ARTICLE

Impairment of Cognitive Function in Women Receiving Adjuvant Treatment for High-Risk Breast Cancer: High-Dose Versus Standard-Dose Chemotherapy

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Background: **Although high-dose chemotherapy is rapidly gaining acceptance as a treatment option for a number of cancers, the long-term toxic effects of such therapy are a concern. Cognitive deficits (e.g., problems with memory and concentration) are not uncommon after chemotherapy, but they have not been documented systematically. In this study, we assessed the prevalence of cognitive deficits in a group of patients with high-risk breast cancer who were randomly assigned to receive either high-dose or standard-dose adjuvant chemotherapy plus tamoxifen, and we investigated whether high-dose chemotherapy impaired cognitive functioning more than standard-dose chemotherapy.** ***Methods:*** **Cognitive functioning was evaluated by use of a battery of neuropsychologic tests. In addition, patients were interviewed with regard to cognitive problems, health-related quality of life, anxiety, and depression. Results from patients who received adjuvant systemic therapy were compared with results from patients who had early stage breast cancer not treated with such therapy (control patients).** ***Results:*** **The study population consisted of 34 patients treated with high-dose chemotherapy plus tamoxifen, 36 patients treated with standard-dose chemotherapy plus tamoxifen, and 34 control patients. For all patients, the average time since the completion of last nonhormonal therapy was 2 years. Cognitive impairment was found in 32% of the patients treated with high-dose chemotherapy, in 17% of the patients treated with standard-dose chemotherapy, and in 9% of the control patients. In comparison with the control patients, patients treated with high-dose chemotherapy appeared to have an 8.2-times higher risk of cognitive impairment (odds ratio; 95% confidence interval [CI] = 1.8–37.7); in comparison with the patients who received standard-dose chemotherapy, this risk of impairment was 3.5-times higher (95% CI = 1.0–12.8).** ***Conclusion:*** **High-dose chemotherapy appears to impair cognitive functioning more than standard-dose chemotherapy. Central nervous system toxicity may be a dose-limiting factor in high-dose chemotherapy regimens. [J Natl Cancer Inst 1998;90:210–8]**

Despite its widespread application in clinical practice in the United States, the efficacy of adjuvant high-dose chemotherapy with autologous bone marrow transplantation (HDC–ABMT) for breast cancer has yet to be proven *(1)*. Likewise, the impact of high-dose chemotherapy on quality of life in comparison with conventional chemotherapy remains to be determined.

This article reports on an aspect of quality of life after HDC–ABMT that has received little attention to date. In an ongoing randomized study in The Netherlands that is comparing high-dose versus standard-dose chemotherapy as adjuvant treatment for breast cancer in patients with four or more positive axillary lymph nodes *(2)*, it was noted that a number of patients complained of memory and concentration problems, even years after the completion of treatment.

Although cognitive complaints after chemotherapy are not uncommon, they have not been systematically investigated. Since 1980, only 13 studies *(3–15)* on this subject have been reported, and the results lack consistency. Moreover, most of the studies have limited power because of their small sample size and the lack of uniform patient populations and treatment regimens. Another shortcoming in most of the studies is that a control group of cancer patients not treated with chemotherapy, which is necessary to determine whether cognitive deficits are

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See ''Notes'' following ''References.''

caused by the psychologic burden of having cancer or by its treatment, is missing. Finally, none of the reported studies was carried out within the framework of a randomized trial, which makes it difficult to draw conclusions concerning the cause of the cognitive impairment.

Therefore, in our study, we investigated the neuropsychologic status of patients with high-risk breast cancer who were randomly assigned to receive either high-dose or standard-dose chemotherapy. In this way, a comparison of the impact of the different treatments on cognitive functioning could be made. Furthermore, patients in this randomized trial were being treated with chemotherapy as part of an adjuvant strategy; they had not undergone previous postsurgical treatment. Consequently, possible cumulative effects of chemotherapy could be excluded.

To control for the impact on neuropsychologic status of being confronted with treatment for cancer, the results of the patients with high-risk breast cancer who were treated with chemotherapy were compared with findings from patients with stage I breast cancer who had not undergone such therapy.

The aim of our study was to assess systematically the prevalence of cognitive deficits in a group of women receiving adjuvant treatment for high-risk breast cancer and to investigate whether high-dose chemotherapy impairs cognitive functioning more than standard-dose chemotherapy in this patient population.

Methods

Patients and Therapy

Three groups of patients were used in this study as follows: a group of patients with high-risk breast cancer treated with high-dose chemotherapy, a group of patients with high-risk breast cancer treated with standard-dose chemotherapy, and a control group of patients consisting of women with stage I breast cancer not treated with chemotherapy. All patients were recruited from The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital. All subjects gave written informed consent, and the study was approved by the ethical committee of the hospital.

The patients with high-risk breast cancer participated either in a multicenter prospective randomized trial *(2)* or in a preparatory single institution trial conducted by The Netherlands Cancer Institute *(16)*. In these trials, the curative potential of intensive adjuvant chemotherapy was studied in women younger than 55 years of age who were treated for high-risk breast cancer [stages II and III, involving $\geq$4 tumor-positive axillary lymph nodes with no evidence of distant metastases *(17)*]. After surgery, the patients were randomly assigned to receive either standard-dose or high-dose chemotherapy. The experimental treatment arms (the CTC [*see below*] arms) consisted of four cycles of FEC chemotherapy (fluorouracil, 500 mg/m^2 intravenously; epidoxorubicin, 90–120 mg/m^2 intravenously; and cyclophosphamide 500 mg/m^2 intravenously) and a fifth course of high-dose combination chemotherapy (cyclophosphamide, 6 g/m^2 intravenously; thiotepa, 480 mg/m^2 intravenously; and carboplatin, 1.6 g/m^2 intravenously [CTC]) with autologous hematopoietic progenitor cell support. After the chemotherapy, the patients received locoregional radiotherapy. Patients in the conventional treatment arms (the FEC arms) received four or five cycles of FEC chemotherapy, followed by locoregional radiotherapy. In both the high-dose and the standard-dose chemotherapy arms, the patients were treated with tamoxifen (40 mg periorally once per day) for a period of 2 years.

Exclusion criteria for participation in the neuropsychologic study were as follows: 1) the presence of metastatic disease or relapse, 2) a history of neurologic/psychiatric signs or symptoms that might lead to deviant neuropsychologic test results, 3) the use of medication that might lead to deviant neuropsychologic test results, and 4) alcohol and/or drug addiction. Basic proficiency in the Dutch language was an inclusion criterion. Only patients who were off nonhormonal treatment for at least 6 months were enrolled in the cognitive functioning study.

The control group consisted of patients with stage I breast cancer treated either with a mastectomy followed by radiotherapy or with breast-conserving surgery followed by radiotherapy. The patients in the control group did not receive any systemic therapy. These patients were matched to the patients with high-risk breast cancer on the basis of age and time since therapy. Inclusion and exclusion criteria were the same as for the patients with high-risk breast cancer.

The patients in this study were treated from September 1991 through January 1996.

Measures

The neuropsychologic status of all patients was assessed with a standard battery of neuropsychologic tests. The patients were also interviewed concerning cognitive problems, health-related quality of life, and anxiety and depression as experienced in daily life.

Neuropsychologic tests. A battery of 13 neuropsychologic tests (comprising 19 test indices), covering a broad range of functions, was used in this study. The tests were selected for reliability, for validity and availability of (Dutch) norms, and for their sensitivity in measuring cognitive functions. The cognitive functions described below are routinely evaluated in a neuropsychologic examination *(18)*.

Rey Auditory Verbal Learning test (19,20). This test measures immediate memory span, provides a learning curve, measures both short-term and longer-term retention following interpolated activity, and allows for a comparison between retrieval efficiency and learning. The Dutch version includes five learning trials of a 15-word list, an interval of 20 minutes (filled with nonverbal tests), a delayed recall, and a recognition trial consisting of the target words interspersed with 15 distractor words.

Complex Figure test: copy and recall (21,22). Copy evaluates visuoconstructional ability and recall evaluates visual memory. The subject is asked to copy a complex figure and, after a few minutes, the subject is asked to reproduce the figure without previous warning.

Digit Span of the Wechsler Adult Intelligence Scale (WAIS) (23). This subtest of the WAIS involves forward and backward repetitions of series of digits and provides measures of concentration and speed.

Digit Symbol of the WAIS (23). This test examines psychomotor performance relatively unaffected by intellectual prowess, memory, or learning. The task consists of pairing numbers with nonsense symbols as quickly as possible.

Trailmaking A and B (24). This test examines visual conceptual and visuomotor tracking. It is given in two parts, A and B. The subject must first draw lines to connect consecutively numbered circles on one work sheet (part A) and then connect the same number of consecutively numbered and lettered circles on another work sheet by alternating between the two sequences (part B). The subject is urged to connect the circles as fast as possible.

D2 test (25). The D2 test assesses many functions, e.g., the capacity for sustained attention. Visual scanning and the activation and inhibition of rapid responses are also necessary for the successful performance of this cancellation task. The test consists of rows of letters randomly interspersed with a designated target letter. The subject is instructed to cross out all target letters.

Stroop test (26,27). This test assesses the ability to substitute an alternative response for a more obvious reaction (e.g., naming the ink color of a word denoting a different color) and is sensitive to disorders of executive (frontal) function. The test exists of three stimulus cards containing 100 words, 100 colored rectangles, and 100 color-words, respectively.

Word Fluency subtest from the Dutch Aphasia Society test (28). This simple test requires the generation of words from a specific semantic category (e.g., animals) within a limited time. Impairment can be related to a language disorder, frontal dysfunction, or deterioration of semantic memory.

Fepsy Finger Tapping Task (29). This test provides a measure of motor speed. The speed of finger tapping is measured five times for a period of 10 seconds each for the index finger of the right and left hand separately.

Fepsy Visual Reaction test (29). This test measures basic perceptuomotor performance. Stimuli (e.g., a white square on a screen) are presented at random intervals by a computer.

Fepsy Binary Choice test (29). In this test, the subject has to react differently to a red square presented on the left side of a computer screen than to a green square presented on the right side. The reaction time reflects motor speed and the decision making process.

Fepsy Visual Searching test (29). This test gives an indication of the accuracy of information processing and mental speed. The task consists of finding a single

grid pattern among 24 that matches the one in the center of a computer screen. Overall, 24 different grid patterns have to be found.

Dutch Adult Reading test (30). This Dutch version of the National Adult Reading Test provides a surrogate measure of premorbid intelligence based on verbal ability. It measures the ability to read correctly a list of phonetically irregular words. The results of the test can be affected by severe cerebral pathology but are generally not affected by mild cognitive deterioration *(31).*

Cognitive Problems in Daily Life checklist. All patients were interviewed with regard to cognitive problems (memory, attention, thinking, and language) encountered in daily life and were asked to indicate on a 5-point Likert scale (0 = not at all, 1 = slightly, 2 = moderately, 3 = quite a bit, or 4 = extremely) the extent to which problems in each of these domains occurred in their daily life. The questions of this semistructured interview originated from a Dutch instrument designed to assess psychopathologic symptoms *(32).*

Health-related quality of life, depression, and anxiety. Health-related quality of life was assessed by use of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, a questionnaire developed for use in clinical trials involving cancer patients. Its validity, reliability, and sensitivity in cancer patients are well established *(33).* The EORTC QLQ-30 is a 30-item questionnaire that consists of five function scales (physical function, role function, cognitive function, emotional function, and social function), three symptom scales (fatigue, pain, and nausea and vomiting), and a general health and quality-of-life scale. Some single items measure complaints often reported by patients with cancer (loss of appetite, dyspnea, sleep disturbance, constipation, and diarrhea). Of special interest for this study were the fatigue and cognitive functioning scales. It is well known that fatigue may influence a patients' test performance *(34).* The cognitive functioning scale consists of two questions in which the patient is asked to indicate the occurrence and the extent of concentration and memory difficulties. To examine whether psychologic distress played a role in a patients' cognitive problems *(34),* the Hopkins Symptom Checklist-25 (HSCL-25) was administered *(35).* The HSCL-25 contains 15 depression and 10 anxiety-related items and was specially developed for ease and appropriateness in medical settings.

Procedure

All patients were asked by their physician to take part in this study. The tests and questionnaires were administered in the same order to each subject and took approximately 2 hours to complete.

Statistical Methods

The Statistical Package for Social Sciences WINDOWS 6.0 was used for all statistical analyses *(36).*

Each neuropsychologic test score was converted into a standard score (z score) by use of the mean test score of the control group as a reference. Furthermore, a mean overall composite z score was computed. Neuropsychologic impairment was determined as follows: a patient who scored two standard deviations below the mean of the control group on a test was considered as impaired on that test *(34).* An overall impairment score was calculated for each individual patient by counting all tests on which the patient was impaired. The fifth percentile of the control patients was used as a cutoff score for neuropsychologic impairment *(37).*

The data from the questionnaires (EORTC QLQ-C30 and HSCL-25) were converted to scores by use of standard scoring rules.

Descriptive statistics were performed for all of the variables. Between-group differences in sociodemographic characteristics were analyzed by use of the chi-squared test for contingency tables and the Student's *t* test. The between-group differences in raw neuropsychologic test scores, the average overall score, and the scores on the questionnaires were tested by use of analysis of variance. For between-group post hoc comparisons, Tukey's Honestly Significance Difference test was used.

Relationships between neuropsychologic test performances and psychologic distress, time since therapy, cancer-specific functioning, and symptoms and subjective measures of cognitive functioning were analyzed by use of Spearman rank order correlations.

Logistic regression analysis was used to determine the risk of being classified as cognitively impaired. Whether a patient was categorized as being impaired or not was used as the dependent variable. The independent variable consisted of the kind of therapy (high-dose chemotherapy, standard-dose chemotherapy, or no chemotherapy). Odds ratios were calculated with adjustment for age and education. ''Time since treatment,'' ''anxiety and depression,'' and ''fatigue'' were included as possible confounding factors to assess their effect on the risk of cognitive impairment.

All reported *P* values are two-sided.

Results

Sociodemographic and Clinical Characteristics

At the time of the study, 83 patients with high-risk breast cancer who were treated at The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital and who were enrolled in trials comparing adjuvant high-dose chemotherapy with standard-dose therapy were off nonhormonal treatment for at least 6 months. Eleven patients declined to participate in the study because of the inconvenience of an additional hospital visit, and two patients did not want to be confronted with issues related to their disease. Fifty patients with stage I breast cancer were also asked to take part in the neuropsychologic study. Eleven of these patients declined to participate because they were not willing to pay an additional visit to the hospital, and five patients refused for emotional reasons. The total sample size, therefore, consisted of 34 patients with high-risk breast cancer who were treated with high-dose chemotherapy (the CTC group), 36 patients with high-risk breast cancer who were treated with standard-dose chemotherapy (the FEC group), and 34 patients with stage I breast cancer who were not treated with chemotherapy (the control group) (Fig. 1).

The sociodemographic and clinical characteristics of the patients are shown in Table 1. There were no statistically significant differences among the three groups with regard to age and premorbid intelligence, which was estimated by performance on the Dutch Adult Reading Test [*see* ''Methods'' section and *(30)*], although the education level of the patients in the control group was lower than the education level of the patients in the two other groups. The mean time since the completion of nonhormonal therapy was, on average, 2 years. Patients in the control group had been off treatment an average of 5 months longer than the patients treated with chemotherapy. The use of alcohol, psychoactive drugs, and antiemetics was negligible in all groups. None of the patients received additional therapy after the prescribed initial therapy (i.e., surgery, chemotherapy, radiotherapy, and hormonal therapy for the high-risk patients and surgery plus radiotherapy for the stage I patients) was completed. At the time of testing, 13 high-risk patients were already off tamoxifen (five patients in the high-dose chemotherapy group and eight patients in the standard-dose chemotherapy group). There were no statistically significant differences between the high-risk patients who were still receiving tamoxifen and the high-risk patients who had completed hormonal therapy on any of the outcome measures. All 34 patients treated with high-dose chemotherapy were postmenopausal because of the impact of the cytostatic drugs on ovarian functioning. Only two of the 36 patients treated with standard-dose chemotherapy were premenopausal, as defined by the occurrence of regular menstrual cycles. In the control group, 13 patients were postmenopausal and 21 patients were premenopausal. We compared the results of the premenopausal and postmenopausal stage I breast cancer patients and observed no statistically significant differences.

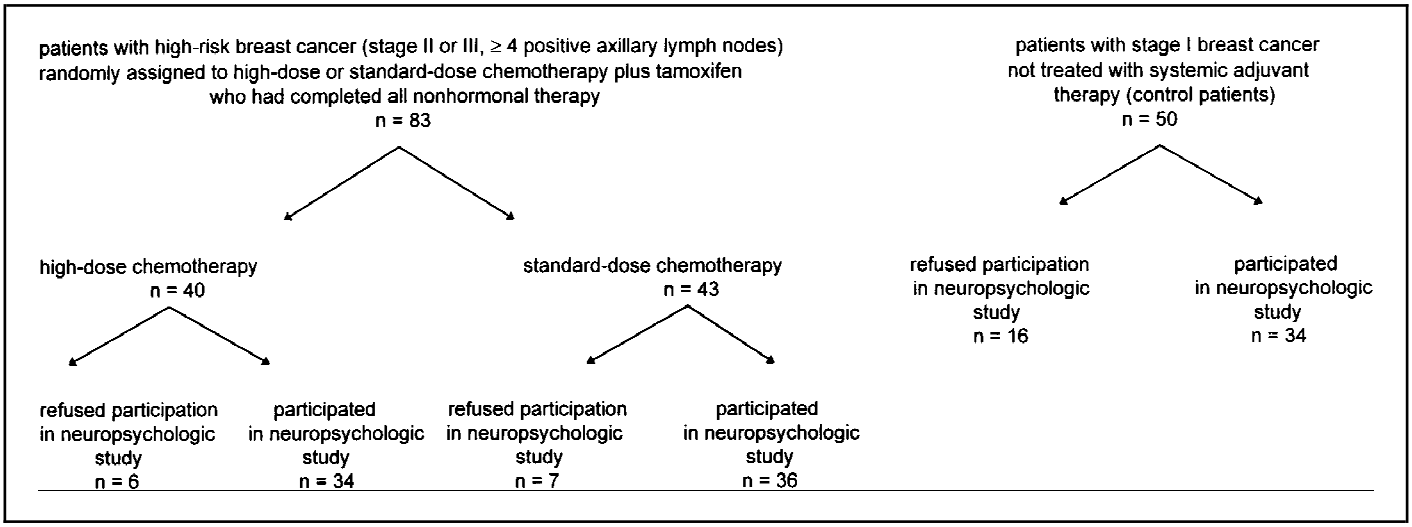

Fig. 1. Study scheme.

Cognitive Problems in Daily Life Checklist

Table 2 shows the percentage of patients who reported having cognitive problems in one of the four domains (concentration, memory, thinking, and language). Only a score of 2 or more was considered as a complaint about cognitive functioning in the domain concerned. In three of the four domains, patients who were treated with chemotherapy and tamoxifen expressed having substantially more cognitive problems than patients who were not treated with systemic therapy. There were no statistically significant differences between the two chemotherapy groups. All patients except one (in the standard-dose chemotherapy group) reported that their problems had started during their treatment. In most cases, the patients reported that they had become aware of the problems only after recovery from their nonhormonal treatment and resumption of their daily routine.

Table 1. Sociodemographic and clinical characteristics of the study subjects

Characteristics	Treatment group*		
	CTC (n = 34)	FEC (n = 36)	Control (n = 34)
Mean age, y (SD)†	45.5 (6.2)	48.1 (6.8)	46.1 (5.2)
Level of education‡			
Low	32%	31%	41%
Middle	32%	25%	41%
High	36%	44%	18%
Mean time since last therapy, y (SD)	1.6 (0.8)	1.9 (1.1)	2.4 (1.0)
Premorbid IQ§ (Dutch Adult Reading test)≠	102.7 (12.3)	105.7 (10.1)	103.9 (8.6)

*CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

†SD = standard deviation.

‡Low = primary school; middle = secondary school; high = university and graduate school; and % = percent of patients in treatment group.

§IQ = intelligence quotient.

≠The Dutch Adult Reading test is a surrogate measure of pretreatment intelligence. The results of the test are generally insensitive to mild cognitive deterioration. *See* ''Methods'' section and *(30,31)* for more details.

Health-Related Quality of Life, Depression, and Anxiety

The mean scores on the EORTC QLQ-C30 quality-of-life questionnaire are shown in Table 3. On three of the five individual function scales (i.e., physical function, role function, and social function) and on the global quality of life scale, the mean scores of the patients treated with high-dose chemotherapy were significantly below the mean scores of the patients treated with standard-dose chemotherapy. On the physical, the role, the cognitive, and the social function scales, the patients treated with high-dose chemotherapy scored significantly below the patients in the control group. On the global quality-of-life scale, the mean score of the patients treated with high-dose chemotherapy did not differ significantly from the mean score of the control patients. There were no statistically significant differences between the patients treated with standard-dose chemotherapy and the control patients on any of these scales.

In general, the symptom scales of the EORTC QLQ-C30 did not indicate significant differences among the three treatment groups. There was, however, one noticeable exception. Patients treated with high-dose chemotherapy reported being more fatigued than patients in the control group ($P = .025$).

The scores on the Hopkins Symptom Checklist (HSCL-25)

Table 2. Cognitive problems in daily life*

Domain	Treatment group†			
	CTC, % (n = 34)	FEC, % (n = 36)	Control, % (n = 34)	P‡
Concentration	38	31	6	.006
Memory	32	28	3	.006
Thinking	21	11	0	.022
Language	12	11	3	.351

*Results are shown as the percentage of patients in each treatment group who reported having cognitive problems in each of the designated domains.

†CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

‡Two-sided *P* values.

Table 3. EORTC QLQ-C30* mean scores

	Treatment group†			
	CTC (n = 34) Mean (SD)‡	FEC (n = 36) Mean (SD)	Control (n = 34) Mean (SD)	P§
Function scales‖				
Physical	71.8 (19.1)	81.1 (16.5)	88.2 (13.1)	.000¶,#
Role	68.1 (27.3)	84.7 (19.7)	88.2 (22.7)	.001¶,#
Cognitive	72.1 (24.5)	78.2 (29.0)	89.2 (16.9)	.014¶
Emotional	77.7 (28.4)	82.9 (20.6)	81.6 (19.2)	.623
Social	77.5 (28.7)	93.1 (13.4)	92.6 (19.3)	.004¶,#
Global quality of life	75.0 (20.3)	86.1 (13.4)	83.8 (17.0)	.020#
Symptom scales and/or items‖				
Fatigue	35.3 (26.2)	25.3 (27.7)	18.6 (20.4)	.025¶
Nausea and vomiting	3.4 (14.7)	3.2 (11.8)	0	.346
Pain	12.3 (19.8)	14.4 (21.1)	17.2 (20.7)	.617
Dyspnea	13.7 (20.3)	16.7 (27.0)	8.8 (20.6)	.358
Sleep disturbance	30.4 (31.1)	19.4 (31.2)	23.5 (29.0)	.322
Appetite loss	5.9 (15.3)	2.8 (9.3)	1.0 (5.7)	.173
Constipation	5.9 (15.1)	7.4 (21.2)	6.9 (16.0)	.936
Diarrhea	0	5.6 (18.7)	2.0 (8.0)	.145
Financial impact	16.7 (31.0)	13.0 (29.0)	3.9 (10.9)	.140

*EORTC = European Organization for Research and Treatment of Cancer; EORTC QLQ-C30 is a health-related quality-of-life questionnaire (*see* ''Methods'' section for more details).

†CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

‡SD = standard deviation.

§Two-sided *P* values.

‖Scores on function scales range from 0 to 100, with a higher score meaning better functioning; scores on symptom scales and/or items range from 0 to 100, with a higher score meaning more bothered by complaint.

¶Mean raw score of CTC group significantly lower than mean raw score of control group (two-sided $P<.05$).

#Mean raw score of CTC group significantly lower than mean raw score of FEC group (two-sided $P<.05$).

are shown in Table 4. The high-dose chemotherapy patients had significantly elevated scores on the depression subscale in comparison with the patients in the control group ($P = .041$), whereas the patients in all three groups were comparable with regard to their scores on the anxiety subscale.

Neuropsychologic Tests

Table 5 shows the mean scores, the standard deviations, and the *P* values of the univariate F tests for the separate neuropsychologic tests. For the patients in the control group, there were no statistically significant differences between the scores on any of the individual neuropsychologic tests and the published norms for those tests. With the exception of one test, i.e., the Fepsy Visual Reaction (nondominant) test, the scores of the two chemotherapy groups on the neuropsychologic tests were not significantly different. On seven of the 19 test indices, the univariate F tests revealed statistically significant differences between the high-dose chemotherapy group and the control group ($P<.05$). If the Bonferroni method of correcting for multiple comparisons *(38)* is applied, setting alpha at .002, none of these differences remain significant. Since consideration of group means may obscure cognitive impairment evaluation at the level of the individual, we calculated an overall individual impairment score. The fifth percentile of the control patients was used as a cutoff point to determine whether a patient was considered cognitively impaired. The fifth percentile of the control patients corresponded to failure on three or more of the tests. Thus, for a patient to be classified as a cognitively impaired, a score of two standard deviations below the mean of the control group on at least three tests was required. Table 6 shows the percentage of patients who met the criteria for cognitive impairment according to this definition; 32% of the patients treated with high-dose chemotherapy were classified as cognitively impaired compared with 17% of the patients treated with standard-dose chemotherapy and 9% of the patients not treated with chemotherapy[1] ($P = .043$).

The medical records of all patients who were classified as being cognitively impaired were examined for the period of time

Table 4. HSCL-25 anxiety and depression mean scores*

	Treatment group†			
	CTC (n = 34) Mean (SD)‡	FEC (n = 36) Mean (SD)	Control (n = 34) Mean (SD)	P§
HSCL-25 total score	19.0 (18.6)	13.5 (10.5)	11.3 (11.6)	.070
Anxiety	19.4 (15.4)	14.1 (13.5)	14.3 (15.9)	.255
Depression	18.8 (22.0)	13.1 (11.0)	9.3 (10.1)	.041‖

*HSCL-25 = the Hopkins Symptom Checklist-25 *(33)*. Scores range from 0 to 100; a higher score indicates more complaints.

†CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

‡SD = standard deviation.

§Two-sided *P* values.

‖Mean raw score of CTC group significantly lower than mean raw score of control group ($P<.05$).

Table 5. Mean raw scores and standard deviations of neuropsychologic tests*

Measurement	Neuropsychologic test	Treatment group† CTC (n = 34) Mean (SD)‡	FEC (n = 36) Mean (SD)	Control (n = 34) Mean (SD)	*P* (F test)§
Attention/concentration	WAIS Digit Span (forward)	12.4 (2.9)	12.7 (2.4)	13.0 (2.5)	.681
	WAIS Digit Span (backward)	9.1 (2.0)	9.6 (2.4)	10.5 (2.4)	.041‖
	WAIS Digit Symbol	53.4 (9.7)	56.3 (11.5)	60.6 (9.2)	.017‖
	Trailmaking A	33.9 (14.0)	34.7 (8.5)	33.1 (0.4)	.835
	D2 (GZ-F score)	384.5 (70.5)	400.8 (62.9)	420.5 (77.1)	.103
Mental flexibility	Stroop color word	39.7 (23.2)	43.0 (32.7)	35.7 (19.1)	.499
	Trailmaking B	71.4 (24.3)	85.7 (30.8)	70.5 (25.0)	.033¶
Speed of information processing	Fepsy visual reaction (dominant)	320.3 (99.3)	280.7 (69.4)	267.8 (41.3)	.011‖
	Fepsy visual reaction (nondominant)	318.7 (124.7)	268.2 (36.5)	266.0 (36.4)	.008‖,#
	Fepsy Binary Choice	434.6 (134.4)	416.9 (75.0)	415.6 (112.2)	.725
	Fepsy Visual Searching	11.9 (3.2)	12.3 (3.0)	11.8 (4.0)	.759
Memory (Verbal)	REY 15 words test recall	48.2 (10.3)	52.0 (8.9)	51.0 (7.5)	.196
	REY 15 words test delayed recall	10.4 (2.9)	11.0 (3.3)	11.3 (1.9)	.347
	REY 15 words test recognition	28.8 (1.9)	28.9 (2.7)	29.5 (1.1)	.269
Memory (Visual)	Complex figure	18.2 (5.6)	20.6 (6.2)	22.0 (5.4)	.028‖
Verbal function	Word fluency	24.9 (5.6)	24.3 (6.2)	27.1 (5.9)	.110
Visuospatial	Complex figure (copy)	34.5 (1.8)	34.9 (1.4)	35.3 (1.1)	.068
Motor function	Fepsy Finger Tapping (dominant)	55.6 (7.7)	57.8 (7.4)	60.7 (9.7)	.041‖
	Fepsy Finger Tapping (nondominant)	49.8 (7.5)	52.4 (6.6)	56.1 (8.6)	.004‖

*See ''Methods'' section for details of individual tests. Lower score means lower performance, except for Trailmaking A and B, Fepsy Visual Reaction, Fepsy Binary Choice, and Fepsy Visual Searching Tests.

†CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

‡SD = standard deviation.

§Two-sided *P* values.

‖Post hoc comparison (Tukey's honestly significant difference test): mean raw score of CTC group significantly lower than mean raw score of control group (two-sided $P<.05$).

¶Post hoc comparison (Tukey's honestly significant difference test): overall difference; there was no significant difference between any two groups.

#Post hoc comparison (Tukey's honestly significant difference test): mean raw score of CTC group significantly lower than mean raw score of FEC group (two-sided $P<.05$).

from the start of the chemotherapy to the time of neuropsychologic testing for medical complications that might affect cognitive functioning, i.e., infections, damage to the liver, etc. No such conditions were found.

Table 6. Percentage of patients with deviant neuropsychologic test scores

No. tests failed (impairment determination)†	Treatment group* CTC (n = 34) No. (%)‡	FEC (n = 36) No. (%)	Control (n = 34) No. (%)
0–2 (not impaired)	23 (68%)	30 (83%)	31 (91%)
⩾3 (impaired)	11 (32%)	6 (17%)	3 (9%)
	Chi-squared test:		*P* = .043§

*CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

†The fifth percentile of the control patients was used as a cutoff point to determine whether a patient was cognitively impaired. The fifth percentile of the control patients corresponded to failure on three or more of the tests. Thus, a score of two standard deviations below the mean of the control group on at least three tests was required for a patient to be classified as cognitively impaired. *See* text for more details.

‡No. = number of patients; % = percent of patients in treatment group.

§Two-sided *P* value.

Neuropsychologic Impairment and Self-Reported Measures

We calculated whether there was a relationship between the overall score of cognitive impairment and the score on the cognitive functioning scale of the EORTC QLQ-C30. The correlation was negligible (Table 7). Furthermore, no relationship was found between the overall score of cognitive impairment and the cognitive problems reported at the interview. A significant relationship was found, however, between the cognitive problems reported at the interview and the cognitive functioning scale of the EORTC QLQ-C30. Additional calculations showed that there was no relationship between the time since last therapy and anxiety and depression on one hand and the overall score of cognitive impairment on the other. A significant relationship was found between the cognitive functioning scale of the EORTC QLQ-C30 and the anxiety and depression subscale of the Hopkins Symptom Checklist. The problems reported at the interview and the anxiety and depression subscale of the Hopkins Symptom Checklist were related. A relationship was also found between the cognitive functioning scale and the emotional functioning scale of the EORTC QLQ-C30. All correlations are displayed in Table 7.

Logistic regression analysis showed that the risk of cognitive impairment was highly elevated for patients in the high-dose chemotherapy group when compared with the patients in the

Table 7. Spearman rank-order correlations of the Overall Score of Cognitive Impairment (OSCI), time since last therapy, and self-reported measures*

	OSCI	EORTC-CF	EORTC-EF	HSCL Anxiety	HSCL Depression	Concentration†	Memory†	Language†	Thinking†
EORTC-CF	−.03	—	—	—	—	—	—	—	—
EORTC-EF	−.05	.39‡	—	—	—	—	—	—	—
HSCL Anxiety	.21	−.44‡	−.71‡	—	—	—	—	—	—
HSCL Depression	.21§	−.47‡	−.71‡	.71‡	—	—	—	—	—
Concentration†	.00	−.79‡	−.33‡	.44‡	.43‡	—	—	—	—
Memory†	.08	−.77‡	−.23§	.34‡	.37‡	.67‡	—	—	—
Language†	.08	−.36‡	−.08	.18	.15	.30‖	.50‡	—	—
Thinking†	.03	−.60‡	−.29‖	.35‡	.32‡	.61‡	.62‡	.29‖	—
Time since last therapy	−.06	−.17	−.03	−.01	−.02	.12	.13	−.07	.04

*EORTC = European Organization for Research and Treatment of Cancer; CF = cognitive functioning scale of the EORTC QLQ-C30 questionnaire; EF = emotional functioning scale of the EORTC QLQ-C30 questionnaire; and HSCL = Hopkins Symptom Checklist-25. *See* text for more details.

†Problems reported at interview.

‡Two-sided $P<.001$.

§Two-sided $P<.05$.

‖Two-sided $P<.01$.

control group (odds ratio [OR] = 8.2; 95% confidence interval [CI] = 1.8–37.7; $P = .006$). When compared with the patients in the standard-dose chemotherapy group, the risk was lower, and the lower bound of the CI just included one (OR = 3.5; 95% CI = 1.0–12.8; $P = .056$). Although the standard-dose chemotherapy group also showed an elevated risk in comparison with the control group, this elevated risk was not statistically significant (OR = 2.4; 95% CI = 0.5–11.5; $P = .287$). The odds ratios were calculated with adjustment for age and education. Adjustment for time since treatment, anxiety, depression, and fatigue did not appreciably alter the risk of being classified as cognitively impaired; these factors, therefore, were not included in the model (Table 8).

Discussion

The aim of this study was to assess the prevalence of cognitive deficits in a group of women receiving adjuvant treatment for high-risk breast cancer and to investigate whether high-dose chemotherapy impaired cognitive functioning more than standard-dose chemotherapy in this patient population. The results indicated that cognitive deficits were substantial in the patients following treatment with adjuvant chemotherapy and hormonal therapy. Furthermore, the patients treated with high-dose chemotherapy had an 8.2-times higher risk of cognitive impairment than the control patients who were not treated with systemic therapy and a 3.5-times elevated risk in comparison with the patients who were treated with standard-dose chemotherapy; however, this latter finding was only of borderline statistical significance. The results were not related to anxiety, depression, fatigue, and the time since treatment. Furthermore, no systematic impaired performance could be detected on any of the separate tests or domains across patients.

Table 8. Risk of cognitive impairment

Treatment group*	Comparison group	Odds ratio†	95% Confidence interval	P‡
CTC	FEC	3.5	1.0–12.8	.056
CTC	Control	8.2	1.8–37.7	.006
FEC	Control	2.4	0.5–11.5	.287

*CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; and control = no adjuvant chemotherapy. *See* ''Methods'' section for definitions of the CTC and FEC chemotherapy regimens.

†Adjusted for age and education.

‡Two-sided *P* values.

A considerable number of patients in both chemotherapy groups reported cognitive problems, whereas, in the control group, only a minority of patients complained about such problems. However, the patients who complained of having problems are not necessarily the same as those who were identified as being cognitively impaired. The correlations between the scores on the cognitive functioning scale of the EORTC QLQ-C30, the complaints reported at the interview, and the impaired caseness scores were negligible. It is a common finding that objective test results and subjective reports of patients about their cognitive functioning are often not related *(15,34,39–42)*. In a recent study by Cull et al. *(15)* among patients with lymphoma, in which the EORTC QLQ-C30 cognitive functioning scale was used, no relationship could be demonstrated between self-reported difficulties of the patients and their performance on objective tests. It was found that subjective reports were more related to anxiety and depression. In our study, a strong relationship between self-reported cognitive problems and psychologic distress was found as well. This finding might imply that complaints of patients about their cognitive functioning are more indicative of emotional distress than of cognitive deficits.

Although in a cross-sectional study it is difficult to determine whether cognitive impairments are related to the chemotherapy or to pre-existing cognitive problems, the results of the patients in our control group, who had stage I breast cancer and who had not been treated with systemic therapy, showed that it is implausible that the elevated risk in the high-dose chemotherapy group derived from pre-existing cognitive problems; there were no differences between the scores of the control group and the scores of healthy reference groups. This result is substantiated by the fact that almost none of the patients stated that their cognitive problems existed before diagnosis. It can be concluded that it is highly unlikely that the cognitive impairments we found are a consequence of being diagnosed as a cancer patient or of surgical and/or radiotherapeutic procedures.

Another explanation for the observed differences in cognitive functioning might be menopausal status. In the literature, there

are some indications that estrogen, by itself, affects cognitive functioning *(43,44)*. In our study, all of the high-risk patients were postmenopausal, except for two who were treated with standard-dose chemotherapy. It is possible, however, that the actual estrogen levels in the chemotherapy groups differed, since high-dose chemotherapy causes chemical castration and the effect of standard-dose chemotherapy on ovarian function may be reversible. Still, we consider it improbable that the cognitive impairments found in this study are hormone mediated rather than a consequence of the effects of cytostatic drugs on the central nervous system; we compared the test results of the premenopausal and postmenopausal patients with stage I breast cancer, and we observed no differences. In theory, it cannot be excluded that the differences observed between the patients with high-risk breast cancer and the control patients might be due, in part, to tamoxifen *(45)*, since the patients treated with chemotherapy received tamoxifen, whereas the control patients did not. The influence of tamoxifen on cognitive function warrants further exploration.

High-dose chemotherapy with autologous bone marrow transplantation or peripheral blood progenitor cell support is rapidly gaining acceptance as a curative treatment option for a number of cancers. The adjuvant treatment of premenopausal women with high-risk breast cancer has become, by far, the most frequent indication for this approach *(46)*, although its efficacy is exclusively based on single-institution phase II studies *(47,48)*. Several large, randomized studies are now in progress, both in the United States and in Europe. None of these studies will, however, yield sufficiently mature data for even a preliminary analysis before 1999. Despite this, adjuvant high-dose chemotherapy has been adopted as the more or less standard treatment for premenopausal women with high-risk breast cancer in parts of the United States *(1,2)*.

Our study is, to our knowledge, the first randomized study in which two chemotherapeutic regimens that differ in intensity have been evaluated with regard to their late central neurotoxicity. Late neurotoxicity of the agents used in this study has not been reported previously, although acute neurotoxicity has been observed in a few patients receiving thiotepa *(49)*. However, the dosages associated with acute neurotoxicity far exceed the dosage used in this study. The fact that the cognitive deficits were observed, on average, 2 years after the last chemotherapy course makes the results of our study of particular clinical significance.

Central neurotoxicity should not be taken lightly, since high-dose adjuvant chemotherapy for cancer aims to achieve long-term survival and should allow patients to regain a socially and professionally acceptable lifestyle after the completion of treatment. Long-term cerebral impairment, even when relatively subtle, may have profound consequences for the daily life of patients *(34,50)*.

On the basis of our findings, which are indicative of neurotoxicity caused by systemic chemotherapy in adult patients, we believe that central neurotoxicity might become a dose-limiting factor in high-dose chemotherapy regimens.

Because the demands for high-dose chemotherapy are likely to increase in the coming years *(46,51)*, the least that can and should be done is the recognition and investigation of central neurotoxicity of specific high-dose regimens before they are introduced into routine clinical practice.

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Notes

[1]Because of the restricted range of the scores and rounding, the fifth percentile cutoff point for the control group includes 9% of the patients.

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