Effects of High-Dose and Conventional-Dose Adjuvant Chemotherapy on Long-Term Cognitive Sequelae in Patients with Breast Cancer: An Electrophysiologic Study

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Abstract

Background: The mechanisms underlying cognitive deficits found in a number of patients with breast cancer treated with adjuvant chemotherapy are still unclear. In the current study, we used a combination of measures of brain electric activity and cognitive performance during information processing to elucidate the origin of these cognitive deficits. Patients and Methods: Twenty-nine patients at high risk with breast cancer treated with adjuvant conventional-dose cyclophosphamide/epirubicin/5-fluorouracil or adjuvant high-dose cyclophosphamide/thiotepa/carboplatin were compared with 23 patients with stage I breast cancer not treated with chemotherapy approximately 4 years after completion of treatment. We studied reaction times and the amplitudes and latencies of the P3, an electrophysiologic index of information processing, in a task with different conditions related to input, central, and output processing of information. Results: The amplitude of the P3 component was significantly reduced in patients with breast cancer treated with high-dose cyclophosphamide/thiotepa/carboplatin compared with patients with breast cancer not treated with chemotherapy. We observed no significant differences in reaction times and P3 latency between the treatment groups. Conclusion: Our data show electrophysiologic alterations in patients with breast cancer treated with high-dose chemotherapy 4 years after completion of treatment. The observed P3 reduction might be a result of suboptimal phasic cortical arousal and problems with the allocation of processing resources in these patients.


Key words: Cognitive deficits, Information processing, Long-term side effects, Neurotoxicity, P3

Introduction

Increased survival in patients with breast cancer treated with adjuvant chemotherapy and the clinical observation that some of these patients experienced cognitive problems up to a few years after completion of treatment triggered studies into cognitive functioning after cytostatic treatment.1-6 Neuropsychologic studies showed cognitive deficits in a broad domain of functioning (memory, information processing, and attention) up to several years after treatment. Although, in most studies, the effects of adjuvant standard-dose regimens were reported, adjuvant high-dose regimens might result in even more problems in cognitive functioning after treatment. In an earlier study in 104 patients with breast cancer an average of 2 years after completion of treatment, we observed cognitive impairment...
in 32% of the patients treated with high-dose chemotherapy (4 courses of FEC chemotherapy [5-fluorouracil 500 mg/m² intravenously (i.v.), epirubicin 120 mg/m² I.V., and cyclophosphamide 500 mg/m² i.v.] and 1 course of the high-dose CTC regimen [cyclophosphamide 5 g/m² I.V., thiota 480 mg/m² I.V., and carboplatin 1.6 g/m² I.V.] with peripheral blood progenitor cell transplantation), in 17% of patients treated with standard-dose chemotherapy (5 courses of FEC chemotherapy), and in 9% of the patients with stage I disease not treated with chemotherapy. Furthermore, a neuropsychologic evaluation in a subgroup of these patients revealed asymmetric symmetry of the alpha rhythm (i.e., oscillatory brain electric activity at frequencies of approximately 10 Hz) in 41.2% of patients treated with high-dose chemotherapy, 12.5% of patients treated with standard-dose chemotherapy, and none of the control patients. Thus, the incidence of long-term neurocognitive problems and neuropsychologic alterations appeared to be higher in patients treated with the high-dose CTC regimen compared with patients treated with the standard-dose FEC regimen. At the time we started the current study, the value of high-dose chemotherapy as adjuvant treatment for breast cancer was unknown. Nevertheless, many women were treated with high-dose regimens within and outside clinical trials. Because high-dose chemotherapy might be associated with more iatrogenic effects, it is of high importance to study its side effects compared with the conventional-dose therapy, including the effects on cognitive functioning.

The mechanisms underlying neurocognitive problems after exposure to chemotherapy remain to be elucidated. In a series of studies, we used a combination of measures of brain electric activity and cognitive performance during information processing to try to clarify the origin of cognitive deficits after chemotherapy. In the previous study, patients treated with conventional CMF (cyclophosphamide/methotrexate/5-fluorouracil) chemotherapy were studied, whereas in the current study, patients with breast cancer treated with high-dose CTC or conventional-dose FEC adjuvant chemotherapy will be compared with patients with stage I breast cancer not treated with chemotherapy.

Brain activity is monitored continuously during task performance. Event-related potentials (ERPs) consist of a series of electric potentials that are elicited while events are processed. One of the ERP components, the P3 potential, is easily observed and has been widely used because it is able to detect subtle cognitive deviations. 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.

Abnormalities in the P3 component-like amplitude reduction and latency prolongation are observed in various psychiatric and neurologic disorders associated with neurocognitive problems. Studies in cancer survivors observed a prolonged P3 latency in long-term acute lymphoblastic leukemia survivors who had received combination chemotherapy and mostly prophylactic cranial irradiation and intrathecal methotrexate, as well as in patients treated for solid tumors outside the central nervous system (CNS) who received similar chemotherapy but did not receive prophylactic treatment to the CNS. Because both groups had similar changes in P3 latency, they suggested that similarity in treatment, rather than specific disease, was the cause (directly or indirectly) of the neurocognitive deficits observed.

In our previous study, patients with breast cancer treated with CMF chemotherapy showed an earlier and reduced P3 component compared with patients with breast cancer not treated with chemotherapy on all conditions of an information-processing task. These results suggested abnormalities in brain functioning in these patients ≤5 years after completion of treatment.

Because speed of information processing appeared to be affected in patients with cancer treated with chemotherapy and problems in information processing might underlie various other neurocognitive problems, we used an information processing task to collect P3 as well as reaction-time data. This computer task is based on the Additive Factors Method, which rests on the assumption that information processing proceeds through a series of discrete and serially organized stages. The duration of processing in each stage can be influenced separately by experimental manipulations that target these stages. Reaction time can be used to measure the efficiency of processing within these stages. The task variables, i.e., stimulus discriminability, stimulus-response compatibility, and response complexity, are assumed to affect the duration of stimulus identification (related to input or perceptual processing), response selection (related to central processing), and response preparation (related to output or motor processing), respectively. The effects of the different chemotherapy regimens on different information processing stages can be examined by studying the effects of the independent task variables and treatment on reaction time and P3 amplitude and latency.

Consistent with previous findings, we expect to observe a slowing of information processing in patients treated with chemotherapy as reflected in longer reaction times, with a more pronounced slowing in patients treated with high-dose chemotherapy than in patients treated with conventional-dose chemotherapy. When the chemotherapy regimen affects particular stages of information processing, interaction effects will be observed between the treatment group and the task variables associated with these processing stages. Such interaction effects will reflect a larger increase in reaction time in the difficult compared with easy conditions in the groups treated with chemotherapy compared with the control group. Furthermore, because P3 latency appears to be proportional to the duration of stimulus-evaluation processes and is relatively independent of the time required for response selection and execution, it might help to locate effects of treatment in stimulus evaluation– or response-related processes. Differences between
the treatment groups in P3 amplitude might indicate differences in the intensity of activation of neural structures during information processing. These data might help us in understanding the mechanisms underlying neurocognitive deficits found in a number of patients with breast cancer treated with adjuvant chemotherapy.

**Patients and Methods**

**Patients**

Three groups of patients participated in the current cross-sectional study approximately 4 years after treatment: a group of patients at high risk with breast cancer treated with high-dose adjuvant chemotherapy, a group of patients at high risk with breast cancer treated with standard-dose chemotherapy, and a control group consisting of patients with stage I breast cancer not treated with chemotherapy. The patients were recruited from a database of a prospective neuropsychologic study performed in the Antoni van Leeuwenhoek Hospital/Netherlands Cancer Institute. The study was approved by the institutional review board. The patients at high risk with breast cancer participated in a multicenter randomized trial. In this trial, patients aged < 50 years who had ≥ 4 tumor-positive axillary lymph nodes were randomly assigned to receive conventional-dose adjuvant treatment or high-dose treatment. The conventional-dose group received 5 courses of FEC (5-fluorouracil 500 mg/m², epirubcin 90 mg/m², and cyclophosphamide 500 mg/m²) I.V. every 3 weeks. In the high-dose group, the fifth course of FEC was replaced by a course of CTC with autologous peripheral blood hematopoietic progenitor cell transplantation. All patients received locoregional radiation therapy after completion of chemotherapy and were treated with tamoxifen (40 mg daily) for 2.5 years if they had hormone receptor-positive cancer. Patients in the third group had undergone surgery followed by locoregional radiation therapy and had not received chemotherapy.

Patients had to fulfill the following inclusion criteria: (1) no presence of metastatic disease or relapse, (2) no history of neurologic or psychiatric signs that might lead to deviant test results, (3) no use of medication that might lead to deviant test results, (4) no alcohol or drug abuse, and (5) sufficient command of the Dutch language. Written informed consent was obtained from all participants according to institutional guidelines.

**Study Measures**

**Cognitive Problems.** A semistructured interview about problems in memory, concentration, thinking, and language experienced in daily life was administered.7,23

**Psychological Distress.** Hopkins Symptom Checklist-25 (HSCL-25) was used to assess the occurrence of depression and anxiety.24-26 Patients had 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 past week.

The Profile of Mood States (POMS) is a questionnaire for the measurement of moods.27 The shortened version consists of 32 items measuring 6 dimensions (depression, anger, fatigue, vigor, and tension). The POMS is frequently used in physiologic studies and pharmacologic studies to control for changes in mood during the experimentation session and is also used in neurocognitive outcome studies in patients with cancer.28 The POMS was administered at the beginning and end of the experimentation session.

**Fatigue.** Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20).29,30 The MFI-20 consists of 20 items on 5 subscales (general fatigue, physical fatigue, mental fatigue, reduction in activity, and reduction in motivation).

**Electrophysiologic Recording.** Patients were examined at the Department of Clinical Neurophysiology of the Slotervaart Hospital in a semidark soundproof room. The electroencephalogram (EEG) was recorded with a 32-channel tin-electrodes Quickcap® referenced to the left mastoid. We used the Pz channel to mastoid for further calculations. Eye movements were recorded from bipolar tin-electrode pairs placed above and below the left eye and left and right of the outer canthus of both eyes. The AFs channel served as a ground electrode. Impedances were kept below 5 kΩ. The EOG signals were amplified by a SynAmps® amplifier. Signals were recorded for a 2048-millisecond period starting 200 milliseconds before stimulus presentation, digitized at 250 Hz, and bandpass filtered between 0.15 Hz and 40 Hz.

**Information-Processing Task.** To examine the effects of chemotherapy on specific stages of information processing, we used an experimental task based on a frequently used paradigm whose intrinsic validity is well documented in the literature.20,21 Subjects were seated in a comfortable chair with response boxes attached to the armrests on both sides and in front of a 17-in. monitor located 80 cm from the subject.

The subject’s task was to determine the direction of a double arrowhead and to give the designated response. The arrowheads were presented in a clearly discernable shape (easy condition stimulus discriminability) or in a shape that requires more thorough perceptual processing to identify its direction (difficult condition stimulus discriminability). Subjects were required to respond “spatially compatible,” with the hand at the same side of the direction of the arrowheads (easy condition stimulus-response compatibility), or “incompatible,” with the hand opposite to the direction indicated by the arrowheads (difficult condition stimulus-response compatibility). In addition, subjects had to respond with the index finger alone (simple response, easy condition response complexity) or a sequence of the index, ring, and middle finger (complex response, difficult condition response complexity).

Patients had to respond as quickly and accurately as possible. In each condition, a similar number of trials were pre-
sented. Stimuli were delivered by an experimental response time system in 4 different task blocks. The stimuli were presented within a framework of 2.8 cm (width) by 2.1 cm (height) in the center of the screen. This framework served as an onscreen fixation area. The target stimulus consisting of 2 arrowheads was presented for 1000 milliseconds. The interstimulus interval varied between 2718 milliseconds and 3219 milliseconds.

Reaction time was measured from the onset of the stimulus to the onset of the button press of the index finger. Responses were scored as correct when all button presses were executed in the correct order within 1500 milliseconds.

First, subjects received onscreen instructions and practiced each block (32 trials). Before each block, subjects were informed onscreen whether they had to respond in a compatible or incompatible way and with a simple or complex response. Experimental blocks consisted of 200 trials each with a short break after every 25 trials. Block order was varied across subjects. The task took approximately 50 minutes to complete (800 trials).

Each patient went through the same order of data collection. The experiment session lasted 2.5 hours, including electrode positioning and removal and an auditory discrimination task with concurrent EEG registration and standard EEG in eyes-open and eyes-closed conditions. These latter data will be reported elsewhere.

**Data and Statistical Analysis**

**Offline Electrophysiologic Data Processing and Analysis.** Electroencephalogram data were low-pass filtered at 16 Hz with 96 dB/octave roll-off (zero phase shift). Three minutes of EEG and electrooculograph were recorded while patients fixated on a cross in the center of the screen to detect spontaneous eye blinks. This file was used to compute an average blink for each patient individually. The resulting file was used in the linear derivation procedure in Neuroscan to correct for blinks.

According to standard procedures, EEG epochs that contained extensive horizontal eye movements or contained voltages in excess of plus or minus 100 μV and epochs that coincided with incorrect behavioral responses were excluded. Electroencephalogram epochs for each condition and each participant were then averaged and aligned to a baseline (i.e., the average amplitude during the 200-millisecond preceding stimulus presentation was subtracted from each signal). To assure reliable ERP analysis, average waveforms consisting of < 20 epochs that could be evaluated (because of previous exclusion) were excluded from subsequent analysis.

Averaged waveforms were subsequently smoothed with an unweighted moving average of 84 milliseconds. The P3 component peak latencies were quantified by scanning for the most positive peak within a specified time window (280-600 milliseconds) at the Pz channel. An automatic peak-picking program with confirmatory visual inspection of the waveforms was used for this procedure.

**Statistical Analysis.** The Statistical Package for Social Sciences 12.0 software and the Statistical Analysis Systems package were used for statistical analyses. Differences in demographic and clinical characteristics between groups were analyzed by χ² tests and univariate analysis of variance (ANOVA).

Questionnaire scores were recoded using standard scoring rules. Differences in questionnaire scores between groups were analyzed by means of ANOVA. Scores on the 5 subscales of the POMS before and after the examination were entered in an ANOVA for repeated measures.

Group differences in reported cognitive complaints from the semistructured interview were analyzed by χ² tests.

To examine the effects of the factors’ stimulus discriminability, stimulus-response compatibility, response complexity, and treatment on reaction time, performance accuracy, P3 amplitude, and latency, the MIXED procedure in Statistical Analysis Systems was used to fit the model with repeated effects for the factors’ stimulus discriminability, stimulus-response compatibility, and response complexity. The restricted maximum likelihood method was used for the estimation of the model with unstructured correlation as repeated covariance type. If there were group differences in patient characteristics, these variables were entered in the model as covariates.

The correlations between performance and ERP measures, sociodemographic variables, anxiety/depression, fatigue, and self-reported measures of cognitive functioning were examined using Spearman rank order correlations. For all analyses (2-sided), a P value < 0.05 was required for significance.

**Results**

**Patients**

Seventy-nine patients (17 patients treated with high-dose chemotherapy, 23 patients treated with conventional-dose chemotherapy, and 39 control patients) from the Antoni van Leeuwenhoek Hospital fulfilled the inclusion criteria. Twenty patients (25.3% of the total group; 2 patients treated with high-dose chemotherapy, 5 treated with conventional-dose chemotherapy, and 13 control patients) declined from participating in the neurophysiologic study. Reasons for withholding participation were lack of interest, too busy, uncomfortable with EEG examination, and participation in other studies. Additionally, 2 patients could not be traced and 5 patients cancelled their appointment. Nonparticipants did not significantly differ from participants in age or education. To determine whether nonparticipants differed from participants in self-reported cognitive problems, nonparticipants were asked whether they were willing to answer the cognitive complaints interview. Sixty-three percent of the nonparticipants answered these questions and did not differ from participants in self-reported cognitive problems.

The final study population consisted of 17 patients treated with conventional-dose chemotherapy, 12 patients treated with high-dose chemotherapy, and 23 patients not treated with chemotherapy. Sociodemographic and clinical characteristics of these patients are presented in Table 1.
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sociodemographic and Clinical Characteristics of the Study Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td><strong>Patient Group</strong></td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td>51.5 (5.6)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>40.58</td>
</tr>
<tr>
<td><strong>Time Since Treatment (Years)</strong></td>
<td>3.7 (0.8)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>2.7-5.3</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>1 (83)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>3 (25)</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>8 (66.7)</td>
</tr>
<tr>
<td><strong>Menopausal Status</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Premenopausal</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Perimenopausal</strong></td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Postmenopausal</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

*Values are in parentheses unless otherwise indicated.

**Cognitive Problems**

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Reported Cognitive Problems in Daily Life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Problem</strong></td>
<td><strong>High-Dose Therapy (n = 11)</strong></td>
</tr>
<tr>
<td>Memory</td>
<td>72.7</td>
</tr>
<tr>
<td>Concentration</td>
<td>72.7</td>
</tr>
<tr>
<td>Thinking</td>
<td>27.3</td>
</tr>
<tr>
<td>Language</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*Values are in percentages unless otherwise indicated.

**Psychologic Distress**

No differences between the 3 groups were found in reported psychologic distress. Patients were comparable with regard to their scores on the depression and anxiety subscales of the HSCL-25 (mean [standard deviation] HSCL-25 total for patients treated with high-dose chemotherapy, 13.2 [7.5]; for patients treated with conventional-dose chemotherapy, 11.6 [9.3]; and for patients not treated with chemotherapy, 14.1 [15]; higher scores reflect more problems). Mood as reflected on the subscales of the POMS did not significantly differ between the 3 treatment groups before and after the experimental session.

**Fatigue**

The subscales and total score of the MFI did not indicate significant differences between the 3 treatment groups (mean [standard deviation] MFI total for patients treated with high-dose chemotherapy, 49.8 [16.7]; for patients treated with conventional-dose chemotherapy, 44.8 [21.4]; and for patients not treated with chemotherapy, 44.3 [19.6]; higher scores reflect more problems).

All scores (HSCL, POMS, and MFI) were within the normal range compared with age-related, healthy, normal groups.

**Information-Processing Task**

Performance Accuracy and Reaction Times. Performance accuracy did not differ significantly between the 3 treat-
Table 3  Mean Reaction Times for Correct Responses on Simple Trials as a Function of Stimulus Discriminability and Stimulus-Response Compatibility by Treatment Group

<table>
<thead>
<tr>
<th>Response Parameter</th>
<th>Stimulus Discriminability</th>
<th>High-Dose Group (n = 11)</th>
<th>Conventional-Dose Group (n = 17)</th>
<th>Control Group (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stimulus-response compatibility</td>
<td>stimulus discriminability</td>
<td>reaction time, milliseconds (standard deviation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy condition</td>
<td>Easy condition</td>
<td>494 (57)</td>
<td>475 (60)</td>
<td>458 (44)</td>
</tr>
<tr>
<td></td>
<td>Difficult condition</td>
<td>524 (63)</td>
<td>523 (83)</td>
<td>503 (53)</td>
</tr>
<tr>
<td>Difficult condition</td>
<td>Easy condition</td>
<td>511 (75)</td>
<td>533 (90)</td>
<td>499 (55)</td>
</tr>
<tr>
<td></td>
<td>Difficult condition</td>
<td>554 (82)</td>
<td>578 (103)</td>
<td>541 (67)</td>
</tr>
</tbody>
</table>

P3 Latency, milliseconds (Standard Deviation)

| Easy condition     | stimulus discriminability | reaction time, milliseconds (standard deviation) |
| Difficult condition| stimulus discriminability | reaction time, milliseconds (standard deviation) |
| Easy condition     | Easy condition            | 456 (56)                 | 457 (37)                        | 453 (45)               |
| Difficult condition| Easy condition            | 466 (59)                 | 444 (47)                        | 470 (53)               |

P3 Amplitude, µV (Standard Deviation)

| Easy condition     | stimulus discriminability | reaction time, milliseconds (standard deviation) |
| Difficult condition| stimulus discriminability | reaction time, milliseconds (standard deviation) |
| Easy condition     | Easy condition            | 9.2 (3.2)                 | 12.6 (5.8)                      | 13.3 (3.5)             |
| Difficult condition| Easy condition            | 8.7 (3)                  | 10.2 (4.7)                      | 11.8 (3.2)             |

Table 4  Main Effects and Interaction Effects of Stimulus Discriminability, Stimulus-Response Compatibility, and Treatment on Reaction Times (N = 51)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reaction Times</th>
<th>P3 Latencies</th>
<th>P3 Amplitudes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F*</td>
<td>P Value*</td>
<td>F*</td>
</tr>
<tr>
<td>Stimulus Discriminability</td>
<td>134.66</td>
<td>0.0001</td>
<td>4.27</td>
</tr>
<tr>
<td>Stimulus-Response Compatibility</td>
<td>30.65</td>
<td>0.0001</td>
<td>17.19</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.66</td>
<td>0.2011</td>
<td>0.05</td>
</tr>
<tr>
<td>Stimulus Discriminability/Stimulus-Response Compatibility</td>
<td>0.42</td>
<td>0.5191</td>
<td>0.92</td>
</tr>
<tr>
<td>Stimulus Discriminability/Treatment</td>
<td>0.53</td>
<td>0.5935</td>
<td>1.62</td>
</tr>
<tr>
<td>Stimulus-Response Compatibility/Treatment</td>
<td>1.58</td>
<td>0.2175</td>
<td>0.74</td>
</tr>
<tr>
<td>Stimulus Discriminability/Stimulus-Response Compatibility/Treatment</td>
<td>1.8</td>
<td>0.1758</td>
<td>3.69</td>
</tr>
</tbody>
</table>

*Degrees of freedom: denominator = 47.

All P values are corrected for age differences between groups.

Event-Related Potentials and Reaction Time After Adjuvant Chemotherapy
compatibility (longer reaction times for difficult compared with easy conditions), and no interaction effects (Table 4). This indicates that the experimental manipulations succeeded for these factors.

In all conditions, patients in both chemotherapy groups responded slower than patients in the control group (Table 3). Overall reaction time, however, did not differ significantly between the 3 treatment groups (Table 4). No significant differences in overall reaction time were observed between the high-dose chemotherapy group and the control group and between the conventional-dose chemotherapy group and the control group (Table 5). No interaction effects were observed on reaction time between treatment and any of the task factors (Table 4). When the 2 chemotherapy groups were combined into 1 chemotherapy group and compared with the control group, we observed a trend toward significance for the main effect of treatment on reaction time ($F_{1,48} = 3.38; P = 0.0719$). Patients treated with chemotherapy responded slower than patients not treated with chemotherapy. There were no interaction effects on reaction time between treatment and any of the task factors.

**Event-Related Potentials**

*P3 Peak Amplitude.* For patients treated with high-dose chemotherapy, lower P3 peak amplitudes were measured than for patients treated with conventional-dose chemotherapy, and for these, lower P3 peak amplitudes were measured than for control patients (Figure 1; Table 3). We found significant differences in P3 amplitude between the treatment groups. Patients treated with high-dose chemotherapy had a significantly reduced P3 component compared with control patients (Table 5). Patients treated with conventional-dose chemotherapy did not differ significantly from the control.
patients in P3 amplitude. The experimental factors stimulus discriminability and stimulus-response compatibility each produced main effects, with more difficult conditions associated with smaller peaks.

A 3-way interaction was observed for stimulus discriminability/stimulus-response compatibility/treatment. Figure 2 shows that the reduction in P3 amplitude in the incompatible condition compared with the compatible condition is comparable for easy condition stimulus discriminability and difficult condition stimulus discriminability in control patients. In the patients treated with conventional-dose chemotherapy, this reduction in P3 amplitude in the incompatible compared with the compatible condition is more pronounced in the easy condition stimulus discriminability, whereas...
in the patients treated with high-dose chemotherapy, this reduction is more pronounced in difficult condition stimulus discriminability. There is a main effect of chemotherapy on P3 amplitude (F(1, 48) = 6.99; P = 0.011) when both chemotherapy groups are combined and compared with the control group. No interaction effects were observed on P3 amplitude between chemotherapy and any of the task factors.

P3 Peak Latency. P3 latencies (Table 3) were not significantly different between the 3 treatment groups (Table 4). Main effects were found for the experimental factors stimulus discriminability and stimulus-response compatibility, with more difficult conditions associated with later peak latencies. A 3-way interaction effect was observed for stimulus discriminability/stimulus-response compatibility/treatment. Figure 3 shows that the slowing in P3 latency in the incompatible compared with the compatible trials in control patients is relatively less pronounced in difficult condition stimulus discriminability compared with easy condition stimulus discriminability, whereas in the patients treated with high-dose chemotherapy, this slowing is more pronounced in difficult condition stimulus discriminability compared with easy condition stimulus discriminability. In the patients treated with conventional-dose chemotherapy, the P3 latency in difficult condition stimulus discriminability is even shorter than in easy condition stimulus discriminability in the compatible trials. When patients treated with chemotherapy were compared with patients not treated with chemotherapy, no main effect for chemotherapy on P3 latency was observed. Furthermore, a 3-way interaction was observed for stimulus discriminability/stimulus-response compatibility/treatment (F(1, 48) = 6.99; P = 0.011).

No significant differences were found between the patients treated with high-dose therapy and the control patients and between the patients treated with conventional-dose therapy and the control patients (Table 5).

Relations Between Behavioral, Neuropsychologic, and Self-Reported Measures

In all patients, reaction times correlated positively with P3 latency (Spearman’s ρ = 0.439; P = 0.001) and negatively with mean P3 amplitude (Spearman’s ρ = -0.388; P = 0.004). Self-reported cognitive complaints did not correlate significantly with any of the behavioral or neuropsychologic measures.

Discussion

In this study, we examined the effects of high-dose and conventional-dose chemotherapy on information processing with the concurrent use of behavioral and neuropsychologic measures approximately 4 years after completion of treatment.

We observed a significant overall reduction in amplitude of the P3 component in the patients treated with high-dose chemotherapy compared with controls. This statistically sig-

ificant P3 reduction was not observed in patients treated with conventional-dose chemotherapy (P = 0.1775), though they had lower P3 peaks (mean, 10.6 μV) than the control patients (mean, 11.8 μV). In general, patients treated with chemotherapy (high-dose as well as conventional-dose) appeared to be slower on all task conditions compared with controls, although this was not statistically significant. In addition, the P3 seemed to peak somewhat later in the high-dose group, but there were no significant differences observed in P3 latency between the groups.

Because we did not observe 3-way interactions with treatment for the factors stimulus discriminability and stimulus-response compatibility on any of the outcome measures, the treatment regimens under study do not appear to affect specific stages related to input or central processing (but see below for the 3-way interactions of stimulus discriminability/stimulus-response compatibility/treatment on P3 amplitude and latency). Unfortunately, the response complexity manipulation posed substantial problems. The complex response pattern proved to be too difficult for a considerable number of patients (independent of treatment). Therefore, we could only evaluate the effects of the treatment regimens on input- and central processing-related stages. To evaluate motor- or output-related processing, a complex response condition ought to be developed that is still challenging but performable. Furthermore, the duration of stimulus evaluation processes does not seem to be affected significantly by the chemotherapy regimens under study, because there were no significant differences in P3 latency between the groups.

The high error rate in the response complexity condition resulted in the removal of the complex response condition from the model. In earlier comparable studies, the response complexity manipulation did not pose similar problems, but in these studies, participants were considerably younger and more highly educated. Because we did not include a healthy control group of similar age and education, we can only speculate about the failure of this condition.

Several hypotheses can be formulated regarding the functional significance of the P3 reduction in the high-dose group. Variations in amplitude are supposed to be related to the intensity of information processing and the allocation of processing resources. P3 amplitude is primarily sensitive to changes in the mobilization of energetic mechanisms that are related to perceptual processes. The amplitude of the P3 is also hypothesized to be related to the phasic activity of the locus coeruleus and the norepinephrine system and to the amount of information transmitted to the subject. The P3 reduction in the high-dose chemotherapy group might therefore indicate a loss in information transmission because of deterioration of the focusing of attention toward important stimuli, which results from a reduction of energetic resources and suboptimal phasic cortical arousal, potentially originating from problems in the locus coeruleus/norepinephrine system. Difficulty of focusing attention is in line with the commonly heard complaint of patients treated...
with chemotherapy, ie, that they experience problems having a conversation or reading a book or newspaper while the television is turned on. Furthermore, the complex 8-way interaction on P3 amplitude and P3 latency of the factors stimulus discriminability, stimulus-response compatibility, and treatment shows overadditivity in patients treated with high-dose chemotherapy; the reduction of P3 amplitude and the delay of P3 latency in the difficult condition of stimulus-response compatibility compared with the easy condition were more pronounced in the difficult condition of stimulus discriminability than in the easy condition. Because stimulus discriminability is supposed to be related to perceptual processing, the difficulties in the patients treated with high-dose chemotherapy appear to be especially evident when the information processing system is taxed by a task that demands more perceptual resources.

This P3 amplitude reduction, which was also observed in patients treated with CMF chemotherapy, might be an underlying phenomenon of problems in information processing. Anecdotally, patients treated with adjuvant chemotherapy report that they are able to perform all sorts of tasks but that it just costs more effort than it did in the past. Because of suboptimal neural functioning, these patients might experience more problems in cognitive functioning, which is not always expressed in task performance. However, in the present study, patients treated with high-dose chemotherapy did not differ in cognitive complaints from patients treated with conventional-dose chemotherapy, who did not significantly differ in P3 amplitude from control patients. Nevertheless, future research should be focused on more effortful processing in which the patient has no opportunity to compensate for suboptimal neural functioning, for example in multitask situations (performing an auditory and visual task concurrently).

No P3 data are available of healthy controls using the same task as we used in the current study. A direct comparison of our data on P3 response with that of healthy controls is therefore not possible. However, from the existing literature using highly comparable tasks, there is no indication to assume that our breast cancer controls differ from healthy controls on P3 response.

Physiologic causes for P3 reduction could be different orientation of the neurons that generate the P3, fewer neurons firing, or fewer neurons firing synchronously. So, the P3 reduction might indicate that there has been an insult to neural tissue in the high-dose chemotherapy group, possibly induced by cytotoxic agents that crossed the blood-brain barrier. 5-Fluorouracil is known to cause neurotoxicity and to cross the blood-brain barrier, but late neurotoxicity is not reported. In our patients, 5-fluorouracil is administered in similar doses in the high-dose as in the conventional-dose regimen, and is therefore not a plausible explanation for the P3 reduction in the patients who received high-dose therapy. The other agents in the regimens under study are not known for their neurotoxicity or to cause changes in the CNS, and long-term neurologic implications have not, to our knowledge, been studied so far. Although cyclophosphamide is also not known for its CNS involvement, the cumulative dose of cyclophosphamide in patients receiving the high-dose regimen is much higher than in patients receiving the conventional-dose regimen.

Because we compared our chemotherapy groups to breast cancer controls, other disease-related factors might have affected the results in all groups. Breast cancer survivors have also been treated with surgery and radiation therapy and might have experienced distress over their disease. The effects of surgery and local radiation therapy on P3 are largely unknown, but it is unlikely that they affect information processing on average 4 years after completion of treatment. Reduced P3s have been reported in posttraumatic stress disorder, but the incidence of posttraumatic stress disorder in patients with breast cancer appears to be small. Our aim was to study the effects of chemotherapy on information processing; therefore, we used a control group that was comparable on as many factors as possible with the chemotherapy groups. In this way, the differences between the groups could not be attributed to other disease-related factors on information processing. Furthermore, we did not find differences in psychologic distress between the 3 groups under study.

Because all patients in the chemotherapy groups received tamoxifen compared with only 2 patients in the control group, the role of tamoxifen in these results should be considered as well. The effect of tamoxifen on cognitive ability is debated, some studies suggesting a negative effect, others reporting no effect, or even a positive effect. In a previous study comparing patients treated with CMF chemotherapy with patients not treated with chemotherapy, we compared current tamoxifen users, past users, and never users. Although the current users appeared to have a smaller P3, no significant differences were found between the 3 groups. To our knowledge, the impact of tamoxifen on P3 has never been investigated in other psychophysiological studies. In the current study, it was not possible to analyze the effects of this hormonal therapy because all patients were treated with tamoxifen. Also, because all patients treated with chemotherapy were treated with tamoxifen and only the high-dose group differed significantly from the control group in P3 amplitude, their amplitude reduction is not likely to be related solely to tamoxifen treatment.

Differences in menopausal status might also be a confounding factor for differences in levels of cognitive functioning. None of the patients treated with chemotherapy were premenopausal, whereas a number of patients in the control group were premenopausal. In 2 previous neuropsychological studies, cognitive performance of premenopausal and postmenopausal women was compared within the group not treated with chemotherapy. In the first study, no differences were found between the 2 groups; in the second study, postmenopausal women performed worse than premenopausal women. However, this latter finding might as well be explained by differences in age.
The lack of group differences might be caused by a lack of power. Comparable studies in which information processing is examined combined with ERP measures use similar sample sizes. However, because the literature suggests that only a subgroup of survivors experience neurocognitive problems after exposure to chemotherapy, it is possible that our study lacks power to detect differences between the groups. Different chemotherapy regimens might have different effects on the brain and cognitive functioning. The use of heterogeneous treatment groups in examining the effects of chemotherapy on cognitive functioning might obscure effects of different regimens. Therefore, we chose not to combine our chemotherapy groups into 1 group to increase power in our main analyses.

Conclusion
The use of high-dose chemotherapy results controversial. In a Cochrane review based on 9 studies, the authors conclude that there is insufficient evidence to support the use of high-dose chemotherapy with autologous bone marrow or peripheral stem cell transplantation for women with early-stage poor prognosis breast cancer outside of a clinical trial. Nevertheless, because it has been viewed as a worthwhile treatment for high-risk breast cancer in the past, many women in the United States have been treated outside of a clinical trial, especially during the 1990s. Because the differences in survival between high-dose and conventional-dose regimens appear to be small, other endpoints like CNS toxicity and neurocognitive function become more important.

Different chemotherapy regimens appear to have differential effects on the P3 component. In the previous study, patients treated with CMF chemotherapy showed an earlier and reduced P3 component compared with control patients, whereas in the present study, no differences in P3 latency were found between the chemotherapy groups and the control patients. These differential effects indicate the importance of studying the effects of chemotherapy on cognitive functioning in homogenous subgroups treated with equal treatment regimens. The potential impact to neural tissue by various chemotherapy regimens and the long-term effects of these regimens on neurocognitive function should be investigated in more detail, for instance, by using animal models (ie, to study the effects of the separate components of the chemotherapy regimens) and imaging techniques like functional magnetic resonance imaging and positron emission tomography (ie, to study functional and structural changes in the CNS).

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