Cognitive functioning following chemotherapy: a study in breast cancer patients

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Chapter 5

Cognitive Deficits after Postoperative Adjuvant Chemotherapy for Breast Cancer

Schagen SB, van Dam FSAM, Muller MJ, Boogerd W, Lindeboom J, Bruning PF.
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Abstract

Background: A number of patients who have undergone adjuvant (CMF) chemotherapy for operative primary breast carcinoma have reported impaired cognitive function, sometimes even years after completion of therapy. The possible role of cytostatic treatment as a causative factor has scarcely been investigated. The objective of the current study was to examine the late effects on neuropsychologic functioning of CMF adjuvant chemotherapy given to patients with breast carcinoma.

Methods: Thirty-nine breast carcinoma patients who had been treated with adjuvant CMF (6 courses) followed (n = 20) by 3 years of tamoxifen 20 mg daily or not (n = 19) were examined with neuropsychologic tests and interviews. The control group consisted of 34 age-matched axillary lymph node negative breast carcinoma patients who received the same surgical and radiation therapy but no systemic adjuvant treatment. The CMF patients were examined a median of 1.9 years after the sixth CMF course, and the controls a median of 2.4 years after surgery of the primary tumor.

Results: Patients treated with CMF reported significantly more problems with concentration (31% vs. 6%, \( P = 0.007 \)) and with memory (21% vs. 3%, \( P = 0.022 \)) than the control patients. No relation was found between reported complaints and results on the neuropsychologic tests. Impairment in cognitive function was found in 28% of the patients treated with chemotherapy compared with 12% of the patients in the control group (odds ratio 6.4 [95% confidence interval 1.5-27.6] \( P = 0.013 \)). Hormonal therapy had no influence on patients' self-reports of symptoms or cognitive function. Cognitive impairment following chemotherapy was noticed in a broad domain of functioning, including attention, mental flexibility, speed of information processing, visual memory, and motor function.

Conclusion: Breast carcinoma patients treated with adjuvant CMF chemotherapy have a significantly higher risk of late cognitive impairment than breast carcinoma patients not treated with chemotherapy (OR 6.4). This cognitive impairment is unaffected by anxiety, depression, fatigue, and time since treatment, and not related to the self-reported complaints of cognitive dysfunction.

Introduction

The rationale for adjuvant chemotherapy given after local treatment of primary breast carcinoma is to eradicate the growth of possible occult metastases that would otherwise become fatal. Although adjuvant chemotherapy given to patients treated with curative intent has a proven beneficial effect on relapse free and overall survival, the rates of recurrence even for women treated for Stage I breast carcinoma are still 20-30% at 10 years after surgery. In choosing an adjuvant therapy regimen, potential benefits must be weighed against both short term and long term side effects.
The adjuvant chemotherapy regimen most widely used is the combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), as first reported in 1976 by Bonadonna et al. Over the past two decades, various toxicities associated with chemotherapy have been investigated and documented extensively.

One possible side effect of chemotherapy that has received little attention until now is long term cognitive impairment. Neuropsychologic symptoms, in particular memory and concentration problems, are frequently reported by cancer patients treated with chemotherapy, even years after completion of treatment. In spite of this, there are few studies that have systematically evaluated these reports of cognitive problems with standardized neuropsychologic tests. Moreover, most studies lack sufficient patient numbers or uniformity to allow definite conclusions on this topic. Aside from this, most research conducted in this area has addressed the neuropsychologic status of patients treated with chemotherapy for metastatic disease, which makes it difficult to draw conclusions about the effect of chemotherapy, as in the past patients in an advanced stage of their disease were usually treated with other cytostatic regimens. Furthermore, studies that have evaluated the cognitive function of patients following chemotherapy as part of an adjuvant treatment strategy have often focused on high dose regimens with autologous bone marrow transplantation. Little is known of late cognitive impairment in cancer patients treated with conventional adjuvant chemotherapy.

The only study that has evaluated the neuropsychologic status of breast carcinoma patients treated with conventional adjuvant chemotherapy revealed substantial deficits. Wienieke and Dienst examined the cognitive functioning of a group of 28 Stage I and II breast carcinoma patients 3-18 months after completion of CMF chemotherapy. Seventy-five percent of the patients scored 2 standard deviations below published test norms of healthy individuals corrected for age, education, and gender on 1 or more of the 16 test measures. These findings emerged in the context of no medically evident comorbidity, and they appeared unrelated to depression or to demographic or treatment variables other than the length of chemotherapy. A limitation of that study was the absence of a control group of cancer patients not treated with chemotherapy. A control group is required to differentiate between cognitive deficits caused by the psychologic burden of having cancer or by its treatment. Therefore, the status of the cognitive deficits reported by Wienieke and Dienst remains unclear.

The current study was designed to examine the neuropsychologic functioning of breast carcinoma patients following standard adjuvant chemotherapy with CMF, in comparison with an appropriate control group consisting of breast carcinoma patients not treated with chemotherapy, matched for age and time since treatment.
Methods

Patients and Therapy

The study population consisted of two groups of patients: a group of operable primary breast carcinoma patients with metastasis to axillary lymph nodes treated with adjuvant chemotherapy (n = 39) and a control group consisting of axillary lymph node negative breast carcinoma patients not treated with adjuvant chemotherapy (n = 34). The study samples represent consecutive series of patients. At the time of the investigation, all patients were clinically free of disease. Written informed consent was obtained from all patients. The study was approved by the ethical committee of the hospital.

The breast carcinoma patients treated with chemotherapy had received six 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 this chemotherapy was followed by tamoxifen 20 mg daily for 3 years (n = 20), according to the protocol of a prospective randomized Phase III trial of the European Organization for Research and Treatment of Cancer (EORTC 10901), the objective of which was to study the effects on survival and relapse free survival of tamoxifen sequentially given after chemotherapy.

To be eligible for the neuropsychologic study, patients had to meet the following inclusion criteria: 1) no evidence of relapse or metastatic disease; 2) no history of neurologic/psychiatric signs or symptoms that might lead to deviant neuropsychologic test results; 3) no use of medication that might lead to deviant neuropsychologic test results (for example, antidepressants or benzodiazepines); 4) no abuse of alcohol or drugs; and 5) sufficient command of the Dutch language. Only patients who were off chemotherapy for at least 6 months were enrolled in the cognitive functioning study.

The control group consisted of breast carcinoma patients not treated with chemotherapy, matched for age and time since treatment. Inclusion criteria were the same as for the breast carcinoma patients treated with chemotherapy.

Measures

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

Neuropsychologic tests

A battery of 14 neuropsychologic tests (comprising 21 test indexes), covering a broad range of functions, was used in this study. The tests were selected for reliability, validity, and availability of (Dutch) norms, as well as their sensitivity for measuring cognitive functions.
Cognitive deficits after conventional CMF chemotherapy

The cognitive functions described below are routinely evaluated in a neuropsychologic examination. The following functions are examined: verbal function, memory, attention/concentration, speed of information processing, motor function, visuoconstructional function, and mental flexibility. The tests are described here in order of administration. For each test the domain is indicated.

Rey Auditory Verbal Learning Test. This test measures both short term and longer term retention following interpolated activity and allows for a comparison between retrieval efficiency and learning. The Dutch version includes 5 learning trials of a 15-word list, an interval of 20 minutes (filled with nonverbal tests), a delayed recall, and a recognition trial consisting of the target words interspersed with 15 distractor words (verbal memory).

Fepsy Finger-Tapping Task. This test provides a measure for motor speed. The speed of finger tapping is measured for the index finger of the right and left hand separately, 5 times for a period of 10 seconds each (motor function).

Fepsy Visual Reaction Test. This test measures basic perceptuomotor performance. Stimuli (a white square on the screen) are presented at random intervals by the computer (speed of information processing).

Fepsy Binary Choice Test. This test reflects motor speed and gives information about the decision-making process. The subject has to react differentially to a red square presented at the left side of the screen and to a green square presented at the right side of the screen (speed of information processing).

Fepsy Visual Searching Test. This test gives an indication of the accuracy of information processing and mental speed. The task consists of finding 1 grid pattern out of 24 that matches the one in the center of the screen. Twenty-four different grid patterns have to be found (speed of information processing).

Stroop Test. This test assesses the ability to substitute an alternative response for a more obvious reaction (naming the ink color of a word denoting a different color) and is sensitive to disorders of executive (frontal) function. The test consists of 3 stimulus cards containing 100 words, 100 colored rectangles, and 100 color-words, respectively (mental flexibility).

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

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

**Complex Figure Test: Copy and Recall.** In this test, copy evaluates visuococonstructional ability and recall evaluates visual memory. The subject is asked to copy a complex figure, and then after a few minutes the subject is asked to reproduce the figure without prior warning (visuococonstructional function and visual memory).

**Word Fluency Subtest from the S.A.N. Test.** This subtest involves a simple task requiring the generation of words from a specific semantic category (animals) within a limited time. Impairment revealed by this subtest can be related to language disorder, frontal dysfunction, or deterioration of semantic memory (verbal function).

**Digit Symbol of the Wechsler Adult Intelligence Scale.** This test involves a symbol substitution task that requires visual-motor coordination, motor persistence, and sustained attention. The test has been shown to be sensitive in detecting brain damage. The task consists of pairing numbers to nonsense symbols as quickly as possible (attention/concentration).

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

**Visual Reproduction Subtest of the Wechsler Memory Scale, Revised: Immediate and Delayed Recall.** This visual memory test requires the subject to reproduce from memory 4 geometric designs, each shown for 10 seconds. After a delay of 20 minutes, the subject is again asked to draw the figures; this is with prior warning (visual memory).

**Dutch Adult Reading Test.** This Dutch version of the National Adult Reading Test provides a measure of premorbid intelligence quotient (IQ).

**Self-reported complaints of cognitive functioning**

All patients were interviewed about cognitive problems (memory, attention, thinking, and language) encountered in daily life and were asked to indicate on a 5-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). The questions of this semistructured interview originated from a Dutch instrument designed to assess psychopathologic symptoms.

**Health-related quality of life, depression, and anxiety**

Health-related quality of life was assessed with the EORTC QLQ-C30, a questionnaire developed for use in clinical trials involving cancer patients. Its validity, reliability, and sensitivity when administered to cancer patients are well established. The EORTC QLQ-30 is a 30-item questionnaire that consists of 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, nausea and vomiting), and a general health and quality-of-life scale. Five single items measure complaints often mentioned by cancer patients (loss of appetite, dyspnea, sleep disturbance, constipation, and
diarrhea). To determine whether psychologic distress played a role in the patients' cognitive problems, the Hopkins Symptom Checklist-25 was administered. The HSCL-25 contains 15 depression and 10 anxiety items and was specially developed for ease and appropriateness in medical settings.

Procedure
The medical records of patients were examined by the researchers to verify the inclusion criteria. All eligible patients were asked by their physicians to take part in the current study. The tests and questionnaires were administered in the same order to each subject and took approximately 2 hours to complete.

Statistical Methods
The Statistical Package for Social Sciences (SPSS) Windows 6.0 software was used for all statistical analyses. Each neuropsychologic test score was converted into a standard score (z-score) by using the mean test scores of the control group as a reference. A summary score for each of the domains was computed by summing the z-scores for the separate tests in that domain. The data from the questionnaires (EORTC QLQ-C30 and HSCL-25) were converted to scores according to standard scoring rules.

Differences in sociodemographic characteristics between groups were analyzed by means of the chi-square test for contingency tables and Student's t test. The differences in questionnaire scores between groups were determined by univariate analysis of variance (ANOVA). Differences in raw neuropsychologic test scores between groups were tested for descriptive purposes by univariate ANOVA. Because comparisons of group means may obscure cognitive impairment evaluation at the level of the individual patient, an individual approach with respect to the determination of neuropsychologic impairment was used. Neuropsychologic impairment was determined as follows: first, a patient who scored 2 standard deviations (SD) below the mean of the control group on a test was considered impaired on that specific test. Second, an overall impairment score (OSCI) was calculated for each individual patient by counting all tests on which the patient was impaired. And finally, the fifth percentile of the overall impairment scores of the control patients was used as a cutoff score for neuropsychologic impairment.

The correlations between neuropsychologic test performance and anxiety/depression, time since therapy, cancer specific symptoms, and subjective measures of cognitive functioning were analyzed by using Spearman rank order correlations.

Multivariate stepwise logistic regression analysis was used to determine the risk of being classified as impaired in neuropsychologic functioning. The following variables were entered into the analysis: type of therapy (adjuvant chemotherapy, yes or no), age, IQ, time since treatment, anxiety and depression, and fatigue. A forward stepwise selection was performed, in which by each step the variable with the smallest significance level for the score statistic,
i.e., an overall chi-square test, was entered in the model. All variables in the forward stepwise block that were entered were then examined to determine whether they met removal criteria. This was done with the likelihood-ratio test. With this procedure, the change in the log-likelihood was tested when each variable was deleted. For all analyses, a \( P \) value less than 0.05 was required for significance.

**Results**

**Sociodemographic Characteristics**

Fifty lymph node positive breast carcinoma patients who had received 6 cycles of adjuvant CMF with or without subsequent tamoxifen were eligible for the neuropsychologic study, i.e., met the inclusion criteria. Eleven patients declined to participate in the study. Ten patients did not wish to be reminded of their illnesses by returning to the hospital for tests, and one patient was too busy to participate. Of the 50 eligible control patients who were asked to take part in the study, 11 declined to pay an additional visit to the hospital and 5 refused for emotional reasons. The total sample size therefore consisted of 39 breast carcinoma patients treated with CMF chemotherapy and 34 control patients not treated with systemic therapy. Eighteen patients treated with chemotherapy were currently receiving tamoxifen and 19 were treated with chemotherapy alone (2 patients were already off tamoxifen at the time of testing). There were no detectable differences between patients treated with chemotherapy plus tamoxifen and those treated with chemotherapy alone on any of the outcome measures; therefore, the groups were taken together in further analysis.

<table>
<thead>
<tr>
<th>Table 1. Sociodemographic characteristics of the study subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean AGE in years (sd)</strong></td>
</tr>
<tr>
<td>Mean Time since last therapy, y (sd)</td>
</tr>
<tr>
<td>Premorbid IQ (Dutch Reading Test)</td>
</tr>
</tbody>
</table>

CMF: patients who received cyclophosphamide, methotrexate, 5-fluorouracil. IQ: intelligence quotient.

*Low: primary school; Middle: secondary school; High: university and graduate school."
Cognitive deficits after conventional CMF chemotherapy

The patients' sociodemographic and clinical characteristics are described in Table 1. The groups did not differ in mean age. Our study population had a relatively young age because adjuvant chemotherapy in our hospital is still largely restricted to premenopausal patients. The mean time since last therapy was on average 2 years. The interval was somewhat longer in the control group than in the chemotherapy group (P = 0.028). Premorbid cognitive ability (IQ), as measured by the Dutch Adult Reading Test, and educational level, as determined by a Dutch standardized scoring system, were higher in the chemotherapy group (P = 0.004 and P = 0.012 respectively).

All patients treated with chemotherapy were postmenopausal, due to the impact of the cytostatic drugs on ovarian functioning (except for 3 patients who were already postmenopausal before diagnosis). In the control group, 13 patients were postmenopausal and 21 patients were considered to be premenopausal (defined by regular menstrual cycles). We compared the results for the pre- and postmenopausal control patients and observed no differences.

Self-Reported Complaints of Cognitive Functioning

Data on self-reported cognitive problems (concentration, memory, thinking, and language) are presented in Table 2. A score of 2 (moderate) or more was considered a distinct complaint about the cognitive functioning in the domain concerned. Thirty-one percent of the patients treated with chemotherapy reported concentration problems (23.1% rated 2, 7.7% rated 3, none rated 4) and 21% expressed memory problems (17.9% rated 2, 2.6% rated 3, none rated 4). These prevalence rates were significantly higher than in the control patients (6% and 3%, respectively, P = 0.007 and P = 0.022; none rated 3 or 4). With regard to complaints about thinking and language, there were no statistically significant differences between the groups.

Table 2. Cognitive problems in daily life

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>CMF</th>
<th>Surgery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 39</td>
<td>N = 34</td>
<td></td>
</tr>
<tr>
<td>Concentration</td>
<td>31%</td>
<td>6%</td>
<td>.007</td>
</tr>
<tr>
<td>Memory</td>
<td>21%</td>
<td>3%</td>
<td>.022</td>
</tr>
<tr>
<td>Thinking</td>
<td>8%</td>
<td>0%</td>
<td>.099</td>
</tr>
<tr>
<td>Language</td>
<td>8%</td>
<td>3%</td>
<td>.373</td>
</tr>
</tbody>
</table>

CMF: patients who received cyclophosphamide, methotrexate, 5-fluorouracil.

*Only patients who rated their cognitive problem at least 2 (moderate) in a distinct domain were considered as having a complaint about their cognitive functioning in that domain.
Health-Related Quality of Life, Depression, and Anxiety

Data on the EORTC QLQ-C30 quality-of-life scale are presented in Table 3. Patients treated with chemotherapy had significantly lower scores on the physical and cognitive functioning scales than the control patients ($P = 0.035$ and $P = 0.021$, respectively). On the symptom scales of the EORTC QLQ-C30, there were no differences between the groups.

Table 3. EORTC QLQ-C30: Quality of life

<table>
<thead>
<tr>
<th></th>
<th>CMF (n = 39)</th>
<th>Surgery (n = 34)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
<td></td>
</tr>
<tr>
<td>Function scales$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>81.0 (15.2)</td>
<td>88.2 (13.1)</td>
<td>.035</td>
</tr>
<tr>
<td>Role</td>
<td>85.0 (22.9)</td>
<td>88.2 (22.7)</td>
<td>.552</td>
</tr>
<tr>
<td>Cognitive</td>
<td>79.5 (18.1)</td>
<td>89.2 (16.9)</td>
<td>.021</td>
</tr>
<tr>
<td>Emotional</td>
<td>76.7 (19.9)</td>
<td>81.6 (19.2)</td>
<td>.289</td>
</tr>
<tr>
<td>Social</td>
<td>88.0 (18.3)</td>
<td>92.6 (19.3)</td>
<td>.299</td>
</tr>
<tr>
<td>Global QoL new</td>
<td>80.6 (16.5)</td>
<td>83.8 (17.0)</td>
<td>.408</td>
</tr>
<tr>
<td>Symptom scales and/or items$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25.6 (21.7)</td>
<td>18.6 (20.4)</td>
<td>.161</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.4 (2.7)</td>
<td>0</td>
<td>.354</td>
</tr>
<tr>
<td>Pain</td>
<td>9.8 (18.6)</td>
<td>17.2 (20.7)</td>
<td>.116</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11.1 (15.9)</td>
<td>8.8 (20.6)</td>
<td>.595</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>29.9 (28.4)</td>
<td>23.5 (29.0)</td>
<td>.346</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>2.6 (9.0)</td>
<td>1.0 (5.7)</td>
<td>.381</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.6 (11.8)</td>
<td>6.9 (16.0)</td>
<td>.191</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.1 (14.4)</td>
<td>2.0 (8.0)</td>
<td>.258</td>
</tr>
<tr>
<td>Financial impact</td>
<td>6.0 (18.5)</td>
<td>3.9 (10.9)</td>
<td>.572</td>
</tr>
</tbody>
</table>

EORTC: European Organization for Research and Treatment of Cancer; CMF: patients who received cyclophosphamide, methotrexate, and 5-fluorouracil; QoL: quality of life.

$^a$ Higher score means better functioning, scale 0-100.

$^b$ Higher score means more bothered by complaint, scale 0-100.

From the results of the Hopkins Symptom Checklist, it appeared that patients treated with chemotherapy had significantly higher scores on the depression subscale than the control patients (CMF: mean, 16.9 [SD 13.7], control: mean, 9.3 [SD 10.1]; $P = .010$). There were no differences between the groups on the anxiety subscale (CMF: mean, 15.5 [SD 12.4], control: mean, 14.3 [SD 15.9]; $P = .718$).

Neuropsychologic Tests

There were no differences between the scores of the control patients and the published norms corrected for age, education, and gender on any of the individual tests. The mean values, their standard deviations, and the $P$ values of the univariate F-tests of the separate tests are
<table>
<thead>
<tr>
<th>Cognitive ability</th>
<th>Type of test</th>
<th>CMF (n = 39) mean (sd)</th>
<th>Control (n = 34) mean (sd)</th>
<th>IQ-corrected P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/Concentration</td>
<td>Digit span (forward)</td>
<td>13.4 (2.7)</td>
<td>13.0 (2.5)</td>
<td>.429</td>
</tr>
<tr>
<td></td>
<td>Digit span (backward)</td>
<td>9.8 (2.8)</td>
<td>10.5 (2.4)</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td>WAIS digit symbol</td>
<td>57.4 (10.9)</td>
<td>60.6 (9.2)</td>
<td>.036</td>
</tr>
<tr>
<td></td>
<td>Trailmaking version A</td>
<td>35.9 (10.6)</td>
<td>33.1 (0.4)</td>
<td>.082</td>
</tr>
<tr>
<td></td>
<td>Test D2 (GZ-F)</td>
<td>402.5 (69.9)</td>
<td>420.5 (77.1)</td>
<td>.060</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td>STROOP Color word test</td>
<td>37.8 (27.4)</td>
<td>35.7 (19.1)</td>
<td>.288</td>
</tr>
<tr>
<td></td>
<td>Trailmaking version B</td>
<td>80.4 (29.4)</td>
<td>70.5 (25.0)</td>
<td>.006</td>
</tr>
<tr>
<td>Speed of information processing</td>
<td>FEPSY visual reaction (dominant)</td>
<td>323.4 (131.2)</td>
<td>267.8 (41.3)</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>FEPSY visual reaction (non dominant)</td>
<td>320.1 (117.4)</td>
<td>266.0 (36.4)</td>
<td>.010</td>
</tr>
<tr>
<td></td>
<td>FEPSY Binary Choice</td>
<td>429.5 (71.9)</td>
<td>415.6 (112.2)</td>
<td>.149</td>
</tr>
<tr>
<td></td>
<td>FEPSY Visual Searching</td>
<td>11.8 (3.4)</td>
<td>11.8 (4.0)</td>
<td>.294</td>
</tr>
<tr>
<td>Memory (Verbal)</td>
<td>Rey 15 words test recall</td>
<td>49.4 (7.0)</td>
<td>51.0 (7.5)</td>
<td>.125</td>
</tr>
<tr>
<td></td>
<td>Rey 15 words test delayed recall</td>
<td>10.6 (2.4)</td>
<td>11.3 (1.9)</td>
<td>.026</td>
</tr>
<tr>
<td></td>
<td>Rey 15 words test recognition</td>
<td>29.2 (1.4)</td>
<td>29.5 (1.1)</td>
<td>.119</td>
</tr>
<tr>
<td>Memory Visual</td>
<td>Complex figure (recall)</td>
<td>20.1 (6.0)</td>
<td>22.0 (5.4)</td>
<td>.027</td>
</tr>
<tr>
<td></td>
<td>WMS immediate recall</td>
<td>35.7 (4.1)</td>
<td>37.5 (2.7)</td>
<td>.010</td>
</tr>
<tr>
<td></td>
<td>WMS delayed recall</td>
<td>33.0 (7.8)</td>
<td>36.2 (3.9)</td>
<td>.006</td>
</tr>
<tr>
<td>Verbal function</td>
<td>Word fluency</td>
<td>24.7 (5.8)</td>
<td>27.1 (5.9)</td>
<td>.025</td>
</tr>
<tr>
<td></td>
<td>Complex Figure Test (copy)</td>
<td>35.0 (1.4)</td>
<td>35.3 (1.1)</td>
<td>.118</td>
</tr>
<tr>
<td>Motor function</td>
<td>FEPSY tapping (dominant)</td>
<td>57.5 (8.8)</td>
<td>60.7 (9.7)</td>
<td>.040</td>
</tr>
<tr>
<td></td>
<td>FEPSY tapping (non dominant)</td>
<td>51.7 (7.7)</td>
<td>56.1 (8.6)</td>
<td>.003</td>
</tr>
</tbody>
</table>

CMF: patients who received cyclophosphamide, methotrexate, 5-fluorouracil.


b Presented mean values are unadjusted.
presented in Table 4. These analyses were performed by using IQ as covariate, because the patients treated with chemotherapy scored significantly higher than the control patients on the Dutch Adult Reading Test, a measure for estimating the premorbid IQ of the subjects. On 12 of the 21 test indexes, significant differences ($P < 0.05$) were found between the chemotherapy group and the control group, with the chemotherapy patients performing worse than the control patients each time.

**Attention/concentration**
The patients treated with chemotherapy scored significantly lower than the control patients on the digit span backward and the digit symbol task. On the digit span forward, the Trailmaking A Test and the D2 Test, there were no differences between the groups.

**Mental flexibility**
The results showed that the chemotherapy group was slower on Trailmaking B than the control group. The groups did not differ significantly on the Stroop Color Word Test.

**Speed of information processing**
On a task that measured basic perceptuomotor performance, it appeared that reaction time was significantly slower among the patients treated with chemotherapy than among control patients. There were no differences between the groups regarding performance of the binary choice or visual searching tasks.

**Memory**
On the Rey Auditory Verbal Learning Test, the groups did not differ regarding immediate recall or recognition. However, patients in the chemotherapy group recalled, on average, fewer words at a 20-minute delay than the patients in the control group. There were no differences between the groups in visuoconstructional ability as measured by the Complex Figure Test, but the performance of the chemotherapy patients on the visual recall condition was worse than the performance of the control patients. The same pattern was found in the Visual Reproduction Subtest; the chemotherapy patients recalled fewer elements than the control patients, both in the immediate and in the delayed recall condition.

**Motor function**
Data showed that the chemotherapy patients had significantly slower motor speed than the control patients, for dominant and nondominant hand.

**Verbal functioning**
The patients treated with chemotherapy produced fewer words than the control patients.

**Neuropsychologic Impairment Risk**
For each patient, an overall score of cognitive impairment was calculated, in the event that group mean values obscured cognitive impairment evaluation at the level of the individual.
This was done by counting all tests on which the patient was impaired (a patient who scored two standard deviations below the mean of the control group on a test was considered impaired on that specific test). The fifth percentile of the control patients was used as a cutoff to determine whether a patient was impaired in cognitive functioning. The fifth percentile of the control patients corresponded with 3 tests failed. Thus, for a patient to be classified as impaired in cognitive functioning, a score of two standard deviations below the mean of the control group on at least three tests was required. According to this criterion, 28% of the patients treated with chemotherapy were classified as impaired in cognitive functioning, compared with 12% of the patients in the control group. (Because of the restricted range of the scores and rounding, the fifth percentile cutoff point for the control group included 12% of the patients.) This classification was tested for differences between treatment groups by use of a multivariate logistic regression model. Type of therapy (adjuvant chemotherapy, yes or no), age, IQ, time since treatment, anxiety and depression, and fatigue were included as possible factors in the model. Type of therapy and IQ met the inclusion criteria. Age, time since treatment, anxiety and depression, and fatigue appeared to have no significant contribution to the model. The results of the final model are shown in Table 5. The risk for cognitive impairment was highly increased for patients treated with chemotherapy as compared with the control patients (odds ratio [OR] = 6.4; confidence interval [CI], 1.5-27.6; \( P = 0.013 \)).

**Table 5. Relative Risk Cognitive Impairment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>0.9</td>
<td>0.8 - 1.0</td>
<td>.007</td>
</tr>
<tr>
<td>Treatment *</td>
<td>6.4</td>
<td>1.5 - 27.6</td>
<td>.013</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI confidence interval; IQ intelligence quotient.

*Control patients as reference group.

**Neuropsychologic Impairment and Self-Reported Measures**

The correlation between self-reported cognitive symptoms and neuropsychologic impairment found on formal testing was investigated. There appeared to be no correlation between the overall score of cognitive impairment and the cognitive problems reported at the interview. Also, no correlation was found between the summary scores for the distinguished cognitive domains and the cognitive problems reported at the interview, and no correlation was found between the overall score of cognitive impairment and the score on the cognitive functioning scale of the EORTC QLQ-C30.

There was, however, an association between the cognitive problems reported at the interview and the scores on the cognitive and emotional functioning scale of the EORTC QLQ-C30. The
Table 6. Spearman rank-order correlations of Overall Score of Cognitive Impairment (OSCI), time since last therapy and self reported measures

<table>
<thead>
<tr>
<th></th>
<th>OSCI</th>
<th>CF</th>
<th>EF</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Concentration</th>
<th>Memory</th>
<th>Language</th>
<th>Thinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-CF</td>
<td>-.01</td>
<td>-</td>
<td>.52</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EORTC-EF</td>
<td>.06</td>
<td>.49</td>
<td>-52</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HSCL Anxiety</td>
<td>.16</td>
<td>-.59</td>
<td>-77</td>
<td>.55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Memory</td>
<td>-.20</td>
<td>-.45</td>
<td>-.22</td>
<td>.13</td>
<td>-.20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Language</td>
<td>-.12</td>
<td>-.47</td>
<td>-.51</td>
<td>.08</td>
<td>-.30</td>
<td>-.53</td>
<td>-.54</td>
<td>-.55</td>
<td>-</td>
</tr>
<tr>
<td>Thinking</td>
<td>.12</td>
<td>-.37</td>
<td>-.34</td>
<td>.29</td>
<td>-.26</td>
<td>.25</td>
<td>.30</td>
<td>.30</td>
<td>.29</td>
</tr>
<tr>
<td>Time since last</td>
<td>.12</td>
<td>-.02</td>
<td>.28</td>
<td>.03</td>
<td>-.18</td>
<td>-.01</td>
<td>-.15</td>
<td>-.30</td>
<td>-.00</td>
</tr>
</tbody>
</table>

OSCI: overall score of cognitive impairment; CF: cognitive function; EF: emotional function; EORTC: European Organization for Research and Treatment of Cancer; HSCL: Hopkins Symptom Checklist.

* P < 0.05.

*P < 0.01.

* P < 0.001.
problems reported at the interview and the scores on the HSCL anxiety and depression subscale were also related.

The EORTC QLQ-C30 cognitive functioning scale was strongly correlated with the emotional functioning scale of the same questionnaire. The scores on these scales were also strongly associated with the HSCL anxiety and depression subscale. All correlations are presented in Table 6.

Discussion

The current study shows that breast carcinoma patients treated with CMF chemotherapy as part of an adjuvant therapy strategy have a significantly higher risk for cognitive impairment than breast carcinoma patients not treated with chemotherapy. The risk for cognitive impairment found in this patient population was unaffected by anxiety, depression, fatigue, or time since therapy. These findings support the results of the study of Wienke and Dienst, in which considerable cognitive deficits were found in a group of breast carcinoma patients treated with CMF chemotherapy. In that study, the test results of the patients were compared with published age-adjusted normative data. The current study included a control group of axillary lymph node negative breast carcinoma patients not treated with chemotherapy, and a much stricter criterion for cognitive impairment, based on the control group, was held. Nevertheless, cognitive deficits were found in a substantial number of patients treated with chemotherapy. The finding of cognitive deficits an average of 2 years after the completion of chemotherapy makes the results particularly relevant.

In the literature, there are some indications that estrogen alone may have a positive effect on certain aspects of cognitive functioning. However, in our study we did not find any differences in test performance between patients treated with chemotherapy plus tamoxifen and patients treated with chemotherapy alone. A comparison between the pre- and postmenopausal control patients did not reveal any differences either. Nonetheless, it was difficult to draw firm conclusions with regard to the role of estrogen in cognitive functioning, because of the small sample size of patients in the different subgroups.

Almost one-third of patients treated with chemotherapy reported cognitive problems. However, these reports could not be related to cognitive functioning as measured by standardized tests. Self-reported cognitive problems appeared to be related to anxiety and depression, but the neuropsychologic impairment based on standardized tests was not. There is a considerable body of research on the correlation between subjective cognitive functioning and objective test performance. From these studies, it can be concluded that the correlation between perceived cognitive functioning and performance is far from simple. It is a common finding that objective test results and subjective reports of patients about their cognitive functioning are not related. It is often argued that the absence of clear correlations
between patients' self-reported symptoms and objective test performance may be due to shortcomings of the different measures used. For example, the ecologic relevance of most neuropsychologic tests is low. The domains assessed by traditional tests of cognitive function have little overlap with the everyday experience on which patients base their self-reports: traditional neuropsychologic tests are, in terms of everyday cognitive function, highly artificial. For example, in the case of memory tests, the material that has to be memorized and the way in which the material is presented to the patient show little resemblance to everyday memory tasks, whereas in an interview, questions explicitly focus on problems in daily-life situations. Furthermore, many people, especially those who are forgetful, have difficulty in objectively assessing their own daily cognitive failures. Another reason for the finding that correlations between test performance and self-reported problems are often elusive is that beliefs of patients about their cognitive functioning are influenced by personality variables, such as neuroticism or affective status, whereas performance on formal testing is much less often affected by these kind of variables. In our study, we indeed found that the self-reported problems of patients were related to anxiety and depression, whereas the objective test performance was not. Although the self-assessment of patients' cognitive function might not provide an accurate measure of the actual incidence of cognitive failures, in a number of studies it has been found that the opinion of an observer (for example, a relative) has greater validity. Future studies might include these proxy ratings to get more insight in the exact meaning of deficits found in formal evaluations for patients' everyday living.

In evaluating the current study and the study of Wieneké and Dienst in terms of patterns of cognitive deficits found, the following statements can be made. Although the test programs differed between the studies, there was also substantial overlap. Attention, speed of information processing, motor speed, and visual memory seemed to be the most frequently impaired functions. We have recently reported cognitive deficits in a group of high-risk breast carcinoma patients who were randomly assigned to receive either high-dose adjuvant chemotherapy and peripheral stem cell transplantation or standard-dose adjuvant chemotherapy, using the same tests as in the current study. It was found that high risk breast carcinoma patients treated with high dose chemotherapy had a 8.2 times higher risk for cognitive impairment as compared with a nontreated control group consisting of axillary lymph node negative breast carcinoma patients (OR = 8.2; 95% CI, 1.8-37.7; P = 0.006) and a 3.5 times higher risk as compared with breast carcinoma patients treated with standard-dose adjuvant chemotherapy (OR = 3.5; 95% CI, 1.0-12.8; P = .056). The pattern of deficits suggests that cognitive impairment is not restricted to a specific modality, but rather appears to be generalized, i.e., it is not possible to indicate a specific region of the brain that is affected. Because the patients in our study were not randomly assigned (or not assigned) to adjuvant chemotherapy, it may be argued that other variables linked to the reason why some patients receive adjuvant chemotherapy and others do not could explain, at least in part, observed differences in cognitive functioning. In accordance with treatment policy in the Netherlands, CMF chemotherapy was given to patients with operable breast carcinoma staged as axillary N1 (M0) and not to patients with operable disease staged as axillary N0 (M0).
Patients readily comply with this treatment policy, so individual choice hardly played any role. Also, at the time of testing, all patients were clinically disease free. In theory, factors related to prognosis, such as anxiety and depression, could account for observed differences in cognitive functioning, but the results from our study showed that depression and anxiety had no influence on the cognitive test performances of the patients.

The current study suggests that chemotherapy itself caused the cognitive impairment observed in a number of our patients. It may be speculated whether this late neurotoxicity was caused by the combination of cytostatic drugs or by one drug in particular. Cyclophosphamide has never been associated with neurotoxicity except for a rarely occurring SIADH syndrome (syndrome of inappropriate secretion of antidiuretic hormone). Neurotoxicity is an infrequent complication of 5-fluorouracil that may consist of an acute cerebellar syndrome or, even more rarely, an acute encephalopathy. These syndromes are acute and reversible, and they probably do not occur at conventional doses of 10mg/kg or less, as employed in the treatment of our patients. Methotrexate (MTX) is the cytostatic agent that is most frequently associated with late cognitive impairment. Symptoms of MTX-induced late neurotoxicity may range from personality changes and memory loss to progressive dementia. However, this late neurologic complication usually occurs after combined treatment of cranial radiation therapy (RT) with intrathecal MTX or high dose intravenous MTX. Late neurotoxicity following conventional doses of MTX, as given to our patients, without cranial RT or intrathecal MTX, has never been reported. Comparison of the late side effects of CMF with other adjuvant regimens, such as cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) and 5-fluorouracil, epidoxorubicin, and cyclophosphamide (FEC), might be useful in elucidating the possibility that conventional dose MTX causes damage to brain function.

The objective of adjuvant chemotherapy for patients with breast carcinoma is to cure, and any irreversible toxicity from treatment may affect the quality of life of patients for many years. Because cognitive deficits can be profoundly disabling, it is essential to document these neuropsychologic problems in a systematic manner. Our results suggest that proper evaluation of cognitive functioning cannot be solely based on self-reports of patients in quality-of-life measures, and that objective testing by means of standardized neuropsychologic tests is the method of choice in assessing neuropsychologic problems. Our findings stress the importance of evaluating impaired cognition as a side effect of chemotherapy. We believe that cognitive deficits after chemotherapy will be increasingly addressed as a major area for research.

References
Cognitive deficits after conventional CMF chemotherapy


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