High-Dose Chemotherapy and Autologous Bone Marrow Support as Consolidation After Standard-Dose Adjuvant Therapy for High-Risk Primary Breast Cancer

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Purpose: **We studied high-dose cyclophosphamide, cisplatin, and carmustine (CPA/cDDP/BCNU) with autologous bone marrow support (ABMS) as consolidation after standard-dose adjuvant chemotherapy treatment of primary breast cancer involving 10 or more axillary lymph nodes.**

Patients and Methods: **One hundred two women with stage IIA, IIB, IIIA, or IIIB breast cancer involving 10 or more lymph nodes at surgery were registered; 85 were eligible, treated, and assessable. Patients were treated with four cycles of standard-dose cyclophosphamide, doxorubicin, and fluorouracil (CAF), followed by high-dose CPA/cDDP/BCNU with ABMS.**

Results: **Actuarial event-free survival for the study patients at a median follow-up of 2.5 years is 72% (95% confidence interval, 56% to 82%). Comparison to three historical or concurrent Cancer and Leukemia Group B (CALGB) adjuvant chemotherapy trials selected for similar patients showed event-free survival at 2.5 years to be between 38% and 52%. Therapy-related mortality was 12%; pulmonary toxicity of variable severity occurred in 31% of patients. Quality-of-life evaluations indicate that patients are functioning well without major impairments.**

Conclusion: **High-dose consolidation with CPA/cDDP/BCNU and ABMS after standard-dose CAF results in a decreased frequency of relapse in patients with high-risk primary breast cancer compared with historical series at the median follow-up of 2.5 years. Evaluation in a prospective, randomized trial is warranted and currently underway.**

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ADJUVANT CHEMOTHERAPY has been demonstrated to produce modest but consistent improvements in long-term disease-free and overall survival in patients with primary breast cancer.[1] These improvements are achieved with chemotherapy programs that are not curative in metastatic disease. Further, there is increasing evidence both from retrospective analyses[2] and from prospective randomized clinical trials that dose intensification is sometimes associated with superior outcomes in metastatic[3-6] and primary breast cancer.[7] We have reported that high-dose cyclophosphamide, cisplatin, and carmustine (CPA/cDDP/BCNU) and autologous bone marrow support (ABMS) can produce frequent and rapid complete responses in metastatic breast cancer,[8] and that some of these responses are durable.[9] However, relapses occurred frequently and primarily at pretreatment sites of bulk disease. Further, the use of high-dose chemotherapy and autologous bone marrow transplantation as consolidation following standard-dose induction therapy has been reported by several groups, including our own, to augment the frequency of complete responses in patients with metastatic breast cancer. However, these results were achieved with considerable treatment-related morbidity and mortality, although the rates of morbidity and mortality have recently been reduced.[10-14]

The prognosis for patients with extensive axillary lymph node involvement at the time of presentation with primary breast cancer is poor, despite standard-dose adjuvant therapy. Analysis of treatment outcomes in patients with 10 or more involved axillary lymph nodes indicates that between 55% and 87% of patients will relapse by 5 years and 70% to 90% will relapse by 10 years.[15] Comparison to historical series in which adjuvant chemotherapy was not used indicates that little, if any, impact of adjuvant therapy is seen in the first 4 years and that benefit from adjuvant therapy becomes apparent only after this time and is generally clinically modest,[16] although statistically significant. Contemporary results from cooperative groups do not appear to improve meaningfully on these earlier results.

Because of the inadequacy of standard adjuvant chemotherapy in high-risk primary breast cancer and the limitation of disease bulk in the use of high-dose chemotherapy for metastatic breast cancer, we chose to com-

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bine these modalities in the treatment program reported here. The study reported here thus represents an evolution in treatment strategy for breast cancer by coupling a standard-dose adjuvant chemotherapy regimen and high-dose consolidation with combination alkylating agents and ABMS. We chose to use an adjuvant chemotherapy program (cyclophosphamide, doxorubicin and fluorouracil [CAF]) that has been widely used and is being simultaneously evaluated in a cooperative group setting (Cancer and Leukemia Group B [CALGB] 8541) in a similar patient population. Further, we used a high-dose chemotherapy program of CPA/cDDP/BCNU, which has been extensively evaluated in both advanced and early metastatic breast cancer to characterize more carefully and control the expected toxicities of high-dose therapy.

PATIENTS AND METHODS

Patient Population

We entered 102 patients onto this trial between February 1987 and January 1991. The patients presented here represent 85 eligible and assessable women who received high-dose chemotherapy. Characteristics of the patients are listed in Table 1. Of the 11 eligible patients not transplanted, one was lost to follow-up and six of the remaining 10 had recurrence of breast cancer. All patients received high-dose therapy at the Duke University Medical Center and the same entry and evaluation procedures were used throughout the study period. Between July 1987 and July 1989, 40 of the entered patients were simultaneously registered on a pilot protocol of identical design and conduct within the CALGB (protocol 8782); of these 40, 37 are assessable, two were not treated with high-dose consolidation for financial reasons, and one relapsed during CAF and is excluded from subsequent analyses. There were no important differences between the CALGB subset of patients and the remainder of patients; this report will describe the characteristics of the entire population subsequently.

The median age for these 85 patients was 38 years (range, 23 to 56). Ninety-five percent were between 25 and 50 years old; only three were older than 50 years. All patients were treated with a modified radical mastectomy, except one who received a segmental resection. The distribution of patients by stage, number of axillary lymph nodes involved with cancer histologically, and hormone receptor characteristics of the primary tumor is listed in Table 1.

Table 1. High-Dose CPA/cDDP/BCNU and ABMS for Stage II/III Breast Cancer Involving 10 or More Axillary Lymph Nodes

	CALGB 8782*	Entire Duke Series Including 8782
No. of patients entered	40	102
Ineligible	0	4
Treated before referral and evaluation	0	3
Relapsed before starting treatment	0	1
Not transplanted	2	11
ICRTP	2	6
Hepatitis		1
Psychotic		1
Refused		3
Relapsed during CAF induction	1	2
Systemic relapse	1	1
Local relapse	0	1
Eligible and assessable	37	85
Median age at surgery, years	38	38
Surgical treatment	37	85
Mastectomy	37	84
Segmentectomy	0	1
Stage		
IIA	9	20
IIB	22	44
IIIA	5	20
IIIB	1	1
No. of involved lymph nodes		
Median	13	14
10-12	15	28
13-15	9	22
16-19	8	25
over 20	5	10
Hormone receptor status		
ER-negative/PR-negative	15	34
ER-negative/PR-positive	2	7
ER-positive/PR-negative	5	10
ER-positive/PR-positive	15	34

Abbreviations: ICRTP, insurance company refused to pay; ER, estrogen receptor; PR, progesterone receptor.

*CALGB 8782 represents a subset of the entire Duke series. All patients in CALGB are included in the entire Duke series.

Treatment Program

Patients were eligible if they had histologically proven invasive breast cancer, stage II or III, which at mastectomy involved 10 or more axillary lymph nodes. Patients were excluded if they had a history of prior cancer or treatment for the breast cancer. Pretreatment evaluation requirements included history and physical examination; computed tomography of the head, chest, abdomen, and pelvis and bone scans showing no evidence of cancer; rest and exercise left ventriculography (ejection fraction > 45% at rest and < 5% decrease with exercise); pulmonary function testing (forced vital capacity, forced expiratory volume in 1 second, and diffusing capacity of the lung for carbon monoxide all > 60% of predicted); and bilateral bone marrow aspirations and biopsies showing no evidence of cancer and cellularity greater than 20%. Evaluation and initiation of therapy were prescribed by protocol to be within 56 days of mastectomy; however, due to delays in evaluation and chemotherapy initiation, six patients received their first chemotherapy treatment from 58 to 64 days after mastectomy. These were considered minor protocol violations and they are not excluded from analysis. The median time from mastectomy to first cycle of chemotherapy was 41 days (range, 9 to 64).

The treatment program involved the sequential use of an outpatient chemotherapy induction program of CAF followed by high-dose chemotherapy consolidation with CPA/cDDP/BCNU with ABMS, radiation therapy, and tamoxifen as shown in Fig 1. All patients were treated with four cycles of CAF (cyclophosphamide 600 mg/m^2 day 1, doxorubicin 60 mg/m^2 day 1, and fluorouracil 600 mg/m^2 days 1 and 8) with each cycle lasting 28 days. No patient had doses reduced from those prescribed by protocol; colony-stimulating factors (CSFs) were not administered during the CAF chemotherapy. Between the

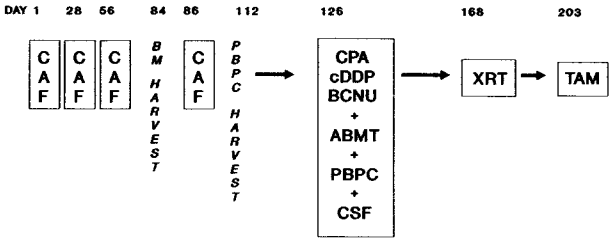

Fig 1. Schema for treatment. BM harvest, bone marrow harvest; PBPC harvest, CSF-primed PBPC harvest; ABMT, autologous bone marrow transplant; CSF, colony-stimulating factor; XRT, radiation therapy to chest wall and draining lymph node regions; TAM, tamoxifen 10 mg orally twice daily for 5 years.

third and fourth cycles of CAF, a bulk bone marrow harvest was obtained under general anesthesia from the posterior iliac crest and processed as described later. Cellular and cytokine support evolved during the protocol and, in addition to bone marrow, 65 patients had CSF-primed peripheral-blood progenitor cells (PBPC) collected after the fourth cycle of CAF. CSF-priming and collection of PBPC required 9 days, and a washout period of 5 days was allowed to elapse before initiation of high-dose chemotherapy. Patients were then admitted to the next available bed in the transplant unit and were cared for in private rooms with positive-pressure, high-efficiency particle filtration (HEPA) air systems. During the high-dose consolidation phase of treatment, access to patient rooms required masks, gloves, gowns, and shoe covers; a low-bacterial, low-fungal content diet was prescribed.

All patients had a triple-lumen central venous catheter placed for access within 3 weeks of beginning high-dose chemotherapy. Per unit policy, patients were transfused until a hematocrit greater than 42% was reached; hematocrit was maintained at this level until leukocyte and platelet recovery. Before initiation of the high-dose chemotherapy, bladder irrigation was begun with 1 L/h urologic saline containing 2 mL of neomycin and polymixin B. This was continued until 24 hours after the last dose of cyclophosphamide to minimize hemorrhagic cystitis. Aggressive hydration with 5% dextrose/0.45% saline supplemented with electrolytes at 200 to 250 mL/m^2/h was used, and urine output replaced on a milliliter-for-milliliter basis throughout chemotherapy. If urine output fell below 200 mL/h, additional hydration was provided. An average 13,375 mL of fluid was administered to patients on a daily basis between day −6 and day −3. High-dose chemotherapy was always begun between 8 AM and noon.

The high-dose chemotherapy program was cyclophosphamide (1,875 mg/m^2/d) administered as a 1-hour intravenous infusion on 3 successive days (days −6, −5, and −4 from day of bone marrow infusion [day +1]), cisplatin (55 mg/m^2/d, days −6, −5, and −4) administered as a 72-hour continuous intravenous infusion, and carmustine (600 mg/m^2) administered on day −3 as an intravenous infusion at a rate of 5 mg/m^2/min, unless hypotension not responsive to fluid challenge (systolic blood pressure < 80 mm Hg) occurred, at which time the dose rate was reduced to 2.5 mg/m^2/min. If hypotension persisted, dopamine was begun and titered to maintain a systolic blood pressure greater than 80 mm Hg. If patients were more than 20% over ideal body weight, the administered doses of CPA/cDDP/BCNU in the high-dose portion of this program were calculated from the average of the surface areas based on actual and ideal body weight.

We have previously reported that high-dose CPA/cDDP/BCNU induces a functional platelet defect, which is partially corrected by transfusion of allogeneic platelets.[17] All patients were therefore transfused twice with single-donor pheresed platelets 24 hours after completion of chemotherapy (day − 2), regardless of the measured platelet count. Throughout the remainder of the treatment course, single-donor platelets were administered to maintain a platelet count greater than 25,000/μL if possible.

Daily cultures were performed for bacterial or fungal infection if a patients temperature was greater than 38.3°C not associated with blood products or amphotericin B administration. Febrile, neutropenic patients were empirically treated with a standardized antibiotic protocol, which included, if indicated, empiric antifungal therapy; these patients continued to receive antibiotics until the granulocyte count was greater than 500/μL.

Cellular Support

Bone marrow. All patients treated with high-dose CPA/cDDP/BCNU received ABMS. Bone marrow was collected when the leukocyte count was greater than 3,000/μL—approximately 28 days after the third cycle of CAF. Marrow was collected as described previously from the posterior iliac crests under general or regional anesthesia.[18] A buffy-coat concentrate was prepared using a Cobe 2991 cell washer (Cobe Industries, Lakewood, CO), mixed with 20% autologous plasma, 20% TC-199 (GIBCO, Grand Island, NY), and 10% sterile, nonpyrogenic dimethylsulfoxide (Research Laboratories Corp, Midvale, UT); the concentrate was frozen using a controlled-rate program technique. No bone marrow purging technique was used. Marrow was stored in the liquid phase of nitrogen until administration. Bone marrow was thawed rapidly at 37°C in a water bath and infused over 10 minutes without further processing through the central venous catheter. A mean 0.76 ± 0.39 × 10^8 nucleated cells per kilogram patient weight was infused (range, 0.32 to 2.3 × 10^8 nucleated cells per kilogram patient weight) (Table 2). Approximately one half of the harvested bone marrow was retained as a backup in case of graft failure. Four patients with persistent thrombocytopenia received their backup bone marrow 56, 77, 222,

Table 2. Cellular and CSF Support

Bone Marrow Administered	PBPC Administered	CSF	No. of Patients	Bone Marrow Infused* (nucleated cells/10^8/kg)	PBPC Infused* (nucleated cells/10^8/kg)
Yes	No	G-CSF	15	0.68 ± 0.17	—
Yes	Yes	G-CSF	22	0.81 ± 0.36	10.72 ± 3.86
Yes	No	GM-CSF	5	0.61 ± 0.11	—
Yes	Yes	GM-CSF	43	0.69 ± 0.24	6.44 ± 5.54
Total				0.76 ± 0.39	7.65 ± 5.47

*Values are expressed as mean ± SD.

and 739 days after the first infusion; each had less than 0.65×10^8 nucleated cells per kilogram patient weight infused during their first bone marrow infusion. Three of these four patients subsequently became platelet transfusion–independent.

CSF-primed PBPC. In addition to bone marrow, 65 patients received CSF-primed PBPC. CSF-priming was begun after the leukocyte count recovered to greater than 3,000/μL following the fourth cycle of CAF and before high-dose chemotherapy.[10] In the afternoon, patients received either granulocyte CSF ([G-CSF] filgrastim; Amgen, Inc, Thousand Oaks, CA) at 6 μg/kg/d subcutaneously for 8 days (22 patients), G-macrophage CSF ([CHO-glycosylated GM-CSF] regramostim; Sandoz Pharmaceuticals, Nutley, NJ) at 8 μg/kg/d as a daily 4-hour intravenous infusion for 8 days (eight patients) or 16 μg/kg/d as a daily 4-hour intravenous infusion for 8 days (four patients) or 14 days (five patients), or GM-CSF ([*Escherichia coli* GM-CSF] molgramostim; Schering-Sandoz Pharmaceuticals, Nutley, NJ) at 10 μg/kg/d subcutaneously for 8 days (19 patients) or 10 μg/kg/d as a daily 4-hour intravenous infusion for 8 days (seven patients). Significant differences between the type, dose, and schedule of GM-CSF used for priming in this study were not seen and they are analyzed together for the purposes of this report. No other growth factors were used.

All 65 CSF-primed patients were leukapheresed three times. Patients who received 8 days of CSF-priming were leukapheresed the morning after the fifth, seventh, and eighth doses of CSF; patients who received 14 days of CSF-priming were leukapheresed the morning after the eleventh, thirteenth, and fourteenth doses. Each leukapheresis was performed via a central catheter using a Cobe Spectra (Cobe Industries) with an approximate processed volume of 9 L over 3 hours. A mononuclear-cell fraction of approximately 200 mL was collected with each pheresis. The total nucleated-cell collections for the three collections are shown in Table 2. The PBPC were mixed with 10% dimethyl sulfoxide, controlled-rate cryopreserved at −1°C/min until −90°C, and then stored in the liquid phase of nitrogen until used.

CSF-primed PBPC were intravenously administered via a central catheter. One third of the available CSF-primed PBPC were administered on the day of bone marrow infusion (day +1) and for 2 subsequent days (days +2 and +3; eight patients) or, in the remaining 57 patients, daily for 3 days beginning 2 days before marrow infusion (days −1, 0, and +1).

CSF Administration. After high-dose chemotherapy, CSF administration was begun on the day of bone marrow infusion or on the first day of progenitor-cell infusion. All CSF-primed PBPC patients received either G-CSF 16 μg/kg/d as a daily 4-hour infusion for up to 21 days from marrow infusion (22 patients), or GM-CSF 10 μg protein by amino acid analysis per kilogram per day as a daily 4-hour infusion for 7 days, then reduced to 5 μg/kg/d again for up to 21 days following marrow infusion (43 patients). The same cytokine that was used to prime for progenitor-cell collection was used after cell infusion. Patients who received only bone marrow were given G-CSF at doses ranging from 5 to 80 μg/kg/d as a 14-day continuous intravenous infusion (seven patients), G-CSF at doses ranging from 10 to 80 μg/kg/d as a daily 4-hour infusion for up to 21 days (eight patients), or GM-CSF at doses ranging from 5 to 20 μg/kg/d as a 14- or 21-day continuous intravenous infusion (three patients) or a daily 4-hour intravenous infusion for up to 21 days (two patients).

Radiation Therapy

The protocol did not initially prescribe locoregional radiation therapy. However, after three of the first nine patients recurred in the surgical area, the protocol was amended to include locoregional radiation therapy following recovery from the high-dose chemotherapy and bone marrow transplantation. Patients received 45 to 50 Gy to the chest wall and regional lymph nodes (internal mammary, supraclavicular, ± axillary) with a 10- to 15-Gy scar boost at 1.8 to 2.0 Gy per fraction, in approximately 6 to 7 weeks, using standard radiation techniques.

Tamoxifen

Patients with hormone receptor–positive tumors (measured estrogen or progesterone receptor level > 7 fmol/mg protein) were prescribed tamoxifen 10 mg by mouth twice daily for 5 years.

Evaluations Performed After Transplant

Six weeks after high-dose chemotherapy, patients were fully evaluated using the same tests as pretreatment except for bone marrow aspiration, biopsy, and bone scan. Patients were then monitored at 6-week intervals with physical examination, and at 12-week intervals with computed tomography of the chest, abdomen, and pelvis for the first 2 years. Evaluations after 2 years were performed at 6-month intervals or more often as clinically indicated.

Quality-of-Life Evaluation

Between May 1991 and April 1992, 52 patients who were more than 1 year after high-dose chemotherapy were asked to complete a quality-of-life evaluation; 43 (83%) provided assessable information. Patients received mailed questionnaires, and data collection was completed with follow-up telephone interviews. The questionnaire consisted of the Functional Living Index-Cancer (FLIC)[19] and the Symptom Distress Scale (SDS).[20]

Hospital Charges

Actual hospital charges for all patients transplanted under this protocol were retrieved and analyzed. In this presentation, no discounting or other manipulation of the data was performed. There was no significant change in the cost structure of charges that occurred during the time of the study except for annual adjustments for inflation. Charges presented do not include those related to harvesting of bone marrow (median, $6,276), harvesting of PBPC ($5,100), or physician costs (~ $8,500). Except for 11 of 22 patients who received G-CSF–primed PBPC who were charged for the CSF, the CSFs were provided free of cost.

Comparison Populations

Patient populations obtained for comparison were derived from the clinical trials of adjuvant chemotherapy in stage II breast cancer conducted by the CALGB during the past 17 years. Three trials had been performed and used for comparison: (1) CALGB 7581 compared schedules of cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP) with or without immunotherapy.[21] Postoperative radiation therapy was discouraged, but not prohibited. The available radiation treatment data indicate that 10 of the 104 patients selected received radiation therapy, but this analysis is compromised in that information is available on only 19% of the patients. (2) CALGB 8082 compared schedules of CMFVP with CMFVP followed by intensification with vinblastine, doxorubicin, thiotepa, and fluoxymesterone (VATH).[22] None of these patients received radiation therapy. (3) CALGB 8541 compared three doses and schedules of CAF[7]; none of these patients received radiation therapy. To provide groups of patients comparable to eligible and assessable transplant patients, we selected patients who, at surgery, had 10 or more involved

axillary lymph nodes, were age 56 years or younger, and did not relapse during the first 4 months of therapy. For protocol CALGB 8541, only patients who received the exact same dose and schedule of CAF ("high-dose" CAF) as in the current trial were selected.

Statistical Methods

Kaplan-Meier estimates were determined from the date of initiation of study chemotherapy using statistical software developed at our institution. Nonparametric confidence limit intervals were calculated using previously described methods.[23] For the patients reported in this study, the calculation of time intervals is from the first day of chemotherapy with CAF. This date may be later by several days to 1 week or more from the registration date used in the CALGB studies, since patients may be registered on study and receive their first dose of chemotherapy slightly later. The last date of follow-up for patients in CALGB was the last confirmed clinic visit date or status confirmation; for the current study, inquiry about the patient status evaluation was performed May 1, 1992 and this is used as the last follow-up date. Median follow-up time was calculated using the method reported by Korn.[24] Numerical data are reported as the mean ± SD or median with range.

RESULTS

Eighty-five patients registered on this protocol were eligible and treated. The minimum follow-up duration for these patients is 16 months from the initiation of chemotherapy, the maximum 5.2 years, and the median 2.5 years. The median age is 38 years, with a range of 25 to 56 y. Only three patients were older than 50 years (51, 52, and 56 years). Table 1 lists the distribution of the patients by stage, number of lymph nodes involved with malignancy, and hormone-receptor characteristics. Sixty-four patients (75%) were stage IIA or IIB, and the median number of involved lymph nodes was 14 (range, 10 to 39). Fifty-one patients (60%) were hormone receptor–positive.

Treatment Results

Twelve patients have relapsed following transplant (Table 3). The actuarial probability of relapse at 30 months is 19% (95% confidence interval, 0.10 to 0.44). Five patients relapsed locally on the chest wall or regional nodes. In three of these patients, posttransplant radiation therapy had not been prescribed, and, in one additional patient, relapse occurred in supraclavicular nodes following radiation therapy that excluded the area. In the three patients in which radiation therapy was not administered initially, subsequent radiation therapy was unable to control disease. Details of the effects of the radiation therapy in these patients are described elsewhere.[25] Seven patients relapsed systemically at 12 to 24 months from start of therapy. One of these patients clinically relapsed in a single site in bone, although the biopsy of this site was negative; localized radiation therapy was administered. Eighteen patients have died; the Kaplan-Meier estimate of survival at 2.5 years is 79% (95% confidence interval, 0.64 to 0.88). The Kaplan-Meier estimate of event-free survival (which includes all local and systemic relapses and all therapy-related mortality) at a median follow-up of 2.5 years is 72% (95% confidence interval, 0.56 to 0.82); no events have occurred after 28 months.

Ten patients died of therapy-related complications. Refractory thrombocytopenia with complicating hemorrhage and liver toxicity were the cause of death in one patient each, lung toxicity in two patients, and hemolytic-uremic syndrome in three. Two patients died of infection with Candida species complicating multiple organ failure despite amphotericin B therapy after full hematopoietic recovery, and one patient died of cytomegalovirus infection.

Treatment Conduct and Nonfatal, Treatment-Associated Toxicity

CAF-associated toxicity. CAF was generally well tolerated. No patient required dose reduction because of complications. Nineteen patients (22%) were hospitalized for treatment of fever and neutropenia. Sixteen patients (19%) had mild to moderate mucositis. There were no therapy-related deaths. Bone marrow was harvested after the third cycle in all patients. There were no major complications of marrow harvesting (three patients had moderate postoperative local bleeding, two moderate to severe local pain, and one mild oral bleeding on extubation), and sufficient marrow was obtained for a primary infusion and a reserve in all but one case. Following the bone marrow harvest, a fourth cycle of CAF was administered, generally within 2 to 5 days of the harvest.

Harvest of CSF-primed PBPC. Following recovery from the fourth cycle of CAF, PBPC were harvested from 65 patients by leukapheresis after treatment with CSF. Three of 22 patients who received G-CSF developed mild to moderate generalized aching, and one developed nausea, vomiting, and headache. Twenty-seven patients who received GM-CSF for priming were assessable for toxicity. One patient experienced a first-dose effect with the initial GM-CSF dose,[26,27] consisting of acute hypotension, dyspnea, and chest pain, which required hospitalization for observation. Additional patients who received GM-CSF (n = 27) developed myalgias (five), fever (nine), headache (six), bone pain (eight), mild hypotension (two), flu-like syndrome (four), heartburn (three), or rash (two) associated with growth factor administration during the generation and collection of the PBPC.

Acute toxicity during high-dose CPA/cDDP/BCNU. Nausea and vomiting occurred in nearly all pa-

Table 3. Relapses and Treatment-Related Deaths Occurring in Transplanted Patients

Patient No.	Site of Relapse or Cause of Death	Time to Relapse or Death (months)	Comments/Cellular and Cytokine Support
Relapses			
165	Local	11	No radiation therapy; progressed in mediastinum and pleura after local radiation therapy; died during second autograft at 29 months from start of study
177	Local	13	No radiation therapy; progressive local disease after local radiation therapy; died of disease 48 months from start of study
207	Local	15	No radiation therapy; progressive local and systemic disease after local radiation therapy
357	Regional	21	Incomplete radiation therapy; progressive in lung and bone at 26 months; died of progressive disease
310	Sternum	28	Alive, free of disease after radiation therapy
233	Retroperitoneal lymph nodes	12	Dead of progressive disease at 14 months
334	Local-regional, lung	16	Dead of progressive disease at 22 months
342	Pleural fluid, nodes	12	Dead of progressive disease at 30 months
452	Single bone	17	Alive, free of disease after radiation therapy
479	Liver, diffuse visceral	11	Dead of progressive disease after 12 months
588	Liver	13	Dead of progressive disease after 13 months
460	Ovary	24	Alive, free of disease after surgery and tamoxifen
Treatment-related deaths			
232	Hemorrhage	7	Bone marrow alone + G-CSF
272	Hepatotoxicity	6	Bone marrow alone + G-CSF
285	Pulmonary toxicity	6	Bone marrow alone + G-CSF
338	Cytomegalovirus	8	Bone marrow + GM-CSF PBPC
449	Persistent *Candida*	7	Bone marrow + GM-CSF PBPC
492	Pulmonary toxicity	11	Bone marrow + GM-CSF PBPC
532	Hemolytic-uremic syndrome	9	Bone marrow + GM-CSF PBPC
497	Hemolytic-uremic syndrome	14	Bone marrow + GM-CSF PBPC
530	Candidiasis	7	Bone marrow + GM-CSF PBPC
609	Hemolytic-uremic syndrome	12	Bone marrow + G-CSF PBPC

tients and was partially controlled by antiemetics. Despite the intensity of chemotherapy, no recorded emesis occurred after high-dose chemotherapy in 56 patients (66%) on at least 1 day and in 31 patients (35%) on at least 2 days. Carmustine administration was associated with systolic hypotension less than 90 mm Hg in 44 patients (52%) and less than 80 mm Hg in 19 patients (22%). These effects generally resolved within 4 hours following completion of the carmustine infusion. Five patients (6%) reported mild to severe chest pain during carmustine infusion; ECGs in three patients showed acute ST segment depression, but cardiac enzymes were not diagnostic for myocardial infarction. ECG changes returned to normal in each case. We have described this syndrome previously.[28]

Acute bone marrow infusion toxicity. Marrow infusion was associated with bradycardia less than 60 beats/min in 27 patients (32%), diastolic hypertension greater than 100 mm Hg in 22 patients (26%), and both bradycardia and hypertension in nine patients (11%). In one case, the marrow infusion was associated with a 15-second atrial pause. These problems reversed promptly and no lasting effects were encountered.

Hematologic reconstitution following high-dose chemotherapy. Following high-dose chemotherapy, profound myelosuppression occurred. The median time from bone marrow infusion to a leukocyte count greater than 1,000/μL was 10 days (range, 8 to 17), and the median time to a granulocyte count greater than 500/μL was 12 days (range, 8 to 29). The severity of the myelosuppression and the rate of hematopoietic reconstitution was less with

the use of PBPC and had an impact on the resource utilization as determined by analysis of the hospital charges incurred during the transplant.[29] The average number of packed RBC transfusions used was 24 ± 15, and the average number of platelet transfusion events was 26 ± 26.

Infectious Complications

Positive blood cultures for bacterial or fungal organisms were recovered in 16 patients (19%). Five patients were infected with gram-negative organisms, including *E coli* (two), *Klebsiella oxytoca* (two), and *Pseudomonas aeruginosa* (one); 10 patients had gram-positive organisms. Two patients had both bacteria and yeast recovered. In one case, *Candida albicans* was identified from blood, which was not eradicated despite greater than 1 g of amphotericin B therapy.

Herpes zoster occurred in 23 patients (27%) from 3 to 8 months after ABMS; one patient developed this infection during CAF therapy.

Pulmonary Drug Toxicity

Approximately 1 to 6 months after the high-dose consolidation program, patients frequently developed a pulmonary syndrome of variable severity characterized by the sudden onset of progressive exertional dyspnea and a slight dry cough, often with fever, which was occasionally high and spiking. Pulmonary function testing showed restriction, a reduced diffusing capacity for carbon monoxide, and hypoxemia. Chest radiographs were sometimes normal and sometimes displayed interstitial changes. Blood and sputum cultures were negative for bacterial or fungal organisms. Lung biopsy showed pulmonary drug toxicity, with an increase in type II pneumocytes, and increased hyaline and alveloar damage.[30] Treatment with prednisone 1 mg/kg/d orally generally resulted in dramatic resolution of symptoms, usually in about 5 days, occasionally in 24 hours. Corticosteroid treatment could usually be tapered and stopped in 6 weeks; however, about one third of patients were intolerant of early corticosteroid withdrawal, and pulmonary symptoms would flare, which required resumption of corticosteroid medication. While symptoms usually resolved rapidly, pulmonary function tests often remained abnormal for extended periods. Long-term effects of this syndrome have not yet been adequately characterized.

Twenty-six patients (31%) developed some degree of this pulmonary toxicity syndrome, and two died. Seven patients developed the syndrome during locoregional radiation therapy, necessitating prolonged treatment interruptions or discontinuation before full dose in four patients. While the clinical syndrome is consistent with pulmonary drug toxicity, there is a suggestion that the syndrome may have been exacerbated by the locoregional radiation therapy in five patients. Four of these five patients were treated with an anterior internal mammary portal. Radiation-associated dyspnea occurred in four of 20 (20%) and one of 12 (8%) patients treated with an anterior portal and wide tangents, respectively.

Hemolytic-Uremic Syndrome

A second syndrome, again varying widely in severity, developed in seven patients, (8%) usually between 1 and 6 months after transplant, although one patient presented at 25 months after marrow infusion. The syndrome was characterized by sudden onset, severe thrombocytopenia, anemia with hemolysis, occasional schistocytes, altered mental status, hypertension, mild renal insufficiency, occasionally hyperbilirubinemia, and respiratory insufficiency. Two patients developed retinopathy, with optic neuritis in one and vasculitis in the other. Underlying infections were usually present in the patients with hemolytic-uremic syndrome. Treatment with corticosteroids and of the underlying infection when present appeared helpful, although in two patients multiple interventions were undertaken, including plasmapheresis through a Prosorba (Imré Corp., Seattle, WA) column.

Quality of Life and Costs of Therapy

Forty-three of 52 patients (83%) completed the quality-of-life questionnaires and interview. All 52 patients were more than 1 year post–high-dose chemotherapy and had been contacted regarding participation in the quality-of-life evaluation. Median follow-up from high-dose chemotherapy was 2 years. The mean FLIC score (possible range, 22 to 154) measuring overall quality of life was 132 ± 18. This score is higher than the mean FLIC score (126) reported by Schag et al[31] in 109 stage II breast cancer patients assessed 13 months after diagnosis. Patients in our series reported few significant symptoms as assessed by the SDS. The most commonly reported symptoms included difficulty sleeping (43%), fatigue (27%), and worry (25%).

The hospital charges during the high-dose consolidation for patients treated in this protocol were a median of $88,836 and ranged from $48,734 to $384,821. The charges were heavily influenced by the type of supportive care used.[29] A detailed cost-effectiveness analysis of these data will be presented elsewhere.

DISCUSSION

During the past decade, the use of high-dose chemotherapy and ABMS for the treatment of breast cancer has

generated enthusiasm, skepticism, new studies, and controversy. We present here data using a sequential program that combines traditional outpatient CAF adjuvant chemotherapy followed by high-dose CPA/cDDP/BCNU chemotherapy consolidation with ABMS, radiation therapy, and hormonal therapy in patients with well-defined pretreatment characteristics. These data show an apparent benefit for the entire high-dose consolidation program; however, the data must be interpreted with caution, since follow-up duration remains short, the study is not randomized, and the treatment carries substantial morbidity and mortality.

The actuarial event-free survival probability (defined as freedom from any local or systemic relapse or early or late therapy-related death) determined by product-limit estimates is 72% at 30 months (Fig 2B). Given the evolving nature of supportive care, and the reduction of treatment toxicity since the introduction of CSF-primed PBPC, presentation of the time to relapse is relevant. The Kaplan-Meier estimate for probability of any local or systemic relapse at 30 months is 19% (Fig 2A).

Comparison to historical populations is subject to many potential biases. Differences in patient selection, staging evaluation, age, hormone receptor status, dose-intensity, follow-up duration, and unknown factors may complicate comparisons. However, the prognosis of patients with high-risk primary breast cancer involving 10 or more axillary lymph nodes is poor in all reported series.[15] We have selected for comparison patients treated over the past 17 years on previous and concurrent CALGB trials of adjuvant chemotherapy for primary breast cancer. While two trials used different chemotherapy programs and were

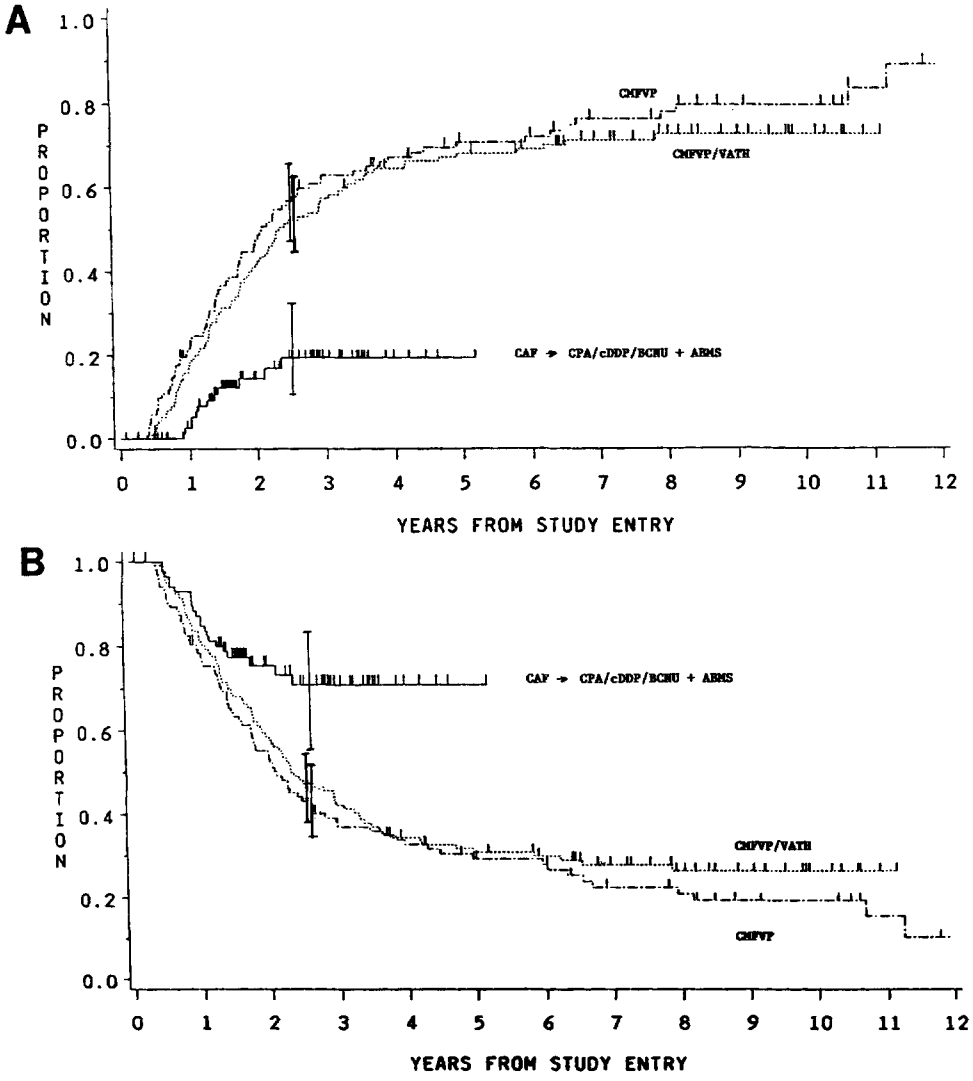

Fig 2. (A) Actuarial probability of relapse or (B) event-free survival for eligible and treated patients (CAF → CPA/cDDP/BCNU + ABMT) and for similar patients selected from two trials using adjuvant CMFVP (CALGB 7581) or CMFVP/VATH (CALGB 8082). Vertical bars represent the 95% confidence intervals for each data set determined at 30 months. Tick marks indicate censored events.

conducted before the current trial, CALGB 8541 was concurrent and, in the selected patients, used the same dose and schedule of standard-dose chemotherapy (CAF) as in the reported trial; unfortunately, the number of patients who met these selection criteria for this study was small. The age, distribution of involved nodes, hormone receptors, and local recurrence frequency for these comparison groups is listed in Table 4. While the patient characteristics are similar, several differences should be noted. The median age for the control populations is approximately one decade older than in the current study. The percentage of patients with more than 20 involved lymph nodes is higher in the nontransplant trials. Dose-intensity was maintained in this trial, and analysis of CALGB 8541 indicated that in the high-dose arm the median protocol prescribed and actually administered doses were within 2% for each drug; no data on administered dose-intensity are available for either of the two CALGB trials using CMFVP. The frequency of local recurrences was lower in the current study (6%) versus the comparison trials (8%, 10%, and 16%; Table 4), consistent with the use of local radiation therapy in the current study. Adjusting for the prognostic factors listed in Table 4 did not alter qualitatively the estimates for our study relative to the other three CALGB trials at 30 months. Figure 2A and B presents the probability of relapse and comparative event-free survival for the current trial and compare the two CALGB trials that involved CMFVP with subsequent randomized addition of VATH in 8082. The vertical bars indicate the 95% confidence intervals around the data sets determined at the median follow-up for the currently reported trial. Most relapses in the comparison trials occur in the first 3 to 4 years, consistent with observations from previous studies in this patient population. Figure 3A and B shows the comparison of probability of relapse and event-free survival of patients in the present study to patients from CALGB 8541 who received the same dose and schedule of CAF, but did not receive high-dose chemotherapy as consolidation. Because of the small number of patients in the nontransplant trial, there is considerable overlap of the 95% confidence intervals determined at the median follow-up for the transplant trial, although the trends appear similar. Longer follow-up periods will be required to determine the impact, if any, on overall survival; no meaningful difference in overall survival is seen at this time between any of the series, since the median time to death in the control series is more than 4 years.

Features of the treatment program other than high-dose chemotherapy may contribute to the improvement in disease-free interval. In this study, locoregional radiation therapy was used to assist in control of chest wall and regional lymph node recurrences. This addition might delay, but ultimately not control, systemic relapses. The frequency of local recurrences in the studies is listed in Table 4 and does not fully account for the much larger differences in relapses between studies at this follow-up. While tamoxifen was administered to patients with hormone receptor–positive cancers in CALGB 8541 and the current study, this intervention was not used in either of the two CMFVP trials. In addition, patients who entered the transplant program were evaluated more thoroughly than is traditional for patients entering other adjuvant chemotherapy programs. We estimate that approximately 5% of referred patients were excluded from entry onto the protocol because the pretreatment evaluation showed metastatic

Table 4. Characteristics of Historical and Concurrent Comparison Groups

Characteristic	Current Study (CAF → ABMS)	CALGB 7581 (CMFVP)	CALGB 8082 (CMFVP/VATH)	CALGB 8541 (CAF high-dose arm)
Total no. of patients entered*	102	898	944	1,572
No. assessable†	85	104	116	25
Median age, years	38	48	47	48
No. of involved lymph nodes (%)				
10-12	33%	41%	30%	20%
13-15	26%	17%	26%	28%
16-19	29%	18%	18%	32%
20+	12%	24%	26%	20%
Hormone receptor–negative (%)	40	25‡	38	36
Local recurrences (%)	6	16	10	8

NOTE. The definitions of the treatment programs, CAF → ABMS, CALGB 7581, CALGB 8082, and CALGB 8541 are in the text.

*Total number of patients entered on the study regardless of node number or treatment arm.

†Number of patients used in the comparisons representing the number of patients meeting the selection criterion used. The comparisons are as defined in the text.

‡Hormone receptor status was not determined in 38% of patients on this study.

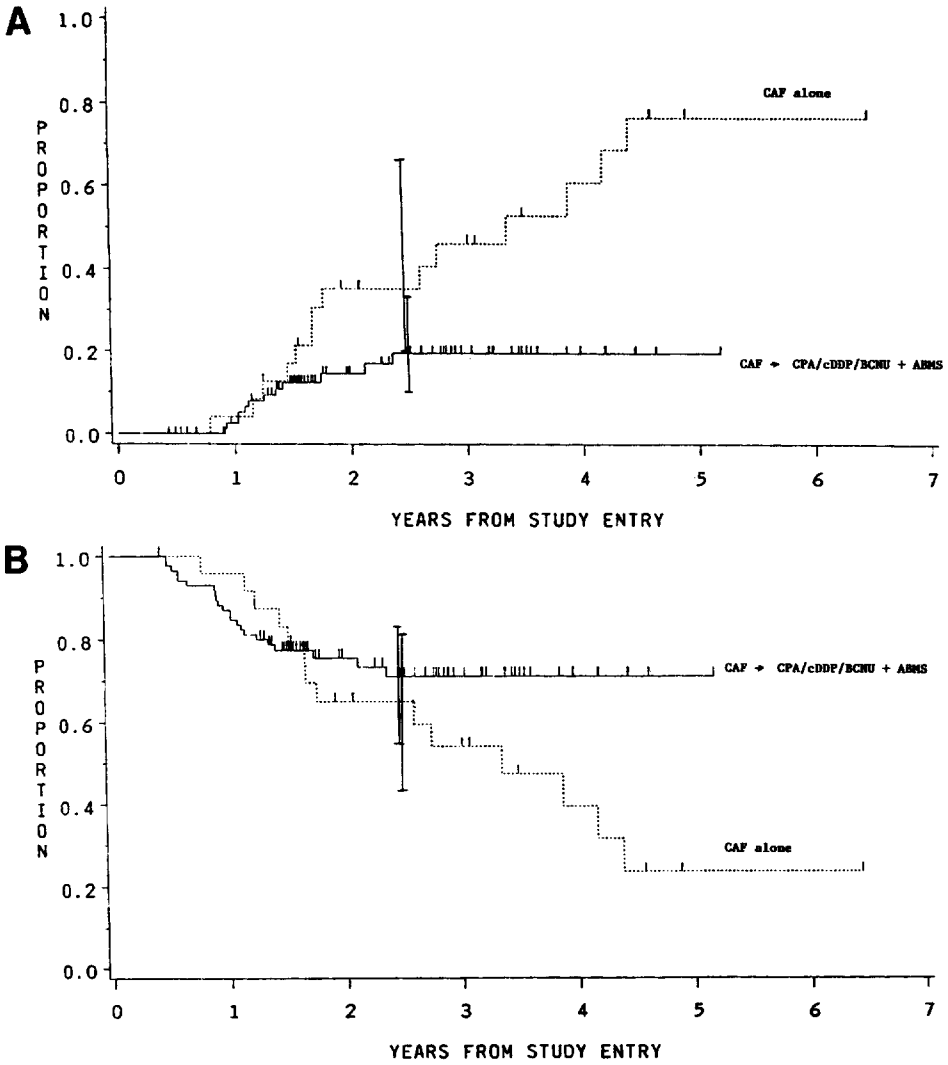

Fig 3. (A) Actuarial probability of relapse or (B) event-free survival for eligible and treated patients (CAF → CPA/cDDP/BCNU + ABMT) and for similar patients selected from the concurrent CALGB trial 8541. Patients received the same dose and schedule of CAF in both trials. Vertical bars represent the 95% confidence intervals at 30 months.

disease that had not been detected with routine evaluation. On the other hand, the intensity of follow-up, again using repetitive computed tomography, would be expected to detect relapses at a slightly earlier time than for patients monitored without such evaluations. These issues may be clarified during the ongoing, randomized clinical trial.

We believe that the confirmation of these results in a prospective randomized trial, as is being currently undertaken, is important before this therapy can be accepted for widespread use. Nonetheless, there is cause for initial encouragement that the principle of dose-intensity, well established in other malignancies such as leukemia and lymphoma, may be applicable to more common epithelial tumors. Only time and further careful evaluation will allow wider use of this technology to be undertaken more comfortably.

The necessity for confirmation in a prospective randomized clinical trial is magnified by the toxicity associated with this treatment. Because toxicity is fatal in 12% of patients and has significant and occasionally life-threatening morbidity in many other patients, careful evaluation of quality of life will be important in addition to monitoring disease-free survival. Evaluation of quality of life of a major subset showed encouraging results in that quality of life appears acceptable compared with previously reported nontransplant regimens, and few patients reported significant limitations 1 year or longer after treatment. These data emphasize the importance of a prospective, repetitive analysis of quality of life using valid instruments in a randomized trial.

These uncontrolled data must also be interpreted with caution, since many new therapies, initially promising, fizzle. The general applicability of this type of compli-

cated treatment program to other institutions is not assured. Programs, apparently valuable at one institution, may not find similar success elsewhere for a variety of reasons. The careful evaluation of the therapeutic and toxic outcomes in the context of a cooperative group trial is thus important. However, total despair over the magnitude of the toxicity is probably not warranted. Advances in supportive care, such as CSF-primed PBPC, CSFs, and approaches to alloimmunization, argue that reductions in the toxicity may be possible with careful study. Our data indicate that the selection of supportive care measures may have important effects on resource utilization, as was measured by the hospital bill.[29]

Despite these caveats, current standard-dose therapies for this disease produce poor results and argue that eligible patients should be enrolled, whenever possible, in trials to test this treatment approach. Two prospective National Cancer Institute high-priority intergroup randomized trials are now underway through the CALGB (CALGB 9082) and Southwest Oncology Group (SWOG 9114) or through the Eastern Cooperative Oncology Group (ECOG 2190). Rapid completion of these randomized trials will allow assessment of the important components of treatment and provide an understanding of the generalizability, if any, of this treatment approach.

The economic implications of these data should not be ignored or overemphasized. We estimate that approximately 3,000 patients are diagnosed with breast cancer annually in the United States who are younger than 50 years of age with 10 or more involved axillary lymph nodes. Treatment of all of these patients would have major economic consequences, unless the treatment costs can be reduced. Extension to other treatment settings would severely strain available medical and financial structures. The toxicity, cost, and especially the complexity of the treatment argue that this treatment approach should, at present, only be offered at major academic centers of excellence with experience in autologous transplantation for solid tumors and in which patients are entered, whenever possible, onto randomized comparative trials.

Finally, this trial has brought into focus again the fragmented and uneven nature of the American health insurance system. Most patients were covered by their health insurance; 7% of eligible and interested patients were unable to receive the therapy due to the aggressive use of the experimental therapy exclusion by certain health insurance companies as a cost-containment mechanism and due to the lack of individual financial capability. The anguish this caused to these patients is not quantitated, but was severe. Hopefully, what we learn from development of this therapeutic procedure will translate into more rational development of other new therapies.

NOTE TO THE PROOF

An update analysis of this study was performed with a minimum follow-up of 2.2 years, a lead follow-up of 6.1 years, and a median follow-up of 3.3 years. No event (relapse or therapy-related death) has occurred after 28 months. At the median follow-up, the actuarial event-free survival is 72% (95% confidence interval, 55% to 82%) and the overall survival is 77% (95% confidence interval, 62% to 87%).

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