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CONVENTIONAL-DOSE CHEMOTHERAPY COMPARED WITH HIGH-DOSE CHEMOTHERAPY PLUS AUTOLOGOUS HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR METASTATIC BREAST CANCER

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ABSTRACT

Background We conducted a randomized trial in which we compared high-dose chemotherapy plus hematopoietic stem-cell rescue with a prolonged course of monthly conventional-dose chemotherapy in women with metastatic breast cancer.

Methods Women 18 to 60 years of age who had metastatic breast cancer received four to six cycles of standard combination chemotherapy. Patients who had a complete or partial response to induction chemotherapy were then randomly assigned to receive either a single course of high doses of carboplatin, thiotepa, and cyclophosphamide plus transplantation of autologous hematopoietic stem cells or up to 24 cycles of cyclophosphamide, methotrexate, and fluorouracil in conventional doses. The primary end point was survival.

Results The median follow-up was 37 months. Of 553 patients who enrolled in the study, 58 had a complete response to induction chemotherapy and 252 had a partial response. Of these, 110 patients were assigned to receive high-dose chemotherapy plus hematopoietic stem cells and 89 were assigned to receive conventional-dose chemotherapy. In an intention-to-treat analysis, we found no significant difference in survival overall at three years between the two treatment groups (32 percent in the transplantation group and 38 percent in the conventional-chemotherapy group). There was no significant difference between the two treatments in the median time to progression of the disease (9.6 months for high-dose chemotherapy plus hematopoietic stem cells and 9.0 months for conventional-dose chemotherapy).

Conclusions As compared with maintenance chemotherapy in conventional doses, high-dose chemotherapy plus autologous stem-cell transplantation soon after the induction of a complete or partial remission with conventional-dose chemotherapy does not improve survival in women with metastatic breast cancer. (N Engl J Med 2000;342:1069-76.)

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MOST women with metastatic breast cancer have a response to various combinations of conventional-dose chemotherapy, but less than 5 percent of them are alive 10 years after the detection of metastatic spread.¹ Several phase 2 trials performed in the late 1980s reported promising results for high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation in patients with chemotherapy-responsive metastatic breast cancer.²⁻⁶ These trials consistently reported high overall rates of response (combined complete and partial responses), ranging from 73 to 100 percent. Despite a median survival of only 10 to 24 months, 7 to 18 percent of patients in these studies remained free of progressive disease for up to 5 years after the treatment. This result was perceived to be an improvement as compared with that in historical controls. The incidence of severe adverse effects, however, was thought to be greater than that reported in historical controls; the transplantation-related mortality ranged from 0 to 22 percent, but improved supportive care and better patient selection promised reduced toxicity in the future.⁷

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By the late 1980s, interest in hematopoietic stem-cell transplantation increased quickly among patients and physicians. Demands on insurers for financial coverage increased, and breast cancer became the most common indication for such transplantations in North America,⁸ despite the lack of studies comparing stem-cell transplantation with conventional-dose chemotherapy.

The unresolved question about what constituted optimal therapy for women with metastatic breast cancer led the Philadelphia Bone Marrow Transplant Group to design and conduct a study of postremission therapy. Later, to increase the accrual rate, the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group (SWOG), and the North Central Cancer Treatment Group (NCCTG) joined the study, which had been designated a high priority by the National Cancer Institute. Patients who had not received prior chemotherapy for metastatic disease were first given conventional-dose chemotherapy, and patients with an objective response were randomly assigned to receive a prolonged course of cyclophosphamide, methotrexate, and fluorouracil in conventional doses or high-dose chemotherapy with carboplatin, thiotepa, and cyclophosphamide plus autologous stem-cell transplantation. The primary objective of this study was to compare the overall survival, the time to progression, and the toxicity associated with these two treatment regimens.

METHODS

Patients

Enrollment began in Philadelphia in December 1990 and ended in December 1997. The NCCTG joined the study in 1990, and ECOG and SWOG joined in 1994. The coordination of the study was transferred to ECOG in 1995, the same year it was designated a high-priority study by the National Cancer Institute. To be eligible, women had to be 18 to 60 years old; to have adequate renal and hepatic function, a normal cardiac ejection fraction, and an ECOG performance status of 0 or 1; to have locally recurrent or distant metastatic breast cancer; and to have received no previous chemotherapy for metastatic disease. If a patient had received adjuvant chemotherapy after surgical treatment of the primary tumor, the adjuvant therapy had to have been concluded more than six months before enrollment in the study. Patients could be premenopausal or postmenopausal, and if they had a positive estrogen-receptor assay, they must have had at least one prior hormonal treatment unless life-threatening visceral disease was present. Patients were excluded if they had metastases to the central nervous system, an uncontrolled infection, or any illness that would preclude the possibility of subsequent stem-cell transplantation. All patients provided written informed consent.

Induction Chemotherapy

For patients who had previously received a total dose of less than 400 mg of doxorubicin per square meter of body-surface area, induction chemotherapy consisted of oral cyclophosphamide (100 mg per square meter per day for 14 days), intravenous doxorubicin (30 mg per square meter on day 1 and day 8), and intravenous fluorouracil (500 mg per square meter on day 1 and day 8) (Fig. 1). For patients who had previously received a total dose of 400 to 500 mg of doxorubicin per square meter, induction chemotherapy consisted of oral cyclophosphamide (100 mg per square meter

per day for 14 days), intravenous methotrexate (40 mg per square meter on day 1 and day 8), and intravenous fluorouracil (600 mg per square meter on day 1 and day 8), with optional treatment with prednisone (40 mg per square meter orally for 14 days), given at the discretion of the treating physician. Four to six cycles of chemotherapy were given at intervals of 28 days.

Randomization

After receiving induction chemotherapy, patients were reevaluated. Patients were eligible to undergo randomization if they had had a complete remission (defined as no evidence of disease), a partial remission (defined as a reduction of at least 50 percent in the size of all measurable tumor areas in more than 50 percent of involved organ sites), or a partial remission restricted to bone (defined as bone lesions that remained stable on bone scans and x-ray films for a period of at least eight weeks in association with an improvement in the ECOG performance status, a decrease in the requirement for analgesia, or both). Patients were withdrawn if they had new lesions or progression (defined as an increase of more than 25 percent in the size of measurable lesions). Eligible patients had to have no detectable involvement of bone marrow by the tumor; adequate hematopoietic function; normal renal, cardiac, pulmonary, and hepatic function; and no severe medical or psychiatric problems.

All patients again provided written informed consent at the transplantation center. Randomization had to occur within eight weeks after the last dose of induction chemotherapy. Patients who did not have a complete or partial remission after six cycles of therapy were withdrawn from the study.

High-Dose Chemotherapy and Stem-Cell Transplantation

Hematopoietic stem cells were harvested from the blood before the start of high-dose chemotherapy in all patients who were to undergo autologous stem-cell transplantation. In the initial stage of the protocol, granulocyte-macrophage colony-stimulating factor was administered to stimulate the mobilization of stem cells from the bone marrow. A minimum of 2×10^8 nucleated cells per kilogram of body weight was also harvested from the bone marrow and cryopreserved.⁹ The bone marrow and blood stem cells were combined and infused after high-dose chemotherapy. Later in this investigation, the protocol was amended to allow stimulation with granulocyte colony-stimulating factor, with an optional bone marrow harvest. If only stem cells from the blood were used, a minimum of 6×10^8 nucleated cells per kilogram was harvested.

The preparative regimen for autologous stem-cell transplantation lasted four days and consisted of a continuous infusion of cyclophosphamide (1500 mg per square meter; total dose, 6000 mg per square meter), carboplatin (200 mg per square meter; total dose, 800 mg per square meter), and thiotepa (125 mg per square meter; total dose, 500 mg per square meter).¹⁰ Stem cells were infused on day 0, approximately 48 hours after the completion of chemotherapy, and granulocyte-macrophage colony-stimulating factor (250 mg per square meter) was administered to stimulate hematopoietic recovery (i.e., until the absolute neutrophil count exceeded 1000 per cubic millimeter for a period of three days).

Conventional-Dose Chemotherapy

Patients who were randomly assigned to receive maintenance therapy received cycles of cyclophosphamide, methotrexate, and fluorouracil in the same doses as those used for induction chemotherapy and according to the same schedule. Treatment continued until treatment-limiting toxic effects or disease progression occurred or until 24 cycles had been administered (Fig. 1).

Statistical Analysis

The study was originally designed to have a power of 90 percent to detect a doubling of the median survival with high-dose chemotherapy and stem-cell transplantation within the complete-response subgroup and the partial-response subgroup. The original design required the randomization of 99 eligible patients with a complete response and 247 eligible patients with a partial re-

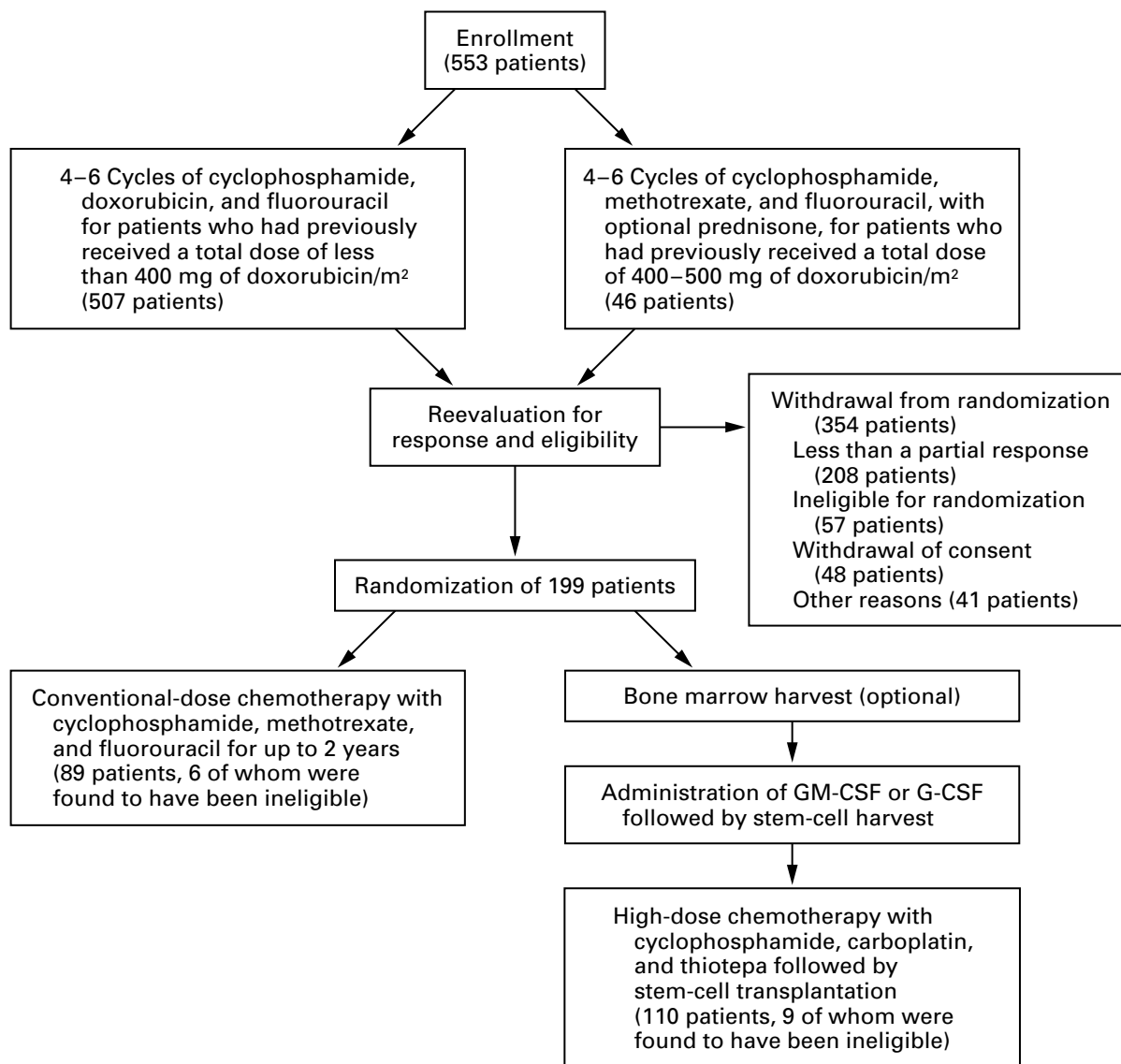


Figure 1. Enrollment of Patients, Induction Chemotherapy, and Randomization to High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation or Conventional-Dose Chemotherapy.

GM-CSF denotes granulocyte–macrophage colony-stimulating factor, and G-CSF granulocyte colony-stimulating factor.

sponse. In the fall of 1996, the design was modified due to low enrollment. In the revised design, there were no longer separate accrual goals or analyses planned on the basis of response status. Instead, the analysis was to be stratified according to the response to induction chemotherapy (complete response or partial response). The revised design required the randomization of 164 eligible patients. For design purposes, we assumed the following: one third of the randomized patients who had a response to induction chemotherapy would have a complete response, and two thirds of the randomized patients would have a partial response; for the patients who were randomly assigned to receive conventional-dose chemotherapy, median survival would be 2.5 years for those with a complete response and 1 year for those with a partial response; 10 percent of all patients would be found to be ineligible after randomization; and 10 percent of each group would be noncompliant with treatment. Two interim analyses were planned — the first after

66 randomized patients had died and the second after 96 patients had died — and a final analysis was scheduled after 120 patients had died. The stopping boundaries used at each interim analysis for decision making were calculated from the O'Brien–Fleming use function.¹¹ This design gave the study a power of 85 percent to detect a doubling of the median survival with a two-sided alpha level of 0.05, with use of a stratified log-rank test.

The primary analysis was conducted on an intention-to-treat basis and included eligible randomized patients. Randomization was stratified according to five factors: the type of response to induction chemotherapy (complete or partial), the predominant site of distant metastasis (visceral or other), age (≤ 42 years or > 42 years), estrogen-receptor status (positive or negative), and cooperative group. Overall survival was measured from the time of randomization until death from any cause. Progression was measured from the time of randomization until progression of the disease. Data

on one patient who died without progression were censored when she was last known to be in remission.

The first interim analysis was conducted in November 1997 after 65 deaths had occurred, and the second was conducted in November 1998 after 93 deaths had occurred. At the time of the second interim analysis, the data-monitoring committee recommended that the study be unblinded because the likelihood that the study would show a significant difference in favor of stem-cell transplantation at the final analysis was very low (a conditional-power calculation showed that the likelihood was less than 1 percent). The unadjusted 95 percent confidence interval of the hazard ratio for the likelihood of survival with conventional-dose chemotherapy as compared with high-dose chemotherapy plus stem-cell transplantation was 0.52 to 1.22. On the basis of the method of Jennison and Turnbull,¹² the 95 percent repeated confidence interval for the hazard ratio with use of the O'Brien-Fleming use function was 0.48 to 1.32. Given the actual rate of noncompliance, a true hazard ratio of 2.0, the target alternative hypothesis, equates with an observed hazard ratio of approximately 1.72. Since 1.72 is outside the repeated confidence interval, the data at the second interim analysis were inconsistent with the alternative hypothesis.

At the time of the final analysis, after 114 deaths had occurred, the 95 percent repeated confidence interval for the hazard ratio for the likelihood of survival after conventional-dose chemotherapy, as compared with high-dose chemotherapy plus stem-cell transplantation, was 0.53 to 1.17. Given the actual rate of noncompliance, a true hazard ratio of 1.25, for example, would equate with an observed hazard ratio of 1.19. Since 1.19 is outside the repeated confidence interval, even a 25 percent improvement in survival as a result of transplantation is inconsistent with our data.

RESULTS

Enrollment of Patients

A total of 553 patients were enrolled for induction chemotherapy. The accrual rate was 70 patients per year before June 1994, and it subsequently increased to 88 patients per year after ECOG and SWOG joined the study. Of the 553 patients, 58 had a complete response and 252 had a partial response. Of these, 110 were randomly assigned to receive high-dose chemotherapy and autologous stem-cell transplantation and 89 were assigned to receive conventional-dose chemotherapy. The skewed assignment resulted from an attempt to balance the randomization for numerous stratification factors.

The remaining 354 patients did not undergo randomization. A total of 208 patients had less than a partial response to induction chemotherapy: 105 had stable disease, 74 had disease progression, and in 29 the disease or its status could not be evaluated. Thirty-two patients were found to have been ineligible for induction therapy: in 11 the laboratory evaluation before enrollment was inadequate, 6 were estrogen-receptor-positive and had received no prior hormonal therapy or had no visceral disease, the disease could not be evaluated in 4, 3 had received prior chemotherapy for metastatic breast cancer, 2 had central nervous system involvement, 2 had an ECOG performance status of more than 1, 1 had undergone oophorectomy less than four weeks before entry into the study, 1 had received prior radiotherapy to the pelvis and lower spine, 1 had inadequate data, and 1 had no metastatic disease. Among the remaining 114 patients with a

complete or partial response after induction chemotherapy, 48 declined to undergo randomization or withdrew from the study, 21 had breast-cancer cells in the bone marrow, 4 were not eligible for other reasons, 3 died or had disease progression in the interim before randomization, and 38 did not undergo randomization for unknown or other reasons. The group of eligible patients who did not undergo randomization was not significantly different from those who did undergo randomization (data not shown).

Characteristics of Patients

Of the 199 randomized patients, 15 were found to be ineligible and were not included in the primary analysis: 9 did not have a documented response to induction chemotherapy, 3 were estrogen-receptor-positive and had received no prior hormonal therapy or had no visceral disease, 2 had disease progression in the interval before randomization, and 1 had no data other than documentation of a response. Nine of the 15 ineligible patients were assigned to receive high-dose chemotherapy and to undergo stem-cell transplantation, and 6 to receive conventional-dose chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. Nine additional randomized patients were ineligible according to eligibility criteria specified in the protocol but were included in the primary analysis. In the case of these patients the reasons for ineligibility were minor: inadequate laboratory evaluation before registration in four; bone marrow cellularity of less than 30 percent but adequate stem-cell collection in two; receipt of a course of appropriate induction chemotherapy before registration, a practice that was allowed early in the course of the study, in one; prior radiotherapy to the pelvis or lower spine but subsequent adequate stem-cell collection in one; and prior chemotherapy for locally recurrent disease in one. Of these nine patients, five were assigned to the transplantation group and four to the conventional-chemotherapy group.

Therefore, of the 199 randomized patients, 184 were included in the primary analysis; 101 had been assigned to autologous stem-cell transplantation and 83 to conventional-dose chemotherapy (Table 1). After induction chemotherapy, 24 percent of these 184 patients were in complete remission. No significant differences between the two treatment groups were found with respect to demographic and stratification factors, including age, predominant site of metastasis, or estrogen-receptor status. In addition, the two groups were well balanced with respect to prior treatment with adjuvant chemotherapy, adjuvant hormonal therapy, and hormonal therapy for metastatic disease. The numbers of patients with complete or partial responses did not differ significantly between the treatment groups; however, the number of patients who underwent randomization while in complete remission was small.

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	HIGH-DOSE CHEMOTHERAPY PLUS STEM-CELL TRANSPLANTATION (N=101)	CONVENTIONAL- DOSE CHEMOTHERAPY (N=83)
Response to induction chemotherapy		
— no. (%)		
Complete	29 (29)	16 (19)
Partial	72 (71)	67 (81)
Age at randomization		
≤42 yr — no. (%)	36 (36)	25 (30)
>42 yr — no. (%)	65 (64)	58 (70)
Median — yr	46	47
Range — yr	30–60	32–61
25th percentile — yr	40	42
75th percentile — yr	52	53
Predominant site of metastatic disease		
— no. (%)		
Visceral	58 (57)	43 (52)
Other	43 (43)	40 (48)
Sites of metastatic disease — no. (%)		
Soft tissue and nodes	52 (51)	42 (51)
Bone	37 (37)	44 (53)*
Bone only	9 (9)	8 (10)
Lung and pleura	37 (37)	26 (31)
Liver	26 (26)	26 (31)
Estrogen-receptor status — no. (%)		
Negative	46 (46)	38 (46)
Positive	50 (50)	38 (46)
Unknown	5 (5)	7 (8)
Prior therapy — no. (%)		
Adjuvant chemotherapy	61 (60)	43 (52)
Doxorubicin	23 (23)	19 (23)
Adjuvant hormonal therapy	32 (32)	27 (33)
Hormonal therapy for metastatic disease	19 (19)	16 (19)

*There were no significant differences between the groups with respect to any characteristic except bone metastasis ($P=0.04$).

Twenty of the 184 eligible randomized patients (11 percent) refused their treatment assignment. Of the 101 patients assigned to undergo autologous stem-cell transplantation, 6 (6 percent) refused the therapy; 5 received either no therapy or conventional-dose chemotherapy, and 1 patient underwent autologous stem-cell transplantation with an alternative regimen. In comparison, of the 83 patients assigned to receive conventional-dose chemotherapy, 14 patients (17 percent) refused the therapy. Ten underwent autologous stem-cell transplantation (all of whom relapsed and eight of whom died), three patients received no therapy, and in the case of one patient the data were insufficient to determine the result of off-protocol therapy. In addition, three patients who received conventional-dose chemotherapy subsequently received high-dose chemotherapy and underwent autologous stem-cell transplantation after relapse.

Outcome

By April 1999, 114 deaths had occurred among the 184 eligible randomized patients. The median follow-

up was 37 months (minimum, 4; maximum, 96). The median follow-up for the 70 patients who were alive at that time was 25 months. The median number of cycles of cyclophosphamide, methotrexate, and fluorouracil received by the group assigned to conventional-dose chemotherapy was 8 (range, 1 to 24).

The 3-year survival rate, calculated from the date of randomization, among all 184 eligible patients was 33 percent, and the median survival was 25 months. As Figure 2 shows, there was no significant difference in survival between the two treatment groups ($P=0.23$, with stratification according to response to induction chemotherapy). The median survival in the group treated with high-dose chemotherapy and stem cells was 24 months, with a 3-year survival rate of 32 percent. The median survival in the conventional-dose chemotherapy group was 26 months, with a 3-year survival rate of 38 percent. The results were similar when the analysis included all 199 patients who underwent randomization ($P=0.14$, with stratification according to the response to induction chemotherapy).

Similarly, there were no significant differences in survival between the two treatment groups when the groups were analyzed according to the extent of the response to induction chemotherapy (complete or partial), age (≤ 42 years or > 42 years), estrogen-receptor status (negative or positive), or predominant site of metastatic disease (visceral or other). Among patients who were older than 42 years, those who received conventional-dose chemotherapy appeared to have a survival advantage over those who received high-dose chemotherapy and underwent stem-cell transplantation. Since this analysis was within a subgroup, the results must be interpreted with caution. Patients consistently had a higher rate of survival if they were in complete remission at the time of randomization, but there was no significant difference in the rates between the two treatment groups (Table 2).

As Figure 3 shows, there was no significant difference in the time to progression in the two treatment groups ($P=0.31$, with stratification according to response to induction chemotherapy). The median time to progression for patients who received high-dose chemotherapy and autologous stem cells was 9.6 months, and the 3-year rate of progression-free survival was 6 percent. The median time to progression for the group given conventional chemotherapy was 9.0 months, and the 3-year rate of progression-free survival was 12 percent. Similarly, there were no significant differences in the time to progression within the various subgroups. Again, the patients who were in complete remission before randomization fared better than those who were in partial remission (Table 2). The results were similar when the analysis included all 199 randomized patients ($P=0.30$, with stratification according to response to induction chemotherapy).

One hundred thirty-nine patients were in partial

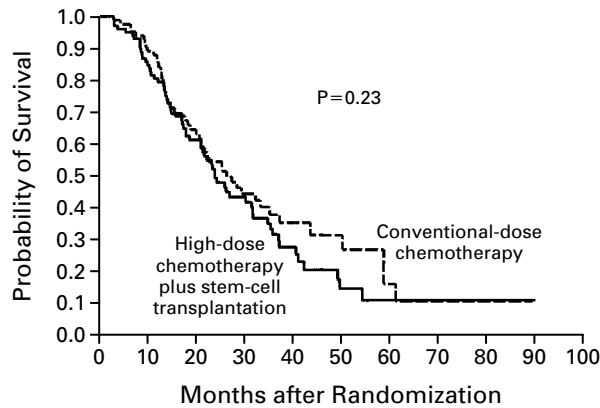


Figure 2. Kaplan–Meier Estimates of Overall Survival of Patients with Metastatic Breast Cancer Who Were Randomly Assigned to Treatment with Conventional-Dose Chemotherapy Alone or High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation.

The median survival was 26 months in the group assigned to receive conventional-dose chemotherapy and 24 months in the group assigned to receive high-dose chemotherapy plus stem-cell transplantation. The survival rates at three years were 38 percent and 32 percent, respectively (P=0.23).

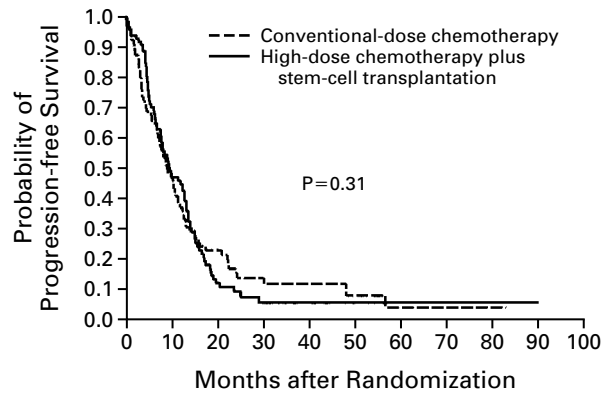


Figure 3. Kaplan–Meier Estimates of Progression-free Survival of Patients with Metastatic Breast Cancer Who Were Randomly Assigned to Treatment with Conventional-Dose Chemotherapy Alone or High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation.

The median time to progression was 9.0 months in the group assigned to receive conventional-dose chemotherapy and 9.6 months in the group assigned to receive high-dose chemotherapy plus stem-cell transplantation. The rates of progression-free survival at three years were 12 percent and 6 percent, respectively (P=0.31).

TABLE 2. RATES OF OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL AT THREE YEARS.*

GROUP	NO. OF PATIENTS	OVERALL SURVIVAL	PROGRESSION-FREE SURVIVAL
		percent (95% CI)	
High-dose chemotherapy plus transplantation			
All patients	101	32 (21–42)	6 (0.1–11)
Patients with complete response to induction chemotherapy	29	42 (22–62)	16 (0.7–32)
Patients with partial response to induction chemotherapy	72	27 (14–40)	0
Conventional chemotherapy			
All patients	83	38 (26–50)	12 (4–19)
Patients with complete response to induction chemotherapy	16	49 (21–77)	25 (2–48)
Patients with partial response to induction chemotherapy	67	36 (22–49)	8 (0.7–16)

*There were no significant differences between groups. Survival was measured from the time of randomization. CI denotes confidence interval.

remission at the time of randomization, 72 of whom were assigned to high-dose chemotherapy plus stem-cell transplantation and 67 of whom were assigned to conventional-dose chemotherapy. Of these 139, 12 subsequently had a complete remission: 5 after receiving high-dose chemotherapy and autologous stem

cells (7 percent of the 72 patients in this group who were in partial remission at randomization) and 7 after treatment with conventional-dose chemotherapy (10 percent of the 67 patients in this group who were in partial remission at randomization). There was no significant difference in the rate of conversion to complete remission with these two treatments.

Table 3 shows the incidence of moderate and severe, but nonfatal, adverse effects in the two groups. Patients who underwent autologous stem-cell transplantation had a higher rate of severe leukopenia, thrombocytopenia, and anemia as well as infection, diarrhea, and vomiting than those who received conventional-dose chemotherapy. The incidence of severe mucositis was similar in the two groups. No lethal adverse effects were reported in the conventional-chemotherapy group. One patient died from venoocclusive disease of the liver 49 days after autologous stem-cell transplantation.

DISCUSSION

Our findings demonstrate that women with metastatic breast cancer who have a complete or partial response to standard chemotherapy and then receive high-dose chemotherapy and undergo autologous stem-cell transplantation do not survive longer or have a longer time to progression of disease than women who receive maintenance therapy with conventional doses of cyclophosphamide, methotrexate, and fluorouracil. The incidence of nonfatal but serious adverse effects was greater in the group assigned to high-

TABLE 3. INCIDENCE OF MODERATE AND SEVERE ADVERSE EFFECTS AFTER RANDOMIZATION.*

ADVERSE EFFECT	HIGH-DOSE CHEMOTHERAPY PLUS STEM-CELL TRANSPLANTATION	CONVENTIONAL-DOSE CHEMOTHERAPY
	percent	
Leukopenia	96	52
Thrombocytopenia	95	5
Anemia	69	6
Infection	31	3
Diarrhea	25	1
Hepatic complications	9	1
Vomiting	8	1
Cardiac complications	8	0
Pulmonary complications	7	1
Neurologic complications	6	0
Mucositis	5	2

*The Common Toxicity Criteria of the National Cancer Institute were used to define moderate adverse effects (grade 3) and severe adverse effects (grade 4).

dose chemotherapy plus transplantation, in which myelosuppression, infection, diarrhea, and vomiting were common. Even so, the treatment-related mortality (i.e., deaths occurring within 100 days after the initiation of therapy) was virtually the same in the two groups.

The study was designed to have a high power to detect a doubling in median survival with high-dose chemotherapy plus stem-cell transplantation. Nonetheless, our data show that this treatment was unlikely to be associated with even a moderate improvement (e.g., a 6-month increase in median survival, from 24 months to 30 months), even when the possible effect of noncompliance was taken into consideration. The number of patients who survived for three years without signs of disease progression was so low that it is unlikely that the results will change significantly with continued follow-up. In addition, the treatment-related mortality rate of less than 1 percent after high-dose chemotherapy plus stem-cell transplantation could not have influenced the survival results. And since the methods we used for high-dose chemotherapy and hematopoietic stem-cell rescue are the current standard approach, our results should reflect outcomes being obtained currently.

The fact that a substantial proportion of enrolled patients withdrew from the study and thus did not receive the assigned treatment is potentially problematic. In published studies of patients with acute myeloid leukemia who received stem-cell transplantation, 33 to 50 percent of the patients who were initially in complete remission declined to undergo randomization and were withdrawn.¹³ The rate was

similar in our study: approximately 28 percent declined to undergo randomization. No substantial difference in the distribution of known prognostic factors was found between the patients who remained in the study and those with a complete response or a partial response who declined to undergo randomization.

Though there was no discernible difference in outcome with the two treatments for patients who had a complete response to induction chemotherapy, the number of such patients was admittedly small — 45 patients in all, 29 in the group treated with high-dose chemotherapy and stem-cell transplantation and 16 in the group treated with conventional-dose chemotherapy. A number of ongoing studies may be able to provide more information on this subgroup of patients with complete responses. Nevertheless, the likelihood that a significant difference in outcome will be found is low. Moreover, the difficulty of enrolling patients in a randomized trial of this sort is so great that any conclusions that are drawn may ultimately require extrapolation of the results of completed or ongoing trials involving high-risk patients with primary breast cancer.

It is possible that the promising results of pilot studies of high-dose chemotherapy and autologous stem-cell rescue were due in part to selection bias.¹⁴⁻¹⁶ Patients undergoing this treatment for metastatic breast cancer are generally younger and healthier, and have had better responses to induction chemotherapy, than those who are treated with conventional therapies. To account for selection bias, we analyzed our results on an intention-to-treat basis. Even so, the outcomes were no different for the 106 patients who actually received high-dose chemotherapy and underwent autologous stem-cell transplantation than for the 101 patients who were randomly assigned to the treatment.

A French multicenter, randomized trial, which compared a single course of high-dose chemotherapy plus stem-cell rescue with conventional-dose chemotherapy for patients with chemotherapy-responsive metastatic breast cancer, was stopped prematurely after the enrollment of 61 patients because of a low rate of enrollment.¹⁷ After five years of follow-up, there was no significant difference between the groups in progression-free survival (9 percent in each group) or overall survival (29.8 percent in the group treated with high-dose chemotherapy and autologous stem-cell rescue and 18.5 percent in the conventional-chemotherapy group, $P=0.12$). This small trial had a low statistical power to detect large differences, but the design was similar to ours. Our results contradict those of an earlier, single-center trial that purported to find an advantage of tandem cycles of high-dose chemotherapy.¹⁸ This study is now under review as part of a misconduct investigation.¹⁹

A number of other randomized studies of patients with metastatic breast cancer are ongoing, and the results of several studies of patients with locally ad-

vanced but not metastatic breast cancer have yet to be reported. Our results should be interpreted in the context of those trials and cannot and should not be extrapolated to patients with nonmetastatic cancer who have multiple positive axillary nodes.

Our results lead us to conclude that the routine practice of administering several cycles of conventional induction chemotherapy followed by a single course of high-dose chemotherapy and stem-cell rescue cannot be recommended for women with metastatic breast cancer. Alternative strategies to improve the results of this therapy are being evaluated and include efforts to minimize the development of resistance to chemotherapy during induction chemotherapy; attempts to improve the processing and purging of stem cells; post-transplantation chemotherapy, hormonal therapy, and immune modulation to eliminate minimal residual disease; and the use of multiple cycles of dose-intensive therapy. These and other approaches should be investigated in well-designed trials to improve the treatment options and outlook for patients with metastatic breast cancer.

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APPENDIX

The following members of the Philadelphia Bone Marrow Transplant Group also participated in the study: University of Pennsylvania Cancer Center: J. Bird, D.L. Porter, P.A. Mangan, and P.A. Cassileth; Fox Chase Cancer Center: M. Daly, R. Krigel (deceased), and R. Schilder; Hahnemann University Hospital: M. Styler, and D. Marks; Temple University Hospital: S. Goldberg and L. Glenn; and Christiana Cancer Center: D. Biggs.

REFERENCES

- Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission follow-

- ing combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996;14:2197-205.
- Peters WP, Shpall EJ, Jones RB, et al. High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol* 1988;6:1368-76.
- Williams SF, Mick R, Desser R, Golick J, Beschoner J, Bitran JD. High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. *J Clin Oncol* 1989;7:1824-30.
- Kennedy MJ, Beveridge RA, Rowley SD, Gordon GB, Abeloff MD, Davidson NE. High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intensive induction as initial therapy for metastatic breast cancer. *J Natl Cancer Inst* 1991;83:920-6.
- Antman K, Ayash L, Elias A, et al. A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *J Clin Oncol* 1992;10:102-10.
- Williams SF, Gilewski T, Mick R, Bitran JD. High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report. *J Clin Oncol* 1992;10:1743-7.
- Antman KH, Rowlings PA, Vaughan WP, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol* 1997;15:1870-9.
- Distribution and frequencies of autotransplants performed between 1992 and 1997 and registered with the ABMTR. Vol. 5. ABMTR Newsletter. December 1998:5. (Milwaukee: IBMTR/ABMTR Statistical Center.)
- Thomas ED, Storb R. Technique for human marrow grafting. *Blood* 1970;36:507-15.
- Eder JP, Elias A, Shea TC, et al. A phase I-II study of cyclophosphamide, thiotepa, and carboplatin with autologous bone marrow transplantation in solid tumor patients. *J Clin Oncol* 1990;8:1239-45.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Jennison C, Turnbull BW. Interim analyses: the repeated confidence interval approach. *J R Stat Soc [B]* 1989;51:305-61.
- Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med* 1998;339:1649-56.
- Rahman ZU, Frye DK, Buzdar AU, et al. Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin-containing chemotherapy in patients with metastatic breast cancer. *J Clin Oncol* 1997;15:3171-7.
- Garcia-Carbonero R, Hidalgo M, Paz-Artes L, et al. Patient selection in high-dose chemotherapy trials: relevance in high-risk breast cancer. *J Clin Oncol* 1997;15:3178-84.
- Crump M, Goss PE, Prince M, Girouard C. Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. *J Clin Oncol* 1996;14:66-9.
- Lotz JP, Cure H, Janvier M, et al. High-dose chemotherapy (HD-CT) with hematopoietic stem cell transplantation (HSCT) for metastatic breast cancer (MBC): results of the French Protocol PEGASE 04. *Proc Am Soc Clin Oncol* 1999;18:43a. abstract.
- Bezwoza WR, Seymour L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. *J Clin Oncol* 1995;13:2483-9.
- Researcher under investigation. Press release of the University of the Witwatersrand Medical School, Johannesburg, South Africa, February 3, 2000. (See <http://www.wits.ac.za/depts/wcs/media/index.htm>.)