Cognitive functioning following chemotherapy: a study in breast cancer patients

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Chapter 8

Discussion
Introduction

The main aim of this thesis is the study of cognitive deficits following chemotherapy in adult cancer patients. The rationale to start this study was based on complaints expressed by patients after treatment with cytotoxic agents and, as a consequence, on the need to investigate this potential late effect of cancer therapy. The results found in the different studies and directions for future research are discussed in this chapter.

In earlier years evaluation parameters in health services and clinical research were predominantly focused on biomedical endpoints such as prolonged survival and control of major physical problems. Nowadays, however, the impact of disease and its treatment on physical, psychological and social health of patients has become an increasingly important outcome measure. Particularly in oncology, the literature on health-related quality of life studies has expanded rapidly, and the concept has acquired a definite place within this field.

Quality of life assessment

Quality of life refers to an omnibus term summarizing a range of related, interacting dimensions. Despite great diversity, it is generally accepted that quality of life assessments should be multidimensional in nature. There is also consensus on the subjective nature of the quality of life concept. It is considered that the patient is the most appropriate source of information on his/her quality of life. Although in selective situations the patient self may not be able to provide adequate quality of life ratings, thus making alternative informants necessary, the basic principle of the quality of life evaluation remains the subjective judgment of a degree of functioning.¹

Cognitive functioning is one of the domains traditionally included in questionnaires evaluating the impact of a medical condition or its treatment on the well-being of a patient. In oncology, one of the most widely used quality of life questionnaires is the EORTC QLQ C30.² In this questionnaire, cognitive functioning of patients is assessed by the following items: "Have you had difficulty in concentrating on things, like reading a newspaper or watching television?" and "Have you had difficulty remembering things?" Although the psychometric properties of the EORTC QLQ C30 are well established, its validity has only been examined in terms of the ability of the different scales to distinguish between subgroups of patients on the basis of their clinical and treatment status.

Relation between subjective and objective cognitive functioning

From the literature it is well known that the relationship between cognitive complaints and cognitive functioning as assessed by a neuropsychological examination is far from straightforward.³⁹ The correlation between subjective cognitive functioning as measured with interviews or self-reported questionnaires, and performance on neuropsychological tests is in general low. Often, 10% of the shared variance is maximally accounted for. In fact, to believe
that subjective experiences are a valid measure for cognitive impairment is sometimes viewed as one of the pitfalls of clinical neuropsychology.\textsuperscript{10}

**Toxicity grading systems**

The evaluation of cognitive deficits as a potential side-effect of cytotoxic treatment is similar to the discussion on the toxicity of drugs, and it can be helpful to view the different assessment methods that are usually applied for these purposes. Several systems have been developed for reporting and grading chemotherapy induced-toxicities. Although the systems used for the evaluation of neurotoxicity differ from one another (e.g. WHO, ECOG, NCIC-CTC), traditionally they all use a combination of quantitative neurological methods and clinical observations.\textsuperscript{11-12} In a recent article on chemotherapy-induced peripheral neuropathy, Postma et al. argued in favor of the inclusion of patients’ perspective in neuropathy grading, in order to obtain the patients’ own experience of daily functional impairment due to neurotoxic chemotherapy.\textsuperscript{13} In their article, the question was asked as to who should score the severity or the extent of abnormalities, the physician or the patient. Whereas it is the physician who assesses the degree of, for example, muscle weakness, it is the patient who experiences a handicap in daily life and the impact of a symptom on his/ her quality of life. The answer is probably entirely dependent on the kind of information that is required to be collected. The fact that self-perceptions on cognitive status may, for example, not be valid estimates of actual functioning, does not automatically imply that these perceptions can not be of considerable importance. In fact, they may have a substantial impact on the behavior of people in everyday situations in which cognition is called upon. In principle, to rely on the patient’s perspective with regard to cognitive functioning can be of considerable value. When the aim is, however, to evaluate cognitive functioning per se, the method of choice remains ‘objective’ testing of the different functions by a neuropsychological examination.

To summarize, the appropriate choice of evaluation methods is dependent on the endpoint of the research under consideration, i.e. on the level of functioning that needs to be assessed. Thus it is that choice which is essential for outcome measures to be valid and clinically meaningful.

**Neuropsychology and the Classification of Impairments, Disabilities, Handicaps**

A practical system for the illustration of the different levels at which the impact of chemotherapy on cognitive functioning can be evaluated is the International Classification of Impairments, Disabilities and Handicaps, as formulated by the World Health Organization.\textsuperscript{14} According to the WHO concept, three levels of functioning can be distinguished: impairment, disability and handicap. In this system, *impairment* refers to the level the functioning of organs, i.e. the loss or abnormality of body structure or of a physiological or psychological function, whereas *disabilities* are related to the behavioral capacities of an individual and
handicap involves the social consequences. Meyers (2001) recently discussed this classification in a review article on neurocognitive functioning in cancer patients. In that article, the levels were translated in terms of clinical neuropsychology as follows: impairment is the deficit occurring in brain functioning, manifested by neurological or cognitive changes. Disability is the impact of the deficit on the patient’s ability to perform usual work and home activities, and handicap refers to the more social adverse effects encountered by the patient, i.e. the impact of the disability on the person’s overall well-being and satisfaction.

Deelman and Eling (1997) re-formulated this model in terms of neuropsychology. As neuropsychology is concerned with the behavioral expression of brain dysfunction, cognitive deficits should in principle refer to disabilities in the classification of the ICIDH terminology, rather than to impairments. Certain central nervous system illnesses or damages (e.g., a cerebrovascular accident) lead to a certain injury in the brain (impairment). This can result in a decline in language functioning (disability). This decline can cause, in turn, a number of problems in the daily life of a patient (handicap).

Neuropsychological testing acts at the level of disabilities, whereas problems in daily activities of patients are more related to the handicap level. The fact that the relationship between cognitive impairment on neuropsychological testing and cognitive complaints in self-evaluations is not straightforward, may be explained by the different levels that they call upon. Interviews and self-reported evaluations often explicitly focus on problems in everyday situations, while neuropsychological testing elicits behavior samples in a standardized, replicable and more or less artificial situation. Its strength lies in this standardization of the test situation for each subject, for it is the sameness that enables to compare behavior samples between individuals, over time, or in comparison to reference groups. But its weakness also lies in the sameness, in that these test observations are limited to the behaviors occasioned by the test situation. They do not include observations of patients in more familiar settings engaging in their usual daily activities.

Different levels of functioning in the present thesis

The work described in this thesis started with patients treated with chemotherapy and their complaints about memory and concentration problems encountered in daily life. A series of studies was set up which included a neuropsychological and a neurophysiological examination, a semi-structured interview on cognitive problems experienced by the patients, an anxiety and depression questionnaire and a health-related quality of life questionnaire in which, in addition to a cognitive functioning scale, questions on fatigue were also included. It was thought that by examining the different outcome measures and the presence or absence of mutual relations, a more complete picture could be formed on the existence of cognitive impairment following chemotherapy, on whether these impairments were reflected in daily

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1 A revised version of the classification as formed in 1980 is currently in progress. In this revision the domains are described from body, individual and societal perspectives by two basic lists: (1) body functions and structures (2) activities and participation. These terms will replace the formerly used terms “impairment, disability and handicap”, and extend their meanings to include positive experiences.
life activities, and on the determinants of these potential impairments. Does cytotoxic treatment influence cognition or does anxiety, depression, fatigue or other confounding factors mediate cognitive dysfunction?

Such a distinction is necessary from both a scientific and a clinical perspective. Assessment of the occurrence of any adverse effect on the central nervous system and its origin is a legitimate research aim in itself, but is also crucial to guide interventions because the type of intervention that is most effective will differ depending on the etiology.

Results in perspective

The following sections will discuss the results of this thesis, the methods by which the findings are assessed, the degree of certainty of the findings and the explanations for the findings.

Overview of study results

Study 1: Cognitive impairment following adjuvant chemotherapy for high-risk breast cancer: high-dose CTC chemotherapy versus standard-dose FEC chemotherapy

In the first neuropsychological study, the sample consisted of high-risk breast cancer patients who, in the context of a randomized trial, had received either standard-dose (FEC) chemotherapy or high-dose (CTC) chemotherapy with peripheral stem cell transplantation (n=36 and n=34 respectively). All patients in both groups additionally received tamoxifen treatment. The high-risk patients were compared with a control group of stage I breast cancer patients that had not received any systemic treatment (n=34). Cognitive functioning was evaluated with a comprehensive battery of neuropsychological tests. All patients answered questions on cognitive problems experienced in daily life, health-related quality of life, and anxiety and depression. The mean time since completion of non-hormonal treatment ranged from 1.6 years to 2.4 years. Patients treated with chemotherapy reported more cognitive problems than patients not treated with chemotherapy. Impairment in cognitive functioning was found in 32% of the patients treated with high-dose CTC chemotherapy, 17% of the patients treated with standard-dose FEC chemotherapy and in 9% of the control patients. Compared with control patients, patients treated with high-dose chemotherapy had an 8.2-times higher risk of cognitive impairment. When compared with patients in the standard-dose group, this risk was lower (OR 3.5). Patients treated with FEC chemotherapy showed no significantly elevated risk compared with the control patients (OR 2.4). No relation could be detected between the self-reported cognitive complaints and the neuropsychological test performance. Complaints on cognitive functioning appeared to be related to anxiety and depression. The cognitive impairment observed on formal testing was not related to anxiety, depression or fatigue. Deficits were found in a broad domain of functioning, including attention, visual memory, mental flexibility, speed of information processing and motor functioning.16
**Study 2: Cognitive impairment following adjuvant conventional-dose CMF chemotherapy for breast cancer**

The population of the second neuropsychological study consisted of breast cancer patients who were treated with conventional adjuvant CMF chemotherapy (n=39), as given in routine clinical practice. In half of these patients, chemotherapy was followed by hormonal treatment according to the protocol of a randomized trial. This second investigation shared the same stage I breast cancer control group as the first neuropsychological study. Again, all subjects were examined with neuropsychological tests, questions on cognitive problems in daily life, health-related quality of life, and psychosocial distress. The assessment took place 1.9 years after completion of cytotoxic treatment. The patients treated with chemotherapy reported more cognitive problems than patients in the control group, and 28% of the patients undergoing cytotoxic therapy exhibited cognitive impairment on neuropsychological testing compared to 12% of the patients in the control group (OR 6.4)\(^2\). Similar to the first study, cognitive complaints were related to anxiety and depression and not to test performance. Again, cognitive impairment found on formal testing was unaffected by anxiety, depression and fatigue. Hormonal treatment had no influence on patients' self-reported problems or cognitive functioning. The pattern of deficits found was similar to the pattern of test performance observed in the high-risk breast cancer group.\(^{17}\)

**Study 3: Neurophysiological evaluation of late effect of adjuvant chemotherapy on cognitive functioning**

The third study was designed to examine potential neurophysiological correlates as clues to the pathophysiology of the observed neuropsychological differences, which may represent damage to the brain as a consequence of chemotherapy. In a non-selected subgroup of high-risk breast cancer patients participating in the neuropsychological study, a neurophysiological examination was performed. Of 17 breast cancer patients treated with high-dose (CTC) chemotherapy and 16 patients treated with standard-dose (FEC) chemotherapy quantitative EEG and Event Related Potentials (P300) were examined. Results of patients treated with chemotherapy were compared with results of 14 stage I breast cancer control patients not treated with chemotherapy. All patients were tested within one week of the neuropsychological assessment. Asymmetry of the alpha rhythm of ≥ 0.5 Hz, which is indicative of cortical or subcortical dysfunction, was found in 7 patients of the high-dose CTC group (41%), 2 patients of the standard-dose FEC group (13%) 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 test performance, except for an overall relation between the P300 latencies and the total number of deviant test scores, with higher P300 latencies corresponding with more deviant test results.\(^{18}\)

\(^2\) Due to additional test indices included in the second study, the percentage of control patients classified as cognitively impaired is not entirely comparable across studies (9% versus 12%).
Study 4: Late effects of adjuvant chemotherapy on cognitive functioning in breast cancer patients: a follow-up study

In examining cognitive functioning of cancer patients, the persistence of deficits potentially caused by organic impairment attributable to the cytotoxic treatment, is of great relevance. A fourth study was set up to obtain insight in the long-term sequelae of the neuropsychological deficits and their course over time. The cognitive functioning of all patients who participated in the first neuropsychological studies and who were still free of disease, was tested for a second time with an additional two years test-retest interval, i.e. 4 years after completion of chemotherapy. Thus, 22 of the original 34 CTC patients, 23 of the 36 FEC patients, 31 of the 39 CMF patients and 27 of the 34 control patients were re-examined with a neuropsychological battery of tests, identical to the previous investigations. For all chemotherapy groups improvement in test performance was observed, while in the control group a slight deterioration of test results was seen. None of the previously observed differences in cognitive functioning between patients treated with high-dose chemotherapy, patients treated with various regimes of conventional dose chemotherapy and patients who received no systemic therapy for breast cancer, could be detected. Also, no significant differences were seen in self-reported complaints on cognitive functioning for the patients treated with CTC or FEC chemotherapy in comparison to the control patients, while the patients treated with CMF chemotherapy expressed significantly more cognitive problems in daily life than the patients in the control group. Similar to the findings of the first examinations, no clear relation was found between test performance on the one hand and anxiety, depression, fatigue and self-reported complaints of cognitive functioning on the other hand. A differential attrition was observed among the groups, with a relatively high percentage of initially cognitively impaired patients from the CTC group dropping out due to factors related to disease progression.19

Comments on study design

In order to investigate cognitive deficits following chemotherapy, some choices concerning the selection of patients were made in the above-described studies, as well as choices about the methods by which the deficits could be assessed. The following section discusses these choices and their consequences.

Study population

At the time of the completion of the neuropsychological pilot study, a randomized trial was in progress in the Netherlands Cancer Institute and elsewhere in the Netherlands to investigate the curative potential of very intensive adjuvant chemotherapy in high-risk breast cancer patients. The aim of this trial was determine whether adjuvant high-dose chemotherapy should be offered on a routine basis to young patients (under 55 years of age) with operable stage II or III breast cancer, who had 4 or more tumor-positive axillary lymph nodes but no distant metastasis.20 In this trial, patients were randomized to receive either high-dose
adjuvant (CTC) chemotherapy with hematopoietic stem cell support following standard-dose adjuvant (FEC) chemotherapy or FEC chemotherapy alone. For several reasons, this patient group was believed to form a good research model to start the investigation on the impact of cytostatic drugs on cognitive functioning.

First, patients were randomized to receive high-dose or no high-dose chemotherapy, which enabled a more precise comparison of these treatments and the assessment of a possible dose-response relationship. Secondly, but of equal importance, the patients in this trial were treated adjuvantly, i.e. there was no evidence of distant metastases, and no prior radiotherapy or chemotherapy was allowed. Furthermore, the issue of high-dose adjuvant chemotherapy for this patient population was of substantial clinical significance. Adjuvant high-dose chemotherapy in breast cancer was and still is a subject of considerable controversy. Preliminary research findings are consistent with a modest benefit on relapse-free survival, but strong evidence for this is still lacking. At present there is no justification for the use of adjuvant high-dose chemotherapy in breast cancer outside clinical studies. High-dose therapy is costly and is associated with both acute and chronic toxicity. Unrecognized pharmacological interactions between high-dose agents and long-term toxicity, such as deficits in cognitive functioning, further complicate the issue.

Another advantage in studying the potential impact of chemotherapy on cognition in a breast cancer population was the availability of relevant comparison groups. Breast cancer patients with a more favorable prognosis but still requiring adjuvant chemotherapy (with 1-3 positive axillary lymph nodes) were, until recently, treated with the widely used cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy regimen. Over the past decades various toxicities associated with this regimen have been investigated and documented, but its potential influence on cognition has not yet been studied.

The breast cancer model also provided the opportunity to include a stage I breast cancer control group that had not received any adjuvant systemic treatment. The use of such a disease-specific comparison group allowed to control for the impact of the diagnosis of cancer on psychosocial distress, that in itself can affect cognitive functioning.

Finally, for the several breast cancer groups the course of the disease is, to a certain degree, predictable, and a fairly long period of disease-free survival could be expected for the total population. In addition, the relatively young age of these women reduced the risk of test results confounded by age-related factors such as hearing or sight difficulties or general frailty.

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3 In this thesis, no formal comparison was made between the patients treated with CTC or FEC chemotherapy and the patients treated with CMF chemotherapy. Such a comparison is however performed, and the results of this analysis are described in a Dutch article: Ned Tijdschr Geneeskd 2000;144:2354-9.
Despite the many advantages of studying the effects of chemotherapy on cognition in breast cancer patients, there were several complicating factors that deserve attention. The fact that in our study only the high-risk breast cancer patients were randomly assigned to the different treatment regimens could in theory preclude unambiguous interpretation of the impact of adjuvant chemotherapy on cognitive function. It can be argued that differences between patients treated with various chemotherapy regimens and control patients can not with certainty be attributed to chemotherapy, because these differences could be due to an unexamined third variable (e.g. stage of disease or individual choice) linked to the reason why some women received specific regimens of chemotherapy and other women did not.

Although at the time of neuropsychological testing all patients were clinically free of disease, factors related to prognosis (e.g. anxiety and depression) could potentially have accounted for differences between patients in cognitive functioning. It appeared, however, that depression and anxiety had no influence on the cognitive test performance of the patients.

Cross-sectional character of studies
Since there was little information available on the hypothesized prevalence of cognitive impairment following chemotherapy for breast cancer, a cross-sectional design was chosen for the initial neuropsychological study. A cross-sectional study can be used to determine whether or not a relationship exists between cognitive impairment and chemotherapy. There are, however, several problems associated with such a design that should be addressed. The first issue concerns the representativeness of the study sample for the general population. Clearly, the selection of a sample can affect the observed prevalence of a disorder. In our study, patients were selected who were free of disease or other medical complications, of relatively young age, and with the potential to survive for fairly long periods of time. Although this selection was made specifically in order to study the effects of chemotherapy on cognitive functioning with as few confounding influences as possible, it should be kept in mind that, by doing so, a selection bias was introduced. Additional problems can also arise from a selection bias due to response rates. In our studies, the response rate for participation in the neuropsychological studies for the various groups was reasonably high and in concordance with those found in other studies conducted in the Netherlands Cancer Institute. Also, the reasons reported for declining participation were mainly of emotional or practical origin. None of the patients refused participation because of the prevalence of cognitive complaints or the lack of such complaints. In spite of this, we cannot completely exclude that there might be potential significant differences between the patients who did or did not participate in the neuropsychological studies. Another inherent weakness of cross-sectional studies addressing associations with a specific disease or treatment concerns the sequence in time of the disorder of interest and the possible risk factor. In theory, it might be conceivable that the observed deficits in cognitive functioning assessed after completion of treatment are

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4 At the time of this study, CMF chemotherapy was considered the standard adjuvant regimen for breast cancer in the Netherlands. Recently published overview data that compared anthracycline-containing regimens with CMF-like regimens indicated, however, a very modest but significant difference in favor of anthracycline use. By now, most university hospitals in the Netherlands prefer anthracyclin-based regimens.
not related to the chemotherapy but refer to pre-existing cognitive problems. Although only a prospective study with a pre-treatment baseline assessment could answer this question, the existence of pre-treatment cognitive impairment is not likely. The control group of stage I breast cancer patients who received surgery and radiotherapy but no chemotherapy did not differ in their neuropsychological test performance from published test norms of healthy individuals. The observed cognitive impairments are, therefore, unlikely the consequence of surgical or radiotherapeutical procedures. Nor are they likely to be mediated by the fact that our patients were confronted with the diagnosis of cancer.

**Assessment times**

Closely linked to the choice for a cross-sectional design with its specific advantages and disadvantages, is the choice for the time point of assessment. In the first assessment points, only patients who were off treatment for at least 6 months were included. This period was selected to examine the influence of chemotherapy in a setting in which the impact of an active disease process or the presence of acute toxicities associated with treatment could be excluded. As stated earlier, the probability of an event of interest occurring is strongly related to the initial selection of patients, but it is also related to the point in time at which the event of interest is chosen to be measured. Our primary interest were the long-term and potentially non-reversible effects of chemotherapy, and the first assessment took place, on average, two years after completion of non-hormonal therapy.

At the time of the completion of the first neuropsychological studies, objective evidence from the literature on the existence of deterioration in cognitive function after chemotherapy was still sparse, as was information on the kind of deficits occurring in brain functioning manifested by cognitive changes and on the mechanisms responsible for causing such deficits. Consequently, no clear expectations could be formulated on the (ir)reversibility of the observed adverse effects and the time frame in which recovery was potentially supposed to occur or was no longer expected.

Although the rate and trajectory of recovery following onset of any kind of brain damage is dependent on the nature, site, and severity of the damage, improvement generally occurs most rapidly in the first two years with further improvement following very slowly. This is, however, not an ironclad rule. For example, in the case of neurotoxins, some adverse effects may take a substantial time to evolve, first appearing only years after exposure or exacerbating pre-existing central nervous system dysfunction.

Because data from sequential neuropsychological examinations can provide an indication of whether the underlying condition is changing and, if so, in what ways, it was decided to test breast cancer patients who were still free of disease for a second time with an additional two-year test-retest interval. The rationale for this specific point in time was (in part) based on observations by clinicians regarding the reduction in patient's complaints of anxiety and depression after a relatively large number of years post therapy.
However, the choice of this late assessment point in time combined with the exclusion of patients with metastatic disease or relapse, meant that a very distinctive group of patients was tested. In interpreting the overall research findings, it should be kept in mind that these factors may have possibly been of influence on the rate of occurrence of cognitive impairment observed following chemotherapy, and that this sample is only partially representative for a normal population of breast cancer patients.

Selection of neuropsychological measures

One of the difficulties in the interpretation of published reports on cognitive problems following chemotherapy is the diversity of measures used (see chapter 2). Some of the conducted studies have focused on selected areas of cognitive functioning, without clear reasons for the omission of others. Based on the literature and on our own pilot study, no hypotheses could be formulated about the direction or pattern of deficits expected after chemotherapy. From what was learned so far, cognitive deficits following cytotoxic treatment occur in a wide spectrum of functions, and there is no well-defined reason for the inclusion or omission of specific functions in the neuropsychological battery. It was therefore decided to design a battery that would detect possible deficits in the major domains of cognitive behavior, i.e. memory, attention, mental flexibility, speed of information processing, motor function, verbal function and visuospatial function.

The test battery was selected in consultation with two experienced neuropsychologists, with the aim to minimize patient burden while still providing coverage of a broad range of cognitive functions. The selected tests are nationally and internationally widely used standardized psychometric instruments, and general population norms are available for most of the tests included in the neuropsychological battery (for a detailed description of the specific tests used see chapter 5).

Selection of self-reported measures of cognitive functioning in daily life

In addition to the neuropsychological test battery, a semi-structured interview on cognitive problems in daily life was conducted with all patients. The questions included in this interview were (in part) adapted from a Dutch instrument designed to assess psychopathological symptoms. As stated previously, most measures of subjective cognitive functioning do not show a reliable or robust correlation with objective measures of cognitive abilities. In cancer population studies these subjective measures of cognitive functioning often consist of a concise inquiry. It was thought that in attempting to obtain reliable self-reported data on cognitive functioning, detailed questions would have to be asked. A disadvantage of the interview that was developed for this purpose was that no comparison data based on healthy subjects were available, i.e. comparison was possible only between the different groups of breast cancer patients.
Selection of subjective measures of quality of life and anxiety and depression

Self-administered questionnaires were applied to collect data on health-related quality of life, fatigue and psychosocial distress to examine if these factors would be of influence on the results of the neuropsychological examination. For this purpose two questionnaires especially designed for the ease and appropriateness of medical settings were included, the Quality of Life questionnaire QLQ C30\(^2\) and the Hopkins symptoms checklist.\(^{26,27}\) No data on healthy populations are available for either of these questionnaires.

Selection of neurophysiological methods

Neuropsychological testing is a common measure for assessing cerebral injury. The judgments made on the basis of a neuropsychological examination remain nonetheless judgments in terms of behavior. These statements can by no means automatically be translated into neuronal concepts. As such, cognitive function in cancer patients following chemotherapy may be compromised by organic impairment due to treatment, but deficits can equally well be the reflection of psychosocial distress or fatigue, factors that are recognized as very common in cancer patients. Although in our studies no relation was detected between anxiety, depression or fatigue and neuropsychological test performance, an unexamined variable other than organic impairment per se could be responsible for the observed cognitive deficits. In summary, cognitive impairment observed on neuropsychological tests can not (even in the absence of, or after controlling for, potentially confounding variables) provide evidence for the existence of organic brain injury, it can only make such injury plausible.

Therefore, in an attempt to quantify cerebral dysfunction in cancer patients treated with chemotherapy, a study was conducted in which a neurophysiological examination consisting of qEEG and P300 event-related potentials (ERPs) was performed subsequent to the neuropsychological test battery. EEG generally provides global information on the nature and extent of activity of the brain, while ERPs can be viewed as a measure for the way in which information is processed.\(^{28}\)

It should be noted that EEG and ERPs are functional methods, which allow more insight in the underlying nature of impairment following chemotherapy. These techniques do not elucidate the causes or the mechanisms by which chemotherapy may induce brain damage.

Comments on the determination of findings

The following section discusses several methodological problems, divided into methods (neuropsychological or neurophysiological) and moment in time (first assessment and second assessment).
Sample size on T1

The main idea behind sample size calculations in studies is to increase the chance of detecting a significant effect if it exists, and thus to be reasonably sure that no such effect exists if none is found. Research performed in a setting such as medical oncology sometimes entails conducting studies within the restrictions set by the (often) limited number of patients available at a specific time. In the first neuropsychological study, we tested the maximum amount of patients available at that time. Although the number of participating patients was higher than in most comparable studies and significant differences were observed between the different patient groups, the wide confidence intervals in the logistic regression analyses indicate that the sample size of the study is still rather small. Consequently, we can consider the observed effect in our sample as strong, for it would otherwise have gone unnoticed given our small study, but we do not know, however, how stable this observation is.

Determination of cognitive impairment on T1

In neuropsychology, the most basic approach of analyzing test data is to compare the mean of an experimental group with the mean obtained from published norms of a healthy control group. In our study, we have deviated from this method on two important points. First, we have included a disease-specific control group in our study consisting of stage I breast cancer patients not treated with chemotherapy. Although we have used published norms of a non-diseased normal population for comparison with the results of the stage I breast cancer patients, our own control group served as a reference for all further analyses. Secondly, our central outcome measures were not based on comparisons of group means of the chemotherapy patients and the control patients, but on an individual approach with respect to the determination of cognitive impairment. The reasons for these choices are well-grounded and offer many advantages. There are, however, several problems that need further discussion.

One essential reason led to the inclusion of a control group rather than the usually employed published normative data of healthy subjects. The focus of our study was on the potential impact of chemotherapy on cognitive functioning in cancer patients and not on the impact of cancer per se. In order to properly address this issue, it was necessary to control for the impact of the diagnosis of cancer, as this in itself might affect cognitive functioning. If only a healthy control group had been used for the comparison of cognitive performance of patients treated with cytostatic agents, this confounding effect could not have been controlled for.

It can be argued that norms based on a true normal population could provide more reliable estimates of the mean and especially of the variance, if the reference data are based on a reasonably large tested population. Our control group consisted of 34 patients, which is rather small compared with available normative data for some of the neuropsychological tests used in the study. There are, on the other hand, several widely used neuropsychological tests included in our battery that provide norms relevant for a specific age or gender group which are based on far fewer subjects. Although our control group may be well matched to other
published reference groups with regard to the sample size, this does not alter the fact that a larger number of control patients would have been preferable to increase the reliability of our findings.

The second point on which we deviated from more common methods, concerns the individual approach used in our studies for the determination of cognitive deficits. In many studies conclusions are based on comparisons between group means, but such analyses do not address the heterogeneity of cognitive deficits after chemotherapy. One subgroup of patients may be impaired in several areas of neuropsychological functioning, while others are not. This would result in an increased variability in the chemotherapy groups compared to a control group, but the group mean of the chemotherapy patients may not be different from the group mean of the control patients. Because the consideration of group means can obscure cognitive impairment evaluation at the level of the individual, an individual approach for the determination of cognitive impairment was used. Neuropsychological impairment was determined in 3 steps: first, a patient who scored 2 standard deviations below the mean of the control group on a test (i.e. < 95% correct) was considered as impaired on that specific test. Only 2.6% of the population would be expected to score in this range in a normal distribution. In neuropsychological practice, a score lower than 2 standard deviations below the mean of a control group is generally accepted as abnormal. Second, for each individual patient an overall impairment score was calculated, by counting all tests on which the patient was impaired. Finally, the fifth percentile of the overall impairment scores of our control patients was used as a cut-off point to determine whether a patient was classified as cognitively impaired. This classification of impairment is much stricter than used in comparable clinical studies. Moreover, it is based on the distribution of impaired scores in the control group, which is again contrary to most studies. In most studies, patients are classified as not, mildly, moderately or severely impaired on the basis of unfounded or unspecified criteria.

Nevertheless, the use of cut-off scores, i.e. forcing a choice between impaired and not impaired patients, remains to a certain degree an arbitrary manner of expressing results, because minor changes to the data could alter the distribution of impaired and not impaired cases.

**Multiple comparisons on T1**

Neuropsychological test data are often criticized because of the multiple comparisons made. Multiple significance testing gives a high probability of finding a significant difference just by chance, i.e. each test has a 5% chance of a false positive result when there is no real difference (type I error). Several statistical models deal with this problem (e.g. Bonferroni or Duncan) by aiming to keep the overall type I error rate at no more than 5%. A disadvantage of all these methods is that they are highly conservative.

In our studies, multiple comparisons were made with regard to the neuropsychological test results. But the differences in mean neuropsychological test scores between groups were
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tested by univariate analysis for descriptive purposes only. When the Bonferroni method of correcting for these multiple comparisons was applied, setting alpha at 0.002, none of the differences between the various chemotherapy groups and the control group remained significant. However, in our studies we focused on the determination of cognitive impairment at the level of the individual patient as the most important outcome variable, and only this variable was tested for differences in a multivariate logistic regression analysis. Due to this approach the problems associated with multiple testing were circumvented. 32

**Validity and reliability of the neuropsychological tests on T1**

The primary aim of the first neuropsychological assessments was to determine of the presence of cognitive deficits. The tests used were selected on their proven value for the detection of cerebral dysfunction. The diffuse pattern of deficits that was found, i.e. the differences between the groups were not attributable to one test in particular, did not allow to formulate specific hypotheses about the observed impairment. Consequently, no in-depth analysis was made on specific meanings and properties of separate tests. No comments were formulated on the internal consistency of a specific test or on the construct that a test is supposed to refer to, e.g. the reliability and validity of the tests used have hardly been subjected to discussion. From the literature, however, it is known that most instruments used in our study have reasonably good psychometric properties, and a significant amount of data is available on the functions that the different tests are supposed to assess. 4 Therefore, we believe that the validity and reliability of the neuropsychological tests used do not lead to specific problems with regard to the interpretation of the neuropsychological data. It is more likely that the judgment of test results in relation to expected performance levels gives rise to problems in interpretation.

**Sample size on T2**

Whereas in the first neuropsychological assessment (T1) the relatively small sample size could have precluded unambiguous interpretation of the prevalence of cognitive impairment after chemotherapy, this is certainly true for the second neuropsychological assessment (T2). In fact, the key limitation of the follow-up study is its power. Loss to follow-up is the main difficulty of such studies, and the longer the follow-up period the more the sample will reduce due to attrition and missing data. In the current study, difference in survival between groups has led to additional complications. Especially problematic was that the percentage of patients impaired on T1 that was lost to follow-up was not comparable across groups. Consequently, it is uncertain how representative this limited sample may be. Due to these problems, any findings from the second neuropsychological assessment should be interpreted with great caution.

**Determination of changes in cognitive functioning from T1 to T2**

Besides the low power and selective attrition of patients on T2, the problem remains assessing the response of the patients that did participate on T1 and T2. There are several methods for
analyzing longitudinal neuropsychological data. Of the various techniques used to compare groups with regard to cognitive change, the simplest method is to compare the mean test scores for the separate neuropsychological tests on T1 and T2. This kind of analysis may not be very meaningful, because the mean test scores of a specific group can conceal individual scores that have deteriorated or improved.

Contrary to the statistical models for comparing groups with regard to neuropsychological change, techniques for detecting changes in individuals are less well developed. Apart from deciding on a statistical method for analyzing change, one has to decide how much change in a test score will be considered significant, i.e. at which point a deviation from T1 is considered unlikely to be the result of chance. The adequacy to reflect true changes in cognitive functions for an individual is a function of several factors, including the reliability and stability of the test procedures over time. In the literature several models for predicting retest scores are described. These methods include the Reliable Change Index and models based upon regression by which potential confounding factors such as test-retest reliability, practice effects and duration of test interval can be taken into account. 33 35

The question as to which model is best suited for which research goal is often not established and, consequently is open to different interpretations. Moreover, other problems have to be considered. The time period held by test publishers to examine test-retest reliability estimates is relatively short. Another problem with using data derived from population-based standardized samples is the assumption that patients with disorders will show the same relative degree of practice effect as neurologically intact individuals. Also, this information on test features required for the analysis has to be derived from data published in either the test manuals, the original article describing the test, or texts describing the tests. This means that the standard against which deviations should be measured is based upon a different control group for each test.

Thus, to adequately determine the improvement, deterioration or stabilizing of cognitive functioning of patients treated with chemotherapy after the first assessment, it is necessary to know whether the observed changes exceed those expected due to natural fluctuation alone. This expectation has to be based either upon information on reliability and practice effects derived from the 13 different test-manuals and articles, or on data of our own reference group consisting of breast cancer patients who were not treated with chemotherapy. Both options are, however, problematic. Information on estimated test-retest change scores (i.e. stability of tests) and re-test effect data (i.e. practice effects) among standardized samples is not available for each neuropsychological instrument. Re-test data of the reference group of breast cancer patients not treated with chemotherapy would be representative, but in our case this information would be inaccurate due to a small sample estimate.

Our follow-up study used the concept of the classification of a patient into the category of cognitively impaired or intact, according to the criterion used on T1, as this was believed to
be the most transparent and straightforward report to describe the cognitive effects perceived. It was claimed that a change has occurred provided that the patient’s change in test scores from T1 resulted in a shift from the classification of cognitively impaired to cognitively intact (or visa versa) on T2. However, by solely using this method which is based on a very strict criterion, the more subtle degree of changes within the continuum on either side of the classification cognitively intact/impaired would remain unnoticed. Thus, it would not be possible to evaluate whether an equal degree of improvement of test scores has resulted differently in a change in the distribution of impaired versus intact cases. Therefore, in spite of the drawbacks, a change in performance was defined as a change in a test score from T1 to T2 according to a fixed external definition of at least 1 standard deviation. The mean number of tests on which a patient improved, deteriorated or maintained a stable performance (irrespective of the criteria for cognitive impairment), was calculated according to this definition. Although this definition for change is common\textsuperscript{4}, it does not become less arbitrary or unfounded. Sometimes the choice is justified by explaining that a downward change of 1 standard deviation on a test of cognitive functioning indicates a reduction of 20\% in cognitive functioning on that test. Some authors even tried to put it in context by illustrating that on a very common test such as the Digit Symbol subtest, for which good age-related norms are available, a 20\% decline is similar to the difference in function between 40- and 60-year-old subjects.\textsuperscript{36} To determine whether such a decline is sufficient or not, additional information on stability of performance in appropriate reference groups is needed before such a statement can be made.

In summary, we do not know if the method we used in our study to operationalize change is a good reflection of the genuine change rate of neuropsychological test performance in our patients. Future research should include the assessment of a true control group (age and education matched non-treated females) over time, which is sufficiently large to provide adequate normative change data to show the normal variance of change, e.g. what should occur on neuropsychological tests over time.

**Study population and sample size of neurophysiological assessment**

Of the high-risk breast cancer patients from the randomized trial comparing the efficacy of high-dose adjuvant chemotherapy with standard-dose chemotherapy that were examined using neuropsychological tests, a cohort of consecutive and unselected patients was asked to participate in the neurophysiological study. The results of these patients were compared with the results of breast cancer patients not treated with chemotherapy. With respect to the representativeness of the findings, it may be risky to select only a subgroup of patients, even when this selection is conducted randomly. However, the subgroup of patients that was tested neurophysiologically, appeared to be a representative sample of the total patient group participating in the neuropsychological study, because the distribution of the percentage of patients classified as cognitively impaired in the different treatment groups was similar to the distribution of the percentage of patients with cognitive deficits found in the total study population. Nonetheless, the total number of patients that underwent a neurophysiological
examination was small, and the insufficient number of patients can cause complications in interpretation of the study data. For example, no differences in P300 latencies were detected among the different groups, but a significant relation was found between the latency of P300 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. The fact that this observation could not be traced back to differences between the groups may be due to the lack of a satisfactory number of patients.

**Determination of neurophysiological response**

Although neurophysiological data are thought to provide a more direct assessment of brain function than neuropsychological data, the interpretation of neurophysiological material also requires some form of subjective judgment. In the current study, the EEG data were subjected to visual inspection by an experienced researcher and clinician, blinded to the treatment condition of the patients. Alpha peak frequency, alpha blocking and asymmetry of alpha rhythm, as well as latency of P300 were compared between the three patient groups. For all parameters, mean outcome measures were compared between groups, except for asymmetry of alpha rhythm. A criterion of 0.5 Hz was held for asymmetry, and the data were compared between the groups according to this definition. In neurophysiological practice, asymmetry of alpha rhythm set at 0.5 Hz is the standard classification for asymmetry, and its power to discriminate between neurologically impaired or intact patients is proven many times. Still, arguments similar to those applied to the neuropsychological data can be formulated against the use of a forced choice to differentiate between impaired and not impaired patients, as minor changes could alter the distribution of the two subgroups.

**Interpretation of findings**

The considerations described in the previous sections on the design and the power of the studies, the instruments applied and the strategies chosen for the determination of sub-optimal performance clearly show that the outcomes of this study can not be definitive, because several limitations exist. However, the need remains to discuss the results in terms of their meaning and their potential origin. When taking the results as a reliable reflection of reality, what have we in fact found?

**Pattern of deficits**

Current thinking in neuropsychology recognizes brain damage as a measurable multidimensional phenomenon. The behavioral consequences of brain damage vary with the nature, extent, location and duration of a lesion, with the age and physical condition of a patient, and with individual neuroanatomical and physiological differences. The concept of brain damage only becomes meaningful in terms of specific behavioral dysfunctions and their implications regarding underlying brain pathology.
One way of gaining insight in the etiology of cognitive impairment is to study the pattern of deficits found. For example, several common patterns of impairment associated with well-understood neurological conditions, such as certain kinds of cerebrovascular accidents, have been shown to involve the same anatomical structures with predictable regularity. It should, however, always be kept in mind that to localize a symptom is not the same as to localize a function. The question is to what extent certain behavioral deficits can be explained by deficits in specific components of the brain, where components can refer to either nerve cells, neurotransmitter systems, to separate lobes or even to the different hemispheres.

From the studies describing the nature of neuropsychological impairment in patients treated with chemotherapy, we learned that no specific domain of cognitive function seemed more frequently characterized by impaired performance than others. The results of our neuropsychological studies were consistent with those of other studies. Deviant performance was found on several cognitive domains, including attention, memory, speed of information processing and mental flexibility. Measures of more specific cognitive abilities, such as tests of visuospatial functioning, were not affected in the patients treated with adjuvant chemotherapy. Deficits in such specific skills are often noticed in patients with focal lesions.

The global pattern of neuropsychological deficits in our breast cancer patients treated with chemotherapy, which is suggestive for diffuse brain dysfunction, seems to be the most consistent with the diffuse cerebral dysfunction seen secondary to radiation therapy side-effects, or with diffuse pathology seen in disorders such as closed head injury.

This global nature of the deficits, combined with the apparent improvement of performance, has important implications for the mechanism proposed by which cytotoxic agents may cause cognitive disorders. These issues are discussed in the final section of this chapter.

Relation between self-reported cognitive problems, neuropsychological test performance and neurophysiological parameters

In our studies, no relation was found between self-reported cognitive complaints and cognitive functioning as measured with the neuropsychological tests. At the interview the self-reported complaints on memory, attention, thinking and language and the complaints expressed on the EORTC QLQ 30 cognitive function scale did not correlate with the overall scores of cognitive impairment as defined for each individual, nor with neuropsychological test performance corresponding to specific domains. Anxiety, depression and fatigue were related to the complaints about cognitive functioning; but these factors were not related to the neuropsychological test results.

The subject of the relation between self-reported cognitive complaints and cognitive functioning as measured with objective cognitive tests is generally viewed as complex and difficult. In trying to understand the discrepancy found between objectively measured
cognitive functioning and reported cognitive complaints, several explanations (that are not necessarily mutually exclusive) have to be considered.5

First of all, the absence of a clear relation between patients' self-reported complaints and objective test performance may be explained by the low ecological relevance of most neuropsychological tests. The domains assessed by neuropsychological tests of cognitive function show little overlap with the everyday experience on which patients base their self-report; traditional neuropsychological tests can be viewed as artificial in terms of everyday cognitive function. Thus, the absence of relationship between laboratory and everyday tasks is not really surprising.39

Secondly, the possibility exists that self-perception could be a more sensitive method to assess subtle cognitive impairment than objective neuropsychological assessment. Particularly for highly educated persons, the tests may not be sensitive enough to measure cognitive impairment, because of ceiling effects. This impairment can nonetheless adversely affect quality of life and cause cognitive complaints.40-42

A third reason concerns the conditions under which the neuropsychological tests are assessed, and the implications of these conditions for the performance measured. Laboratory tasks have been designed to control all except one single critical variable and to minimize the effects of individual differences. Unlike real-life demands, laboratory tasks are experienced under conditions of minimal distractions and stress. Patients are reassured and encouraged to do their best, leading to the full use of their potential cognitive abilities. In this respect, neuropsychological testing measures the capacity of a patient within the optimal circumstances of a test situation. The ability, however, to learn a list of words in a quiet atmosphere of a test room does not guarantee that a patient will remember the name of a person he/she was introduced to at a noisy social gathering, or what goods he/she had intended to purchase at a busy supermarket. Furthermore, normal test results may be achieved only with an abnormal expenditure of effort. Patients may be able to perform well during a relatively short test period, but their daily functioning may be compromised and give rise to cognitive complaints. In other words, patients may be able to mobilize cognitive resources for a short time during a test session, but they are not able to sustain this for longer periods of time during everyday activities.39,43-45

A fourth possibility that has to be considered is that complaints of cognitive functioning do not reflect actual cognitive deficits. It is recognized that patients' complaints are also related to affective status or personality factors such as neuroticism, whereas performance on formal testing is much less affected by this kind of variable.3,39,46

5 Besides content-related explanations for the absence of a relation between cognitive complaints and neuropsychological test performance, a more prosaic argument has to be mentioned. The fact that we did not find a relationship between cognitive complaints and test performance can, theoretically, also be explained by a too limited distribution in overall impairment scores.
Also, it can be argued that people may have only limited conscious access to their own cognitive processes. Especially subjects with cognitive deficits may have difficulty in objectively assessing their own daily cognitive failures. Whatever the degree of insight into one’s own cognitive abilities can be expected, people can only make relative comparisons, assessing their competence against their ability to cope with the particular demands which their lives make of them. This obviously reflects many more aspects besides cognitive functioning, for example self-respect or confidence.

In considering these arguments, the intuitive logical association between complaints about cognitive functioning and cognitive functioning as measured with neuropsychological tests becomes less self-evident, and its absence can even be satisfactorily explained. But what is the impact of these considerations on our research findings?

The aim of the studies was to investigate whether patients treated with chemotherapy exhibited cognitive deficits. It can be concluded that in a number of patients such deficits are observed. Whether and in what way these problems are reflected in the daily life experiences is less clear.

One of the proposed hypotheses stated that neuropsychological testing is actually the measurement of the capacity of a patient. This implies that a patient can truly experience cognitive problems in daily life, leading to the report of cognitive complaints, without exhibiting impairment on neuropsychological testing, because full use of abilities is being employed at that moment. At the same time, neuropsychological tests may elicit deficits, without bringing about an effect in daily life functioning. In what way the cognitive capacity (as measured with neuropsychological tests) is expressed or experienced in daily life functioning by a patient is dependent on the circumstances (including personal and environmental factors) in which the patient lives. In terms of the classification described in a previous section of this chapter, the injury occurring in brain functioning as a consequence of cytotoxic treatment (impairment) can be manifested in the cognitive capacity (disabilities) measured with the neuropsychological tests, which in turn can lead to a complaint (handicap) in daily life functioning. It is the extent to which a disability becomes a handicap that is determined by a number of factors.

In light of these considerations, it is not surprising that no relation was found between the neurophysiological parameters and the self-reported cognitive complaints, and that the relation between these parameters and neuropsychological test performance was not straightforward.

Impairment, disability and handicap can all be expressions of a single underlying phenomenon, without clear-cut associations between these components. Which components should be accentuated and what outcomes will be most decisive is dependent on the endpoint of the research in question.
Confounding factors

After description of the cognitive impairment observed, as well as its pattern and its interrelated nature with several self-reported problems, the next step is to consider the cause of the impairment. How can the cognitive deficits in a number of breast cancer patients treated with chemotherapy be explained? Is it the chemotherapy that causes these problems or are there other factors that might explain or mediate the cognitive impairment found? The cognitive deficits emerged in the absence of evident co-morbidity. None of the patients had a history of neurological or psychiatric disorders and none had clinical evidence of central nervous system involvement. Patients using opioid analgesics, anxiolytics or antidepressant medications were excluded from the studies. Also, the medical charts of the patients were examined from the start of chemotherapy to the time of the neuropsychological assessments in order to reveal any medical complications that might have affected cognitive functioning such as infections, thyroid dysfunction, damage to the liver, etc. No conditions were found that could account for the observed differences. By means of comparison with stage I breast cancer control patients not treated with chemotherapy, the possible long-term effects of anesthesia could be excluded as a determinant in the cognitive impairment found. Also, depression, anxiety and fatigue were not associated with test performance. However, several factors remain whose potential influence on cognitive functioning can not be excluded.

Role of estrogen in cognitive functioning

After menopause, estrogen levels decrease in women. This decrease is associated with an increased risk of osteoporosis and cardiovascular disease. Decreases in estrogen levels have also been hypothesized to be associated with cognitive decline. Such a relationship between estrogen levels and cognitive functioning is biologically plausible. Mechanisms have been described, proposing alterations in brain enzymes that impact neurotransmitters crucial for specific cognitive processes. Estrogen receptors are known to be present in the hippocampus, locus coeruleus and basal forebrain. They are also present on cholinergic neurons of the basal forebrain, and these neurons project to both the hippocampus and the cerebral cortex. Circulating estrogen increases choline acetyltransferase and thereby increases acetylcholine synthesis. With estrogen depletion, estrogen-sensitive neurons may be lost. Alternative explanations suggest that estrogens reduce monoamine oxidase levels and increase cerebral blood flow.48

Cytotoxic treatment causes chemical castration, inducing early menopause. In theory, it is possible that the observed differences in cognitive functioning between patients treated with chemotherapy and control patients are hormone-mediated rather than the result of direct adverse effects of the chemotherapeutic treatment itself. In this respect, the potential role of tamoxifen, an anti-estrogen, which a large proportion of the patients treated with chemotherapy additionally received, has to be considered as well.

Current literature on the relation between endogenous fluctuations in estrogen levels and cognition, and on cognitive effects of exogenous hormone replacement therapy has shown
Discussion

inconsistent results. Whereas some reported a beneficial effect of exogenous estrogen use on cognitive functioning $^{49}$, and a relation between lower endogenous estrogen levels and cognitive decline $^{50}$, others did not support these findings $^{51}$ or even reported opposite effects. $^{52}$ In studies that were supportive of a positive influence of estrogen on cognition, effects were frequently limited to measures of verbal memory only. A recent study, which for the first time specifically investigated the role of tamoxifen, suggested that its use may adversely affect cognition, while past users and those who never used tamoxifen did not differ in their cognitive performance. $^{53}$

In our studies, almost all patients treated with chemotherapy were postmenopausal at the time of the first neuropsychological assessment (only 2 patients treated with FEC chemotherapy were considered premenopausal). As a consequence, comparisons could be made only between pre- and postmenopausal patients in the control group. No differences in cognitive performance were found between these patients. The value of this observation is however unclear, because it is not known if the disruptive effects of treatment-induced menopause on cognitive functioning are comparable to the effects of a naturally occurring menopause. At the time of the second neuropsychological assessment, the percentage of pre- and postmenopausal women in the control group had changed. This time, significant differences were found in neuropsychological test outcomes between the patients who were premenopausal and those who were postmenopausal, with the postmenopausal patients performing worse. These differences, however, might equally well be explained by the significant difference in age between the two groups, which causes an unresolvable methodological limitation for investigation of the effects of menopausal status in this selection of patients.

Most patients treated with CTC or FEC chemotherapy still received tamoxifen at the time of the first neuropsychological assessment. A comparison between patients receiving tamoxifen and those that do not receive such therapy, could only be made for the CMF group. In this group, patients were randomly assigned to receive tamoxifen or no further treatment. No differences were found in test performance between patients treated with chemotherapy plus tamoxifen and patients treated with chemotherapy alone. For the total study population treated with chemotherapy comparisons at the second assessment showed no differences in neuropsychological outcome measures between patients who completed tamoxifen therapy, who were still on tamoxifen therapy, and those who had never used tamoxifen.

However, the small number of patients in the different subgroups precludes definitive judgments on the influence of estrogen in cognitive dysfunction as observed in our studies. This important potential confounder should be carefully accounted for in future studies.

Co-medication

In addition to the potential neurotoxic effects of chemotherapy, adjuvant medications may also cause cognitive deficits, complicating the assessment of patients receiving multiple medications. Drugs with known cognitive effects include steroids, antiemetics, antibiotics,
pain medications and immunosuppressive agents.\textsuperscript{4} It can not be excluded that some of these medications may have contributed to the occurrence of cognitive deficits in some of our patients.

\textit{Dimethylsulfoxide (DMSO)}

DMSO is a component used for the preservation of stem cells. It is a low-molecular-weight solvent, which is also frequently used to solubilize poorly water-soluble substances and drugs. It has been reported that DMSO might cause a temporary increased permeability of the blood-brain barrier for certain drugs.\textsuperscript{54} These claims are, however, controversial.\textsuperscript{55} Since the infusion of DMSO takes place after wash-out of the cytotoxic drugs, possible effects on the penetration of the drugs in the high-dose CTC regimens is not likely an important issue. Direct adverse effects of DMSO on cognitive functioning remain to be determined.

\textit{Granulocyte-colony stimulating factor (G-CSF)}

G-CSF (filgrastim) is a biological response modifier that regulates the production, maturation and function of cells of the neutrophil lineage. The most prominent effect of administration of G-CSF (as given to our patients treated with high-dose chemotherapy) is to induce an increase of the neutrophil count. Toxic side-effects of G-CSF are generally described as mild. Some patients have reported bone pain, and chronic administration of G-CSF has been associated with benign splenomegaly.\textsuperscript{56}

G-CSF is also used to prevent infections in head injured patients.\textsuperscript{57} Some studies suggested that G-CSF could exacerbate brain injury by causing secondary injuries, such as blood-brain permeability, brain swelling and intracranial pressure.\textsuperscript{58} The role of neutrophils in blood-brain damage in non-injured brain patients is controversial. Animal studies have indicated that administration of G-CSF to rats before traumatic brain injury increases blood-brain damage after controlled cortical impact.\textsuperscript{59} As the action of biologically active substances is strictly species-dependent, the value of these observations is questionable. Further studies on the potential adverse effect of G-CSF either alone or in combination may be needed.

\textbf{Chemotherapy as a causative factor?}

If chemotherapy itself is the cause of the cognitive impairment observed in a number of breast cancer patients, identification of the cytotoxic agents responsible for this impairment and determination of the mechanisms by which the impairment is established, is essential. To differentiate between the effects of the agents is problematic, as all cytotoxic drugs are given in combinations. Therefore it is difficult to identify whether cognitive impairment results from the direct action of a specific drug given, or from a specific combination of drugs.

For the cytotoxic agents employed in the conventional regimens in our studies, late neurotoxicity has not been reported, at least not when administered in the dosages currently used. 5-FU penetrates the blood-brain barrier easily. The major neurotoxicity of 5-FU is an acute (reversible) cerebellar syndrome, but this syndrome is rare and occurs only at high
Dosages. Epidoxorubicin and cyclophosphamide hardly cross the blood-brain barrier. These agents have never been associated with neurotoxicity, except for a rarely occurring SIADH syndrome (syndrome of inappropriate secretion of antidiuretic hormone) with administration of cyclophosphamide. 56,60,61

In explaining the difference observed in cognitive functioning between the breast cancer patients treated with CMF or FEC chemotherapy, it should be noted that the cumulative dose of cyclophosphamide is much higher in the CMF regimen than in the FEC regimen (CMF = 8.4 g/m², FEC = 2.5 g/m²). The difference between the CMF and FEC patients may, however, also suggest that methotrexate (MTX) plays a role in the occurrence of cognitive problems. Late neurotoxicity, ranging from memory and concentration problems to progressive dementia, is a well-known complication of intrathecal MTX administration either alone or in combination with cranial radiation. Neurotoxicity is also reported as a rare complication of high-dose intravenous MTX given as single treatment. However, MTX dosages equivalent to the dosages used in the CMF regimen are known to barely penetrate the blood-brain barrier. 62

Of the cytotoxic agents used in the high-dose CTC regimen, neurotoxicity is described for thiotepa only. Carboplatin causes mild peripheral neuropathy occasionally and only after high-dose intravenous administration. It does not cross the blood-brain barrier easily. The neurotoxic effect of thiothepa is known as an acute encephalopathy, which only occurs after very high-dose administration, well beyond the dosage used in the CTC protocol. 63 Thiotepa easily traverses the blood-brain barrier.

Currently, the pathogenesis of neurotoxicity induced by cytotoxic agents or their metabolites is unknown. The pattern of cognitive deficits in our breast cancer patients treated with chemotherapy bore a resemblance to that of diffuse cerebral dysfunction seen secondary to radiation therapy side-effects.38 The most serious late effect of radiotherapy is necrosis, which is generally considered an irreversible vascular condition. But even without the occurrence of overt necrosis, global cognitive or personality dysfunction after radiation therapy is well recognized. This so-called radiation encephalopathy or diffuse radiation-induced injury is predominantly confined to the subcortical white matter and resembles normal pressure hydrocephalus or leukoencephalopathy. The syndrome is thought to be the result of direct toxic effects of irradiation to the neuroglia or indirect ischemic effects to the neuroglia caused by a radiation-induced microangiopathy. Furthermore, the reported declines in cognitive functioning may be progressive over time or have a delayed onset.64

Although the pattern of deficits observed in the patients treated with chemotherapy is also suggestive of diffuse dysfunction, the impairment does not seem to worsen over time, indicating a marked difference compared to the sequelae of deficits induced by radiation therapy. This difference in course implies that the mechanism thought to be responsible for radiation-induced injury may be dissimilar to the mechanism potentially accounting for chemotherapy-induced injury.
In principle, there are a number of potential mechanisms by which impairment due to cytotoxic agents can be explained. Postulated factors at the histological level of delayed chemotherapy-induced neurotoxicity include direct damaging effects on endothelial cells, on oligodendrocytes and on the microglia, but also on nerve cells themselves. At the biochemical level, possible mechanisms such as changes in synthesis of biogenic amines and neurotransmitters have also been proposed, which might in turn contribute to vascular pathology and ischemic brain injury.

MTX, for example, induces an inhibition of the enzyme dihydrofolate reductase. This enzyme is essential for the synthesis of purines and thymidylate, and plays a role in the synthesis of the neurotransmitters serotonin and dopamine. 5-Fluorouracil, which inhibits the enzyme thymidylate synthase, might play an additional role in the neurotoxicity observed in a number of patients treated with CMF chemotherapy.

Clearly, it is necessary to increase the understanding of the mechanisms involved in the development of impairment and to enable identification of particular agents and their separate, combined or interactive effects mediating cytotoxic brain damage.

Cognitive impairment after chemotherapy: indicator or interference

This thesis addresses the degree to which cognitive function is potentially affected by chemotherapy. The current studies extend the existing empirical literature by providing serial assessments in several homogeneously treated groups of breast cancer patients with an appropriate reference group using a comprehensive neuropsychological test battery. Although our studies were carefully performed, limitations still exist and there is still much to learn about cognitive functioning after chemotherapy. The pattern of deficits, the course of deficits over time and the impact of deficits on daily-life situations, all need to be addressed more comprehensively. Moreover, a number of important confounding factors exists and potential mechanisms by which chemotherapy can adversely affect the brain are insufficiently understood. However, we do know that a number of patients treated with chemotherapy exhibits cognitive impairment two years after completion of treatment, with gradual improvement of performance up to four years post-therapy. At present, it can not be definitely concluded that chemotherapy is the causative factor for these deficits, but its role can not be excluded.

The results of the empirical studies in this thesis confirm data from two other studies in breast cancer patients adjuvantly treated with chemotherapy, on the prevalence of cognitive deficits following such treatment. Wieneke and Dienst tested a group (n=28) of early stage breast cancer patients following standard-dose adjuvant chemotherapy. Adjuvant regimens included 17 patients treated with CMF, 7 patients treated with CMF followed by CAF (cyclophosphamide, doxorubicin, 5-FU) and 4 patients treated with CAF only. At testing, the time since treatment ranged from two weeks up to one year. Effects of drug regimen, length of treatment and level of depression on cognitive functioning were examined. Patients scored below published norms of healthy reference groups on several cognitive functions such as
memory, attention, speed of information processing, mental flexibility, motor function and visuospatial ability. Three quarters of the patients scored 2 standard deviations below the norms on one or more test measures. Level of impairment was unrelated to depression, type of treatment and time since treatment. In the study by Brezden et al. breast cancer patients receiving adjuvant (CMF or CEF i.e., cyclophosphamide, epidoxorubicin, 5-FU) chemotherapy (n=31) were compared with healthy controls (n=36) and with breast cancer patients who had completed chemotherapy a median of two years earlier (n=40). Comparison of mean test scores showed differences between patients currently receiving chemotherapy and healthy controls, with poorer functioning in patients receiving cytotoxic agents. Also, significantly more patients receiving chemotherapy as well as patients who completed this treatment, were classified as having moderate to severe cognitive impairment compared with controls. Observed differences in cognitive functioning were, again, unlikely to be due to mood disturbances. Our follow-up study provided new insights into the course of the cognitive deficits over time, as no previous study assessed their patients after an interval of two years post-treatment. The suggestion of our follow-up study that cognitive deficits following adjuvant chemotherapy in breast cancer patients may be transient, is a finding of major clinical importance.

Currently, the interest in neurocognitive functioning following chemotherapy is rapidly expanding, as is reflected in several recently published reviews on this topic. The question summarized by one of the reviewers on what patients under what conditions experience what type of cognitive deficits (by whose definition) and what difference does it make to them, nicely illustrates the issues that should challenge further research. This question should, however, be expanded by a discussion on the cause of the deficits.

Contributions of the Netherlands Cancer Institute to this field also continue to expand. Neuropsychological and neurophysiological studies are presently underway with larger patient groups in longitudinal settings with different chemotherapeutic agents to gain more insight in the prevalence, the pattern and the impact of cognitive problems following chemotherapy. Also, more basic research is set up to further elucidate the determinants and mechanisms of these cognitive problems.

**Further developments**

In 1998, a large prospective longitudinal neuropsychological study was started in the Netherlands Cancer Institute. A number of interrelated studies are carried out, in which breast cancer patients and lymphoma patients are neuropsychologically tested at three points in time: at baseline (i.e. after surgery and prior to the start of chemotherapy) at 6 months and at 12 months after completion of treatment. Different chemotherapeutic regimens are under investigation. Patients treated with chemotherapy are compared with patients not treated with chemotherapy and with healthy controls, tested at approximately similar points in time. At
each assessment point patients are interviewed with regard to cognitive problems in daily life, work situation, psychological distress and fatigue. Also, for each patient, a partner or close relative is interviewed about his/her opinion of cognitive problems experienced by the patients.

To date, in co-operation with 15 hospitals in the Netherlands, over 700 patients have been tested neuropsychologically. This study will resolve a number of problems encountered in the work described in this thesis, especially with respect to the design and the study power. Hopefully, more insight will be gained in the pattern of deficits and in the impact of deficits on daily life experiences by matching data with occupation-related factors and information gained from the patient’s partner or close relative. The large sample size available should allow better evaluation of patient subgroups, specifically with regard to the influence of menopause and tamoxifen treatment and cognitive functioning. First results of this prospective neuropsychological study are expected in the spring of 2002. The intention is to follow the patients beyond the time point of one year after completion of treatment.

Another way to gain more insight in the nature of late cognitive effects is by asking patients treated with chemotherapy to perform cognitive tasks, while recording event related potentials (ERPs) at the same time. Different components of ERPs can be used to draw precise inferences about different aspects of information processing. Significant features of the separate ERP components are their polarity (positive or negative), intensity or amplitude (reflecting the mobilization of energetical mechanisms involved in task performance) latency (reflecting the timing of information processing) and scalp location (indicating the brain area(s) involved). Energetical aspects of information processing can be distinguished from computational mechanisms. According to the literature, the former refer to the energetical mechanisms of behavior (arousal, activation, effort), whereas the latter refer to cognitive components of information processing (such as stimulus identification, stimulus-response translation, and motor preparation). Thus, ERPs provide information about different aspects of information processing and about the cortical areas involved. Combined measurements of overt task performance and ERPs can yield insight not only into the patients’ task processing efficiency, but also which aspect of performance is enhanced or repressed and which specific areas in the brain are active during different processing stages associated with the task.  

In the year 2000 we started such a psychophysiological study: a joint venture of the Netherlands Cancer Institute, the Faculty of Psychology of the University of Amsterdam and the Departments of Neurology and Clinical Neurophysiology of the Slotervaart Hospital. A subgroup of patients participating in the prospective neuropsychological study is asked to take part in the neurophysiological study. First results of this physiological study are expected in the summer of 2002.
Although EEG and ERP can supply data on the nature of cognitive impairment that supplement behavioral performance, these techniques do not provide additional understanding on the cause or the mechanisms by which chemotherapy may possibly induce such damage.

Studies with animal models of human cognitive functioning after cytotoxic treatment are both complicated and controversial, but they might help to increase the understanding of potential mechanisms involved. In the Netherlands Cancer Institute a series of studies using mice models will be set up, in close cooperation with the Department of Animal Physiology of the University of Groningen. These studies aim to develop a mouse model suitable for the research of cognitive impairment after administration of cytotoxic drugs, to investigate specific cytotoxic agents potentially responsible for cognitive impairment, and to determine neural mechanisms by which cognitive impairment may be caused.

**Implications for clinical practice**

It should be stressed that the basis of current and future research on the effects of cognitive impairment following chemotherapy is patient care and the improvement of this care. As the cognitive sequelae following cytotoxic treatment are still insufficiently understood, it is premature to include this topic in the process of informed decision-making for all patients considered for treatment with cytotoxic agents.

In case of an individual patient complaining of cognitive problems physicians and nurses could be advised to consult a neurologist who, in the absence of signs indicative for brain metastases, can call in a neuropsychologist.

Subsequently, two scenarios are thinkable. On the one hand, no deficits can be observed on neuropsychological testing, and the complaints of the patient can not be objectified. This finding can be explained by the possibility that the neuropsychological tests are not sensitive enough to measure subtle cognitive changes which, nonetheless, can affect quality of life considerably and can cause cognitive complaints. Especially in case of high premorbid capacities of a patient, it can be difficult to prove the existence of impairment, as average scores may actually represent a significant decline in cognitive functioning of this patient. It is also possible that complaints of a patient are an expression of psychoaffective disturbances, rather than the result of an actual decline in cognitive functioning. For this reason, a neuropsychological examination should incorporate an instrument to measure such emotional factors.

On the other hand, if the neuropsychological examination is indicative of cognitive deficits, it can be explained to the patient that that these findings are not unusual and that studies are in progress to elucidate the cause of these cognitive symptoms, with chemotherapy as one of the potential candidates.
In both scenarios, however, a patient can be reassured that the results of the studies described in this thesis indicate that complaints and deficits do not progress over time and may eventually ameliorate.

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