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High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for High-Risk Breast Cancer

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ABSTRACT

BACKGROUND

The use of high-dose adjuvant chemotherapy for high-risk primary breast cancer is controversial. We studied its efficacy in patients with 4 to 9 or 10 or more tumor-positive axillary lymph nodes.

METHODS

Patients younger than 56 years of age who had undergone surgery for breast cancer and who had no distant metastases were eligible if they had at least four tumor-positive axillary lymph nodes. Patients in the conventional-dose group received fluorouracil, epirubicin, and cyclophosphamide (FEC) every three weeks for five courses, followed by radiotherapy and tamoxifen. The high-dose treatment was identical, except that high-dose chemotherapy (6 g of cyclophosphamide per square meter of body-surface area, 480 mg of thiotepa per square meter, and 1600 mg of carboplatin per square meter) with autologous peripheral-blood hematopoietic progenitor-cell transplantation replaced the fifth course of FEC.

RESULTS

Of the 885 patients, 442 were assigned to the high-dose group and 443 to the conventional-dose group. After a median follow-up of 57 months, the actuarial 5-year relapse-free survival rates were 59 percent in the conventional-dose group and 65 percent in the high-dose group (hazard ratio for relapse in the high-dose group, 0.83; 95 percent confidence interval, 0.66 to 1.03; $P=0.09$). In the group with 10 or more positive nodes, the relapse-free survival rates were 51 percent in the conventional-dose group and 61 percent in the high-dose group ($P=0.05$ by the log-rank test; hazard ratio for relapse, 0.71; 95 percent confidence interval, 0.50 to 1.00).

CONCLUSIONS

High-dose alkylating therapy improves relapse-free survival among patients with stage II or III breast cancer and 10 or more positive axillary lymph nodes. This benefit may be confined to patients with HER-2/*neu*-negative tumors.

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A NUMBER OF RELATIVELY SMALL, UNCONTROLLED studies have suggested that adjuvant high-dose chemotherapy with hematopoietic progenitor-cell infusion could be of benefit for high-risk breast cancer.¹ The largest of these studies suggested that high-dose chemotherapy dramatically prolongs progression-free survival as compared with survival among historical controls who had received conventional therapy.² We and others were not able to reproduce this result.³ Clearly, much larger prospective, controlled studies were required to ascertain the efficacy of this treatment.

The Dutch randomized study reported here was designed in 1993, and the original protocol included fewer than 300 patients. When the study had been under way for two years, we recognized that a much larger trial would be required to detect a true relapse-free survival benefit of 15 to 20 percent. The study protocol was amended, but the funding agency stipulated that the results in the first 284 patients would be reported in 2000.^{4,5} In addition, the larger study had specifically to address whether high-dose therapy would also be useful in patients with an intermediate risk of relapse (as defined by the presence of four to nine tumor-positive axillary lymph nodes). Thus, separate analyses of the intermediate-risk (4 to 9 nodes) and high-risk (10 or more nodes) categories were planned. Here, we report the outcome of the study after a median follow-up of 57 months and a maximal follow-up of more than 8 years.

METHODS

PATIENTS

The study was designed to enroll women younger than 56 years of age who had undergone surgery for breast cancer. Patients were eligible if they had at least four axillary lymph nodes with metastases but no distant metastases. The results of chest roentgenography, an ultrasonographic examination of the liver, and a bone scan had to be negative. If the results of bone scanning were equivocal, normal findings on magnetic resonance imaging (MRI) of the involved area were required to resolve the issue. Other eligibility criteria included an Eastern Cooperative Oncology Group–Zubrod performance status of 0 or 1, a white-cell count of at least 4000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a creatinine clearance rate of at least 60 ml per minute, and a serum bilirubin level of 1.46 mg per deciliter (25 μ mol per liter) or less.

The chemotherapy had to begin within six weeks after the last surgery. No other cancers were allowed except adequately treated *in situ* carcinoma of the cervix or basal-cell carcinoma of the skin. Informed consent was obtained from all patients, and the study was approved by the institutional review committees at each of the participating centers.

Eligible patients underwent randomization before treatment and were stratified according to age (younger than 50 years of age vs. 50 years or older), menopausal status (premenopausal vs. postmenopausal), the number of lymph-node metastases (4 to 9 nodes or 10 or more) and tumor size (pT1, pT2, or pT3).

The conventional-treatment group received five courses of fluorouracil, epirubicin, and cyclophosphamide (FEC), radiotherapy, and tamoxifen. Treatment in the high-dose group was identical, except that the fifth course of FEC was replaced by high-dose alkylating chemotherapy.

TREATMENT

The conventional chemotherapy consisted of intravenous injections of fluorouracil (500 mg per square meter of body-surface area), epirubicin (90 mg per square meter), and cyclophosphamide (500 mg per square meter) every three weeks. In the high-dose group, peripheral-blood progenitor cells were mobilized by administering granulocyte colony-stimulating factor (filgrastim) at a dose of 300 μ g daily subcutaneously for 10 days starting the day after the third course of FEC. Peripheral-blood progenitor cells were collected by leukocytapheresis until at least 3 million CD34+ cells per kilogram of body weight had been harvested.⁶ The high-dose chemotherapy regimen consisted of cyclophosphamide (6 g per square meter), thiotepa (480 mg per square meter), and carboplatin (1600 mg per square meter) divided over a four-day period and given in daily infusions of 30 to 60 minutes.^{6,7} The peripheral-blood progenitor cells were administered 48 hours after the last dose of chemotherapy and were followed by daily treatment with filgrastim. Details of supportive care before and after transplantation have been published elsewhere.⁶

The original protocol included treatment with tamoxifen, 40 mg daily for two years, after the completion of chemotherapy. During the course of the trial, however, it became clear that five years of tamoxifen was more efficacious than two years.⁸ Patients with hormone-receptor–positive cancer therefore continued to receive tamoxifen for three more

years after completing the first two years of tamoxifen prescribed in the protocol.

Patients were evaluated at the beginning of every chemotherapy course and at the beginning and end of the radiation therapy. Patients were subsequently seen at least every four months. To monitor patients' menopausal status, the date of the last menstruation was noted and follicle-stimulating hormone and 17 β -estradiol levels were determined at least every year during tamoxifen therapy and after the discontinuation of tamoxifen if any uncertainty regarding postmenopausal status remained. Yearly mammography and chest roentgenography were performed.

PATHOLOGICAL REVIEW

A centralized review of pathological specimens was performed in a blinded fashion by one investigator. Classification included tumor type according to the criteria of the World Health Organization, histologic tumor grade,⁹ mitotic activity index,¹⁰ and the presence or absence of carcinoma in situ and angioinvasion.

Formalin-fixed, paraffin-embedded tissue samples were stained with antibodies against estrogen receptor (1D5; dilution, 1:150; Dako); progesterone receptor (involving standard antigen retrieval, followed by incubation with progesterone-receptor polyclonal antibody [Dako]), HER2/*neu* (3B5; dilution, 1:10,000),¹¹ and p53 (D07; dilution, 1:8000; Dako). Immunohistochemical results were scored semiquantitatively. Tumors were considered positive for hormone receptors if at least 10 percent of the tumor cells showed nuclear staining. Staining for HER2/*neu* was scored as follows: a score of 0, no staining; a score of 1, more than 10 percent of cells were weakly positive; a score of 2, moderate homogeneous staining; and a score of 3, strong homogeneous staining.

STATISTICAL ANALYSIS

The main end points for the comparison of the two treatments were relapse-free survival and overall survival. Relapse-free survival was calculated from randomization to the initial appearance of a relapse of disease or to death from any cause; data on patients known to be alive and without a relapse at the time of an analysis were censored at the time of their last follow-up visit. The occurrence of second breast cancers or other cancers was not counted as an event. Overall survival was calculated from randomization to death from any cause; data on patients known to be alive at the time of an analysis

were censored at the time of their last follow-up visit. All treatment comparisons are based on the intention-to-treat principle. The Kaplan-Meier method was used to estimate curves for relapse-free and overall survival, and comparisons were made with use of the log-rank test. Cox proportional-hazards models were fitted in order to estimate hazard ratios and confidence intervals. Differences in the overall treatment comparison and the treatment comparison within the two groups on the basis of the number of nodes are expressed in terms of hazard ratios with 95 percent confidence intervals. The relative benefit of high-dose treatment with respect to relapse-free survival was further investigated in subgroups of potential prognostic variables by means of forest plots, which showed the hazard ratio with 99 percent confidence intervals. To evaluate whether there were differences in the relative size of the effect in different subgroups, we used a χ^2 test for interaction or, when appropriate, a χ^2 test for trend. All P values are based on two-sided tests. Analyses were performed with use of SAS system version 8.2 and S-Plus version 2000.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between August 1993 and July 1999, 885 patients from 10 centers were enrolled and underwent randomization. Thirty-seven patients were found to be ineligible for the following reasons: prior radiation therapy for unrelated disease (4 patients), evidence of distant metastases (2), prior cervical cancer (1), and abnormalities in laboratory values (30). All 37 stayed in the study, and all patients were included in the intention-to-treat analysis. Pertinent characteristics of the patients are listed in Table 1, as are the results of the pathological review.

FEC CHEMOTHERAPY

Two patients (one in each group) declined chemotherapy after randomization. The median dose intensities were equal in both groups, but the absence of a fifth course of conventional chemotherapy made the cumulative doses of epirubicin and fluorouracil 20 percent lower in the high-dose group. Clinically significant adverse effects included 50 episodes of fever and neutropenia requiring antibiotics (1 percent), grade 3 (moderate) or grade 4 (severe) nausea and vomiting in 388 courses (10 percent), and grade 3 or 4 mucositis in 14 courses (less than 1 percent). Fourteen days after the third course of FEC, one pa-

Table 1. Characteristics of the Patients and Tumors.

Characteristic	Conventional-Dose Group (N=443)	High-Dose Group (N=442)
Age (yr)		
Median	45	46
Range	25–55	23–55
Type of surgery (no. of patients)		
Mastectomy	353	337
Breast-conserving	90	105
Tumor classification (no. of patients)		
T1	105	90
T2	260	274
T3	73	70
Unknown	5	8
No. of positive nodes (no. of patients)		
4–9	284	284
≥10	159	158
Histologic grade (no. of patients)*		
I	76	78
II	154	138
III	182	184
Not determined	31	42
Estrogen-receptor status (no. of patients)		
Negative (<10%)	125	126
Positive (≥10%)	290	289
Not determined	28	27
Progesterone-receptor status (no. of patients)		
Negative (<10%)	172	178
Positive (≥10%)	239	233
Not determined	32	31
HER2/neu score (no. of patients)		
0 (negative)	282	300
1+ or 2+ (negative)	23	15
3+ (positive)	96	85
Not determined	42	42
p53 status (no. of patients)		
Negative (<10%)	202	211
Positive (≥10%)	182	174
Not determined	59	57
Menopausal status at randomization (no. of patients)		
Premenopausal	369	367
Postmenopausal	58	49
Uncertain	16	26
Menopausal status 30 mo after randomization (no. of patients)		
Premenopausal	93	22
Postmenopausal	262	335
Uncertain	88	85
Length of tamoxifen therapy (no. of patients)		
Not started	3	13
Discontinued at relapse, within 2 yr	56	50
2 yr	184	188
>2 yr	178	167
Unknown	22	24

* A higher grade indicates more aggressive disease.

tient in the high-dose group died of cardiac arrhythmia during an emergency hospital admission for diarrhea and an electrolyte imbalance.

MOBILIZATION AND HARVEST OF PERIPHERAL-BLOOD PROGENITOR CELLS

A total of 402 patients in the high-dose group received filgrastim after the third or fourth course of FEC and underwent leukocytapheresis to obtain peripheral-blood progenitor cells. A median of two sessions (range, one to four) was required to obtain at least 3 million CD34+ cells per kilogram of body weight in 394 patients (median yield, 8.9 million; range, 3.0 million to 51.0 million). In seven patients (2 percent), less than the target number of cells was harvested (median yield, 2.6 million; range, 1.3 million to 2.9 million). In a single patient, no CD34+ cells could be mobilized into the peripheral blood.

HIGH-DOSE CHEMOTHERAPY

Of the 442 patients in the high-dose group, 397 received the planned course of high-dose alkylating therapy after four courses of FEC. Reasons for canceling high-dose therapy in the 45 other patients were the withdrawal of informed consent in the case of 15 patients, severe psychological problems in 5 patients, medical complications in 9 patients, early progression in 6 patients, venous access problems in 1 patient, early death in 1 patient, inability to harvest sufficient numbers of peripheral-blood progenitor cells in 1 patient, and unknown reasons in 7 patients. Thirty-four of the 45 patients received a fifth course of FEC instead of the high-dose alkylating therapy. None of the 443 patients who were randomly assigned to the conventional-dose chemotherapy group crossed over to high-dose treatment or received high-dose therapy elsewhere.

In six patients, the high-dose course was terminated early because of high fever (four patients), cardiac arrhythmia (one patient), or possible heart failure (one patient). All other patients received the full course without dose reductions. All patients given high-dose chemotherapy had nausea and vomiting and became transfusion-dependent. There were four deaths within 100 days after the reinfusion of peripheral-blood progenitor cells, two from septicemia and two from cardiac causes.

RADIATION THERAPY

Radiotherapy was administered to 776 patients. Radiation-induced pneumonitis requiring therapy with corticosteroids occurred in 25 patients, 7 of

whom were in the conventional-dose group and 18 of whom were in the high-dose group. The condition of all but one patient improved; severe lung fibrosis developed in this patient, who was in the high-dose group, and the patient died of pulmonary complications 18 months after randomization.

TAMOXIFEN

The durations of tamoxifen therapy are given in Table 1. More patients became postmenopausal after high-dose chemotherapy than after conventional-dose treatment (Table 1).

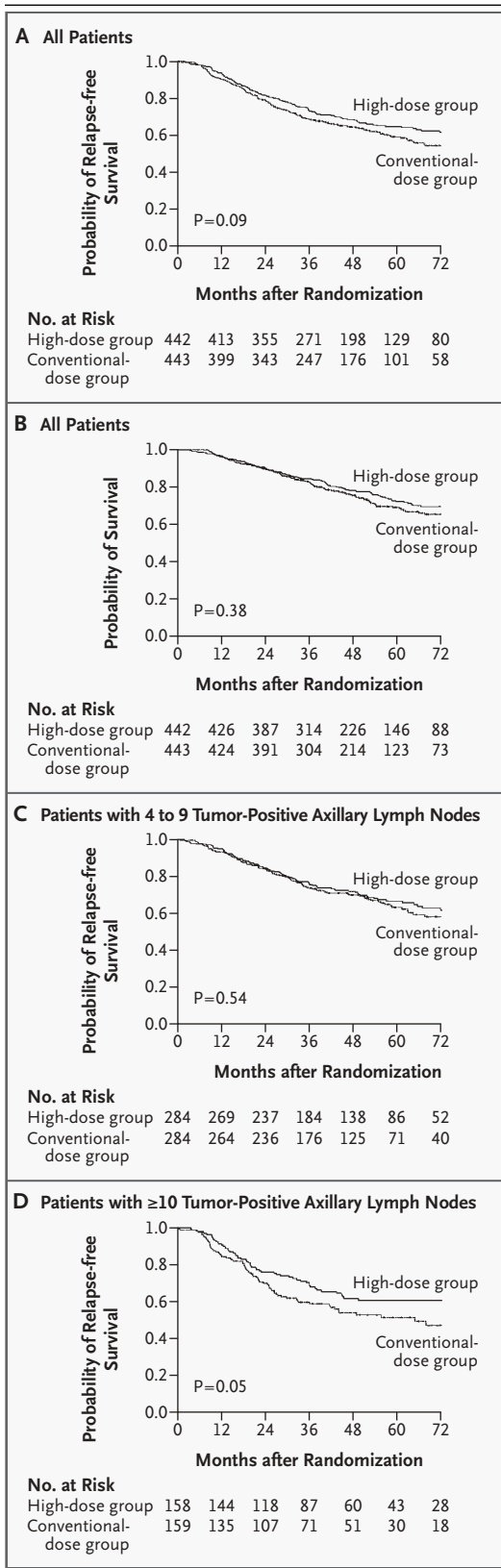
SURVIVAL ANALYSIS

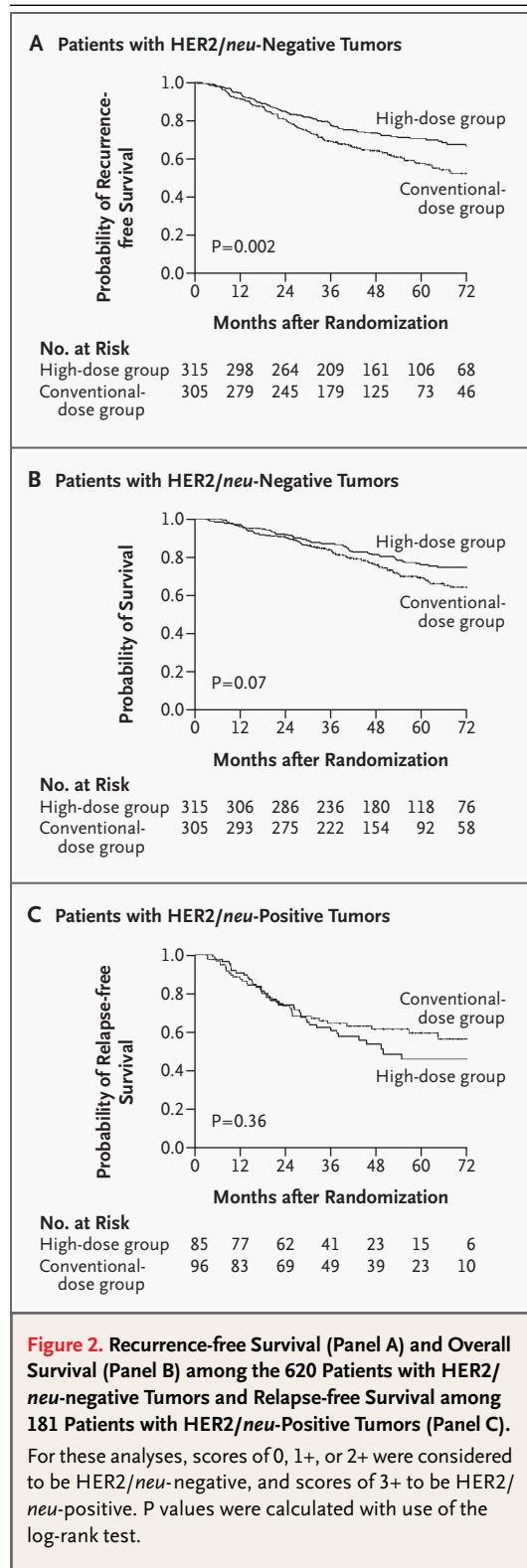
At the time of the analysis, the median follow-up of the surviving patients was 57 months. A total of 319 events (36 percent) had been reported. The five-year relapse-free survival rates were 59 percent (range, 54 to 64) in the conventional-dose group and 65 percent (range, 60 to 70) in the high-dose group. The hazard ratio for relapse in the high-dose group was 0.83 (95 percent confidence interval, 0.66 to 1.03; $P=0.09$) (Fig. 1A). At the time of the last follow-up, a total of 235 patients had died, and there was no significant difference in overall survival between the two groups (Fig. 1B).

The only planned subgroup analyses were for patients at intermediate risk (those with 4 to 9 tumor-positive axillary lymph nodes) (Fig. 1C) and patients at high risk (those with 10 or more positive nodes) (Fig. 1D). Patients with 10 or more axillary lymph nodes had a significantly longer relapse-free survival after high-dose therapy than after conventional therapy ($P=0.05$ by the log-rank test; hazard ratio for relapse, 0.71; 95 percent confidence interval, 0.50 to 1.00), but in both subgroups, high-dose therapy had no significant effect on overall survival. Further subgroup analyses were performed for a range of predictive factors (data not shown). Younger age ($P=0.05$), negativity for HER2/*neu* expression ($P=0.02$), and lower grade ($P=0.002$) were associated with a significant positive effect of high-dose therapy on relapse-free survival.

Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) among all 885 Patients, According to an Intention-to-Treat Analysis, and Relapse-free Survival among Patients with 4 to 9 Tumor-Positive Axillary Lymph Nodes (Panel C) and Patients with 10 or More Tumor-Positive Axillary Lymph Nodes (Panel D).

P values were calculated with use of the log-rank test.





HER2/*neu*-NEGATIVE AND HER2/*neu*-POSITIVE TUMORS

A total of 620 patients had tumors that were negative for HER2/*neu* (as defined by a score of 0, 1+, or 2+) and 181 had tumors that expressed HER2/*neu* (as defined by a score of 3+). Since patients with HER2/*neu*-positive tumors derived no benefit from high-dose therapy, we performed a subgroup analysis of the patients with HER2/*neu*-negative tumors. In this subgroup, relapse-free survival was significantly longer after high-dose therapy than after conventional therapy (Fig. 2A) (hazard ratio for relapse, 0.66; 99 percent confidence interval, 0.46 to 0.94; $P=0.002$). There was also a trend toward an overall survival benefit after high-dose chemotherapy ($P=0.07$) (Fig. 2B).

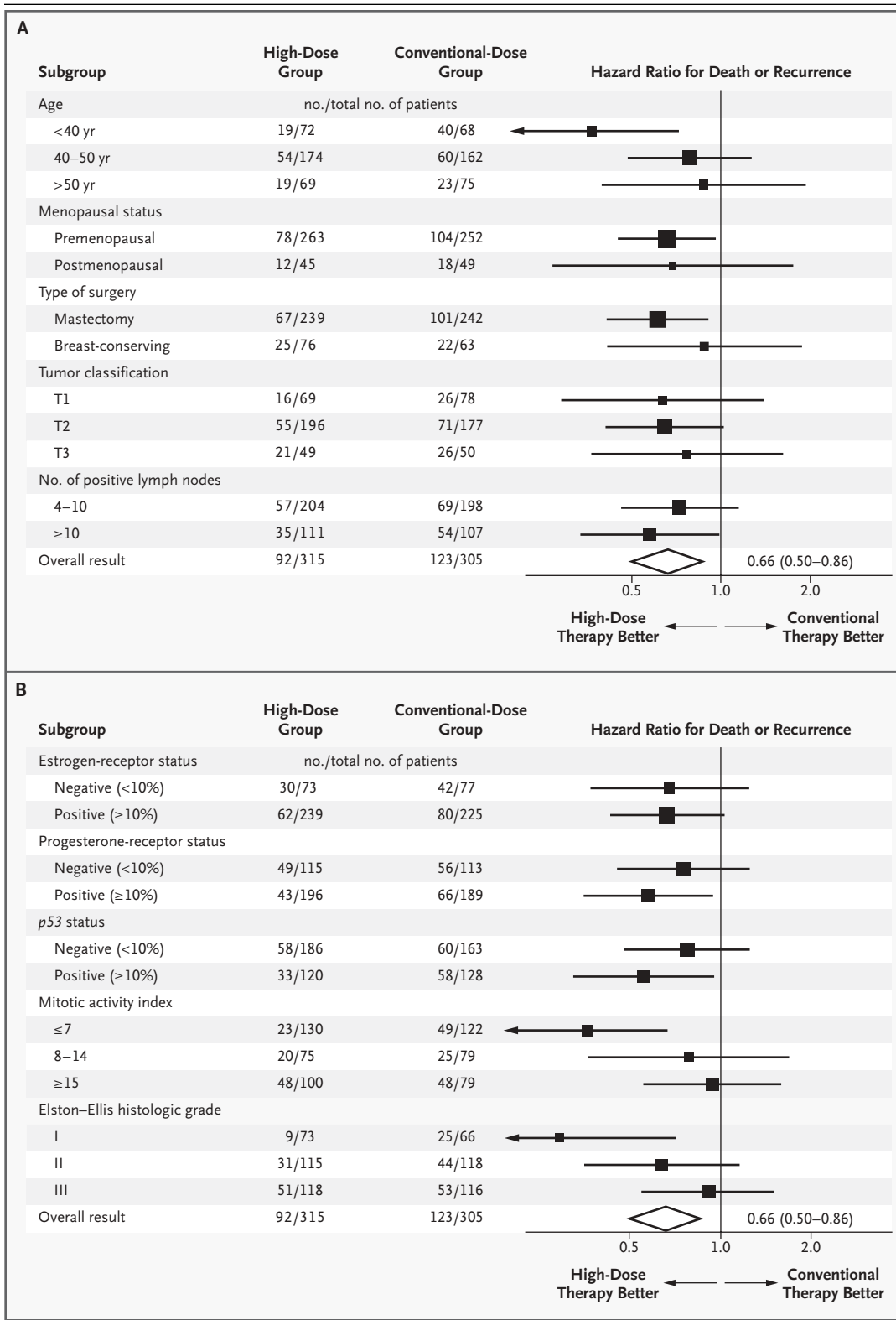
Patients with HER2/*neu*-positive tumors in the high-dose group had a higher frequency of relapses than did such patients in the conventional-dose group, although the difference was not statistically significant (Fig. 2C). Subgroup analyses of the HER2/*neu*-negative group are shown in Figure 3. As was true for the group as a whole, in this subgroup, younger age ($P=0.02$) and a low histologic grade ($P=0.01$) were strong indicators of relapse-free survival after high-dose therapy.

LONG-TERM ADVERSE EFFECTS AND SECOND CANCERS

The main long-term adverse effect was the induction of menopause, which was more frequent in the

Figure 3 (facing page). Characteristics of the Patients (Panel A) and Tumors (Panel B) in Subgroup Analyses for Potential Predictive Factors among 620 Patients with HER2/*neu*-Negative Tumors.

Higher scores for the mitotic activity index indicate more aggressive disease. The Elston–Ellis histologic grades range from I to III, with III indicating more aggressive disease. HER2/*neu*-negative disease was defined by a score of 0, 1+, or 2+. These forest plots show the effect of high-dose therapy on the hazard ratio for recurrence (or death) and the 99 percent confidence interval. The size of the solid squares corresponds to the size of the subgroups. Subgroups for which the line representing the 99 percent confidence interval lies to the left of the vertical line represent subgroups for which high-dose chemotherapy may offer a significant benefit over conventional therapy with respect to relapse-free survival. All subgroup analyses except those associated with the number of lymph nodes were unplanned. The diamonds correspond to the 95 percent confidence intervals. Data were missing for some patients.



high-dose chemotherapy group than in the conventional-dose group (Table 1). Second cancers also occurred slightly more often in the high-dose chemotherapy group (Table 2).

DISCUSSION

This randomized study was designed to determine whether high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin could improve relapse-free survival among patients with node-positive breast cancer. All patients received the regimen of adjuvant therapy that was considered optimal when the study was designed: radiotherapy, chemotherapy, and tamoxifen. The only difference between the groups was that one group received high-dose chemotherapy after four courses of anthracycline-based chemotherapy (FEC). To ensure that any advantage of the high-dose therapy could not simply be ascribed to a difference in the duration of treatment between the groups, a fifth course of FEC was given to the patients in the conventional-dose group.

One potential drawback of our study was that the high-dose alkylating chemotherapy was expected to induce amenorrhea in nearly all patients, whereas a substantial proportion of women in the conventional group would remain premenopausal, creating an imbalance with regard to ovarian function. However, this imbalance proved to be relatively minor, and we have no evidence that chemotherapy-induced amenorrhea contributed heavily to the relapse-free survival benefit of high-dose therapy.

The high-dose chemotherapy regimen caused five deaths (1 percent) and considerable reversible morbidity. This rate is, however, less than the rate of 7.4 percent reported for the regimen of cisplatin, cyclophosphamide, and carmustine in the American Intergroup Study,¹² and one year after high-dose therapy there were no significant differences in the quality of life between the treatment groups (unpublished data).

The relapse-free survival curve for all the 885 patients shows a mean (\pm SD) reduction of 17 ± 10 percent in the hazard ratio for relapse in the high-dose group as compared with the conventional-dose group ($P=0.09$), a degree of improvement for which even a study involving 885 patients is underpowered, but that could be clinically important. The respective reduction in the hazard ratio in the subgroup with 10 or more tumor-positive lymph nodes was 29 ± 15 percent ($P=0.05$). Since this subgroup analysis was planned, the result is statistically significant. The overall survival benefit was not statistically significant, but 5 to 10 years of additional follow-up may be required before a definitive conclusion about overall survival can be made.

We found a significant interaction between HER2/neu status and treatment ($P<0.05$). Although unplanned, the subgroup analyses of HER2/neu-positive disease and HER2/neu-negative disease are important, since the amplification of HER2/neu characterizes a breast-cancer subtype with a distinct molecular signature,¹³ and the sensitivity to alkylating agents and to anthracyclines may differ markedly between HER2/neu-negative and HER2/neu-positive tumors.¹⁴⁻¹⁶

Patients with HER2/neu-positive disease had a higher relapse rate after high-dose therapy than after conventional-dose therapy, but this difference was not statistically significant. Retrospective analyses of uncontrolled studies of high-dose chemotherapy, both as adjuvant chemotherapy and in patients with metastases, have consistently shown that patients with HER2/neu-positive tumors have a very poor response to this approach.¹⁷⁻²³ Since staining for HER2/neu is often among the strongest adverse predictive factors for relapse or survival after high-dose alkylating chemotherapy, high-dose therapy may be inappropriate in such patients.²⁴

In our study, patients in the high-dose group who had HER2/neu-negative tumors had a relapse rate of 30 percent after five years, as compared with a rate of 42 percent among such patients in the conventional-dose group ($P=0.002$). This value corre-

Table 2. Second Cancers.

Type of Cancer	Conventional-Dose Group	High-Dose Group
	number	
Melanoma	1	3
Nonmelanoma skin cancer	1	2
Second breast cancer	9	12
Myelodysplasia or leukemia	1	
Ovarian cancer	1	1
Endometrial cancer	1	2
Head and neck cancer	1	1
Total	15	21

sponds to a 34 ± 11 percent reduction in the hazard ratio. In this subgroup, there is also a trend toward a survival benefit with high-dose therapy.

High-dose chemotherapy significantly decreased the relapse rate, as compared with conventional therapy, among patients younger than 40 years of age (*P* for interaction, <0.05). This held true for patients with HER2/*neu*-negative tumors (*P* for interaction <0.02) but not for those with HER2/*neu*-positive tumors (data not shown). The effect of high-dose therapy was particularly evident among patients with low-grade tumors, as defined by a low mitotic activity index or a low histologic grade (*P* for interaction $=0.01$). Clearly, the results of these retrospective subgroup analyses should be interpreted with caution, but the subgroups are relatively large and the tests for statistical significance indicate that the results are reliable. These findings could have important consequences if they are confirmed, because it has long been assumed that high-dose chemother-

apy should be particularly effective in patients with prognostically unfavorable features of the disease. Another study of conventional adjuvant chemotherapy plus high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer is also reported in this issue.²⁵

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