Persistent Neurocognitive Problems After Adjuvant Chemotherapy for Breast Cancer

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Abstract

Background: Neurocognitive problems have been observed in a number of women previously treated with adjuvant chemotherapy for breast cancer. The present study aims to combine the results of neuropsychological and electrophysiological techniques collected in patients with breast cancer treated with cyclophosphamide/methotrexate/5-fluorouracil (CMF) at different time points. Patients and Methods: Patients with breast cancer treated with adjuvant CMF chemotherapy (n = 63) were examined with neuropsychological tests 1 year after treatment and compared with healthy women (n = 60; T1 portion of the study). Based on neuropsychological test performance, patients were classified as cognitively impaired or unimpaired. Four years later, behavioral and neuropsychological measures (T2 portion of the study) were collected during an information-processing task in a subgroup of patients (n = 26). At T2, we compared the results of cognitively impaired patients (n = 8) with those of patients classified as cognitively unimpaired at T1 (n = 18).

Results: In the initial neuropsychological assessment, 33.3% of the patients were classified as cognitively impaired, compared with 10% of healthy women. At T2, impaired patients who received CMF showed longer P3 latencies, lower P3 amplitudes, longer reaction times, and made more errors in an information-processing task compared with unimpaired patients who received CMF. Conclusion: The results indicate the persistence of neurocognitive problems ≤ 5 years after completion of chemotherapy and consistency across different assessment techniques.

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Key words: Blood-brain barrier, Cognitive dysfunction, Electrophysiology, P3 Latency

Introduction

Previous adjuvant cytotoxic treatment for breast cancer is associated with cognitive deficits and abnormalities in brain functioning.1-7 We found, for example, that 2 years after treatment with cyclophosphamide/methotrexate/5-fluorouracil (CMF), 28% of a group of patients with breast cancer showed cognitive impairment on neuropsychological tests compared with 12% of a breast cancer control group not treated with chemotherapy.8 Also, a neuropsychological study in a similar patient group supported the existence of neurocognitive problems after CMF treatment.9 Although studies that use different techniques to examine the cognitive sequelae of chemotherapy consistently show that a proportion of patients exhibit cognitive deficits, no clear cognitive profile has yet been established.10 Until now, these diverse techniques, like electrophysiological and neuropsychological tests, have hardly ever been combined in studies of neurocognitive problems after cytostatic treatment. Associations between a variety of neurocognitive measures might help elucidate the mechanisms behind these problems.

The present study aims to combine the results of newly acquired neuropsychological data (T1 portion of the study) and neuropsychological techniques (T2 portion of the study)10 collected in patients with breast cancer treated with CMF at different time points. The main goal was to examine the persistence of neurocognitive problems ≤ 5 years after completion of chemotherapy and consistency across different assessment techniques.

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sistence of cognitive deficits over time and the consistency of findings with different techniques. To achieve this goal, we first performed a neuropsychological examination in a new sample of patients treated with CMF chemotherapy approximately 1 year after completion of chemotherapy. A neuropsychological test battery was used to examine performance in various domains of cognitive functioning. The results of the patients treated with CMF were compared with the results of a group of healthy women. Second, to evaluate whether the cognitive problems after chemotherapy have a permanent character and persist on a neuropsychological level of functioning, we performed an electrophysiological examination 4 years later. Because speed of information processing is a domain that appeared to be consistently affected in previous studies that examined chemotherapy-induced cognitive impairment, 6,8 we used an information-processing task, during which behavioral and neurophysiological measures were collected. We compared reaction time, P3 amplitude, and P3 latency between cognitively impaired and unimpaired patients, as was determined at the initial neuropsychological assessment. In a previous study that focused on neurophysiological data, the complete sample of patients with breast cancer treated with CMF chemotherapy were compared with the data of a sample of patients with stage I breast cancer not treated with chemotherapy. 9,10 The P3 component is associated with high-level attention-dependent cognitive processing. 11 Its amplitude is generally assumed to be related to the intensity of activation of neural structures, whereas its latency indexes the duration of stimulus evaluation processes and is relatively independent of the time required for response selection and execution.

Patients and Methods

Patients and Therapy

In the neuropsychological part of the current study, a group of patients with lymph node–positive breast cancer who received adjuvant chemotherapy was compared with a control group of healthy women. The patients with breast cancer 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) after surgery. Before chemotherapy, patients received local radiation therapy. Patients were invited by their treating physician to take part in the neuropsychological study. All subjects gave written informed consent, and the institutional review board approved the study. Exclusion criteria for participation in the neuropsychological study were (1) the presence of metastatic disease or relapse; (2) a history of neurologic/psychiatric signs or symptoms that might lead to deviant neuropsychological test results; (3) the use of medication that might lead to deviant neuropsychological test results; and (4) alcohol and/or drug addiction. Basic proficiency in the Dutch language was an inclusion criterion.

Patients were tested neuropsychologically 6-12 months after completion of therapy (but hormonal treatment could be ongoing). Healthy controls were recruited via patients. Patients were asked to invite a female friend or relative of approximately similar age to serve as a control. Inclusion and exclusion criteria for the control group were the same as for the patients with breast cancer, with the additional exclusion criterion of a medical history of malignancies.

Four years after neuropsychological assessment, patients who still fulfilled the aforementioned inclusion criteria were asked to participate in the neurophysiological part of the study, in which an information-processing task was administered with concurrent electroencephalography registration. In this second part of the study, patients who were classified as cognitively impaired in the neuropsychological part of the study are compared with those who were not cognitively impaired. We were particularly interested if the neurocognitive problems would sustain on another level, i.e., by means of electrophysiological techniques and reaction time analysis. Therefore, we decided not to repeat the exact same neuropsychological examination but to use an information-processing task comparable with one of the tasks in the neuropsychological test battery (the Additive Factors Method [AFM] task). We chose the AFM task because speed of information processing appears to be consistently affected in previous studies of cognitive deficits after chemotherapy. 6,8 In addition, by this procedure we avoid the influence of practice effects on the neurocognitive outcome measures.

Measures

Neuropsychological Examination (T1: 6-12 Months After Chemotherapy). Neuropsychological testing consisted of 10 tests (24 test indices). The tests were divided into focused and sustained attention (Trail Making A, 12 Digit Symbol of the Wechsler Adult Intelligence Scale [WAIS], 13 Stroop Color Word Test cards 1 and 2, 14 Eriksson Task, 15 Working-Memory Updating, 16 verbal memory [Dutch version of the California Verbal Learning Test], 17 visual memory [Visual Reproduction of the Wechsler Memory Scale], 18 processing speed [AFM Task], 19,20 mental flexibility [Trail Making B, 12 Stroop Color Word Test interference score], 14 verbal functioning [Word Fluency 21] and motor functioning [Fepsy Finger Tapping 22]). The Dutch Adult Reading Test was included in the battery to obtain a measure of premorbid intelligence. 23

Neurophysiological Examination (T2: 5 Years After Chemotherapy: Electrophysiological Recording). Patients were examined at the Department of Clinical Neurophysiology of the Slotervaart Hospital (Amsterdam, the Netherlands) in a semidark soundproof room. The electroencephalogram (EEG) was recorded with 32-channel tin electrodes Quickspec® referenced to the left mastoid. Eye movements were recorded from bipolar tin-electrode pairs placed above and below the left eye and left and right of the outer canthi of both eyes. AFz served as a ground electrode. Impedances were kept below 5 kOhm. The EEG signals were amplified by a SynAmps® ampli-
fier. Signals were recorded for a 2048-ms period starting 200 ms before stimulus presentation, digitized at 250 Hz, and band pass filtered between 0.15 Hz and 40 Hz.

**Neurophysiological Examination (T2): 5 Years After Chemotherapy; Information Processing Task.** The subject’s task was to determine the direction of a double arrowhead and to give the designated response. Reaction times and errors were determined. Brain activity was monitored continuously during task performance. Event-related potentials (ERPs) consist of a series of electrical potentials that are elicited while events are processed. One of the ERP components, the P3 potential, is easily observed and has been used widely because it is able to detect subtle cognitive deviations. The amplitude and latency of the P3 component were determined. The P3 peak latency indexes the duration of stimulus evaluation processes and is relatively independent of the time required for response selection and execution. The P3 amplitude is assumed to be related to the intensity of activation of neural structures. For a more elaborate description of this task, see Kreukels et al.

**Anxiety, Depression, and Fatigue (T1 and T2).** To evaluate the possible role of psychological distress and fatigue in neurocognitive outcome, 2 questionnaires were administered at both time points. The Hopkins Symptom Checklist-25 was used to assess the occurrence of depression and anxiety. Patients were required to indicate, on a 4-point Likert scale from 1 (not at all) to 4 (very much), how much they were troubled by a problem in the previous week. Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20). The MFI-20 consists of 20 items on 5 subscales (general fatigue, physical fatigue, mental fatigue, reduction in activity, and reduction in motivation).

**Statistical Analysis**

**Sociodemographic Characteristics and Self-Reported Measures.** Between-group differences in sociodemographic characteristics and depression, anxiety, and fatigue were analyzed by χ² tests for contingency tables and independent samples t tests.

**Neuropsychological Assessment.** Cognitive functioning was evaluated by comparing the neuropsychological test performance between the group of patients with breast cancer treated with chemotherapy and the test performance of the healthy control group. Each neuropsychological test score was converted into a standard score (Z score) using the mean test score and the standard deviation (SD) of the healthy control group as a reference.

Patients who scored 2 SDs below the mean of the reference group on a test were considered impaired on that test. An overall impairment score was calculated for each individual patient by counting all tests on which the patient was impaired. The 95th percentile of the healthy reference group was used as a cutoff score to distinguish between disturbed and unaffected cognitive functioning; the application of this algorithm to the data indicates that a participant is classified as cognitively impaired when she has deviant test scores on ≥ 3 of the 24 test indices. Following this criterion (i.e., 2 SDs below the mean of the reference group on ≥ 3 tests), each participant was classified as cognitively intact or impaired. Binomial testing was carried out to determine whether the observed percentages of patients with breast cancer classified as impaired differed from the fixed 5% of impaired cases in the healthy control group.

Logistic regression models were used to study the contribution of potential confounding factors to the risk of being classified as cognitively impaired. The following variables were entered into the model with the control group as reference: therapy (yes or no), age, IQ, anxiety, depression, and fatigue. A forward stepwise selection procedure was performed to determine whether those variables influenced the model. Because we solely tested the variable of individual cognitive impairment (yes or no) in the multivariate logistic regression analysis, we circumvented problems associated with multiple testing.

**Neurophysiological Assessment (T2).** To determine whether the T2 outcome measures of patients who are cognitively impaired at the neuropsychological assessment differ from those that are cognitively intact, patients that participated in the neurophysiological study were divided into 2 groups (an intact and an impaired group). The P3 component amplitude and latency were quantified by scanning for the most positive peak within a specified time window (240-600 ms) at the Pz channel (for a more elaborate description of neurophysiological data processing, see Kreukels et al). The 2 groups were compared on neurophysiological and behavioral measures, and anxiety, depression, and fatigue with independent samples t tests. If necessary, P values were corrected for potential confounding factors such as age and premorbid IQ by means of univariate analysis of covariance. P values were corrected for multiple comparisons according to Bonferroni. The d-statistic was used to estimate the effect sizes of observed differences between the impaired and unimpaired group (d = the difference between means for 2 groups divided by the pooled SD). In behavioral science, d values of 0.2 are considered small, those of 0.5 moderate, and those of ≥ 0.8 large.

We also examined correlations of our neurophysiological outcome measures with impairment on T1 on a continuous scale (degrees of impairment). Therefore, we used Spearman rank-order correlations to examine the relations between total number of deviant tests on neuropsychological assessment with P3 amplitude, P3 latency, reaction times, and errors. For all analyses, a P value ≤ 0.05 was required for significance.

**Results**

**Sociodemographic and Clinical Characteristics**

Of the 84 patients with breast cancer who were treated with CMF chemotherapy between 1997 and 1998 and who
Table 1: Socioeconomic and Clinical Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CMF Group (n = 63)</th>
<th>Control Group (n = 60)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychological Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>46.6 (6.7)</td>
<td>48.8 (6)</td>
<td>.064</td>
</tr>
<tr>
<td>Mean premorbid IQ score (SD)**</td>
<td>101.8 (13.7)</td>
<td>105.1 (14.1)</td>
<td>.195</td>
</tr>
<tr>
<td>Mean time since treatment, years (SD)</td>
<td>.96 (3.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Postmenopausal (%)†</td>
<td>85.7</td>
<td>38.3</td>
<td>.000</td>
</tr>
<tr>
<td>On Tamoxifen (%)</td>
<td>39.7</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>Neurophysiological Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>51.5 (5.6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean premorbid IQ score (SD)**</td>
<td>100.9 (14.4)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean time since treatment, years (SD)</td>
<td>5.1 (6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Postmenopausal (%)†</td>
<td>92.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>On Tamoxifen (%)</td>
<td>23.1</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

*Two-sided P value: independent samples t test in case of mean age and IQ score, z test in case of menopausal status and tamoxifen use.

†Assessed using the Dutch Adult reading test as a surrogate measure of premortem intelligence.

‡At the time of neuropsychological assessment: postmenopausal status defined by the absence of irregular menstrual cycles (not possible to use the criterion of amenorrhea for 12 months because time since treatment is 12 months on average, and treatment itself affects menopausal status).

§At the time of neuropsychological assessment: postmenopausal status defined by amenorrhea for at least 12 months.

Table 2: Self-Reported Psychological Distress and Fatigue

<table>
<thead>
<tr>
<th>Assessment</th>
<th>CMF Group (n = 63)</th>
<th>Control Group (n = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSCL Total*</td>
<td>16.8 (11.9)</td>
<td>9.2 (7.9)</td>
<td>.000</td>
</tr>
<tr>
<td>HSCL Anxiety*</td>
<td>16.3 (12.3)</td>
<td>8.7 (7.9)</td>
<td>.000</td>
</tr>
<tr>
<td>HSCL Depression*</td>
<td>17.1 (13.6)</td>
<td>9.6 (9.2)</td>
<td>.001</td>
</tr>
<tr>
<td>MFI Total*</td>
<td>47.1 (17.5)</td>
<td>33.7 (12.2)</td>
<td>.000</td>
</tr>
</tbody>
</table>

*Mean scores with SDs in parentheses. Abbreviation: HSCL = Hopkins Symptom Checklist-25

Table 3: Relative Risk for Cognitive Impairment on Average One Year After Completion of Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment*</td>
<td>5.51</td>
<td>1.86-16.28</td>
<td>.002</td>
</tr>
<tr>
<td>Age</td>
<td>1.14</td>
<td>1.04-1.26</td>
<td>.007</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>.96</td>
<td>.93-1.00</td>
<td>.048</td>
</tr>
</tbody>
</table>

*Healthy controls as reference group. Abbreviation: OR = odds ratio (expected)

Risk for Neuropsychological Impairment. The risk for cognitive impairment was significantly increased for patients treated with CMF chemotherapy compared with healthy controls (odds ratio, 5.5; 95% CI, 1.9-16.3; P = .002). Anxiety, depression, and fatigue appeared to make no significant contribution to the model. Age and IQ had a small effect on the risk for cognitive impairment. The results of the final model are shown in Table 3.

Neurophysiological Outcome Measures (T2)

Participants of the neurophysiological study did not differ from nonparticipants in age or premorbid IQ at neurophysiological assessment. Of the participants in T2 (n = 26), the neurophysiological part of the study, 30.8% of the patients were classified as cognitively impaired, which was not significantly different from the percentage of the patients who did not participate at T2 (35.1%; P = .790).

Within the CMF group that participated in T2, cognitively impaired patients were significantly older (n = 8; mean age, 65.5 years; SD, 4.2 years) than unimpaired patients (n = 18; mean age, 49.8 years; SD, 5.3 years; P = .013). Therefore, P values are corrected for age. Menopausal status and tamoxifen use in patients was comparable at neurophysiological assessment for cognitively impaired and unimpaired patients.

met our inclusion and exclusion criteria, 18 (21.4%) declined to participate. Additionally, 3 patients could not be reached. A total of 63 patients with breast cancer and 80 healthy controls participated in the neuropsychological part of the study. Patient demographic and clinical characteristics are summarized in Table 1.

The patients with breast cancer differed significantly from the healthy reference group with regard to menopausal status, and there was a trend toward significance with regard to age. The neuropsychological assessment took place on average almost 1 year after completion of chemotherapy. Of the 63 patients treated with CMF, 25 were on endocrine treatment (ie, tamoxifen) at the time of the neuropsychological assessment.

Four years later, at the time of neuropsychological assessment, 46 patients treated with CMF still fulfilled the inclusion criteria; 17 of these (37%) declined to participate in the neuropsychological study. Additionally, 3 patients cancelled their appointment or could not be reached.

Neuropsychological Test Performance (T1)

According to the criterion for cognitive impairment, 33.3% of the patients treated with CMF could be classified as cognitively impaired, compared with 10% of the subjects in the control group (binomial testing, P < .001). There was no difference in menopausal status between impaired and unimpaired patients. Within the CMF group, tamoxifen use did not differ between cognitively impaired and unimpaired patients. Patients treated with CMF chemotherapy had significantly higher scores than healthy controls on self-reported anxiety, depression, and fatigue (Table 2; higher scores indicate more symptoms).
Patients who were cognitively impaired had longer P3 latencies and lower P3 amplitudes (Table 4; Figure 1). Table 4 further shows that impaired patients had longer reaction times and made more errors in the information-processing task. When the P values are corrected for multiple comparisons according to the Bonferroni method, the differences in P3 latency and reaction time between the 2 groups remained significant.

**Relationships Between Neuropsychological Measures (T1) and Neuropsychological Measures (T2)**

Spearman rank-order correlations showed that the total number of deviant tests correlates positively with the number of errors (ρ = .524; P = .008) and reaction time (ρ = .647; P < .001; behavioral measures). Furthermore, a positive correlation was observed between the total number of deviant tests and P3 latency (ρ = .557; P = .005), and a negative correlation was seen with P3 amplitude (ρ = -.572; P = .002).

A high correlation was observed between processing speed (reaction time) measured during neuropsychological assessment (T1) and reaction time measured during neuropsychological assessment (T2): ρ = .636; P < .001. Furthermore, the correlation between reaction time at T1 and the P3 latency at T2 is ρ = .344; P = .085.

**Discussion**

In the present study, the results of neuropsychological and neurophysiological techniques collected in patients with breast cancer treated with CMF at different time points after treatment were combined. The main goal was to examine the persistence of cognitive deficits over a longer period, while at the same time examining their consistency across different assessment techniques. One year after CMF treatment, 38% of the patients were classified as cognitively impaired on neuropsychological tests, compared with 10% of the healthy controls. Four years later, the patients treated with CMF who were impaired showed longer P3 latencies and longer reaction times in an information-processing task compared with unimpaired CMF patients. Moreover, the cognitively impaired patients had lower P3 amplitudes and made more errors than did unimpaired patients. Also, strong associations appeared between the total number of deviant tests that involved multiple cognitive domains at T1 and the behavioral and neurophysiological outcome measures collected 4 years later restricted to the domain of information processing.

First, the parallel findings of neuropsychological and neurophysiological measures provide strong support for the existence of a negative effect of treatment on the cognitive functioning of a subgroup of patients with cancer. Secondly, our results indicate that the neuropsychological problems found 1 year after treatment are not temporary and persist as neurophysiological abnormalities until ≥5 years after treatment. Thirdly, our data suggest that there might be an underlying process that can account for the wide variety of cognitive problems often observed after chemotherapy; our previous studies and those of others have shown that speed of information processing is one of the domains that seems consistently affected by cytotoxic treatment.6,8,35 For that reason, our neurophysiological assessment was focused on this domain. Although considerable time has elapsed between the 2 measurements, the strong correlations between the broader neuropsychological outcome measure and the information processing measures show that this choice was justified.

Processing speed can be viewed as a fundamental part of the architecture of human cognition.36 The idea that information processing might underlie the deficits found in other cognitive domains bears a resemblance to the processing speed theory of aging that is formulated by Salhouse.37 This theory suggests that a major factor contributing to age-related differences in cognitive functioning is a reduction with increased age in the speed with which many cognitive operations can be executed. Also, based on their metaanalysis of studies on the neuropsychological effects of cancer treatment, Anderson-Hanley and colleagues propose slowing of mental processing as a common underlying theme that might tie the observed deficits across domains together.38 Further support for the slowing of cognitive processes in chemotherapy-treated patients comes from our own data. While exploring the group means on neuropsychological
tests, it appears that especially speeded tasks (Stroop, Digit symbol, Trail making, Eriksen task) differentiate between the patients treated with CMF and the healthy controls. Also, P3 latency was significantly prolonged in the impaired group compared with the unimpaired group. P3 latency is generally prolonged in disorders with cognitive dysfunction (e.g., schizophrenia, dementia). Therefore, for future studies on cognitive dysfunction after cytotoxic treatment, we suggest to pay particular attention to tasks with a time element and to explore the possibility of diminished processing speed as a common cause for cognitive decline more explicitly.

Notwithstanding the interesting results of our study, there are clearly several limitations. First of all, because of the cross-sectional design, we cannot rule out the possibility that the cognitive problems observed in some of the patients treated with CMF were preexistent (present before the start of chemotherapy). Findings of previous studies indicated that patients with breast cancer who received surgery and radiation therapy but no chemotherapy performed on a similar level as healthy controls. We think that it is unlikely that the cognitive deficits we currently observe can be attributed to the fact that patients are confronted with cancer and subsequent surgery and radiation therapy. Second, although all eligible patients treated in our hospital between 1997 and 1998 were asked to participate in both assessments, some patients were lost because of refusal or disease progression, which left us with a rather small and potentially biased sample. However, patients who participated in the second assessment did not differ from nonparticipants in age, pre-morbid IQ, or percentage impaired on the neuropsychological assessment. Third, repetition of the neuropsychological assessment at the time of the neuropsychological examination would have made our study stronger. However, we considered a combination of an extensive neuropsychological and a neuropsychological examination too burdensome for the patients. Nevertheless, we feel that our neuropsychological findings can be interpreted as a confirmation of the persistence of cognitive problems or at least as an indication of abnormalities in brain functioning in these patients. High correlations were found between the reaction times of the patients at T1 (the neuropsychological examination) and T2 (the neuropsychological examination). Also, the P3 component is generally viewed as an expression of cognitive functioning, and in a previous study of our group, the P3 latency was found to be associated with the total number of deviant neuropsychological tests.

Also, other factors might have influenced the cognitive functioning of our patients, such as menopausal status, hormonal treatment, depression, anxiety, and fatigue. However, in line with the results from previous studies, we did not observe a relation between anxiety, depression, and fatigue and the cognitive test results in our patients. Also, at both measurement points there appeared to be no difference in the percentage of tamoxifen users and postmenopausal women between the cognitively impaired group and the cognitively intact group.

The etiologic mechanisms underlying cognitive compromise after adjuvant chemotherapy are still largely unknown. They might vary across different chemotherapy regimens and depend on the ability of the specific components of these regimens to penetrate the blood-brain barrier (BBB). With a few exceptions, anticancer drugs are thought to be barred from the brain by the BBB. Of the currently used CMF regimen, 5-FU is known to cross the BBB, but late neurotoxicity has not been reported. Methotrexate is documented to cross the BBB only in higher dosages than were given to our patients, and neurotoxicity of systemically administered conventional doses has never been described. Cyclophosphamide is not known to easily cross the BBB. Thus, there appears to be no easy explanation for our results in terms of penetration of drugs into the brain. However, recent animal studies show effects of different anticancer agents on the brains of mice and rats. A study by Winocour and colleagues showed the effects of methotrexate and 5-FU on cognitive function in mice. The behavioral pattern of the drug-treated mice indicated primary deficits in executive and memory functions, thought to be controlled by frontal lobe and hippocampal brain regions, respectively. In another study from our own group, a single administration of methotrexate induced a dose-dependent decrease in cell proliferation (a decrease in neurogenesis) in the hippocampal formation in rats that was also reflected in their cognitive behavior. Interestingly, even the lowest dose given to the animals (37.5 mg/kg) already resulted in a significant decrease in cell proliferation.

Few studies in humans have addressed the effects of chemotherapy on brain mechanisms. However, 2 recent studies did find deleterious effects of anticancer agents on the brain. A positron emission tomography study in patients with breast cancer treated with adjuvant chemotherapy showed altered frontocortical, cerebellar, and basal ganglia activity during performance of a short-term recall task 5-10 years after treatment. In addition, Inagaki and
colleagues reported smaller grey and white matter volumes (including prefrontal, parahippocampal, cingulate gyrus, and precuneus) 1 year after treatment but not 3 years after treatment.46 Whereas our study suggests the persistence of neurocognitive problems over a longer period, the Iagnaki study suggests recovery from cognitive impairment 3 years after treatment. In this last study, however, there was a difference in the composition of the study sample between the 1-year study and the 3-year study. In the 1-year study, 78% of the patients were treated with CMF, whereas in the 3-year study, only 51% of the patients were treated with CMF. This difference in sample composition might possibly have accounted for the difference between the findings of the 1-year and 3-year studies.

Conclusion

Gradually, we come to a broader understanding of cognitive deficits after adjuvant chemotherapy in patients with breast cancer. The present study indicates the persistence of neurocognitive problems ≤5 years after completion of treatment. Our results also show consistency over different assessment techniques and give rise to the idea that the slowing of information processing might elicit a diversity of chemotherapy-related neurocognitive problems. Future studies should further investigate problems in information processing as an underlying cause, while also examining the contribution of other cognitive processes in an ERP experiment.

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