

High-Dose Chemotherapy and Hematopoietic Support for Patients with High-Risk Primary Breast Cancer and Involvement of 4 to 9 Lymph Nodes

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ABSTRACT

Despite modern chemotherapy, advanced breast cancer remains a significant cause of cancer morbidity and mortality in women. Patients with disease involvement of multiple lymph nodes represent a subgroup with a high risk of relapse. In particular, 50% of patients with 4 to 9 axillary lymph nodes involved will relapse after standard chemotherapy. In an effort to improve the survival of patients with 4 to 9 involved nodes, we performed a phase II study in which 61 patients with surgically diagnosed stage II or III breast cancer and 4 to 9 positive lymph nodes received 3 cycles of doxorubicin and 5-fluorouracil followed by high-dose chemotherapy consisting of cisplatin, cyclophosphamide, and carmustine and infusion of autologous hematopoietic progenitor cells. All patients received posttransplantation localized radiotherapy unless contraindicated, and all patients with hormone receptor-positive disease received tamoxifen. After a median patient follow-up of 6.7 years (range, 4.6-8.6 years), the 5-year overall survival rate was 79% (95% CI, 69%-90%), with relapse-free survival of 73% (95% CI, 62%-85%). Treatment-related mortality was 3%. Interstitial pneumonitis occurred in 69% of patients but did not contribute to mortality. Our study presents long-term favorable results regarding the use of consolidative HDC with autologous hematopoietic support in previously untreated patients with high-risk primary breast cancer.

KEY WORDS

Multinodal-positive breast cancer • Multinodal involvement • Autologous hematopoietic cell rescue

INTRODUCTION

Breast cancer remains the most common cancer in women and the second leading cause of cancer deaths in women [1]. Although patients with limited-stage disease are often cured with standard multimodality therapy, the prognosis for patients with multinodal-positive disease remains poor. There are considerable data demonstrating the correlation between survival after the diagnosis of breast cancer and the number of lymph nodes involved at the time of surgery. Although adjuvant chemotherapy has improved the outcome in many patients, those with extensive lymph node

involvement continue to suffer high mortality rates. In women with primary breast cancer involving 10 or more lymph nodes, 55% to 87% will relapse within 5 years [2-4]. Results for patients with 4 to 9 positive lymph nodes are also disappointing, with $\geq 50\%$ of patients treated with standard-dose regimens relapsing by 5 years [5-9].

High-dose chemotherapy (HDC) with autologous hematopoietic cell rescue has the advantage of a steep therapeutic dose-response curve, characteristic of many chemotherapeutic agents, without the disadvantage of significant hematopoietic toxicity at higher doses. Initial

phase II trials conducted in the 1980s demonstrated that the response rates in patients with metastatic breast cancer who received combination HDC, with median survival durations of 4.2 to 6.8 months, were superior to those in patients who received standard-dose combination therapy. In particular, with more than 13 years of follow-up, combination chemotherapy with cyclophosphamide, cisplatin, and carmustine (CPB) yielded a response rate of 65% and progression-free survival rate of 14% [10,11]. Although HDC results in high response rates, responses appear durable predominantly in those patients who are able to achieve a complete response following HDC [12-14]. Therefore, incorporation of induction chemotherapy and consolidative hormonal and radiotherapy has been used in later trials in an attempt to increase the number of complete responders.

The Duke University Bone Marrow Transplant Program previously performed a series of studies employing CPB in the treatment of metastatic or locally-regionally recurrent breast cancer. These studies demonstrated complete response rates of 50% and long-term disease-free survival (DFS) rates that showed significant improvement compared to those obtained with conventional-dose therapy [10,15,16]. After these encouraging results were obtained, a pilot study was conducted in which patients with high-risk primary breast cancer with 10 or more positive lymph nodes were treated with intensive induction chemotherapy followed by CPB and autologous hematopoietic support. With a median follow-up of 6.5 years, according to comparison with historical controls, event-free survival (EFS) rates in these patients were almost twice those in patients who received the same or similar induction chemotherapy without CPB and autologous hematopoietic support [17]. The preliminary results of a phase III randomized study in women with 10 or more positive lymph nodes comparing the results of treatment with intermediate versus high-dose CPB showed no difference in overall survival (OS) [18]. Disease-specific survival rates were modestly improved with HDC, but the benefit was offset by treatment-related mortality. Longer follow-up is needed to better assess the utility of HDC in these patients. Conclusions drawn from these data are premature, as demonstrated by the Dutch study [19] that showed, after an adequate follow-up period, that treatment with HDC was beneficial in the initial subset of 284 patients. Because treatment with standard therapy has been shown to result in similar survival rates for patients with 4 to 9 and patients with 10 or more involved axillary lymph nodes, a comparable approach of intensive induction chemotherapy followed by HDC and autologous hematopoietic cell rescue was undertaken in patients with 4 to 9 positive axillary nodes.

MATERIALS AND METHODS

Patient Selection

From August 1992 to February 1996, 72 women with newly diagnosed stage II or III breast cancer and 4 to 9 involved axillary lymph nodes were referred to the Bone Marrow Transplant Program at Duke University. After the initial evaluation, each patient's case was presented at a weekly conference at which patients were reviewed for suitability for enrollment. Eligibility criteria included patient age ≥ 18 years, Karnofsky performance status of $\geq 80\%$, con-

firmation of all pathologic specimens and disease staging at the transplantation center, and insurance approval. Patients could not have received adjuvant chemotherapy. Eleven patients were excluded for the following reasons: bone marrow involvement ($n = 1$), presence of inflammatory breast cancer ($n = 2$), prior therapy ($n = 3$), previous breast cancer ($n = 3$), and patient refusal to participate in study ($n = 2$).

Eligibility Criteria Prior to HDC

The following test results were mandatory for patients undergoing registration and initiation of HDC and were obtained within 4 weeks prior to enrollment: bilateral bone marrow biopsies with $\geq 20\%$ cellularity without evidence of tumor involvement; hemoglobin [Hb] ≥ 10 g/dL; platelet count $\geq 100,000/\mu\text{L}$; absolute neutrophil count (ANC) $\geq 1800/\mu\text{L}$; serum creatinine ≤ 1.8 mg/dL; blood urea nitrogen $\leq 1.5 \times$ normal; estimated creatinine clearance ≥ 60 mL/min; aspartate aminotransferase and bilirubin $\leq 2.5 \times$ normal; negative β -human chorionic gonadotropin, human immunodeficiency virus antibody, and hepatitis B surface antigen; computed tomographic (CT) scans of the head, chest, abdomen, and pelvis and bone scan without evidence of metastatic disease; multiple-gated acquisition scan with ejection fraction $\geq 45\%$ at rest; and pulmonary function tests with corrected carbon monoxide diffusing capacity (DLCO), 1-second forced expiratory volume (FEV1), and forced vital capacity (FVC) all $\geq 60\%$. All 61 patients proceeded to HDC.

Treatment Plan

All patients had previously undergone primary surgery consisting of axillary lymph node dissection in addition to one of the following procedures: radical mastectomy, modified radical mastectomy, or lumpectomy. A minimum number of sampled axillary nodes was not required for any of the patients. Adjuvant chemotherapy included 3 cycles of doxorubicin (80 mg/m²) and 5-fluorouracil (AF) (800 mg/m²) given as intravenous (IV) boluses every 14 days with granulocyte colony-stimulating factor (G-CSF) support on days 3 through 10. Initiation of adjuvant chemotherapy had to occur within 8 weeks of the last breast cancer-related surgery.

Within 3 weeks of the last dose of AF chemotherapy and subsequent hematopoietic recovery, the patients underwent a bone marrow harvest as previously described [20]. A minimum nucleated cell count of $1 \times 10^8/\text{kg}$ was collected. Cells were cryopreserved with dimethyl sulfoxide (DMSO) and maintained in liquid nitrogen.

Peripheral blood progenitor cells (PBPCs) were mobilized with subcutaneous daily injections of G-CSF 5 $\mu\text{g}/\text{kg}$ per day for a total of 5 consecutive days. Patients underwent leukapheresis as previously described [21] on days 4 through 6 of G-CSF priming, and all patients met the goal of $>1 \times 10^{10}/\text{kg}$ nucleated cells or $2 \times 10^6/\text{kg}$ CD34⁺ cells. PBPCs were cryopreserved in liquid nitrogen with 10% DMSO.

After a minimum of 5 days from the last dose of G-CSF, the following HDC regimen was initiated: cyclophosphamide (CPA) 1875 mg/m² per day IV over 1 hour on days -6 to -4 and concurrent cisplatin (cDDP) 55 mg/m² per day via continuous IV infusion on days -6 to -4 , followed by the immediate administration of carmustine (BCNU) 600 mg/m² IV over 2 hours on day -3 . All chemotherapy doses were calculated based on actual body weight (ABW) unless the patient's

body weight was >20% more than ideal body weight (IBW), in which case the mean of the ABW and IBW was used. On days -1 to +1, all patients received autologous PBPCs, which were rapidly thawed at 37°C and infused over several minutes via a large-bore central venous catheter. With a similar procedure, bone marrow was rapidly thawed and reinfused on day +1, approximately 3 hours after the last infusion of PBPCs.

Supportive Care

All patients received daily subcutaneous injections or IV infusions of G-CSF 5 µg/kg per day after PBPC reinfusion, beginning on day -1 and continuing until day +21, unless ANC was ≥2500/mL for 3 days or ≥10,000/mL for 1 day. Beginning on day -2 and continuing until ANC was >500/mL, all patients received prophylactic antibiotics consisting of ciprofloxacin 500 mg orally every 8 hours and rifampin 300 mg every 12 hours [22]. In patients who developed febrile neutropenia (temperature >38.2°C), oral antibiotics were discontinued and broad-spectrum IV antibiotics were initiated, with modification of therapy based on culture results. Antifungal therapy was initiated if the fever persisted for 5 days of treatment with broad-spectrum antibiotics. Criteria for blood-product support included Hb <10 g/dL or platelet count ≤25,000/mL. All patients received irradiated and leukoreduced filtered blood products.

Tamoxifen

Estrogen receptor (ER) and progesterone receptor (PR) status were considered positive if ≥7 fm/mg protein was present or immunohistochemical staining was positive. Women whose disease was hormone-receptor positive were initiated on tamoxifen therapy 10 mg orally twice a day beginning 6 weeks after HDC and continuing for 5 years. A total of 41 patients received tamoxifen. In addition to the 39 women with known hormone-receptor-positive tumors, the 2 patients with unknown ER and PR status also received tamoxifen. Three patients received incomplete therapy because of relapsed disease (n = 1) or prolonged pancytopenia (n = 2). In addition, 2 patients had an interruption in hormonal therapy because of refractory emesis.

Posttransplantation Irradiation

Patients underwent local/regional radiotherapy approximately 6 weeks following completion of HDC unless they had continued transplantation-related toxicities including significant pulmonary toxicity, white blood cell count (WBC) <3000/mL, or platelet count <50,000/mL. Six patients had a delay in therapy because of the development of interstitial pneumonitis. Nine patients did not receive radiotherapy because of prolonged interstitial pneumonitis (n = 7), development of Guillain-Barre syndrome (n = 1), or development of idiopathic thrombocytopenic purpura (n = 1). The remaining 52 patients were scheduled to receive 50.4 Gy irradiation to the chest wall or ipsilateral remaining breast, internal mammary, and supraclavicular nodes via cobalt 60 or higher energy tangential photons, with an additional 10 to 15 Gy to the tumor bed or mastectomy scar region, all in 1.8- to 2.0-Gy daily fractions 5 days a week. Treatment delays were allowed for acute skin desquamation, acute pulmonary toxicity, WBC <1500/mL, or platelet count <30,000/mL. Five patients had delays in receiving a

complete radiotherapy course because of interstitial pneumonitis (n = 4) or the development of hemolytic uremic syndrome (n = 1). An additional 3 patients received only partial therapy because of recurrent interstitial pneumonitis, the development of prolonged pancytopenia, or the development of progressive disease. The radiation therapy may have varied somewhat because patients were treated at multiple sites and the radiation therapy records were not reviewed.

Follow-up

After HDC, patients were evaluated at the transplantation center at 6 weeks, 6 months, and 1 year and annually thereafter. At all follow-up visits, a complete physical examination was performed and samples obtained and analyzed for complete blood count with differential and complete chemistry panel results. Screening CT scans of the chest and abdomen and bone scans were obtained annually.

Interstitial Pneumonitis

Baseline results of pulmonary function tests (PFTs), including FVC, FEV1, and DLCO, were obtained prior to study registration and after standard-dose chemotherapy. Follow-up PFTs were performed 6 weeks after hematopoietic cell transplantation. Additional PFTs were performed if signs/symptoms of pulmonary toxicity developed. DLCO was corrected for Hb using the formula $(1.7 \times \text{Hb}) / (10.2 + \text{Hb})$. FVC, FEV1, and DLCO were expressed as percentage predicted for the corresponding age, sex, and height of the patient. The following criteria were used in the diagnosis of interstitial pneumonitis: (1) no evidence/suspicion for infectious etiologies; (2) development of nonproductive cough and dyspnea, with or without fever, occurring several weeks to months following consolidative HDC, and a fall in DLCO to <60% predicted; (3) decline in DLCO to <50% predicted, with or without symptoms. Patients in whom interstitial pneumonitis was diagnosed were treated with prednisone, beginning at a dosage of 60 mg/day for 2 weeks. Although the dosage for most patients was tapered over 8 weeks, the duration of therapy was individually adjusted based on clinical response. Patients treated with prednisone received concurrent pneumocystis prophylaxis with oral sulfamethoxazole-trimethoprim or aerosolized pentamidine.

Statistical Methods

Cox proportional hazards univariate regression models were used to identify predictors of OS, relapse-free survival (RFS), and EFS. We estimated OS and EFS according to the Kaplan-Meier product limit method. We calculated EFS from time of transplantation to disease progression or death, whichever occurred first. Patients who were alive without progressive disease were censored at the date of last follow-up visit. OS was calculated from time of transplantation to death, and patients who were alive were censored at date of last follow-up visit.

RESULTS

Patient Characteristics

Table 1 lists the characteristics of the 61 patients analyzed in this study. The median age was 44 years (range, 26-58 years), and the majority of patients had stage II breast

Table I. Patient Characteristics

Age at diagnosis, median (range), y	44 (26-58)
Primary tumor size, median (range), cm	3 (1-16)
Time to transplantation from diagnosis, median (range), d	132 (89-472)
Stage, n	
II	45
III	16
Surgery, n	
Mastectomy	2
Modified radical mastectomy	37
Bilateral mastectomy	4
Lumpectomy + axillary lymph node dissection	15
Other	2
Unknown	1
Lymph node involvement, n	
4	9
5	5
6	15
7	7
8	16
9	9
Hormonal status, n	
ER/PR+	28
ER+ only	4
PR+ only	7
Negative	20
Unknown	2

cancer (45 of 61). Prior to chemotherapy, most patients underwent a modified radical mastectomy with a median of 7 involved lymph nodes. Thirty-nine (64%) of patients had a positive hormone-receptor status.

Survival Data

Survival data are shown in Figures 1 and 2. The median follow-up was 6.7 years (range, 4.6-8.6 years). At 3 years, the OS and EFS rates were 87% (95% confidence interval [CI], 79%-96%) and 74% (95% CI, 64%-86%), respectively. RFS was 78% (95% CI, 69%-89%). At 5 years, the OS and EFS

rates were 79% (95% CI, 69%-90%) and 69% (95% CI, 58%-82%), respectively. At the time of analysis, a total of 16 patients had evidence of recurrent disease, with a median time to relapse of 1.72 years (range, 0.36-3.98 years). Although only 3 patients relapsed within the first year after transplantation, all 16 patients relapsed within 4 years. Five of the patients who relapsed had not received radiation or had experienced a delay in receiving radiation, and none of these 5 relapsed locoregionally. Fifteen patients died because of disease; 2 deaths were due to treatment-related toxicity, and 1 was due to previously undisclosed alcoholic liver disease. The median time to death in this group of 16 patients was 2.2 years from transplantation. In the entire group of patients, the median survival was not reached.

Toxicity

Two patients (3%) suffered treatment-related mortality, one of an air embolus that occurred during administration of total parenteral nutrition after transplantation and one of hepatosplenic candidiasis/sepsis. A non-treatment-related death noted at day 592 was a result of previously undisclosed alcoholic liver disease.

Interstitial pneumonitis was the most frequent reported complication, affecting 42 patients (69%) with a median decrease in DLCO of 44% from baseline. The median time to development of pneumonitis was 45 days (range, 10-411 days), with 41 patients diagnosed within the first 6 months. No deaths could be attributed to the development of interstitial pneumonitis. There were no cases of significant regimen-related hepatotoxicity including veno-occlusive disease, nephrotoxicity, central nervous system toxicity, cutaneous changes, microangiopathic hemolytic anemia, or secondary cancers, including myelodysplastic syndrome.

PROGNOSTIC FACTORS

The following variables were analyzed using a univariate Cox proportional hazards regression model to predict RFS: age, tumor size, number of positive lymph nodes, proportion of positive nodes, type of surgery, use of consolidative radiotherapy, ER status, PR status, tamoxifen therapy in

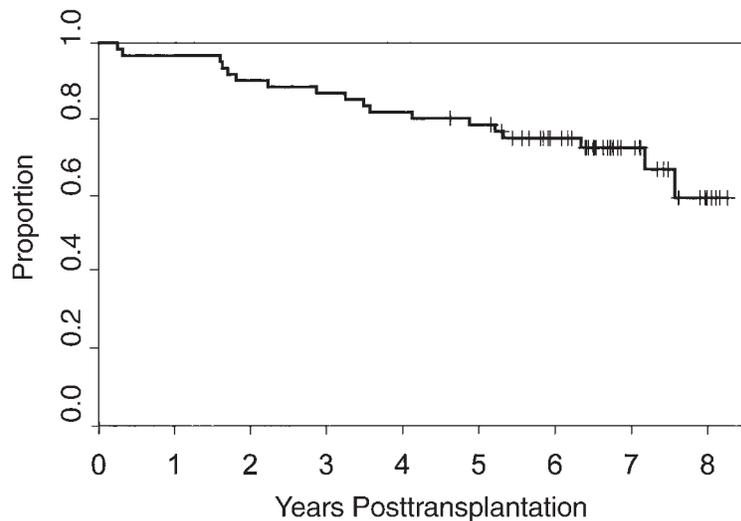


Figure 1. Kaplan-Meier overall survival curve.

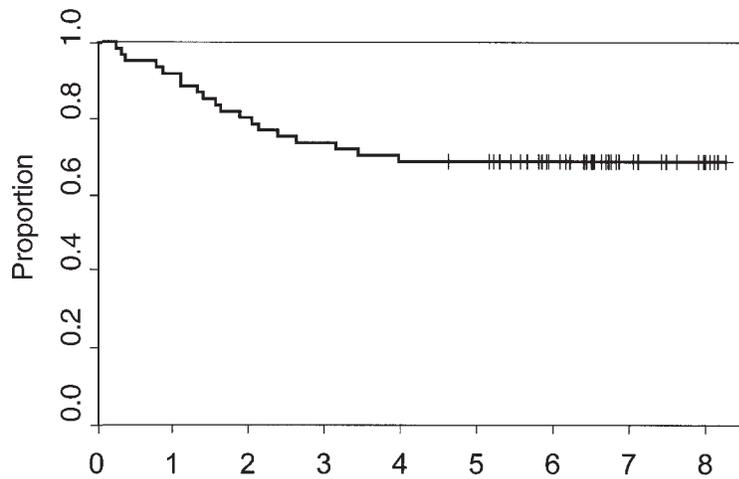


Figure 2. Kaplan-Meier event-free survival curve.

hormone positive or postmenopausal patients, or the development of interstitial pneumonitis. Table 2 outlines the variables and *P* values. The number of positive nodes, proportion of positive nodes, and degree of radicalness of surgery were of borderline significance. Additionally, univariate analyses were performed to predict EFS and OS; consolidative radiotherapy and more radical surgery predicted an improved OS. The HER-2/neu status of the primary tumors was not available.

DISCUSSION

The prognosis of patients with primary breast cancer is inversely related to the number of lymph nodes involved. Despite conventional chemotherapy, patients with 10 or more lymph nodes involved at the time of surgery have relapse rates of 55% to 87% at 5 years [5,7,8,23]. Analysis of the results of treatment outcomes for patients with 4 to 9

positive lymph nodes are equally grim, with a 50% to 60% relapse rate at 5 years, increasing to 70% to 80% by 10 years [5,6,8,24]. In particular, standard-dose CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) and CAF (cyclophosphamide, doxorubicin and 5-fluorouracil), commonly used adjuvant treatments, have led to 5-year DFS rates of only 35% and 54%, respectively [5,25,26].

Because of the poor prognosis of patients with advanced disease, the possibility of improving survival using dose-escalation therapy with non-cross-resistant agents has been studied. Historical studies such as those from the Mayo Clinic and MD Anderson Center (FAC trials) have extensive follow-up on the cohort of patients who achieved complete remissions after extended chemotherapy [27]. Compared to these trials, trials with HDC achieve 2 to 15 times the number of complete remissions. However, inherent difficulties exist in the analysis of nonmatched historical controls. More compelling are the results of the

Table 2. *P* Values of Univariate Analyses for Prediction of EFS and OS

Variable	RFS	EFS	OS	Comparison
Nodes	.083	.36	.32	Continuous
Surgery	.50	.57	.26	Bilateral, lumpectomy, modified radical mastectomy
Radical*	.053	.067	.026	Radical surgery
IP	.65	.54	.30	Interstitial pneumonitis (yes/no)
RT	.47	.10	.038	Radiation therapy (yes/no)
Tam	.94	.93	.94	Tamoxifen (yes/no)
Age	.65	.55	.74	Age dichotomized at 45
Age	.23	.31	.72	Continuous
Prop Nodes ††	.08	.14	.19	Proportion of positive nodes
ER/PR status	.75	.75	.95	Either positive versus both negative
ER status	.92	.85	.92	+ versus -
PR status	.74	.72	.93	+ versus -
Tumor size	.75	.68	.69	Continuous
Tumor size	.95	.70	.87	≤2 cm versus >2 cm

*The more radical the surgery, the higher the group survival rates. Compares bilateral mastectomies or modified radical mastectomy versus lumpectomy or simple mastectomy.

††Formula for the calculation is number of positive nodes divided by number of nodes examined.

Cancer and Leukemia Group B (CALGB) 8541 trial, which compared 3 doses and schedules of CAF adjuvant therapy for stage II/III breast cancer. A significant improvement in OS and DFS was seen in the higher dose arms [5]. Dose escalation of a single agent, as demonstrated in CALGB 9344, with dose escalation of doxorubicin of 60 mg/m² to 90 mg/m², or NSABP B25, with a dose escalation of cyclophosphamide of 1200 mg/m² to 2400 mg/m², did not result in a survival benefit [28,29]. However, in one trial, the addition of a non-cross-reactive agent, such as paclitaxel, resulted in early improvement in DFS and OS in patients with hormone-receptor-negative tumors [29].

Because of initially encouraging data on treatment of metastatic disease, patients with high-risk primary breast cancer have been treated with HDC. In a phase II trial, Peters et al. used HDC and autologous hematopoietic cell rescue as consolidation after 4 cycles of standard-dose CAF adjuvant chemotherapy. All 85 patients received posttransplantation radiotherapy, and patients with hormone-receptor-positive disease received up to 5 years of tamoxifen therapy. With a median follow-up of 6.5 years, patient EFS was 65% [17,30]. Other single-institution studies have reported similar results, and the International Bone Marrow Transplant Registry demonstrated a 3-year EFS after HDC of 65% and 60% for stage II and III disease, respectively, in patients with ≥ 4 positive nodes [14,31-34]. Several prospective randomized multicenter trials that will attempt to better clarify potential benefit are currently underway or have completed enrollment, but to date no results have been published that focus on the 4-to-9-positive-node patient group.

Initial studies using HDC in patients with 4 to 9 involved lymph nodes have shown promising results. In a phase II multicenter trial, 43 patients with stage II or III breast cancer with 4 to 9 involved lymph nodes received standard AFM chemotherapy (adriamycin, 5-fluorouracil, and methotrexate) followed by HDC (cyclophosphamide, thiotepa, and carboplatin) and chemotherapy-mobilized autologous hematopoietic cell rescue. OS was 77% and DFS was 67% at a median of 4 years [31]. Bearman et al. reported similar results, with a DFS of 71% at 4 years, using high-dose cyclophosphamide, cisplatin, and BCNU [32]. In a comparable study, Hudis et al. investigated the use of "dose-dense" adjuvant chemotherapy in patients with 4 or more positive lymph nodes. A sequential schedule was used to optimize time of exposure of doxorubicin and cyclophosphamide, and the 5-year DFS for 73 patients was 51.7% [35].

In a study based on these encouraging results, we investigated the efficacy of CPB HDC in patients with 4 to 9 involved axillary lymph nodes. With 3-year OS and RFS rates of 87% and 78%, respectively, our data demonstrate further improvement over historical data and results similar to those of the other phase II transplantation studies. This improvement may be partially related to the decreased transplantation-related mortality, which is considerably lower than the 10% to 20% reported in previously published trials. The median time to relapse was 1.76 years, with most patients with relapsed disease dying at 3 to 4 years posttransplantation. No correlation could be found regarding delay in any therapy, including transplantation, radiation therapy, or hormonal therapy. However, this conclusion is based on a relatively small sample size. Insufficient data

were available to assess whether relapse correlated with Her-2-neu positivity. The University of Colorado group has shown decreased survival in Her-2-neu-positive patients following transplantation [36].

The incidence of pneumonitis resulting from the HDC regimen was higher in our study than that in studies using other HDC regimens, but was comparable to the incidence in a smaller group of patients previously reported by us [37]. The incidence of pneumonitis in our current study was also markedly similar to the incidence of pneumonitis (72%) seen in 75 patients treated under the CALGB 9082 protocol described below [38]. The mechanism by which these similar regimens lead to a higher incidence of pneumonitis is unclear, but may involve enhanced oxidative lung injury and the development of a proinflammatory environment due to the chemotherapeutic agents used [37,38]. Systemic steroid use appears beneficial in the treatment of interstitial pneumonitis, a result that led our group to complete a study that demonstrates a possible beneficial effect of high-dose inhaled steroid prophylaxis against the development of interstitial pneumonitis [39]. Despite the higher incidence of pneumonitis seen in our study, no deaths resulted from pneumonitis. Deaths were likely prevented by frequent follow-up and rapid administration of steroid therapy upon diagnosis.

Large-scale randomized trials may provide further insight into the use of HDC in high-risk breast cancer patients. In a phase III randomized trial, CALGB 9082 patients with 10 or more positive nodes received 4 cycles of CAF followed by randomization to either intermediate-dose CPB or high-dose CPB therapy and autologous hematopoietic cell rescue, followed by consolidated radiotherapy and tamoxifen. At a median follow-up of 5 years, no statistical difference in EFS between the treatment groups was seen [18]. In the Scandinavian trial, 525 women with either high-risk or metastatic disease to the bone or bone marrow were randomized to receive either 3 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by HDC with cyclophosphamide, thiotepa, and carboplatin (CTCb) with autologous hematopoietic cell rescue or 9 cycles of tailored FEC. The OS was 70% in both arms at a median of 2 years [40]. The intergroup study led by the Southwest Oncology Group, 9623, compared dose-dense anthracycline cyclophosphamide and paclitaxel with 4 cycles of CAF followed by transplantation for patients with 4 to 9 involved lymph nodes. The study is closed to accrual and data should be forthcoming in the next 1 to 2 years.

With a short follow-up time, the available analyses of these trials are premature, and the high up-front mortality rate in the transplantation arms likely contributes to the lack of difference in survival results between treatment groups. After a longer time for analysis, results from a third large-scale trial are now favoring HDC. In the Dutch study, the first 284 out of 885 enrolled patients with ≥ 4 positive axillary lymph nodes received 3 cycles of adjuvant FEC and surgery. The patients were randomized to receive a fourth cycle of FEC followed by either radiation therapy and tamoxifen or high-dose CTCb and autologous hematopoietic cell rescue followed by radiation therapy and tamoxifen. At a follow-up of 3 years, there was a 15% improvement in progression-free survival favoring the HDC group (77% in the high-dose group versus 62% in the conventional-dose chemotherapy group; $P = .009$) [19]. It is important to note

that the HDC was administered as bolus infusions in this study and not continuous infusions as previously reported for that regimen. The bolus infusions resulted in 7-fold increased 4-hydroperoxycyclophosphamide (4HC) levels compared to levels obtained with continuous infusions. We have previously reported on the importance of drug levels and survival [41].

Considerable controversy exists around the use of HDC and autologous transplantation in breast cancer. Patients with multinodal involvement represent a subgroup with a high risk of relapse. Our study presents favorable results regarding consolidative HDC with autologous hematopoietic rescue in previously untreated patients with 4 to 9 involved lymph nodes. Although single-institution studies provide important information regarding feasibility issues, rigid multicenter randomized trials are required to truly compare HDC to other therapies. We hope such trials will provide necessary information regarding the overall benefit of HDC.

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