Cognitive functioning following chemotherapy : a study in breast cancer patients

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Chapter 6

Neurophysiological Evaluation of Late Effects of Adjuvant High-dose Chemotherapy on Cognitive Function

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Abstract

Objectives: to evaluate late neurotoxicity of adjuvant high-dose (HD) chemotherapy versus standard-dose (SD) chemotherapy by event-related potentials (ERP) and quantitative electroencephalography (qEEG).

Patients and Methods: from a randomized study in high-risk breast cancer patients on the efficacy of high-dose versus standard-dose adjuvant chemotherapy, late effects on cognitive functioning were analyzed by neuropsychological tests. Cognitive impairment was found in 32 % of the HD group, 17% of the SD group and in 9% of a control group of stage I breast cancer patients not treated with chemotherapy. In 17 consecutive patients in the HD group and 16 consecutive patients in the SD group neurophysiological tests were performed, consisting of P300 and qEEG. Results of patients treated with chemotherapy were compared with results of 14 control patients not treated with chemotherapy. All patients were tested two years after treatment.

Results: asymmetry of the alpha rhythm of $\geq$ 0.5 Hz was found in 7 HD patients, 2 SD patients and in none of the control patients ($P = 0.01$). No differences were found between the groups with regard to frequency of alpha rhythm, alpha blocking and latency of P300. No correlation was found between neurophysiological parameters and neuropsychological performance, except for an overall relation between the P300 latencies and the total number of deviant test scores.

Conclusion: Although the neurophysiological differences are subtle and the relation with the cognitive functioning in individual patients as measured by the neuropsychological examination is equivocal, the results suggest that there is neurophysiological support for cognitive dysfunction as a late complication of high-dose systemic chemotherapy in breast cancer.

Introduction

In oncology overall survival and recurrence free survival are the main targets of treatment. In recent years high-dose chemotherapy with autologous blood progenitor cell transplantation has been shown to be an effective treatment modality in several chemotherapy-sensitive malignancies, including non-Hodgkin lymphoma, neuroblastoma and germ cell tumors. The most frequent indication is, however, breast cancer, although the superiority of this treatment over conventional therapy is still under investigation in large-scale phase III randomized trials.[1] With the arrival of the possibility of dose escalations of cytotoxic agents above the former dose-limiting myelotoxic level, new and unknown neurological complications may be elicited. One of the complaints reported by patients who have previously been treated with chemotherapy is cognitive problems. In a Dutch randomized study on the efficacy of adjuvant high-dose chemotherapy in high-risk breast cancer, it was found that patients who were

randomized to receive high-dose chemotherapy had an eight times higher risk for cognitive impairment as compared with a non-treated control group consisting of axillary node-negative breast cancer patients. Patients who were randomized to receive only conventional-dose chemotherapy had no significant elevated risk compared to the control patients. In this study, cognitive functioning was evaluated by means of neuropsychological testing. Since the examination was conducted on average two years after the completion of treatment, the cognitive abnormalities found may be irreversible.[2]

It is well known that cancer treatment may be followed by neurotoxic complications.[3] Late central neurotoxicity is reported in patients treated with cranial irradiation as single treatment or in combination with chemotherapy and in patients treated with intrathecal or intravenous chemotherapy. Higher incidence of neurotoxicity is in general associated with combined modality treatment. Late treatment related cognitive problems have been extensively studied in patients following multimodality treatment. [4-6] To a much lesser extent well-designed studies have been undertaken to address late central neurotoxic side-effects of systemic chemotherapy given as single treatment for non-CNS tumors. Little is known about the prevalence and the degree of cerebral dysfunction following this treatment. Although most of the, predominantly, neuropsychological studies on this topic have shown a substantial percentage of patients treated with chemotherapy exhibiting cognitive deficits (for review see Meyers[7]), the characteristics of the impairment found are insufficiently understood. In addition, the pathophysiology of the central nervous system effects of chemotherapy is still unclear.

In the present study, we performed a neurophysiological examination (including quantitative EEG, P300 Event Related Potentials) subsequent to a battery of neuropsychological tests to assess the underlying physiological basis of possibly treatment-related cognitive sequelae in a cohort of high-risk breast cancer patients participating in a randomized trial comparing high-dose versus standard-dose chemotherapy as adjuvant treatment.

Methods

Patients and Treatment

A total of 70 high-risk breast cancer patients who participated in a randomized trial comparing the efficacy of high-dose adjuvant chemotherapy with standard-dose chemotherapy have been examined with a battery of neuropsychological tests.[2] From this neuropsychological study group, a cohort of consecutive and unselected patients were asked to participate in the neurophysiological study as well. In the randomized trial the high-risk breast cancer patients (with four or more axillary lymph node metastases) were treated as follows: following surgery, patients received five courses of 'FEC' chemotherapy (fluorouracil 500 mg/m^2 intravenously, epidoxorubicin 120 mg/m^2 intravenously and cyclophosphamide 500 mg/m^2 intravenously), radiation therapy and tamoxifen. In patients

randomized to receive high-dose therapy, the fifth course of FEC chemotherapy was replaced by the high-dose regimen 'CTC' (cyclophosphamide 6 g/m^2 intravenously, thiotepa 480 mg/m^2 intravenously and carboplatin 1.6g/m^2 intravenously) with peripheral blood progenitor cell transplantation (PBPC).

To be eligible for the neuropsychological and the neurophysiological study, patients had to fulfill the following criteria: (1) no evidence of relapse or metastatic disease; (2) no history of neurologic/psychiatric signs or symptoms that might lead to deviant results; (3) no use of medication that might lead tot deviant results; (4) no abuse of alcohol or drugs; (5) sufficient control of the Dutch language.

The results of the high-risk breast cancer patients were compared with the results of a control group of stage I breast cancer patients treated with surgery followed by radiotherapy. The patients in the control group did not receive any systemic therapy. These patients were matched to the patients with high-risk breast cancer on the basis of age and time since treatment. Inclusion criteria were the same as for the breast cancer patients treated with chemotherapy. Informed consent was obtained from all patients, according to institutional guidelines.

Procedures and Measures

All patients were asked by their treating physician to participate in the study. Of the high-risk breast cancer patients treated with chemotherapy who were asked for the neuropsychological tests, only a cohort of patients was asked to participate in the neurophysiological study as well (the neuropsychological results for the total population are described in detail in a previous publication [2]). A group of stage I breast cancer patients not treated with chemotherapy was especially included to form a comparison with the high-risk breast cancer patients. All control patients were tested both neuropsychologically and neurophysiologically. The study samples represented consecutive series of patients. For all patients testing was conducted in two sessions. Neurophysiological tests were performed no later than within one week of the neuropsychological examination.

Neurophysiological assessment

qEEG was recorded using silver-silver chloride electrodes affixed to the scalp with collodion. Recordings were obtained from 20 electrodes according to the international 10/20 system with a reference electrode over the right mastoid. Off-line 50-60 sec epochs of artifact- free EEG during eyes closed and eyes open conditions were processed against the average reference. The alpha peak frequency and amplitude were measured for each subject. In addition left-right difference of the alpha rhythm and alpha blocking were assessed. Patient data were fed into a Bio-logic System Corp. Brain Atlas III.[8]

The ERP was recorded with an auditory oddball-paradigm method. Stimuli were given with an inter-stimulus interval of 2 sec, with a variability of 20%. Non-target stimuli consisted of

1000 Hz tonebursts for 30 msec, rise and fall time 5 msec, presented at an intensity level of 75 dB. Target stimuli were presented at random in a ratio of 1:5 and consisted of 2000 Hz tonebursts for 30 msec at an intensity of 75 dB. Subjects were instructed to count the number of target tones and to report the count at the end of the test. Stimuli were presented until 30 artifact-free target stimuli and 150-180 non-target stimuli were obtained. The P300 component was regarded the maximum positive deflection of the trace following stimulus onset in a segment between 280 and 420 msec. Latency of P300 was measured to the apex of the highest peak in the global field power.[9]

Neuropsychological assessment

The cognitive status of all patients was assessed with a standard battery of neuropsychological tests, covering a broad range of functions. Verbal function, memory, attention/concentration, speed of information processing and mental flexibility were assessed using 13 separate tests. A detailed description of the tests and the scoring procedures is provided in the previous publication on the neuropsychological findings.[2]

Self reported measures

All patients were interviewed [10] about possible cognitive problems experienced in daily life (memory, attention, thinking, language) and were asked to indicate on a five-point Likert scale the extent to which these problems in each of these domains occurred in their daily lives (0 = not at all, 1 = slightly, 2 = moderately, 3 = quite a bit, 4 = extremely). All participants also completed a quality of life questionnaire, the EORTC QLQ C-30 [11] and an anxiety and depression checklist, the Hopkins Symptom checklist. [12]

Data Analysis

The EEG data were subjected to visual inspection by an experienced researcher (HLH) blind to the treatment condition of the patients and processed with fast Fourier transformation. Mean values of the neurophysiological parameters were compared employing univariate analysis of variance (ANOVA). The neuropsychological data of the stage I breast cancer control patients did not differ from published norms of healthy subjects. Therefore we converted the neuropsychological data to standard-scores (z-scores) using the mean test scores of these control patients who were not treated with chemotherapy as a reference. A summary z-score for each of the domains was computed by summing the z-scores for the separate tests in that domain. Differences in raw neuropsychological test scores between groups were tested by univariate ANOVA. For each individual patient neuropsychological impairment was determined following a strict criterion. At first, the number of tests was calculated by which a patient scored in the impaired range (a score of two standard deviations below the mean of the reference group on a test was considered as impaired). Secondly, a cutoff of 5% of the number of impaired tests of the control group was applied to distinguish between disturbed and unaffected cognitive functioning.[2] Between-group differences in sociodemographic and clinical data were evaluated using chi-square test for contingency tables and Student's t-test. The correlations between neurophysiological data,

neuropsychological test performance, subjective measures and time since last therapy were analyzed by use of the Pearson correlation coefficient. The statistical Package for Social Sciences (SPSS) WINDOWS 9.0 software was used for all analysis.[13]

Results

Sociodemographic characteristics

Of the 70 high-risk breast cancer patients participating in the neuropsychological study, a consecutive and non-selected subgroup of 42 patients was asked to participate in the neurophysiological examination. Twenty patients were randomized to high-dose chemotherapy (HD group) and 22 patients to standard-dose chemotherapy (SD group). A total of 6 patients refused to participate (2 patients of the HD group and 4 patients of the SD group); the reasons for refusal varied from emotional to practical considerations.

Of the 21 stage I breast cancer patients approached to participate in the study, 7 did not want to cooperate. The primary reason for declining to participate was lack of willingness to schedule an additional visit to the hospital.

The total study population consisted of 18 high-risk breast cancer patients treated with high-dose chemotherapy, 18 high-risk breast cancer patients treated with standard-dose chemotherapy and 14 stage I breast cancer patients not treated with chemotherapy.

An additional 3 patients were considered not eligible. One patient from the HD group was subsequently found to have metastatic disease, and 2 patients from the SD group were actually randomized to receive HD therapy, but refused this treatment despite having previously agreed with the policy. The data of these patients were excluded from all analysis.

Table 1. Sociodemographic and clinical characteristics

	Treatment group			
	CTC n = 17	FEC N = 16	Control n = 14	*P*-value
Mean age, y (sd)	46,1 (6.8)	48,7 (7.8)	48,5 (6.6)	.507
Mean time since treatment, y (sd)	1.6 (0.7)	2.0 (1.0)	2.0 (0.3)	.221
Mean IQ (sd)	102 (10.9)	105 (9.4)	101 (10.0)	.569

CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; Control = no adjuvant chemotherapy. See the 'Methods' section for definitions of the CTC and FEC chemotherapy regimens.

The sociodemographic and clinical characteristics of the study sample are listed in Table 1. The three groups were well balanced with regard to age and premorbid IQ, as measured with

the Dutch Adult Reading test. [14] The patients were also highly comparable with regard to time since treatment.

Neurophysiological findings

The neurophysiological findings are summarized in Table 2. qEEG analysis of the alpha peak frequency showed no differences between the groups. The frequency of alpha rhythm was 9.7 Hz (+/- 0.8 Hz) in the high-dose chemotherapy group, 9.5 Hz (+/- 1.3 Hz) in the standard-dose chemotherapy group and 10.0 Hz (+/- 0.7 Hz) in the control group (P =.342). Alpha blocking in the eyes open condition was also equally present in the three groups; 9.8 Hz (+/- 0.8 Hz) in the high-dose chemotherapy group, 9.4 Hz (+/- 1.2 Hz) in the standard-dose chemotherapy group and 10.1 Hz (+/- 0.7 Hz) in the control group (P =.149). Group comparisons showed a significant difference only for the asymmetry of the alpha rhythm. Asymmetry of 0.5 Hz was found in 7 patients of the HD group, 2 patients of the SD group and in none of the control patients (P = .012). No pattern of alpha asymmetry was evident, i.e. there was no hemisphere side showing continuously less activity in comparison with the other. There were no statistically significant differences in latencies of P300 among the groups (341.6 msec (+/- 39.2 msec) in the HD group, 327.7 msec (33.9 +/- msec) in the standard group and 346.3 msec (+/- 19.6 msec) in the control group (P =.309)).

Table 2. Neurophysiological parameters

	Treatment group			
	CTC n = 17	FEC n = 16	Control n = 14	P-value
Alpha Peak frequency (hz)	9.7 ± 0.8	9.5 ± 1.3	10.0 ± 0.7	.342
Alpha blocking (hz)	9.8 ± 0.8	9.4 ± 1.2	10.1 ± 0.7	.149
Asymmetry (hz) of alpha rhythm	41.2% (7)	12, 5% (2)	0 % (-)	.012
P300 latency (msec)	341.6 ± 39.2	327.7 ± 33.9	346.3 ± 19.6	.309

CTC = high-dose adjuvant chemotherapy; FEC = standard-dose adjuvant chemotherapy; Control = no adjuvant chemotherapy. See the 'Methods' section for definitions of the CTC and FEC chemotherapy regimens.

Neuropsychological findings

Six (35%) patients treated with HD chemotherapy were classified as cognitively impaired versus 3 (19%) patients treated with standard-dose chemotherapy and 2 (14%) control patients (P = .336, see Table 3). This subgroup of patients appeared to be a representative sample of the total group of patients participating in the neuropsychological study, i.e. the distribution of the percentage of patients classified as cognitively impaired in the different treatment groups is similar to the distribution of the percentage of patients with cognitive deficits found in the total population (32% of the total HD group was defined was cognitively impaired, compared with 17% of the SD group and 9% of the control group, P = .043).

Table 3. % of patients with deviant neuropsychological test scores

No. tests failed [a]	Treatment group		
	CTC n = 17	FEC n = 16	Control n = 14
0-2 (not impaired)	65%	81%	86%
≥ 3 (impaired)	35%	19%	14%
	Chi-squared test:		$P = .336$

See footnote Table 1.
[a] The fifth percentile of the control patients was used as a cutoff point to determine whether a patient was cognitively impaired. The fifth percentile of the control patients corresponded to failure on 3 or more of the tests. Thus a score of two standard deviations below the mean of the control group on at least three tests was required for a patient to be classified as cognitively impaired.

Self-reported complaints about cognitive functioning, anxiety, depression and fatigue

Akin to the findings in the total sample participating in the neuropsychological study, patients treated with high-dose chemotherapy and patients treated with standard-dose chemotherapy reported more cognitive problems in daily life in comparison to the patients who were not treated with chemotherapy. There were no differences between the groups with regard to depression, anxiety and fatigue (results not shown).

EEG/ERP, neuropsychological performance and self-reported measures

The correlation between the neurophysiological parameters, the overall score of deviant tests and the self-reported complaints of the patients was investigated. In general, there appeared to be no relation between the neurophysiological parameters, the neuropsychological test results and the self-reported complaints including cognitive problems, depression, anxiety and fatigue. A correlation was found between the latencies of P300 and the total number of deviant test scores, with longer P300 latencies corresponding to more deviant test results (PMC = .30, $P = .05$). No relation could be revealed between the summary scores for the distinguished cognitive domains and the neurophysiological parameters.

Discussion

This study continues the investigation on the adverse late effects of chemotherapy on neurocognitive functioning. Although patients' complaints of cognitive problems after chemotherapy are recognized and studies have found deviant performances on formal neuropsychological testing in patients treated with chemotherapy, the neural substrate of the cognitive dysfunction is largely unknown. The present study was conducted to gain more insight in the physiological correlates of possible treatment-related cognitive sequelae found in high-risk breast cancer patients who were randomized to receive either high-dose or standard-dose adjuvant chemotherapy. In addition to neuropsychological testing which

indicated that 32% of patients treated with high-dose chemotherapy had cognitive deficits, compared to 17% of patients treated with standard-dose chemotherapy and 9% of control patients not treated with chemotherapy [2], a neurophysiological examination was conducted in a non-selected subgroup of these patients.

Up till now, functional and structural analysis of late central neurotoxicity of chemotherapy either alone or in combination with neuropsychological testing have been reported sporadically. Meyers et al. reported abnormal results on conventional EEG in a significant percentage of cancer patients previously treated with systemic chemotherapy for non-CNS metastatic disease. The incidence of the abnormal results on EEG was not related to the neuropsychological test performance. Most of the EEG tracings considered abnormal demonstrated mild diffuse slowing of background activity. [15] Van Oosterhout et al. studied central nervous system effects of chemotherapy and prophylactic cranial radiation in three groups of long-term survivors of small cell lung cancer. Patients treated with chemotherapy alone, patients treated with PCI after chemotherapy and patients treated with PCI concurrent with chemotherapy were compared with matched healthy controls using neuropsychological assessment and CT scanning or MR imaging of the brain. Results indicated marked neuropsychometric impairment in all treatment groups compared to healthy controls. Cortical atrophy and white matter abnormalities, primarily periventricular, were also found in all three groups. The extent of the white matter lesions was related to PCI concurrent with chemotherapy, to a high fraction dose and to the number of chemotherapy courses. No other relations were detected in that study.[16] White matter changes were also observed in breast cancer patients treated with systemic chemotherapy undergoing MR imaging and proton MR spectroscopy. In a few studies, patients with advanced breast carcinoma who were treated with high-dose chemotherapy and peripheral blood stem cell support, showed white matter changes on MRI scan 2 months post-treatment, progressively increasing up to about 6 months after high-dose chemotherapy, and stabilizing by 6 months to 1 year after treatment. These white matter changes appeared without significant changes in metabolic ratios and in the absence of central neurologic symptoms. [17,18] The signs of late neurotoxicity after chemotherapy on CT or MRI resembles those attributed to radiation therapy of the brain. Similar white matter changes have also been described as leukoencephalopathy in children treated with systemic chemotherapy and CNS prophylaxis for leukemia. [16] The nature of leukoencephalopathy is largely unknown but it is thought to be the result of direct toxic effects of radiation or chemotherapy to the neuroglia, possibly in combination with indirect ischemic effects to the neuroglia caused by an irradiation or chemotherapy-induced microangliopathy.

In the current study in which a neurophysiological examination consisting of qEEG and P300 event related potentials was performed subsequent to a neuropsychological test battery, a significant difference between three groups of breast cancer patients was found with respect to the asymmetry of the alpha rhythm. Asymmetry of alpha rhythm of 0.5 Hz, which is indicative of certain cortical or subcortical dysfunction[19], was found in 41% of the patients

treated with high-dose chemotherapy, compared to 13% of the patients treated with standard-dose chemotherapy and none of the patients not treated with chemotherapy. Other EEG parameters, i.e. alpha peak frequency and alpha blocking, showed no differences between the groups. The interpretation of the neurophysiological data is complicated by the fact that none of the neurophysiological parameters, including the significant observed differences in asymmetry of alpha rhythm, could be related with any of the neuropsychological outcome measures in the individual patients.

With regard tot the P300, no differences in latencies were detected among the groups. However, a significant relation was found between the latency of P3 component of event related potentials and the total number of deviant test scores per patient, with higher p300 latencies corresponding to more deviant test results, although this observation could not be traced back in differences between the groups. Prolonged P300 latencies have also been reported in lung cancer patients treated with prophylactic radiotherapy. ERP's are deflections in EEG in response to certain stimuli, and thought to be neurophysiological expression of cognitive processes. P300 is more sensitive than other ERP's and, though rather speculative, may provide an index of attention and working memory. [20] Prolonged latencies of P300 have been associated with cognitive impairment in dementia, with a direct correlation between prolongation of latency and severity of cognitive dysfunction. [21]

Although the neurophysiological differences are subtle and the relation with the cognitive functioning in individual patients as measured by the neuropsychological examination is equivocal, the results suggest that there is neurophysiological support for cognitive dysfunction as a late complication of high-dose systemic chemotherapy in breast cancer. Further studies with a larger patient population should inform us on the actual existence and significance of a relationship between the neuropsychological and the neurophysiological parameters.

Almost any study which reports on late effects of cytostatic treatment is suggestive of brain damage, whether these effects were made visible by EEG, MRI, CT, neurologic or neuropsychologic evaluations. Still, we are at an early stage in understanding the fundamental mechanisms of cognitive dysfunction in cancer patients treated with chemotherapy. The structural, metabolic and functional consequences of cyctostatic treatment must be linked to clinical outcome and tools must be put to good use by documenting and unraveling the complexity of these observations and by searching for converging evidence.

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