

ORIGINAL ARTICLE

# Conventional Adjuvant Chemotherapy with or without High-Dose Chemotherapy and Autologous Stem-Cell Transplantation in High-Risk Breast Cancer

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## ABSTRACT

### BACKGROUND

The prognosis for women with primary breast cancer and 10 or more involved axillary lymph nodes is poor. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation has been reported to be effective in the adjuvant setting for patients at high risk for relapse.

### METHODS

We randomly assigned 540 female patients with primary breast cancer and at least 10 involved ipsilateral axillary lymph nodes to receive either six cycles of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil (CAF) or the same adjuvant chemotherapy followed by high-dose chemotherapy with cyclophosphamide and thiotepa and autologous hematopoietic stem-cell transplantation.

### RESULTS

Among the 511 eligible patients, there was no significant difference in disease-free survival, overall survival, or the time to recurrence between those who received CAF alone and those who received CAF plus high-dose chemotherapy and stem-cell transplantation. Among 417 patients fulfilling strict eligibility criteria, the time to recurrence was longer for patients who underwent stem-cell transplantation than for those who received CAF alone. In the transplantation group, nine patients died of transplantation-related complications and a myelodysplastic syndrome or acute myeloid leukemia developed in nine.

### CONCLUSIONS

The addition of high-dose chemotherapy and autologous hematopoietic stem-cell transplantation to six cycles of adjuvant chemotherapy with CAF may reduce the risk of relapse but does not improve the outcome among patients with primary breast cancer and at least 10 involved axillary lymph nodes. Conventional-dose adjuvant chemotherapy remains the standard of care for such patients.

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WOMEN WITH PRIMARY BREAST CANCER and 10 or more involved ipsilateral axillary lymph nodes have a particularly poor prognosis. Only 20 to 30 percent of such patients who receive postoperative (adjuvant) chemotherapy with cyclophosphamide, methotrexate, and fluorouracil are disease-free at five years.<sup>1-4</sup> Among those given doxorubicin-containing adjuvant regimens, approximately 50 percent have not had a relapse at five years.<sup>5</sup> In the 1980s and 1990s, high-dose chemotherapy with autologous hematopoietic stem-cell transplantation was reported to be effective adjuvant therapy for patients with a high risk of relapse. Phase 2 trials and registry data suggested a three-year disease-free survival rate of approximately 65 to 70 percent.<sup>6-11</sup> With these promising results, autologous hematopoietic stem-cell transplantation became a popular yet controversial treatment for high-risk patients despite the lack of a randomized trial to prove its value.<sup>12</sup> Data suggested that this approach had potential complications and an early mortality rate as high as 10 percent.<sup>6</sup> Furthermore, the possibility of selection bias was raised to explain the encouraging early results.<sup>13</sup> To determine the benefit of the addition of high-dose chemotherapy and autologous hematopoietic stem-cell transplantation to standard adjuvant chemotherapy for women with stage II or III breast cancer with a high risk of recurrence, we conducted a randomized clinical trial (Intergroup protocol 0121) to compare the rates of recurrence, disease-free survival, and overall survival.

## METHODS

### ELIGIBILITY FOR STUDY ENTRY

Female patients were eligible to enter the study if they had been given a biopsy-proven diagnosis of epithelial carcinoma of the breast; had at least 10 involved ipsilateral axillary lymph nodes; had undergone a radical, modified radical, or breast-sparing procedure plus axillary dissection with margins that were histologically free of tumor within 12 weeks before study entry; had normal blood counts; were 15 to 60 years of age; had liver-function tests whose results were no more than 1.2 times the normal values; had no evidence of breast cancer in bilateral bone marrow core-biopsy specimens and on bone scanning; had a left ventricular ejection fraction of at least 50 percent on multiple gated acquisition scanning; had a forced expiratory volume in one second (FEV<sub>1</sub>) and a diffusing capacity for carbon

monoxide that were at least 60 percent of the predicted values; and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients provided written informed consent. Patients with T4 disease (extension into the chest wall), bilateral infiltrating cancers that occurred more than six weeks apart, or distant metastases were excluded. No prior therapy was permitted before enrollment except tamoxifen for 21 days or less and one or two cycles of doxorubicin-based chemotherapy. Patients with apocrine, adenocystic, squamous-cell, or inflammatory carcinoma or sarcoma; those who were pregnant or lactating; and those who had symptomatic central nervous system disease of any cause were also excluded. Prior hormone-replacement therapy was allowed, but it had to have been discontinued before enrollment.

### ELIGIBILITY FOR AUTOLOGOUS HEMATOPOIETIC STEM-CELL TRANSPLANTATION

Eligibility for autologous hematopoietic stem-cell transplantation included an Eastern Cooperative Oncology Group performance status of 0 or 1, the absence of active infection, a serum creatinine level of 2.0 mg per deciliter (177  $\mu$ mol per liter) or less, alkaline phosphatase and alanine aminotransferase values that were no more than 1.2 times the normal value, a total serum bilirubin level of 2.0 mg per deciliter (34  $\mu$ mol per liter) or less, the absence of evidence of breast cancer, and an FEV<sub>1</sub> and a diffusing capacity for carbon monoxide that were at least 60 percent of the predicted values.

### TREATMENT

#### *Adjuvant Chemotherapy*

All patients received adjuvant chemotherapy consisting of 100 mg of cyclophosphamide per square meter of body-surface area per day given orally on days 1 through 14, 30 mg of doxorubicin per square meter per day given intravenously on days 1 and 8, and 500 mg of fluorouracil per square meter per day given intravenously on days 1 and 8 (CAF) every 28 days for a total of six cycles.<sup>14</sup> The doses were based on actual body weight. Patients who were randomly assigned to receive CAF alone were to receive a 50-Gy dose of radiation therapy to the breast and chest wall and regional nodes beginning within four weeks after the completion of chemotherapy or when the white-cell count exceeded 2900 per cubic millimeter and the platelet count exceeded 100,000 per cubic millimeter. Tamoxifen, at a daily dose of 20 mg orally, was to be given for 5 years to patients

whose tumors were estrogen-receptor-positive or progesterone-receptor-positive (or both), beginning 28 days after the start of the last CAF cycle.

#### *Preparative Regimen for Transplantation*

Patients who were assigned to receive CAF plus autologous hematopoietic stem-cell transplantation received high-dose chemotherapy as follows: a continuous intravenous infusion of 6 g of cyclophosphamide per square meter and 800 mg of thiotepa per square meter over a four-day period. High-dose chemotherapy was given on days 6, 5, 4, and 3 before the infusion of autologous bone marrow, peripheral-blood stem cells, or both.<sup>15</sup> For patients who received stem cells derived from bone marrow, a minimum of  $1 \times 10^8$  nucleated cells per kilogram of actual body weight was required. For patients who received stem cells derived from peripheral blood, at least  $1 \times 10^9$  nucleated cells per kilogram were required. Radiation therapy to the breast and chest wall and regional nodes (total, 50 Gy) was to be initiated within eight weeks after transplantation. Patients with estrogen-receptor-positive or progesterone-receptor-positive tumors (or both) were to begin tamoxifen after transplantation when the white-cell count exceeded 4000 per cubic millimeter or the absolute neutrophil count exceeded 2000 per cubic millimeter (or both criteria were met).

#### *Modifications to the Treatment Plan*

In July 1994, three years after the study began, the protocol was amended to permit the administration of up to one cycle of CAF before enrollment. In December 1995, a second amendment allowed up to two cycles of any doxorubicin-based chemotherapy to be given before study entry. In the original protocol, patients assigned to autologous hematopoietic stem-cell transplantation after completing adjuvant CAF were to be randomly assigned to one of three regimens of granulocyte-macrophage colony-stimulating factor (GM-CSF): 250  $\mu$ g per square meter per day over a 2-hour period, 250  $\mu$ g per square meter per day over a 6-hour period, or 250  $\mu$ g per square meter per day over a 24-hour period. The amendment in July 1994 eliminated this randomization scheme and left the dose and schedule of growth factors to the discretion of the treating physician. The use of GM-CSF at a dose of 250  $\mu$ g per square meter per day was recommended. Originally, only autologous bone marrow transplants were allowed. The amendment in July 1994 also allowed the use of peripheral-blood stem-cell

transplants alone or in combination with autologous marrow. Initially, tamoxifen was given to patients who were positive for either estrogen receptors or progesterone receptors. The amendment in July 1994 required tamoxifen to be given only to patients whose tumors were positive for estrogen receptors.

#### **STATISTICAL ANALYSIS**

Disease-free survival was defined from the time of randomization to the earliest sign of a recurrence, a new primary breast cancer, or death without recurrence; data were censored on the date a patient was last known to be alive. Survival was defined as the time from randomization to death from any cause. The time to recurrence was defined as the time from randomization to recurrence or a new primary breast cancer; data were censored on the date a patient was last known to be disease-free.

The rates of failure in each group were estimated with use of the method of Kaplan and Meier<sup>16</sup> and compared with use of the log-rank test.<sup>17</sup> A Cox proportional-hazards model was used to estimate hazard ratios and to perform regression analysis.<sup>18</sup> Comparisons were conducted according to the intention-to-treat principle. All P values are based on two-sided tests, and P values of less than 0.05 were considered to indicate statistical significance.

The primary analysis was originally planned to include the subgroup of eligible patients. However, owing to the high rates of ineligibility, this policy was reviewed in July 1999, whereupon we decided to divide protocol violations into major and minor categories and to include patients with minor violations in the primary analysis. Major protocol violations included the lack of a bone scan in one patient, positive resected margins in five patients, the lack of a bone marrow core biopsy in six, the presence of inflammatory carcinoma or peau d'orange in five, possible metastatic disease in one, invasive prior breast cancer in one, diabetes in one, prior therapeutic oophorectomy in two, the lack of a documented left ventricular ejection fraction at base line in one, the lack of a documented pulmonary-function test at base line in three, residual disease in the axilla in one patient, and fewer than 10 positive axillary lymph nodes in one patient. Minor violations included the failure to obtain bilateral bone marrow aspirates and biopsy specimens in a patient with negative findings on unilateral biopsy; the failure to meet the requirements for the assessment of lung volume and diffusing capacity for carbon mon-

oxide in a patient with adequate pulmonary function; violations of prestudy laboratory requirements (mostly in patients who started chemotherapy before entry); failure to document performance status, insurance coverage, or a negative pregnancy test; the receipt of chemotherapy before entry that was not allowed in the protocol; the failure to submit an operative report; and the failure to perform multiple gated acquisition scanning in a patient with adequate cardiac function. Secondary analyses of the subgroups of all randomized patients and eligible patients were also performed.

Three formal interim analyses of disease-free survival were performed. The results were released by the data-monitoring committee when 92 percent of the planned information was available, since it was clear that the primary end point of a difference in disease-free survival would not become significant.

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## RESULTS

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### ENROLLMENT

Between August 1991 and August 1998, 540 patients were enrolled. Data have been analyzed as of September 2002. Of the 540 patients enrolled, 1 had no data submitted and 28 had major protocol violations, leaving 511 patients in the primary analysis (Table 1). An additional 94 patients — 49 in the group assigned to receive CAF alone and 45 in the group assigned to receive CAF, high-dose chemotherapy, and a hematopoietic stem-cell transplant — had minor protocol violations. Among patients who were disease-free after the completion of CAF, 7 percent of those assigned to CAF alone received some form of transplantation therapy, and of those assigned to high-dose chemotherapy with stem-cell transplantation, 14 percent did not receive a transplant and 7 percent underwent transplantation outside the study.

### CHARACTERISTICS OF THE PATIENTS

The base-line characteristics of the patients were similar in the two groups (Table 2). The median age of the 511 patients was 44 years. Approximately one third of the patients in each group were younger than 40 years of age, and approximately one fourth of the patients in each group were postmenopausal. In one fourth of the patients in each group, the size of the primary tumor exceeded 5 cm, and 60 percent of the patients in each group were positive for estrogen receptors, progesterone receptors, or both.

### ADVERSE EFFECTS

#### *CAF Adjuvant Chemotherapy*

There were no drug-related fatalities in the group that received CAF alone. The most common grade 3 (severe) or grade 4 (life-threatening) nonhematologic adverse effects included nausea (11 percent), vomiting (8 percent), stomatitis (4 percent), neurologic effects (6 percent), hyperglycemia (2 percent), phlebitis (1 percent), hepatotoxicity (1 percent), and pulmonary effects (1 percent). Grade 3 or 4 granulocytopenia and thrombocytopenia occurred in 90 percent of patients.

#### *Stem-Cell Transplantation*

The most common nonhematologic adverse effects related to autologous hematopoietic stem-cell transplantation included nausea (32 percent), stomatitis (grade 3 in 26 percent and grade 4 in 11 percent), infection (grade 3 in 19 percent and grade 4 in 2 percent), diarrhea, hyperglycemia, hepatotoxicity, and rash (Table 3).

#### *Lethal Effects of Transplantation*

Nine patients died between 2 days before and 55 days after receiving the transplant (Table 4). All but one death occurred early in the trial, generally when bone marrow–derived stem cells, rather than stem cells from the peripheral blood, were infused (six patients received only bone marrow–derived stem cells, two received stem cells derived from both bone marrow and peripheral blood, and one received stem cells derived from peripheral blood). The use of stem cells derived from bone marrow was invariably associated with more prolonged aplasia than the use of stem cells derived from peripheral blood. The causes of death were as follows: cyclophosphamide-induced myocarditis with pericardial tamponade in one patient, cerebral hemorrhage in one, aspergillosis in two, capillary leak syndrome with multiorgan failure in one, pulmonary toxicity with multiorgan failure in one, graft failure in one, sepsis in one, and infection in one (Table 4).

### SECOND CANCERS

The incidence of second (non-breast) cancers is summarized in Table 5. In the group that received CAF alone, one case of myeloma, one case of lymphoma, and seven solid tumors developed. In the group assigned to high-dose chemotherapy with stem-cell transplantation, solid tumors developed in six patients, a myelodysplastic syndrome developed in six, and acute myelogenous leukemia devel-

oped in three. Of the last three patients, two had had a myelodysplastic syndrome 1.9 and 8.7 years after study entry. Six of the nine patients with a myelodysplastic syndrome or leukemia have died.

#### CAUSES OF TREATMENT FAILURE

All first occurrences of treatment failure in the opposite breast were included as new primary breast cancers, whereas first treatment failures in the ipsilateral breast were regarded as recurrences. Among the 257 patients in the CAF group who were included in the primary analysis, 124 (48 percent) had a recurrence, 4 (2 percent) had new primary breast cancers, and 4 (2 percent) died before the disease recurred. The respective values among the 254 patients assigned to high-dose chemotherapy with stem-cell transplantation were 99 (39 percent), 7 (3 percent), and 19 (7 percent).

#### DISEASE-FREE SURVIVAL

The median follow-up of patients was 6.1 years. The difference in disease-free survival between the two groups was not significant ( $P=0.55$ ) (Fig. 1A). The six-year disease-free survival rate was 47 percent in the group given CAF alone and 49 percent in the group assigned to high-dose chemotherapy with stem-cell transplantation.

#### OVERALL SURVIVAL

The difference in overall survival between the two groups was not significant ( $P=0.32$ ) (Fig. 1B). The six-year overall survival rate was 62 percent in the group given CAF alone and 58 percent in the group assigned to high-dose chemotherapy with stem-cell transplantation.

#### TIME TO RECURRENCE

Time to recurrence in the two groups was not significantly different in the primary analysis ( $P=0.12$ ) (Fig. 1C). At six years, 48 percent of the patients in the group given CAF alone were free of recurrence, as compared with 55 percent of the patients in the group assigned to high-dose chemotherapy with stem-cell transplantation. When only the 417 patients fulfilling strict eligibility were analyzed, the time to recurrence was longer among patients in the group assigned to high-dose chemotherapy with stem-cell transplantation ( $P=0.045$ ). At six years 45 percent of patients in the group given CAF alone were free of recurrence, as compared with 55 percent of patients in the other group.

**Table 1. Status of the 540 Patients Enrolled in the Study.**

Status	Conventional Therapy	High-Dose Chemotherapy + Stem-Cell Transplantation	Total
	<i>no. of patients (%)</i>		
<b>Initial</b>			
Randomized	270	270	540
No data submitted	1	0	1
Major protocol violation	12	16	28
Included in primary analysis	257	254	511
Minor protocol violation	49	45	94
<b>Subsequent</b>			
Early recurrence	11	6	17
Eligible for transplantation	246	248	494
Assigned to transplantation	0	197*	—
Declined to participate after enrollment	—	1	—
Received transplant according to protocol	0	196	—
Received transplant outside the study	18	18	—
Total undergoing transplantation	18 (7)	214 (86)	—

\* There were 51 patients in the group assigned to high-dose chemotherapy plus stem-cell transplantation who were eligible for but who did not undergo transplantation for the following reasons: 22 patients declined, 4 had insurance problems, 2 had subsequently been determined to be ineligible for the study because of a minor violation, 5 had elevations in liver-function test results after chemotherapy that were above the permissible threshold, 6 had a left ventricular ejection fraction of less than 50 percent on multiple gated acquisition scanning, 2 had a diffusing capacity for carbon monoxide that was less than 60 percent of the predicted value, 3 had inadequate lung function on pulmonary testing after chemotherapy, 1 had a fungal infection, 1 had a complication as a result of hemothorax, and 1 had another adverse effect related to chemotherapy. The reason was unknown in four patients.

#### OUTCOME RELATED TO ESTROGEN-RECEPTOR STATUS

There were no significant differences in disease-free survival, overall survival, or time to recurrence between the two groups when estrogen-receptor status was considered (data not shown).

#### ANALYSIS OF PROGNOSTIC FACTORS

To evaluate the possible influence of the patients' characteristics and disease-related characteristics, we designed proportional-hazards regression models incorporating a variety of factors, including treat-

**Table 2. Base-Line Characteristics of 511 Patients Included in the Primary Analysis.\***

Characteristic	Conventional Therapy (N=257)	High-Dose Chemotherapy + Stem-Cell Transplantation (N=254)	Total (N=511)
Median age (yr)	43	45	44
Age <40 yr (%)	32	30	31
Postmenopausal (%)	28	28	28
Breast-sparing primary surgery (%)	21	16	19
>14 positive nodes (%)	47	44	46
Tumor size (%)			
≤2 cm	26	23	25
>2 and ≤5 cm	49	53	51
>5 cm	25	25	25
Estrogen-receptor-positive (%)	59	61	60
Progesterone-receptor-positive (%)	57	62	59

\* Data on tumor size were missing for one patient, and data on progesterone-receptor status were missing for seven patients. Because of rounding, percentages may not total 100.

**Table 3. Severe, Life-Threatening, and Lethal Adverse Effects of Transplantation Occurring in at Least 10 Percent of Patients.\***

Adverse Effect	Severe	Life-Threatening	Lethal
		<i>percent</i>	
Leukopenia	1	97	0
Granulocytopenia	1	93	0
Thrombocytopenia	2	95	0
Anemia	57	5	0
Infection	19	2	2
Nausea	32	0	0
Vomiting	11	5	0
Diarrhea	15	5	0
Stomatitis	26	11	0
Liver effects	10	3	0
Dermatologic effects	10	1	0
Diabetes	13	1	0

\* A total of 208 patients were analyzed, including 12 with major protocol violations who were assigned to and underwent transplantation according to the protocol.

ment assignment, estrogen-receptor status, tumor size (≤2 cm, >2 to 5 cm, or >5 cm), the number of involved lymph nodes (10 to 14 vs. more than 14), age at study entry (younger than 40 years vs. 40 years or older), and menopausal status, for each of the three end points (disease-free survival, overall survival, and time to recurrence). Estrogen-receptor status was significant for all three end points (P=0.006 for disease-free survival, P<0.001 for overall survival, and P=0.005 for time to recurrence), with estrogen-receptor-positive patients having lower rates of treatment failure. Estrogen-receptor status was the only significant factor in the models for disease-free survival and time to recurrence. The only other significant factor in the model for overall survival was age (P=0.04), with better overall survival among patients who were 40 years of age or older. Treatment assignment was not a significant factor with respect to any of the end points (P=0.82 for disease-free survival; P=0.15 for overall survival, with slightly worse overall survival among the patients assigned to high-dose chemotherapy with stem-cell transplantation; and P=0.27 for time to recurrence).

## DISCUSSION

We found that the addition of autologous stem-cell transplantation to six cycles of conventional-dose CAF adjuvant chemotherapy did not significantly increase either disease-free survival or overall survival among women with stage II or III breast cancer and at least 10 involved ipsilateral axillary lymph nodes. However, in a subgroup analysis that excluded patients with minor protocol violations, the time to recurrence was longer among patients assigned to high-dose chemotherapy with stem-cell transplantation, suggesting that the addition of stem-cell transplantation may enhance the antitumor effect more than does six cycles of adjuvant chemotherapy with CAF alone. An apparent late divergence in the rates of disease-free survival, overall survival, and time to recurrence suggests that longer follow-up will be important to determine whether such differences persist or increase. If so, further subgroup analyses may prove useful in future clinical trials.

Five other randomized trials have addressed the potential benefits of autologous hematopoietic stem-cell transplantation after adjuvant chemotherapy in patients with 10 or more involved axillary lymph nodes, and our results are generally consistent with those of other studies. In a small, single-

institution trial, 78 high-risk patients who were given eight cycles of conventional-dose adjuvant chemotherapy were randomly assigned to either two cycles of high-dose chemotherapy with cyclophosphamide, etoposide, and cisplatin plus autologous hematopoietic stem-cell transplantation or no further chemotherapy.<sup>19</sup> No significant difference in relapse-free or overall survival was observed. Investigators at the Netherlands Cancer Institute randomly assigned 81 patients to receive either a fourth cycle of adjuvant chemotherapy with fluorouracil, epirubicin, and cyclophosphamide (FEC) or high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin and stem-cell transplantation.<sup>20</sup> (The final results are reported elsewhere in this issue.<sup>21</sup>) After a follow-up of more than six years, no significant difference was observed in relapse-free or overall survival. In a large intergroup trial, patients were randomly assigned to receive either high doses of cyclophosphamide, cisplatin, and carmustine with stem-cell support or intermediate doses of this regimen with granulocyte colony-stimulating factor support after four cycles of adjuvant chemotherapy with CAF.<sup>22</sup> No statistically significant differences in event-free survival were observed. In a study from Scandinavia, patients were assigned to receive either nine cycles of FEC, with the doses adjusted to achieve targeted nadir blood counts, or three cycles of conventional-dose (unadjusted) FEC followed by cyclophosphamide, thiotepa, and carboplatin with autologous hematopoietic stem-cell transplantation.<sup>23</sup> Follow-up was not long enough to allow a survival analysis, but myelodysplastic syndrome or acute myelogenous leukemia developed in eight patients in the adjusted-dose FEC group. In the Anglo-Celtic trial, 605 patients with 4 or more involved axillary lymph nodes (median, 9+) were randomly assigned to conventional adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil or high-dose chemotherapy.<sup>24</sup> No difference was observed in event-free survival (54 percent vs. 51 percent, respectively) or overall survival (62 percent vs. 63 percent, respectively). All five treatment-related deaths occurred in the high-dose chemotherapy group.

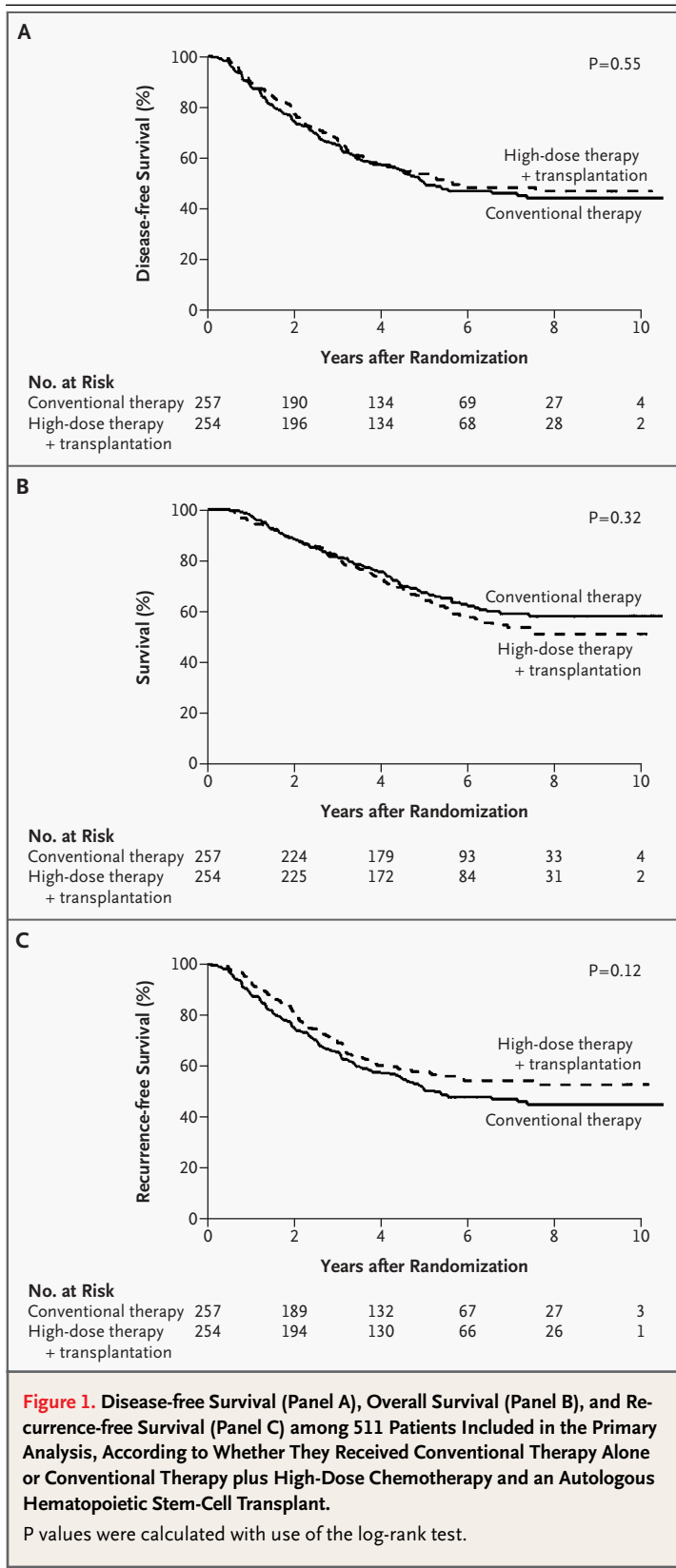
Roche et al. randomly assigned 314 women who were younger than 60 years of age, had more than seven involved lymph nodes, and received four cycles of fluorouracil, cyclophosphamide, and epirubicin to receive either no further chemotherapy or high-dose chemotherapy with cyclophosphamide, mitoxantrone, and melphalan with autologous hematopoietic stem-cell transplantation.<sup>25</sup>

**Table 4. Treatment-Related Cause of Death in Nine Patients Who Received High-Dose Chemotherapy and Underwent Autologous Stem-Cell Transplantation.**

Patient No.	Age yr	Stem-Cell Source	Time of Death	Cause of Death
1	35	Marrow	9 Days after transplantation	Capillary leak syndrome and multiorgan failure
2	36	Marrow	28 Days after transplantation	Aspergillosis of the lungs
3	45	Marrow	37 Days after transplantation	Infection
4	50	Marrow	31 Days after transplantation	Cerebral hemorrhage
5	49	Marrow	37 Days after transplantation	Graft failure
6	45	Blood and marrow	55 Days after transplantation	Pulmonary toxicity (alveolar hemorrhage)
7	50	Marrow	28 Days after transplantation	Cardiovascular failure due to disseminated aspergillosis
8	52	Blood and marrow	21 Days after transplantation	Sepsis
9	28	Blood	2 Days before transplantation	Pericardial tamponade with cyclophosphamide-induced myocarditis

**Table 5. Sites of Second Cancers.**

Site or Type of Cancer	Conventional Therapy	High-dose Chemotherapy + Stem-Cell Transplantation
	<i>number of cases</i>	
Thyroid	1	0
Kidney	2	0
Ovary	0	2
Myelodysplastic syndrome or acute myelogenous leukemia	0	9
Melanoma	2	0
Nonmelanoma skin cancer	1	2
Cervix	0	1
Myeloma	1	0
Sarcoma	0	1
Endometrium	1	0
Non-Hodgkin's lymphoma	1	0
Total	9	15



After a median follow-up of 39 months, an intention-to-treat analysis showed that the 3-year disease-free survival rate was 55 percent in the conventional-treatment group and 71 percent in the high-dose group ( $P < 0.003$ ), and the overall survival rates were 84 percent and 86 percent, respectively ( $P = 0.33$ ). This was the only trial to show an improvement in disease-free survival, but it included patients at somewhat lower risk for recurrence (7 to 10 involved lymph nodes) than our patients and had a relatively short median follow-up.

Our results do not confirm the promise of earlier phase 2 trials.<sup>6-10</sup> Most such studies included relatively small numbers of patients, were not randomized, and were subject to selection bias.<sup>12,13</sup> Factors that may have contributed to the lack of improvement in disease-free survival and overall survival in this trial included nine transplantation-related deaths, most occurring before the introduction of stem cells derived from peripheral blood as a source of hematopoietic reconstitution, and the development of a secondary myelodysplastic syndrome or acute myelogenous leukemia in nine patients in the transplantation group. Although the number of relapses may be reduced by the addition of stem-cell transplantation, the benefit was offset in part by treatment-related deaths. An additional theoretical limitation of high-dose chemotherapy and autologous hematopoietic stem-cell transplantation is the risk of contaminating the harvested stem cells with malignant cells.<sup>26</sup> The degree of contamination may be influenced by the mobilization methods used.<sup>27</sup>

The development of myelodysplastic syndrome or acute myelogenous leukemia in nine patients is a serious concern, since this has become an increasingly recognized, but uncommon, complication of adjuvant chemotherapy<sup>27-31</sup> or autologous hematopoietic stem-cell transplantation<sup>32,33</sup> for breast cancer, and the median survival among patients in whom these therapy-related complications develop is only six months after transplantation.<sup>34</sup> Prior reports suggested a relatively low incidence of these complications: a four-year probability of 1.6 percent in the series by Laughlin et al.<sup>32</sup> and a five-year probability of 3.2 percent in the series by Nichols et al.<sup>33</sup> However, these complications developed in 4 percent of our patients. The individual contribution of the adjuvant chemotherapy or high-dose chemotherapy with two alkylating agents cannot be determined. Furthermore, the two treatments may have an additive effect with respect to leukemogenicity.

We speculate that the development of secondary myelodysplastic syndrome or acute myelogenous leukemia could be avoided and disease-free survival and overall survival improved by collecting peripheral-blood stem cells after one or two cycles of adjuvant chemotherapy, since the type and intensity of pretransplantation chemotherapy with alkylating agents have an important influence on the development of these disorders and conventional-dose chemotherapy before transplantation damages hematopoietic stem cells.<sup>35,36</sup>

Although the addition of autologous hematopoietic stem-cell transplantation to conventional adjuvant chemotherapy did not improve disease-free survival or overall survival, the increased time to recurrence suggests that the long-term outcome may improve if transplantation-related mortality and the development of secondary myelodysplastic syndrome and acute myelogenous leukemia can be avoided. Transplantation-related mortality has been all but eliminated through the use of peripheral-

blood stem cells, and less potentially leukemogenic preparative regimens may decrease the risk of secondary myelodysplastic syndrome or acute myelogenous leukemia. Whether the use of such contemporary transplantation strategies will translate into a survival benefit must be determined in a prospective randomized trial. Conventional-dose adjuvant chemotherapy remains the standard of care for women with primary breast cancer and a high risk of recurrence.

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