Cognitive functioning following chemotherapy: a study in breast cancer patients
Schagen, S.B.

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Chapter 7

Late Effects of Adjuvant Chemotherapy on Cognitive Function: a Follow-up Study in Breast Cancer Patients

Schagen SB, Muller MJ, Boogerd W, Rosenbrand RM, van Rijn D, Rodenhuis S, van Dam FSAM. Accepted for publication in Annals of Oncology
Abstract

Background: Neuropsychological examinations have shown an elevated risk for cognitive impairment two years after therapy in breast cancer patients randomized to receive adjuvant high-dose CTC (cyclophosphamide, thiotepa, carboplatin) chemotherapy compared to a non-treated control group of stage 1 breast cancer patients. Patients randomized to receive standard-dose FEC (5-fluorouracil, epidoxorubicin, cyclophosphamide) chemotherapy showed no elevated risk compared to the controls. However, breast cancer patients treated with conventional CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy showed a higher risk of cognitive impairment. The present study was designed to obtain more insight in these long-term neuropsychological sequelae following chemotherapy and their course in time.

Methods: At 4 years post therapy, 22 of the original 34 CTC patients, 23 of the 36 FEC patients, 31 of the 39 CMF patients, and 27 of the 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.

Conclusion: The results show an improvement of cognitive deficits four years post therapy. It is suggested 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.

Introduction

In cancer patients cognitive decline is increasingly studied as a potential toxicity 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 central nervous system metastasis, toxic effects due to radiation therapy and use of 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 these possible long-term side-effects of cytotoxic treatment on cognitive functioning. Several confounding factors can be absorbed in the adjuvant setting, as patients are clinically free of 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.
Follow-up of late effects of chemotherapy on cognitive function

In the Netherlands Cancer Institute a series of cross-sectional studies was conducted to investigate the prevalence of cognitive deficits 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 CTC (cyclophosphamide, thiotepa, carboplatin) 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 FEC (5-fluorouracil, epirubicin, cyclophosphamide) chemotherapy showed no elevated risk compared with the control group. However, breast cancer patients treated with conventional adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy given in routine clinical practice also showed a higher risk of cognitive deficits 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 two 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 is aimed to obtain more insight in 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.

Methods

Patients, Treatment and Results of the First Assessment

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

1. 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 4 or more positive axillary lymph nodes but no other metastases) were treated as follows:
following surgery, patients received five courses of FEC chemotherapy (5-fluorouracil 500 mg/m² intravenously, epirubicin 90 mg/m² intravenously and cyclophosphamide 500 mg/m² intravenously), 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 intravenously, thiotepa 480 mg/m² intravenously and carboplatin 1.6g/m² intravenously) with peripheral blood progenitor cell transplantation (PBPC), and GM-CSF support.

2. CMF group: comprised 39 breast cancer patients with 1-3 positive axillary lymph nodes treated with conventional chemotherapy in routine clinical practice. The patients received 6 cycles of CMF chemotherapy (cyclophosphamide 100 mg/m² orally on days 1-14, methotrexate 40 mg/m² intravenously on days 1 and 8, and 5-fluorouracil 600 mg/m² intravenously 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.

3. 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 study samples represented consecutive series of patients. At the time of testing, all patients were clinically free of disease. The cognitive status of the patients was evaluated by use of a battery of standard neuropsychological tests. Additionally, all patients were interviewed with regard to cognitive problems experienced in daily life. The average time since completion of the last therapy was 2 years. 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. Following this criterion, 32% of the high-risk patients treated with high-dose CTC chemotherapy was classified as cognitively impaired compared with 9% of the control group (OR 8.2 P = .006, CI = 1.8-37.7). When compared with high-risk patients the risk was lower in the standard-dose FEC group (OR 3.5 P = .056, CI = 1.0-12.8); 17% of this standard-dose group also showed cognitive deficits, but this elevated risk was not significant (odds ratio 2.4 P = .287, CI = 0.5-11.5). Of the breast cancer patients treated with conventional CMF chemotherapy, 28% exhibited cognitive deficits (OR 6.4 P = .013, CI = 1.5-27.6). 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: 1) no evidence of relapse or
Follow-up of late effects of chemotherapy on cognitive function

metastatic disease; 2) no history of neurologic/psychiatric signs or symptoms that might lead to deviant results; 3) no use of medication that might lead to deviant results; 4) no abuse of alcohol or drugs; 5) interval of at least one 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 between June 1997 and 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 7 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, Complex Figure Test: copy and recall, Digit Span of the Wechsler Adult Intelligence Scale (WAIS), Digit Symbol of the WAIS, Trailmaking A and B, D2 Test, Stroop Test, Word Fluency subtest from the Dutch Aphasia Society Test, Fepsy Finger Tapping Task, Fepsy Visual Reaction Test, Fepsy Binary Choice Test, Fepsy Visual Searching Test, Dutch Adult Reading Test. 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.

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). 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, 4 = extremely). Health-related quality of life was assessed for all patients with the EORTC QLQ C-30, which consists of 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales (fatigue, pain, nausea and vomiting) and a general health and quality of life scale. Additional items measure cancer-specific complaints. All patients also completed an anxiety and depression checklist, the Hopkins Symptom checklist.

Data coding, scoring and statistical methods

The Statistical Package for Social Science (SPSS) WINDOWS 10.0 was used for the statistical analyses. Because there are differences in overall survival and disease-free survival between breast cancer patients with 4 or more positive lymph nodes and breast cancer patients with 1,2 or 3 positive lymph nodes, analyses were performed separately for these groups. For both patient groups, results were compared with the control group of stage I breast cancer patients not treated with chemotherapy. Data from the questionnaires were converted to scores according to standard scoring rules. For the interview on cognitive problems in daily
life, only a score of 2 (moderate) or more for the domain concerned was considered as a complaint. To compare scores on neuropsychological tests at a comparable level of measurement, the raw neuropsychological tests scores were converted to standard scores (z-scores), by using the mean test scores of patients not treated with chemotherapy as a reference. To reduce the risk of practice effects, form I of the Complex Figure test used in the first assessment (T1), was replaced by form II in the second testing (T2). Because the recall of form II is known to be considerably easier than form I, we excluded the scores of the recall of Complex Figure test in the analyses for both assessments. For each patient, the number of tests was calculated for which a patient scores in the impaired range (a score of 2 standard deviations (SD) below the mean of the reference group was considered as impaired). Subsequently, a cutoff of 5% of the number of impaired tests of the control group was applied to distinguish between disturbed and unaffected cognitive functioning. Based on this distribution, each patient could be classified as cognitively intact or impaired.

The scores of the control group on the first assessment were used as the standard against which all data were measured, including the scores of the control patients of the second assessment. The 5% cutoff corresponded with an impairment of 2 SD on 3 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 on 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 1 SD, compared to the previous assessment.

On the second assessment, between group differences in social demographic and clinical characteristics were analyzed by use of chi-square 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: (1) the dichotomous outcome to differentiate between impaired and not-impaired patients, and (2) 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 variable was of type of therapy. Age, IQ, time since treatment, and anxiety, depression and fatigue on T2 were included as potential factors in the model. Second, mean changes in test scores irrespective of the classification on T2
were tested for differences between treatment groups in a linear regression model with the following covariates: age on T2, 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 Hopkins 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.

Results

Patient Accrual

**CTC/FEC group:** of the 34 high-risk breast cancer patients randomized to receive high-dose CTC chemotherapy, who were clinically free of disease at the time of the first neuropsychological assessment, 11 patients (32%) relapsed and one patient (4%) declined participation. Ten of the 36 high-risk patients (28%) treated with standard-dose FEC chemotherapy relapsed, and 3 (11%) declined to participate. **CMF group:** of the original sample of 39 breast cancer patients treated with the conventional CMF chemotherapy 6 (15%) were not evaluable for cognitive functioning as a result of recurrence of the disease, and 2 patients (6%) did not want to cooperate. **Control group:** 2 of the 34 control patients (6%) relapsed, and 5 patients (16%) declined to participate in the follow-up assessment. Percentages of attrition 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>
<thead>
<tr>
<th>Ineligible due to:</th>
<th>CTC (T1=34)</th>
<th>FEC (T1=36)</th>
<th>Control (T1=34)</th>
<th>CMF (T1=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness</td>
<td>32% (11)</td>
<td>28% (10)</td>
<td>6% (2)</td>
<td>15% (6)</td>
</tr>
<tr>
<td>Refusal</td>
<td>4% (1)</td>
<td>11% (3)</td>
<td>16% (5)</td>
<td>6% (2)</td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiotepa, carboplatin. FEC: patients who received standard-dose 5-fluorouracil, epidoxorubicin, cyclophosphamide. CMF: patients who had received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.
Sociodemographic and Clinical Characteristics

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, the CTC and the control group for age and premorbid IQ, as measured with the Dutch Adult Reading test. For the patients treated with chemotherapy, the time since completion of therapy was on average 3.5 years. Patients in the control group were on average one year longer free from treatment than the patients in the two chemotherapy groups ($P = .00$). For all patients, the time since the first neuropsychological testing (T1) was on average 2 years. At the time of the second testing (T2), all patients treated with CTC chemotherapy were postmenopausal; 2 patients treated with FEC chemotherapy were premenopausal as defined by the occurrence of regular menstrual cycles, and 3 patients reported irregular menstrual cycles. Of the 22 CTC patients, 15 had finished hormonal treatment and 7 patients still used tamoxifen (40 mg/day). In the FEC group, 19 of the 23 patients had completed hormonal treatment and 4 patients still received tamoxifen.

### Table 2. Sociodemographic and clinical characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>CTC (T2=22)</th>
<th>FEC (T2=23)</th>
<th>Control (T2=27)</th>
<th>$P$-value (ctc/fec/contr)</th>
<th>CMF (T2=31)</th>
<th>$P$-value (cmf/contr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, Yr (SD)$^a$</td>
<td>47.0 (4.8)</td>
<td>50.4 (6.3)</td>
<td>48.8 (5.0)</td>
<td>.12</td>
<td>50.3 (4.5)</td>
<td>.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>.00</td>
<td>3.7 (1.1)</td>
<td>.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>.29</td>
<td>2.0 (0.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Premorbid IQ$^b$</td>
<td>102 (12.4)</td>
<td>104 (12.7)</td>
<td>99 (9.0)</td>
<td>.29</td>
<td>105 (9.4)</td>
<td>.02</td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiotepa, carboplatin. FEC: patients who received standard-dose 5-fluorouracil, epidoxorubicin, cyclophosphamide. CMF: patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.

$^a$ SD: standard deviation.

$^b$ IQ: Intelligence quotient.

**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 ($P = .00$). The interval from diagnosis of the primary tumor was not different between the groups ($P = .85$). For both groups, the time since the first neuropsychological testing was on average 2 years. 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 ($P = .02$). Of the 31 CMF patients participating on T2, 28 were postmenopausal and 3 patients reported irregular menstrual cycles. At the time of the second testing 11 patients used tamoxifen (40 mg/day), 9
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 are given in Table 3. **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.

**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.

**Neuropsychological test results**

*Percentage of individual patients meeting the criteria for cognitive impairment*

Table 4 gives data on the different groups who 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 (T1 s), 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 ($P = .87$) Also, on T2 no differences were seen between the patients treated with CMF chemotherapy and the control group ($P = .83$).
### Table 3. Self-reported complaints by the patients in each group

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Treatment</th>
<th>CTC</th>
<th>FEC</th>
<th>Control</th>
<th>P-value</th>
<th>CMF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n=34)</td>
<td>(n=36)</td>
<td>(n=34)</td>
<td>ctc/fec/</td>
<td>(n=39)</td>
<td>cmf/contr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=22)</td>
<td>(n=23)</td>
<td>(n=27)</td>
<td>contr</td>
<td>(n=31)</td>
<td></td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td>M1</td>
<td>38%</td>
<td>31%</td>
<td>6%</td>
<td>.006</td>
<td>31%</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>32%</td>
<td>30%</td>
<td>7%</td>
<td>.064</td>
<td>26%</td>
<td>.064</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>32%</td>
<td>13%</td>
<td>11%</td>
<td>.130</td>
<td>19%</td>
<td>.387</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td>M1</td>
<td>32%</td>
<td>28%</td>
<td>3%</td>
<td>.006</td>
<td>21%</td>
<td>.022</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>18%</td>
<td>30%</td>
<td>4%</td>
<td>.040</td>
<td>19%</td>
<td>.068</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>18%</td>
<td>17%</td>
<td>11%</td>
<td>.746</td>
<td>29%</td>
<td>.093</td>
</tr>
<tr>
<td><strong>Thinking</strong></td>
<td>M1</td>
<td>21%</td>
<td>11%</td>
<td>0%</td>
<td>.022</td>
<td>8%</td>
<td>.099</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>10%</td>
<td>9%</td>
<td>0%</td>
<td>.280</td>
<td>7%</td>
<td>.179</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>9%</td>
<td>4%</td>
<td>7%</td>
<td>.816</td>
<td>13%</td>
<td>.493</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>M1</td>
<td>12%</td>
<td>11%</td>
<td>3%</td>
<td>.351</td>
<td>8%</td>
<td>.373</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>5%</td>
<td>9%</td>
<td>4%</td>
<td>.722</td>
<td>10%</td>
<td>.360</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>.988</td>
<td>13%</td>
<td>.213</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>M1</td>
<td>19</td>
<td>14</td>
<td>14</td>
<td>.255</td>
<td>16</td>
<td>.072</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>17</td>
<td>15</td>
<td>12</td>
<td>.384</td>
<td>17</td>
<td>.191</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>.268</td>
<td>16</td>
<td>.013</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>M1</td>
<td>19</td>
<td>13</td>
<td>9</td>
<td>.041</td>
<td>17</td>
<td>.010</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>14</td>
<td>14</td>
<td>8</td>
<td>.168</td>
<td>18</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>14</td>
<td>12</td>
<td>9</td>
<td>.312</td>
<td>15</td>
<td>.032</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>M1</td>
<td>35</td>
<td>25</td>
<td>19</td>
<td>.025</td>
<td>26</td>
<td>.016</td>
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<td></td>
<td>M1 s^</td>
<td>27</td>
<td>25</td>
<td>19</td>
<td>.448</td>
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<td>.093</td>
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<tr>
<td></td>
<td>M2</td>
<td>22</td>
<td>24</td>
<td>19</td>
<td>.695</td>
<td>25</td>
<td>.272</td>
</tr>
<tr>
<td><strong>Physical function</strong></td>
<td>M1</td>
<td>72</td>
<td>81</td>
<td>88</td>
<td>.000</td>
<td>81</td>
<td>.035</td>
</tr>
<tr>
<td></td>
<td>M1 s^</td>
<td>75</td>
<td>82</td>
<td>87</td>
<td>.049</td>
<td>77</td>
<td>.015</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>77</td>
<td>83</td>
<td>87</td>
<td>.070</td>
<td>78</td>
<td>.038</td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiotepa, carboplatin. FEC: patients who received standard-dose 5-fluorouracil, epidoxorubicin, cyclophosphamide. CMF: patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.

s: patients on T1 who also participated in the follow-up assessment.

Results are shown as the percentage of patients who reported having cognitive problems in each of the domains at interview.

# Hopkins symptom checklist. Results are mean scores; scale 0-100; higher scores means more bothered by complaint.

EORTC QLQ C30. Results are mean scores; scale 0-100; higher scores means more bothered by complaint except for physical functioning.
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Table 4. Percentage of patients classified as impaired at T1 and T2.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Assessment</th>
<th>Size</th>
<th>Not impaired</th>
<th>Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC</td>
<td>T1</td>
<td>(n = 34)</td>
<td>68% (23)</td>
<td>32% (11)</td>
</tr>
<tr>
<td></td>
<td>T1 s</td>
<td>(n = 22)</td>
<td>77% (17)</td>
<td>23% (05)</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>(n = 22)</td>
<td>86% (19)</td>
<td>14% (03)</td>
</tr>
<tr>
<td>FEC</td>
<td>T1</td>
<td>(n = 36)</td>
<td>83% (30)</td>
<td>17% (06)</td>
</tr>
<tr>
<td></td>
<td>T1 s</td>
<td>(n = 23)</td>
<td>87% (20)</td>
<td>13% (03)</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>(n = 23)</td>
<td>91% (21)</td>
<td>09% (02)</td>
</tr>
<tr>
<td>CMF</td>
<td>T1</td>
<td>(n = 39)</td>
<td>80% (31)</td>
<td>20% (08)</td>
</tr>
<tr>
<td></td>
<td>T1 s</td>
<td>(n = 31)</td>
<td>75% (23)</td>
<td>26% (08)</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>(n = 31)</td>
<td>87% (27)</td>
<td>13% (04)</td>
</tr>
<tr>
<td>Control</td>
<td>T1</td>
<td>(n = 34)</td>
<td>94% (32)</td>
<td>06% (02)</td>
</tr>
<tr>
<td></td>
<td>T1 s</td>
<td>(n = 27)</td>
<td>96% (26)</td>
<td>04% (01)</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>(n = 27)</td>
<td>89% (24)</td>
<td>11% (03)</td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiota, carboplatin. FEC: patients who received standard-dose 5-fluorouracil, epidoxorubicin, cyclophosphamide. CMF: patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.

s: patients on T1 who also participated in the follow-up assessment

T1 differences between groups $P = .047$; T1s differences between groups: $P = .113$; T2 differences between groups $P = .953$

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) i.e. 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 (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 5 gives the individual changes for the different groups over time. None of the changes reached significance. **CTC/FEC group:** for the group treated with FEC chemotherapy, the distribution of patients classified as impaired/intact showed no marked changes over time; one patient (4%) considered to be impaired on T1 was judged cognitively intact on T2. Patients treated with CTC chemotherapy had a different pattern: 18% (n=4) of the CTC group who met the criteria for cognitive impairment on T1, were classified as cognitively intact on T2. For two patients in the CTC group (9%) a deterioration in test scores resulted in a shift from cognitively intact on T1 to impaired on T2. In total, 68% (n=15) of the CTC group and 15%
(n=1) of the FEC group retained the classification of cognitively impaired across both assessments. **CMF group:** of the patients treated with CMF chemotherapy classified as impaired on T1, 16% (n=5) shifted to the category of cognitively intact. One patient (3%) initially classified as intact was now considered impaired. 71% (n=22) remained classified as cognitively intact, and 10% (n=3) retained the classification of cognitively impaired.

**Table 5.** Individual changes over time in the study groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 s a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC</td>
<td>Intact 68% (15)</td>
<td>9% (2)</td>
</tr>
<tr>
<td></td>
<td>Impaired 18% (4)</td>
<td>5% (1)</td>
</tr>
<tr>
<td>FEC</td>
<td>Intact 87% (20)</td>
<td>4% (1)</td>
</tr>
<tr>
<td></td>
<td>Impaired 71% (22)</td>
<td>16% (5)</td>
</tr>
<tr>
<td>CMF</td>
<td>Intact 85% (23)</td>
<td>11% (3)</td>
</tr>
<tr>
<td></td>
<td>Impaired 4% (1)</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiopeta, carboplatin. FEC: patients who received standard-dose 5-fluorouracil, epidoxorubicin, cyclophosphamide. CMF: patients who received standard-dose cyclophosphamide, methotrexate, 5-fluorouracil.
s: patients on T1 who also participated in the follow-up assessment (T2).

**Control group:** the pattern of change in the control group was different from that in the chemotherapy groups. Although a comparable percentage of control group patients maintained the status of cognitively intact in comparison to for example the FEC patients (85% n=23 and 87% n=20, respectively), a relatively high percentage of control patients deteriorated (11%, n=3). Only one patient has improved (4%), and no patient initially defined as cognitively impaired maintained this classification.

**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 $P = .03$; depression $P = .00$; IQ $P = .03$). 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
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potentially contributing to the model, solely age was related to the classification into the categories impaired versus not impaired ($P = .00$).

**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 a 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 6.

**Table 6: Individual changes over time irrespective of the criteria for impairment**

<table>
<thead>
<tr>
<th>Mean number of tests</th>
<th>Treatment</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CTC (T2=22)</td>
<td>FEC (T2=23)</td>
</tr>
<tr>
<td>Stable</td>
<td>13.5</td>
<td>13.1</td>
</tr>
<tr>
<td>Improvement</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Deterioration</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Improvement – deterioration</td>
<td>1.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiotepa, carboplatin. FEC: patients who received standard-dose 5-fluorouracil, epidoxorubicin, 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.
Compared with the control group, the relative improvement in patients treated with CMF chemotherapy did reach significance ($P = .05$).

**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 ($CTC P = .04$, $FEC P = .03$; depression $P = .04$). **CMF group:** only the type of therapy was related to the changes observed for the CMF group compared with the control group ($CMF P = .04$).

**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 1 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 $P = .00$; CMF group $P = .00$; Control group $P = .02$).

**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 .19 to .22). It was also calculated whether there was a relation between the changes in complaints on cognitive functioning (as reported at the interview) and the changes in the neuropsychological tests scores. For all groups, this relation was negligible (results not shown).

**Tamoxifen therapy, menopausal status and neuropsychological test results**
**CTC/FEC group:** for those 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 1 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 = .00).

Lost to follow-up itemized by cognitively impaired versus not impaired
Table 7 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%).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T1</th>
<th>Participation in follow-up</th>
<th>Lost to follow-up death/relapse</th>
<th>Lost to follow-up Refusal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC</td>
<td>Intact</td>
<td>74% (17)</td>
<td>26% (6)</td>
<td>10% (1)</td>
<td>.143</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>45% (5)</td>
<td>45% (5)</td>
<td>10% (1)</td>
<td></td>
</tr>
<tr>
<td>FEC</td>
<td>Intact</td>
<td>67% (20)</td>
<td>27% (8)</td>
<td>7% (2)</td>
<td>.638</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>50% (3)</td>
<td>33% (2)</td>
<td>17% (1)</td>
<td></td>
</tr>
<tr>
<td>CMF</td>
<td>Intact</td>
<td>74% (23)</td>
<td>19% (6)</td>
<td>6% (2)</td>
<td>.273</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>100% (8)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Intact</td>
<td>81% (26)</td>
<td>6% (2)</td>
<td>13% (4)</td>
<td>.340</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>33% (1)</td>
<td>-</td>
<td>67% (2)</td>
<td></td>
</tr>
</tbody>
</table>

CTC: patients who received high-dose cyclophosphamide, thiotepa, carboplatin. FEC: patients who received
standard-dose 5-fluorouracil, epidoxorubicin, cyclophosphamide. CMF: patients who received standard-dose
cyclophosphamide, methotrexate, 5-fluorouracil.

CMF group: none of the CMF patients initially classified as cognitively impaired were lost to
follow-up due to illness or death.

Control group: 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.
Predictors of survival

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 in 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 4 patients compared to T2). Of the 36 patients treated with FEC chemotherapy, 19 patients relapsed (compared to 10 patients on T2). Of the 39 CMF patients, 10 relapsed (compared to 6 on T2). Of 34 patients in the control group, 4 patients were not eligible on T2 due to disease progression, and an additional 2 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 the CTC patients classified as cognitively impaired on T1 relapsed or died, compared to 21% of the impaired cases in the FEC group and 10% of the 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 of 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) is too small in the control group. Covariates examined were: (1) age and IQ, (2) 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), (3) 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 ($P = .09$) and classification into the category of cognitively impaired on T1 ($P = .13$). For the CMF group, complaints on physical functioning as measured with the quality of life questionnaire were a significant predictor for time to progression ($P = .03$).

Discussion

The complaints of breast cancer patients treated with chemotherapy about impaired memory and concentration has led to a series of neuropsychological examinations. Initially, two retrospective studies were performed in breast cancer patients treated with adjuvant chemotherapy. Three clinically different populations were tested two years post therapy; (1) a group of high-risk breast cancer patients (with 4 or more positive lymph nodes and no other
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metastases) who had received either high-dose CTC chemotherapy or standard-dose FEC chemotherapy according to randomization; (2) a group of breast cancer patients with 1-3 positive lymph nodes and no other metastases who had received conventional dose CMF chemotherapy; and (3) a control group of patients who had undergone surgery for stage I breast cancer but had not received any systemic adjuvant therapy. From these first neuropsychological assessments (T1) it appeared that breast cancer patients treated with high-dose CTC chemotherapy and breast cancer patients treated with conventional CMF chemotherapy had a higher risk of cognitive impairment than breast cancer patients not treated with chemotherapy (odds ratio 8.2 and odds ratio 6.4, respectively). Patients treated with FEC chemotherapy showed no elevated risk compared with the control group. All chemotherapy groups (irrespective of the regimen) reported significantly more problems with memory and concentration than the control group, but no relation was found between the subjective reported complaints on memory and concentration and the results on the neuropsychological tests. Anxiety, depression and fatigue were not related to the neuropsychological test outcomes. The subjective complaints of the patients on memory and concentration did correlate with anxiety and depression. 

The present study is a continuation of these earlier examinations, in that this second neuropsychological assessment (T2) of the three groups has an additional two years test-retest interval, i.e. this study takes place four 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 re-test is not simple. Two methods were used to analyze the follow-up data: we constructed a dichotomous outcome to differentiate between impaired and not-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 relation 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, four 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 dose 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 4 or more positive lymph nodes (CTC and FEC group), patients with 1-3 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 leads to further complications and makes interpretation of the results even more problematic. For the second analysis, due to factors related to the disease, the sample included only 45% of the initially cognitively impaired patients in the CTC group, 33% of the impaired cases in the FEC group, and all of the impaired patients in the CMF chemotherapy group. Consequently, the question arises about a potential relation between the cognitive impairment measured and the differential attrition observed in the various treatment groups.

To examine whether variables assessed during the neuropsychological examination were related to disease progression, survival analyses were performed with time to progression defined as event. These analyses were conducted two years after the last follow-up examination, i.e. six years after completion of treatment. The number of patients who relapsed had increased during that period, and the observation that the percentage of impaired versus intact cases lost to follow-up was 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 relation 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 a result of treatment, but an early expression of disease progression. This is, however, unlikely, as the relation 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 it cannot be excluded that this observation is a result of chance.

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.

Second, in repeated neuropsychological examinations, an overall pattern of test susceptibility to practice effects generally emerges. 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 two 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.

It cannot be excluded 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. As indicated previously, our data are prone to some amount of measurement error. But the fact that extreme scores regress toward the mean does not necessary leads 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 run. 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 much debated recent topic is the effect of estrogen on cognitive functioning. Whereas some report a beneficial effect of exogenous estrogen use on cognitive functioning, and a relation between lower endogenous estrogen levels and cognitive decline, others do not support these findings or even report opposite effects. A recent study on tamoxifen suggested that its use may adversely affect cognition, while past users and those who never used tamoxifen did not differ in their cognitive performance. In the present study post hoc comparisons showed no differences in any of the neuropsychological outcome measures between patients who completed tamoxifen therapy, who were still on tamoxifen therapy, and 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 four 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.

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