, are still 6–9 months from attaining their

![Fig. 3. Numbers of patients with breast cancer, according to the number of positive axillary lymph nodes, reported to the Surveillance, Epidemiology, and End Results database of the National Cancer Institute in 1994, the most recent year for which data are available. Node-negative = patients with uninvolved lymph nodes; one to three = patients with one to three positive lymph nodes; four to nine = patients with four to nine positive lymph nodes; 10 or more = patients with 10 or more positive lymph nodes; undetermined = patients with positive lymph nodes with the number unknown, patients in whom lymph node dissection was not performed, and patients with no recorded lymph node information.](image-url)
accrual targets (Table 2). The NCI (i.e., the Cancer Therapy Evaluation Program and the Office of Cancer Communications) investigated the reasons behind this slow accrual (81). In 1995, three focus groups were held during the American Society of Clinical Oncology meetings; two were conducted with oncologists who refer patients to the HDC/ASCR trials, and one focus group was held with physicians who had never referred anyone to these trials. Regardless of their previous referral patterns, all physicians agreed that enrolling patients in clinical trials was extremely difficult. Among the reasons cited were the following: lack of funding by trial groups for data managers and clinical research nurses; varying standards and procedures among trial centers that add administrative burdens and frustrate physicians; and increased time required to enroll patients, especially when patients want to start treatment immediately. Additional obstacles, specific to the transplant trials, were the following: competition among, and even within, academic cen-

### Table 2. National Cancer Institute-supported high-priority randomized trials of high-dose chemotherapy/autologous stem cell rescue (HDC/ASCR) for breast cancer

<table>
<thead>
<tr>
<th>Disease setting</th>
<th>Trial No./sponsor</th>
<th>HDC/ASCR arm</th>
<th>Control arm</th>
<th>Sample size: accrual as of Target completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant therapy for stage II/III disease, No. of involved axillary lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–9</td>
<td>S9623(SWOG, CALGB, ECOG, NCCTG)</td>
<td>AC × 4 → HDC/ASCR: CTCb or CPB</td>
<td>HDSC: A × 3, Tx × 3, C × 3 (only G-CSF support)</td>
<td>1000</td>
</tr>
<tr>
<td>≥10</td>
<td>INT-0121(ECOG, SWOG)</td>
<td>CAF × 6 → HDC/ASCR: CT</td>
<td>CAF × 6</td>
<td>105</td>
</tr>
<tr>
<td>≥10</td>
<td>INT-0163(CALGB, SWOG, NCIC)</td>
<td>CAF × 4 → HDC/ASCR: CPB</td>
<td>CAF × 4 → CPB (only G-CSF support)</td>
<td>760</td>
</tr>
</tbody>
</table>

*Abbreviations are as follows: SWOG = Southwest Oncology Group; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; NCCTG = North Central Cancer Treatment Group; NCIC = National Cancer Institute of Canada; A = doxorubicin; C = cyclophosphamide; T = thiopeta; Cb = carboplatin; B = BCNU (carmustine or 1,3-bis[2-chloroethyl]-1-nitrosourea); Tx = paclitaxel; P = cisplatin; F = fluorouracil; HDSC = high-dose sequential chemotherapy; G-CSF = granulocyte colony-stimulating factor; and M = methotrexate.

### Table 3. Ongoing national and international randomized trials of high-dose chemotherapy/autologous stem cell rescue (HDC/ASCR) for breast cancer

<table>
<thead>
<tr>
<th>Disease setting</th>
<th>Sponsor</th>
<th>HDC/ASCR arm</th>
<th>Control arm</th>
<th>Target sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant therapy for stage II and/or III disease, No. of involved axillary lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>Milan/Italy†</td>
<td>HDSC/ASCR: C × 1, VM × 1, E × 2, LP × 1</td>
<td>E × 3, CMF × 6</td>
<td>200</td>
</tr>
<tr>
<td>≥4</td>
<td>NWPFAST</td>
<td>CEF × 4 → HDC/ASCR: CTCb</td>
<td>CEF × 5</td>
<td>880</td>
</tr>
<tr>
<td>≥4</td>
<td>ACG</td>
<td>LAM × 4 → HDC/ASCR: CT</td>
<td>LAM × 4, CMF × 8</td>
<td>550</td>
</tr>
<tr>
<td>4–9</td>
<td>Response Technologies</td>
<td>CEF × 3 → HDC/ASCR: CTCb</td>
<td>A × 4 → HDC/ASCR: CTCb</td>
<td>246</td>
</tr>
<tr>
<td>≥5</td>
<td>PEGASE</td>
<td>CEF × 4 → HDC/ASCR: CML</td>
<td>CEF × 4</td>
<td>240</td>
</tr>
<tr>
<td>≥10</td>
<td>IBCSG</td>
<td>HDSC/ASCR: EC × 3</td>
<td>EC/AC × 4, CMF × 3</td>
<td>210</td>
</tr>
<tr>
<td>≥10</td>
<td>GABG</td>
<td>EC × 4 → HDC/ASCR: CTM</td>
<td>EC × 4, CMF × 3</td>
<td>420</td>
</tr>
<tr>
<td>≥10 (stage II only)</td>
<td>GABG-IMG</td>
<td>EtiCE × 2 → HDC/ASCR: EdCb</td>
<td>EC × 4, CMF × 3</td>
<td>320</td>
</tr>
<tr>
<td>≥10 (stage III only)</td>
<td>GABG-IMG</td>
<td>EC × 3 → HDC/ASCR: CCPb × 1, Tmt × 1</td>
<td>EC × 3, CMF × 3</td>
<td>300</td>
</tr>
<tr>
<td>Metastatic disease (stage IV) Bone metastases</td>
<td>Duke University</td>
<td>AFM × 2–4 → HDC/ASCR: CBP</td>
<td>AFM × 2–4 → at relapse: HDC/ASCR: CBP</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>PEGASE</td>
<td>CEF × 4 → HDC/ASCR: CT</td>
<td>CEF</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>NCIC</td>
<td>A or Tx × 4 → HDC/ASCR: CMtC × 2</td>
<td>Continue A (to dose limit) or Tx</td>
<td>192</td>
</tr>
</tbody>
</table>

*Abbreviations are as follows: PEGASE = Societe Francaise de Greffe du Moelle, Federation Nationale des Centres de Lutte Contre le Cancer; ACG = Anglo-Celtic Group; NWPFAST = Netherlands Working Party for Autotransplantation in Solid Tumors; IBCSG = International Breast Cancer Study Group; GABG/GABG-IMG = German Adjuvant Breast Chemotherapy Cancer Group—Interdisciplinary Mammary Group; SBG = Scandinavian Breast Group; NCIC = National Cancer Institute of Canada; HDSC/ASCR = high-dose sequential chemotherapy/autologous stem cell rescue; B = BCNU (carmustine or 1,3-bis[2-chloroethyl]-1-nitrosourea); C = cyclophosphamide; A = doxorubicin; E = etoposide; I = ifosfamide; and V = vincristine.

†Istituto Nazionale Tumori.
ters between phase 2 nonrandomized transplant trials and the high priority phase 3 studies; increases in the number of nonacademic centers offering transplantation outside of clinical trials; and unwillingness of many patients to accept trial designs that require acceptance of a random assignment between high-dose therapy and standard-dose therapy. Potential solutions that were offered centered on 1) educational campaigns to inform the public and 2) the reduction of administrative burdens and personnel requirements by finding ways to standardize some protocol requirements and to eliminate unnecessary ones.

Because patient bias was frequently cited by physicians in the focus groups as a major element for the slow accrual, the NCI also performed a series of mini-focus groups and personal interviews from November 1995 through February 1996 with 26 women who entered the NCI-supported randomized trials and with three women who rejected participation (82). The overwhelming message from these women was that their physician’s attitude and interest in the trials and his/her ability to give a balanced presentation of both study arms were the key determinants in their decision-making process. Other important factors noted were insurance coverage, travel costs, and time away from home. The inability to find many women to participate in these interviews who had been offered a trial but decided against participation resulted from the failure of most researchers to keep records of such encounters. In trials that are having accrual difficulties, or that can be predicted to have such problems, it would be worthwhile to record information about such patients, since they represent a potentially valuable resource for helping the investigators diagnose and amend a faulty trial design.

In summary, it is clear, as has been noted in a recent General Accounting Office report (83), that the wide availability of HDC/ASCR is possibly the major reason that researchers are having problems accruing patients to the randomized trials. During the past few years, this problem has been further aggravated by the willingness of insurers to pay for this therapy, whether or not a patient enters a randomized trial, as a result of public relations concerns, threats of litigation, and government mandates. To counter this trend and to improve accrual to randomized trials that involve new technologies, such as HDC/ASCR, as opposed to new drugs, which are controlled more closely by the Food and Drug Administration, efforts are needed on several fronts. More broadly based patient education efforts focused on attracting national media attention, rather than restricting efforts to local hospitals and grass-roots publications, are necessary. The NCI-sponsored Cooperative Groups must also streamline their trials and facilitate participation by community-based oncologists by addressing the clinical research costs. Improved informatics represents a potential solution in this era of increasing cost containment. If user-friendly office management systems can be developed that allow trial data collection to be incorporated into routine office management, then physicians may come to view clinical trials as a routine part of patient care.

**Conclusion**

HDC/ASCR is likely to make a contribution to breast cancer treatment. The results of large, randomized trials will allow physicians and their patients to assess accurately the potential benefits and risks and to determine whether HDC/ASCR is truly their best treatment choice. If randomized trials are positive, additional research will be necessary to identify the subset of patients most likely to benefit from this intensive and costly therapy.

**References**


Notes
1Phase 1 clinical trials determine the relationship between the dose of a drug or treatment and its toxicity when given according to a specified schedule via a specified mode of administration; biologic effects other than toxicity are also of interest. Phase 1 trials help define a treatment dose that is appropriate for use in phase 2 studies. Phase 2 clinical trials are designed to determine the antitumor activity of a drug or treatment with respect to specific tumor types. Phase 1/2 clinical trials first determine a dose for phase 2 studies and then test the recommended dose in a cohort of patients with a specific tumor type. Phase 3 clinical trials are designed to provide evidence that the drug or treatment has effectiveness in patients with a specific diagnosis with a specific recommendation for treatment. Phase 3 trials usually involve a prospective randomization to either the new treatment or the conventional treatment (84).
2Note added in proof: Since this review was accepted for publication, preliminary findings from NSABP B-25 have been reported in abstract form (85). These early results fail to show a statistically significant survival advantage for the higher doses.
3Editor’s note: SEER is a set of geographically defined, population-based cancer registries under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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