Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients

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Background: Neuropsychological examinations have shown an elevated risk for cognitive impairment 2 years after therapy in breast cancer patients randomized to receive adjuvant high-dose cyclophosphamide, thiotepa, carboplatin (CTC) chemotherapy compared with a non-treated control group of stage I breast cancer patients. Patients randomized to receive standard-dose fluorouracil, epirubicin, cyclophosphamide (FEC) chemotherapy showed no elevated risk compared with controls. However, breast cancer patients treated with conventional cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy showed a higher risk of cognitive impairment. The present study was designed to obtain a greater insight into these long-term neuropsychological sequelae following chemotherapy and their course in time.

Patients and methods: At 4 years post-therapy, 22 of the original 34 CTC patients, 23 of 36 FEC patients, 31 of 39 CMF patients and 27 of 34 control patients were re-examined with neuropsychological tests.

Results: Improvement in performance was observed in all chemotherapy groups, whereas in the control group there was a slight deterioration in test results. A differential attrition was observed among the groups, with a relatively high percentage of initially cognitively impaired patients from the CTC group dropping out due to factors related to disease progression.

Conclusions: The results suggest that cognitive dysfunction following adjuvant chemotherapy in breast cancer patients may be transient. Additional studies are needed to investigate the differential attrition of patients with cognitive impairment.

Key words: breast cancer, chemotherapy, cognitive deficits, late effects, neurotoxicity

Introduction

In cancer patients cognitive decline is increasingly studied as a potential toxic effect of chemotherapy [1]. These neuropsychological manifestations often present a diagnostic problem due to the multiplicity of symptoms and signs. Moreover, several factors may complicate identification of these adverse effects of chemotherapy, such as intracerebral metastasis and toxic effects due to radiation therapy and other drugs [2]. The availability of a substantial number of breast cancer patients who have been treated with adjuvant chemotherapy has provided an opportunity to obtain a better understanding of the possible long-term side effects of cytotoxic treatment on cognitive function. Several confounding factors can be absorbed in the adjuvant setting, as patients are clinically free from disease and have not been treated previously with systemic therapy. Another major advantage of testing this particular population is the fact that these patients are often studied in randomized trials and are followed-up over many years.

In The Netherlands Cancer Institute a series of cross-sectional studies was conducted to investigate the prevalence of cognitive deficit in breast cancer patients who received chemotherapy as part of an adjuvant treatment strategy [3, 4]. The results of these studies showed that breast cancer patients who participated in a randomized trial and who had been treated with high-dose cyclophosphamide, thiotepa, carboplatin (CTC) chemotherapy had a higher risk of late cognitive impairment than the control group of matched primary breast cancer patients not treated with chemotherapy. Patients...
randomized to receive standard-dose fluorouracil, epirubicin, cyclophosphamide (FEC) chemotherapy showed no elevated risk compared with the control group. However, breast cancer patients treated with conventional adjuvant cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy given in routine clinical practice also showed a higher risk of cognitive deficit than the matched control group of primary breast cancer patients not treated with chemotherapy. Although the rate of recovery following onset of any kind of brain damage varies with the patient’s age, and the nature, site and severity of the damage, improvement usually (but not necessarily) takes place in the first 2 years. For example, in the case of neurotoxins, some adverse effects may take a substantial time to evolve, only first appearing years after exposure or aggravating pre-existing central nervous system dysfunction [5].

Because in our previous studies [3, 4] the neuropsychological tests were conducted on average 2 years post-therapy in a cross-sectional manner, it is uncertain whether the observed abnormalities are or are not reversible. This is of importance for patients and their caretakers, and for programming rehabilitation strategies.

No data are available on the course of these late cognitive sequelae of cytotoxic agents, because most studies on this topic have tested their patients on only one occasion post-treatment, with an interval ranging from 2 weeks to a maximum of 3 years [6–19].

The present study aimed to obtain more insight into the long-term neuropsychological sequelae following chemotherapy, and their course over time. Therefore, we re-evaluated the cognitive status of all patients still free of disease who had participated in the previous neuropsychological studies.

Patients and methods

Patients, treatment and results of the first assessment

Three groups of breast cancer patients participated in the previous neuropsychological assessment.

CTC/FEC group

The CTC/FEC group comprised 70 high-risk breast cancer patients who participated in a Dutch national study, conducted by the Netherlands Working Party on Autologous Transplantation in Solid Tumors (NWAST). In this randomized trial, patients (with four or more positive axillary lymph nodes but no other metastases) were treated as follows: following surgery, patients received five courses of FEC chemotherapy (fluorouracil 500 mg/m² i.v., epirubicin 90 mg/m² i.v. and cyclophosphamide 500 mg/m² i.v.), radiation therapy and tamoxifen, 40 mg daily (n = 36). In patients randomized to receive high-dose therapy (n = 34), the fifth course of FEC chemotherapy was replaced by the high-dose regimen CTC (cyclophosphamide 6 g/m² i.v., thiopeta 480 mg/m² i.v. and carboplatin 1.6 g/m² i.v.) with peripheral blood progenitor cell transplantation (PBPC) and granulocyte–macrophage colony-stimulating factor (GM-CSF) support [20].

CMF group

The CMF group comprised 39 breast cancer patients with one, two or three positive axillary lymph nodes treated with conventional chemotherapy in routine clinical practice. The patients received six cycles of CMF chemotherapy (cyclophosphamide 100 mg/m² orally on days 1–14, methotrexate 40 mg/m² i.v. on days 1 and 8, and 5-fluorouracil 600 mg/m² i.v. on days 1 and 8). For a number of patients (n = 20), this chemotherapy was followed by tamoxifen 20 mg daily, in accordance with the protocol of a prospective randomized phase III trial examining the effect of tamoxifen (given sequentially after chemotherapy) on survival and relapse-free survival [21].

Control group

A control group (n = 39) consisting of axillary lymph node-negative breast cancer patients treated either with a mastectomy followed by radiotherapy or with breast conserving surgery followed by radiotherapy. These patients did not receive any systemic therapy and were matched for age and time since therapy to breast cancer patients treated with chemotherapy.

The cognitive status of these patients was evaluated by the use of a battery of standard neuropsychological tests, on average 2 years after completion of treatment. At the time of testing, all patients were clinically free from disease. The results of this first examination can be described as follows: patients in the chemotherapy groups expressed significantly more problems with memory and concentration than the patients in the control group. For each patient, neuropsychological impairment was determined following a strict criterion. To control for the impact on cognitive functioning of being diagnosed as a cancer patient, we compared the results of the chemotherapy patients with the results of stage I breast cancer patients not treated with chemotherapy. It should be noted that there are no differences between the neuropsychological scores of these stage I breast cancer patients and published norms for healthy references groups. Thirty-two per cent of the high-risk patients treated with high-dose CTC chemotherapy, 17% of patients treated with FEC chemotherapy and 9% of patients in the control group were classified as cognitively impaired. In comparison with patients in the control group, patients treated with high-dose CTC chemotherapy appeared to have an 8.2-fold higher risk of cognitive impairment [odds ratio (OR) = 8.2; 95% confidence interval (CI) 1.8–37.7; P = 0.006]. When compared with patients in the standard-dose FEC group, the risk was lower (OR = 3.5; CI 1.0–12.8; P = 0.056); although the standard dose FEC group also showed an elevated risk in comparison with the control group, this elevated risk was not statistically significant (OR = 2.4; CI 0.5–11.5; P = 0.287) [3]. Of the breast cancer patients treated with conventional CMF chemotherapy, 28% exhibited cognitive deficits (OR= 6.4; CI 1.5–27.6; P = 0.013) [4]. For all groups, impairment was seen in various domains of cognitive functioning. The cognitive deficits as assessed by the neuropsychological examination were not associated with depression, anxiety, fatigue and time since therapy, and not related to the subjectively reported cognitive complaints.

Patient enrollment in the second assessment

All patients who participated in the first neuropsychological assessment were eligible for the current follow-up study if they fulfilled the following criteria: (i) no evidence of relapse or metastatic disease; (ii) no history of neurological/psychiatric signs or symptoms that might lead to deviant results; (iii) no use of medication that might lead to deviant results; (iv) no abuse of alcohol or drugs; (v) an interval of at least 1 year from the first neuropsychological assessment. Patients were asked by their physician to
take part in the current sequel of the neuropsychological study. Informed consent was obtained from all patients, according to institutional guidelines. All patients were enrolled and tested from June 1997 to February 1999.

**Measures**

**Neuropsychological tests**

In the present study, the cognitive status of all patients was assessed using the same battery of neuropsychological tests used in the first assessment. The battery was designed to assess functioning across seven cognitive domains: verbal function, memory, attention/concentration, speed of information processing, motor functioning, visuospatial functioning and mental flexibility. The following tests were assessed: Rey Auditory Verbal Learning Test [22, 23]; Complex Figure Test, copy and recall [24, 25]; Digit Span of the Wechsler Adult Intelligence Scale (WAIS) [26]; Digit Symbol of the WAIS [26]; Trailmaking A and B [27]; D2 Test [28]; Stroop Test [29, 30]; Word Fluency subtest from the Dutch Aphasia Society Test [31]; Fepsy Finger Tapping Task [32]; Fepsy Visual Reaction Test [32]; Fepsy Binary Choice Test [32]; Fepsy Visual Searching Test [32]; and Dutch Adult Reading Test [33]. To reduce the risk of practice effect, form II (instead of form I) of the Complex Figure Test was used in the second assessment. All other tests were identical to the first test session. In the original article on cognitive functioning in patients treated with CMF chemotherapy, an additional memory test was included. To compare the CMF patients with patients treated with FEC or CTC chemotherapy, this test was excluded from the analyses.

**Self-reported cognitive problems, health-related quality of life, depression and anxiety**

Patients were interviewed about potential cognitive problems experienced in daily life (memory, attention, thinking, language) [34]. They were asked to indicate on a five-point Likert scale the extent to which these problems in each of these domains occurred in their daily lives (0, not at all; 1, slightly; 2, moderately; 3, quite a bit; and 4, extremely). Health-related quality of life was assessed for all patients with the EORTC QLQ-C30, which consists of five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting) and a general health and quality of life scale [35]. Additional items measure cancer-specific complaints. All patients also completed an anxiety and depression checklist, the Hopkin’s Symptom Checklist [36].

**Data coding, scoring and statistical methods**

Statistical Package for Social Science (SPSS) for Windows, version 10.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses. Because there are differences in overall survival and disease-free survival between breast cancer patients with four or more positive lymph nodes and breast cancer patients with one, two or three positive lymph nodes, analyses were performed separately for these groups [37]. For both patient groups, results were compared with the control group of stage I breast cancer patients of the second assessment. The 5% cut-off corresponded with an impairment of two SD on three or more tests. The exclusion of the recall of the Complex Figure Test did not alter the original criteria for cognitive impairment. Additionally, to examine changes in test scores irrespective of the criteria for cognitive impairment, the mean number of tests in which a patient improved, deteriorated or maintained a stable performance was calculated. A change in performance was defined as a change in a test score of at least one SD, compared with the previous assessment [5, 38].

On the second assessment, between-group differences in social demographic and clinical characteristics were analyzed by use of χ² tests for contingency tables and Student’s t-test. Interview and questionnaire scores were tested for differences between the groups by univariate analysis of variance (ANOVA). Changes in these study measures over time were tested by either the general linear model for repeated measures or by McNemar tests. Relations between subjectively reported complaints on T2 and the total number of tests scored in the impaired range per patient on T2 were examined by Spearman rank order correlations. Also, relations between changes in subjectively reported cognitive complaints and changes in test scores of ≥1 SD were examined by Spearman rank order correlations. A change in a cognitive complaint was defined as a shift from a score of 2 (moderate) or more to a score of 0 or 1 (or vice versa) for each of the domains concerned.

Two separate analyses were performed for the evaluation of the neuropsychological test data: (i) the dichotomous outcome to differentiate between impaired and not-impaired patients; and (ii) the changes in test scores over time irrespective of this classification. First, the classification of cognitive impairment on T2 was tested by use of a multivariate logistic regression model. Whether or not a patient was categorized as cognitively impaired was used as the dependent variable; the independent variables were type of therapy, age, IQ, time since treatment, and anxiety, depression and fatigue on T2. For all groups, predictors of change irrespective of the criterion were investigated by means of linear regression analyses. Potential predictors of change included in this analysis were age, IQ, time since treatment, cognitive, emotional and physical functioning and fatigue as measured with the EORTC QLQ-C30 questionnaire on T1, anxiety and depression as measured with the Hopkin’s Symptom Checklist on T1, cognitive complaints reported at the interview on T1 and the total number of tests in the impaired range per patient on T1. Additionally, univariate and multivariate analyses were performed to investigate potential differences between patients with regard to menopausal status and use of tamoxifen on the classification of cognitive impairment and the changes in cognitive functioning irrespective of this classification.
Table 1. Percentage of patients ineligible at the second assessment due to breast cancer recurrence or refusal to participate

<table>
<thead>
<tr>
<th>Reason for ineligibility</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CTC (T1 = 34)</td>
</tr>
<tr>
<td>Illness</td>
<td>32% (11)</td>
</tr>
<tr>
<td>Refusal</td>
<td>4% (1)</td>
</tr>
</tbody>
</table>

CTC, patients who received high-dose cyclophosphamide, thiotepa, carboplatin; FEC, patients who received standard-dose 5-fluorouracil, epirubicin, cyclophosphamide; CMF, patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil; T1, first neuropsychological test.

Table 2. Sociodemographic and clinical characteristics of the study groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CTC (T2 = 22)</th>
<th>FEC (T2 = 23)</th>
<th>Control (T2 = 27)</th>
<th>P value (CTC/FEC/control)</th>
<th>CMF (T2 = 31)</th>
<th>P value (CMF/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>47.0 (4.8)</td>
<td>50.4 (6.3)</td>
<td>48.8 (5.0)</td>
<td>0.12</td>
<td>50.3 (4.5)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean years since treatment</td>
<td>3.3 (1.1)</td>
<td>3.4 (1.2)</td>
<td>4.6 (1.1)</td>
<td>0.00</td>
<td>3.7 (1.1)</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean years since T1</td>
<td>2.0 (0.6)</td>
<td>1.9 (0.6)</td>
<td>2.1 (0.2)</td>
<td>0.29</td>
<td>2.0 (0.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>102 (12.4)</td>
<td>104 (12.7)</td>
<td>99 (9.0)</td>
<td>0.29</td>
<td>105 (9.4)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CTC, patients who received high-dose cyclophosphamide, thiotepa, carboplatin; FEC, patients who received standard-dose 5-fluorouracil, epirubicin, cyclophosphamide; CMF, patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil; IQ, intelligence quotient; SD, standard deviation; T1, first neuropsychological test; T2, second neuropsychological test.

Results

Sociodemographic and clinical characteristics

Percentages of patients ineligible at the second assessment due to breast cancer recurrence or refusal to participate are given in Table 1. The relative number of patients in the different groups who dropped out due to illness-related factors conforms with the current expectation of recurrence-free survival time in (high-risk) primary breast cancer [37].

Table 2 gives the sociodemographic and clinical characteristics of the study sample participating on T2.

FEC/CTC group. There were no significant differences between the FEC, CTC and control group for age and premorbid IQ, as measured with the Dutch Adult Reading Test [33]. For the patients treated with chemotherapy, the time since completion of therapy was 3.5 years on average. Patients in the control group were free from treatment on average 1 year longer than the patients in the two chemotherapy groups (P = 0.00). For all patients, the time since the first neuropsychological assessment (T1) was 2 years on average. At the time of the second assessment (T2), all patients treated with CTC chemotherapy were postmenopausal; two patients treated with FEC chemotherapy were premenopausal, as defined by the occurrence of regular menstrual cycles, and three patients reported irregular menstrual cycles. Of the 22 CTC patients, 15 had finished hormonal treatment and seven patients still used tamoxifen (40 mg/day). In the FEC group, 19 of 23 patients had completed hormonal treatment and four patients still received tamoxifen.

CMF group. There were no differences between the CMF group and the control group for age and time since the first neuropsychological testing. Patients in the CMF group were tested within a shorter time interval since completion of treatment than patients in the control group (P = 0.00). The interval from diagnosis of the primary tumor was not different between the groups (P = 0.85). For both groups, the time since the first neuropsychological testing was 2 years on average. Patients in the control group had lower IQ scores (as measured with the Dutch Adult Reading Test [23]) than the patients in the CMF group (P = 0.02). Of the 31 CMF patients participating on T2, 28 were postmenopausal and three patients reported irregular menstrual cycles. At the time of the second testing 11 patients used tamoxifen (40 mg/day), nine had completed tamoxifen treatment and 11 patients never received (by randomization) hormonal treatment.

Of the women in the control group with stage I breast cancer, 16 were postmenopausal and 11 patients were premenopausal. No control patient received any systemic therapy.

Self-reported cognitive dysfunction, health-related quality of life, anxiety and depression

The self-reported problems can be summarized as follows.
**CTC/FEC group.** On T1, patients in the FEC and CTC group reported significantly more concentration, memory and thinking problems than patients in the control group. On T2, no significant differences in reported complaints were seen between the groups. On T1, patients treated with high-dose CTC chemotherapy reported more complaints on the social, role, physical and cognitive functioning scale of the EORTC QLQ-C30 than the control group. Also, patients in the high-dose group reported more fatigue and depression than the control group. There were no differences between the patients treated with FEC chemotherapy and control patients not treated with chemotherapy at the first assessment. On T2, no differences were observed between the three groups on any of these outcome measures; on all measures, the chemotherapy groups improved to the level of the control group (data not shown).

**CMF group.** On T1, patients treated with CMF chemotherapy reported more memory and concentration problems than the control patients at the interview. They also reported lower physical and cognitive functioning than the control patients on the quality of life questionnaire. Moreover, patients treated with CMF chemotherapy had higher scores (i.e. stronger complaints) on the depression scale than the control patients. On T2, these differences remained significant. An additional difference was observed on the anxiety subscale: patients treated with CMF chemotherapy had higher scores (i.e. more complaints) than the control group (data not shown).

**Neuropsychological test results**

**Percentage of individual patients meeting the criteria for cognitive impairment.** Table 3 gives data on the different groups that met the criteria for cognitive impairment on the first assessment for the entire sample (T1), on the first assessment for patients participating in both examinations (T1s) and on the second assessment (T2).

On T2, no significant differences were found in the neuropsychological follow-up assessment between the high-dose CTC chemotherapy group, the standard-dose FEC chemotherapy group and the control group with regard to the classification of patients exhibiting cognitive deficits ($P = 0.87$). Also, on T2 no differences were seen between the patients treated with CMF chemotherapy and the control group ($P = 0.83$).

Trends of the distributions of patients meeting the criteria for cognitive impairment are reported here for descriptive purposes.

**CTC/FEC group.** In the CTC chemotherapy group, the number of patients classified as impaired on T2 was smaller than the number of patients in this selective group on the first assessment (T1s) [14% ($n = 3$) versus 23% ($n = 5$)]. For the patients treated with FEC chemotherapy, the percentage of impaired cases was more or less stable over time [13% ($n = 3$) on T1s versus 9% ($n = 2$) on T2].

**CMF group.** In the CMF chemotherapy group, the number of patients classified as cognitively impaired on the first assessment...
ment (T1s) was greater than on T2 [26% (n = 8) on T1s versus 13% (n = 4) on T2].

**Control group.** Two patients in the control group classified as not impaired on T1s had become impaired on T2 [4% (n = 1) on T1s versus 11% (n = 3) on T2].

**Shifts in meeting the criteria for impairment over time.** Table 4 gives the individual changes for the different groups over time. As can be inferred from this table, changes in the distribution of patients classified as impaired/intact differed from group to group. None of the changes reached significance.

**Factors contributing to the classification of cognitive impairment.**

**CTC/FEC group.** Logistic regression analysis showed that the risk of being classified as cognitively impaired on T2 was not higher for the high-risk patients treated with either high-dose CTC chemotherapy or standard-dose FEC chemotherapy compared with control patients not treated with chemotherapy. Age, IQ and depression were included in the model as factors relating to the impairment risk (age, P = 0.03; depression, P = 0.00; IQ, P = 0.03). Time since treatment, anxiety and fatigue made no significant contribution to the model.

**CMF group.** The patients treated with CMF chemotherapy showed no elevated risk for cognitive impaired compared with control patients not treated with chemotherapy. Among the variables potentially contributing to the model, solely age was related to the classification into the categories impaired versus not impaired (P = 0.00).

**Changes over time irrespective of the criteria for impairment.** For each patient the mean number of tests was calculated on which the patient improved (defined as an improvement of ≥1 SD), deteriorated (defined as a decline of ≥1 SD) or had stable performance (defined as improvement or decline <1 SD) irrespective of the criteria for the classification of cognitive impairment. Additionally, the ‘relative change’ was calculated by subtracting the number of tests on which the patient deteriorated from the number of tests on which the patient improved. The results of this analysis are given in Table 5.

**Table 4. Individual changes over time in the study groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T2</th>
<th>Intact [% (n)]</th>
<th>Impaired [% (n)]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1s</td>
<td>CTC</td>
<td>68 (15)</td>
<td>9 (2)</td>
<td>0.687</td>
</tr>
<tr>
<td></td>
<td>}</td>
<td>18 (4)</td>
<td>5 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>}</td>
<td>87 (20)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>}</td>
<td>4 (1)</td>
<td>9 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>FEC</td>
<td>71 (22)</td>
<td>3 (1)</td>
<td>0.219</td>
</tr>
<tr>
<td></td>
<td>}</td>
<td>16 (5)</td>
<td>10 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMF</td>
<td>85 (23)</td>
<td>11 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>}</td>
<td>4 (1)</td>
<td>–</td>
<td>0.625</td>
</tr>
<tr>
<td>Control</td>
<td>Intact</td>
<td>85 (23)</td>
<td>11 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>4 (1)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

aS, patients on the first neuropsychological test (T1) who also participated in the follow-up assessment (T2). CTC, patients who received high-dose cyclophosphamide, thiotepa, carboplatin; FEC, patients who received standard-dose 5-fluorouracil, epirubicin, cyclophosphamide; CMF, patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.

**Table 5. Individual changes over time irrespective of the criteria for impairment**

<table>
<thead>
<tr>
<th>Mean number of tests</th>
<th>Treatment</th>
<th>CTC (T2 = 22)</th>
<th>FEC (T2 = 23)</th>
<th>Control (T2 = 27)</th>
<th>P value (CTC/FEC/control)</th>
<th>CMF (T2 = 31)</th>
<th>P value (CMF/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>13.5</td>
<td>13.1</td>
<td>13.4</td>
<td>0.78</td>
<td>14.0</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>2.9</td>
<td>3.0</td>
<td>2.1</td>
<td>0.19</td>
<td>2.6</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td>1.5</td>
<td>1.8</td>
<td>2.5</td>
<td>0.12</td>
<td>1.4</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Improvement – deterioration</td>
<td>1.4</td>
<td>1.2</td>
<td>–0.3</td>
<td>0.07</td>
<td>1.2</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

aStable, improvement or decline <1 SD; improvement, improvement of ≥1 SD; deterioration, decline of ≥1 SD.

CTC, patients who received high-dose cyclophosphamide, thiotepa, carboplatin; FEC, patients who received standard-dose 5-fluorouracil, epirubicin, cyclophosphamide; CMF, patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.
CTC/FEC group. Similar to the evaluation of individual patients following the criterion, based on this method it can be concluded that the patients treated with CTC chemotherapy showed an improvement in test scores (relative improvement on 1.4 tests). For the patients treated with FEC chemotherapy, a similar rate of relative improvement was observed (1.2 tests).

CMF group. For the CMF group, the relative improvement was also 1.2 tests. This result is in concordance with the trend observed in the evaluation of the classification of cognitively impaired versus intact.

Control group. Patients in the control group showed a slight deterioration, i.e. the number of tests on which patients deteriorated was higher than the number of tests on which the patients improved (control = −0.3). The deterioration was in concordance with the changes seen in the distribution of patients defined as cognitively impaired/intact according to the criterion.

Univariate analyses showed that the relative improvement in the FEC/CTC group compared with the relative change in cognitive functioning in the control group approached significance ($P = 0.07$). Compared with the control group, the relative improvement in patients treated with CMF chemotherapy did reach significance ($P = 0.05$).

Factors contributing to change irrespective of the classification. A linear regression model was used to investigate which factors were associated with the relative changes.

CTC/FEC group. Of the variables, type of therapy, time since treatment, age, IQ, anxiety, depression and fatigue, only type of therapy and depression were related to change (CTC, $P = 0.04$; FEC, $P = 0.03$; depression, $P = 0.04$).

CMF group. Only the type of therapy was related to the changes observed for the CMF group compared with the control group (CMF, $P = 0.04$).

Predictors of change over time irrespective of the classification. To examine the existence of factors predicting improvement in neuropsychological functioning over time, a linear regression analysis was performed. Performance on T1 based on the total number of tests scored in the impaired range, age, IQ, time since treatment, cognitive functioning, emotional functioning, fatigue, anxiety, depression and time since treatment were examined as covariates for their potential influence on changes in neuropsychological functioning (measured by the relative improvement according to one SD). For all groups, the total number of tests scored in the impaired range on T1 was related to the relative improvement, i.e. a high number of tests scored in the impaired range on T1 is a predictor for the rate of improvement on T2 (CTC/FEC group, $P = 0.00$; CMF group, $P = 0.00$; control group, $P = 0.02$).

Relation between neuropsychological test results and subjective complaints

For all groups, the potential relationship was investigated between the total number of tests scored in the impaired range per patient on T2 and a number of subjective measures including depression, anxiety, fatigue, cognitive functioning and emotional functioning as reported on T2. In concordance with the findings on T1, the correlations between the objective test results and the subjective measures were low (range 0.19–0.22). It was also calculated whether there was a relationship between the changes in complaints on cognitive functioning (as reported at the interview) and the changes in the neuropsychological test scores. For all groups, this relation was negligible (data not shown).

Tamoxifen therapy, menopausal status and neuropsychological test results

CTC/FEC group. For those patients treated with CTC or FEC chemotherapy, there were no differences between patients who completed tamoxifen therapy ($n = 34$) and those still using tamoxifen ($n = 11$) for the total number of tests scored in the impaired range, the percentage of patients classified as cognitively impaired and the mean number of tests changes according to one SD on T2.

CMF group. There were no differences found between patients treated with CMF chemotherapy who completed tamoxifen therapy ($n = 9$), those still on tamoxifen therapy ($n = 11$) and those who never used tamoxifen ($n = 11$) for any of the neuropsychological test outcomes.

Control group. There were significant differences in neuropsychological test outcomes between the patients in the control group who were premenopausal ($n = 11$) and those who were postmenopausal ($n = 16$), with the postmenopausal patients performing worse. These differences might be explained by the significant difference in age between the two groups (mean age premenopausal patients, 46 years; mean age postmenopausal patients, 52 years; $P = 0.00$).

Lost to follow-up itemized by cognitively impaired versus not impaired

Table 6 gives the percentage of patients per group who participated in the second assessment (T2), who were lost to follow-up due to relapse or death, and who refused further testing, itemized by the classification impaired/intact on T1.

CTC/FEC group. For the high-dose CTC group, 45% of the patients classified as cognitively impaired on T1, could not participate on T2 due to relapse or death; for the standard-dose FEC group, this percentage was lower (33%).
None of the CMF patients initially classified as cognitively impaired were lost to follow-up due to illness or death.

A similar pattern to that of the CMF group was observed. None of the differences in impaired or intact dropouts between the groups reached significance.

Finally, to examine whether variables assessed during the first neuropsychological examination were related to disease progression, survival analyses were performed. For this purpose, the medical records of all patients who participated on T1 were checked for disease recurrence at the time point of April 2001, i.e. 26 months after the last follow-up assessment. Of the 34 patients treated with CTC chemotherapy, 15 eventually relapsed (which is an additional four patients compared with T2). Of the 36 patients treated with FEC chemotherapy, 19 patients relapsed (compared with 10 patients on T2). Of the 39 CMF patients, 10 relapsed (compared with six on T2). Of 34 patients in the control group, four patients were not eligible on T2 due to disease progression, and an additional two patients relapsed since that time. The finding that the percentage of impaired versus not impaired patients who were not eligible for the second assessment due to disease progression was not comparable across the treatment groups remained applicable. Again, 47% of CTC patients classified as cognitively impaired on T1 relapsed or died, compared with 21% of impaired cases in the FEC group and 10% of impaired patients in the CMF group. None of the control patients initially classified as cognitively impaired relapsed or died.

Independent predictors of disease progression were examined using the Cox regression model. Time to progression was determined from the first neuropsychological examination. Patients who were free from disease at the time point of April 2001 were censored. Analyses were performed for the chemotherapy groups only, because the number of events (i.e. disease progression) was too small in the control group. Covariates examined were as follows: (i) age and IQ; (ii) neuropsychological test outcomes (i.e. classification into the category of cognitively impaired on T1 and performance on T1 based on the total number of tests scored in the impaired range); and (iii) subjective complaints on cognitive functioning (i.e. complaints reported at the interview and on the cognition scale of the quality of life questionnaires and subjective complaints on anxiety, depression, fatigue and physical functioning).

For the CTC/FEC group, the only variables that approached significance were subjective complaints on cognitive functioning as reported at the interview ($P = 0.09$) and classification into the category of cognitively impaired on T1 and performance on T1 based on the total number of tests scored in the impaired range; and (ii) subjective complaints on cognitive functioning (i.e. complaints reported at the interview and on the cognition scale of the quality of life questionnaires and subjective complaints on anxiety, depression, fatigue and physical functioning).

For the CMF group, complaints on physical functioning as measured with the quality of life questionnaire were a significant predictor for time to progression ($P = 0.03$).

### Discussion

The present study is a continuation of two earlier examinations, in which cognitive impairment was found in a number of breast cancer patients treated with adjuvant chemotherapy, 2 years after completion of treatment. In this second neuropsychological assessment (T2) the breast cancer patients were tested with an additional 2 years test–retest interval, i.e. this study took place 4 years after completion of therapy.

The rationale for this second cognitive assessment is the lack of knowledge about the long-term sequelae and the reversibility of the potential neurotoxic effects of cytotoxic treatment on cognitive functioning.

The picture emerging from this retest is not simple. Two methods were used to analyze the follow-up data: we
constructed a dichotomous outcome to differentiate between impaired and non-impaired patients, and we studied changes in test scores over time irrespective of this classification. Results from both methods indicate an improvement in test performance for all chemotherapy groups. For the control group, a slight deterioration of test results was observed. The best predictor of improvement in neuropsychological test scores over time was to be the number of tests scored in the impaired range on the first assessment. Whereas there were no significant differences in self-reported complaints on cognitive functioning between the CTC/FEC group and the control patients; patients treated with CMF chemotherapy expressed significantly more cognitive problems in daily life than the control group. Similar to the findings of the first examination, no clear relationship was found between test performance on the one hand and anxiety, depression, fatigue and self-reported complaints of cognitive functioning on the other. In conclusion, 4 years after completion of treatment, we could not demonstrate any of the previously observed differences in cognitive functioning between patients treated with high-dose chemotherapy, patients treated with various regimes of conventional doce chemotherapy and patients who received no systemic therapy for breast cancer.

Our study is clearly limited by a number of factors, the most important being the small power. One of the problems common to all cohort studies is the selection of subjects. In follow-up studies the probability of the event of interest occurring may be strongly related to how the sample was originally obtained, but the main difficulty in such studies is loss to follow-up.

Besides the problem of loss of patients due to refusal or disease progression, our study is also complicated by the inevitable differences in length of survival between the high-risk patients with four or more positive lymph nodes (CTC and FEC group), patients with less than four positive lymph nodes (CMF group) and patients with no metastases to the lymph nodes (control group). Moreover, the fact that the percentage of impaired versus intact cases lost to follow-up is not consistent among the groups still applied, with the relatively high percentage of impaired cases relapsing in the CTC group still manifest. Among the variables examined for their potential relation to time to progression in the CTC/FEC group, classification into the category impaired approached significance, and this relationship was strongest for the CTC group. For the CMF group, the sole factor related to progression was physical functioning.

Is there an explanation for the apparent relation between poor test performance and disease progression in the CTC group? It could be hypothesized that cognitive impairment might not in fact be the result of treatment, but an early expression of disease progression. This is, however, unlikely, as the relationship between cognitive impairment and disease progression was only noticed for the patients treated with CTC chemotherapy, and not for those treated with either FEC or CMF chemotherapy. No simple explanation emerges for the unexpected selective attrition of impaired patients from the CTC group, and the possibility that this observation is the result of chance cannot be excluded.

Apart from the limitations due to small sample size and differential attrition, some remarks on methodology are necessary. First, intrinsic difficulties are associated with the psychometric properties of the neuropsychological tests. Repeated administrations of neuropsychological tests can yield varying results in patients without the existence of a true change in the cognitive status of these patients. Moreover, less than perfect reliability of the instruments used may also have contributed to this phenomenon. In our model, although we controlled for several confounding factors such as age, IQ and time since treatment for the prediction of change, specific test features such as reliability and stability that may affect level of performance in a test–retest situation were not included.

Omission of these factors can be justified because normative data on estimated test–retest change scores among standardized samples are lacking for all neuropsychological instruments, and the use of retest data of our own control group of breast cancer patients would have been inaccurate for this purpose due to the small sample size. The lack of information on base-rate test–retest change scores is an additional reason for caution in interpreting the results.

Secondly, in repeated neuropsychological examinations, an overall pattern of test susceptibility to practice effects generally emerges [5]. As a consequence, the improvement observed in the patients treated with chemotherapy could simply reflect a significant degree of practice. However, besides the plausibility of a positive carryover effect of learning and previous exposure after a test–retest interval of 2 years, practice alone does not seem to be a reasonable justification for the improvement noticed. In our study we tested a group of breast cancer patients for whom chemotherapy was not required. This group was included to enable an optimal interpretation of test scores and changes in patients treated with chemotherapy. If the performance of the control group had exhibited a similar degree of improvement to that observed in
the chemotherapy groups, a practice effect would have been likely. This proved not to be the case, as the test scores of the control group slightly deteriorated, making the improvement of the chemotherapy group even more pronounced, and thereby reducing the likelihood of a practice bias.

The possibility that the main result of our study, i.e. that the performance of patients in the chemotherapy groups improved whilst that of the control group slightly deteriorated, can be explained as a statistical phenomenon called regression to the mean cannot be excluded. As indicated previously, our data are prone to some amount of measurement error. However, the fact that extreme scores regress toward the mean does not necessarily lead to the conclusion of an actual homogenization process; it may equally imply that scores are less than 100% reliable. On the basis of the current data we believe that the only conclusion to be drawn with certainty is that none of the previously observed differences on T1 in cognitive functioning between the groups can be shown on T2.

When taking the observed changes in the groups as a reflection of true changes, how can the pattern found be interpreted? It is possible that the initially adverse effects of chemotherapy on cognitive functioning found in a substantial number of patients smooth out in the long term. This is in contrast to other adverse effects of cancer treatment known to cause delayed neurotoxicity of the central nervous system, which often gradually progress years after therapy.

An alternative explanation could be found in the role of tamoxifen therapy. A recent topic of much debate is the effect of estrogen on cognitive functioning. Whereas some report a beneficial effect of exogenous estrogen use on cognitive functioning [39] and a relationship between lower endogenous estrogen levels and cognitive decline [40], others do not support these findings [41], or even report opposite effects [42]. A recent study on tamoxifen suggested that its use may adversely affect cognition, while past users and those who had never used tamoxifen did not differ in their cognitive performance [43]. In the present study, post hoc comparisons showed no differences in any of the neuropsychological outcome measures between patients who completed tamoxifen therapy, those who were still on tamoxifen therapy and those who had never used tamoxifen. Although the number of patients in the different subgroups is low, it is unlikely that the improvement seen in the chemotherapy groups is due to the completion of tamoxifen therapy in a number of patients.

In conclusion, in spite of the discussed limitations of the present study, the results show that, after initial impairment of cognitive functioning, these deficits improve 4 years post therapy. This suggests that neurocognitive dysfunction following adjuvant chemotherapy in breast cancer patients may be transient, a finding of major importance for this group of patients. Observations related to the differential attrition of patients with neuropsychological impairment highlight a number of challenges for future research on the late effects of cancer treatment on cognitive functioning.

References

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