Cognitive functioning following chemotherapy : a study in breast cancer patients

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Chapter 1

Introduction

General introduction

The introduction of chemotherapeutic agents in the 1940s has led to an improvement in the prognosis of many cancer patients. Currently, chemotherapy has a role in several clinical settings. It is given as palliative treatment for patients with advanced disease, as an adjuvant therapy after control of the primary tumor with local therapy to treat micrometastatic disease, and as primary and curative treatment in chemosensitive malignancies.

One of the important obstacles encountered in the use of chemotherapy is toxicity to normal tissue of the body. At present there are no therapeutic agents that have toxicity limited to neoplastic cells, primarily because no drug target, metabolic pathway, surface protein or mechanism of growth and dividing is found exclusively in cancer cells. Over the past decades, various toxicities associated with chemotherapy have been investigated and documented. Nausea and vomiting, myelosuppression and mucositis are the most prominent acute toxicities. Long-term toxicities include cardiotoxicity, neuropathy, infertility and second cancers. Furthermore, fatigue is a very frequent complaint during treatment as well as after completion of chemotherapy. [1]

Cognitive impairment is a less well known potential side-effect of cytotoxic treatment. Complaints of patients about memory and concentration, sometimes years after cytotoxic treatment, are not uncommon, but have not been the subject of systematic investigation. Research on the late effects of cancer treatment on cognitive functioning has predominantly focused on children. This research mainly concerned children cured of leukemia who had received central nervous system (CNS) prophylaxis including cranial radiation therapy and chemotherapy. It was shown that the developing brain was particularly vulnerable to such treatment. In contrast, studies on cognitive effects in adult patients treated for cancer are sparse and have focused on patients who received cranial radiation therapy. As a consequence, little is known about cognitive deficits following chemotherapy in adult patients. This is surprising because even mild cognitive impairment may influence a patient's quality of life and ability to function.

Background to the current research topic

Major advances in the treatment with chemotherapy are the more effective therapies for the dose-limiting acute side-effects like nausea, vomiting and myelosuppression. As a consequence, high-dose chemotherapy regimens combined with autologous bone marrow transplants or granulocyte colony stimulating factor therapy to circumvent bone marrow suppression are now possible. An intact blood-brain barrier is the mechanism generally assumed to prevent central neurotoxicity of chemotherapeutic agents by limiting their entry to the brain. However, this barrier is not an all-or-nothing phenomenon; several factors like peak dose and cumulative dose play a role in the penetration of drugs to the CNS, so the increased dose intensity of cytotoxic agents may elicit new neurological complications.

To investigate the efficacy, toxicity and applicability of a triple high-dose regimen employing autologous peripheral blood progenitor cells (PBPC) and CTC (cyclophosphamide, thiotepa and carboplatin) chemotherapy, [2] a feasibility study was initiated in 1993 in the Netherlands Cancer Institute. At that time, high-dose chemotherapy with peripheral blood progenitor cells transplantation had become accepted therapy in the management of malignant lymphomas and in acute leukemias. Its role in solid tumors was yet to be defined. Single-course high-dose chemotherapy with autologous bone marrow transplantation had shown to induce a high percentage of complete remissions in patients who were incurable with standard doses of this treatment modality, but long-term disease-free survival was still rare. The rationale for the sequential administration of three courses of high-dose CTC chemotherapy (with PBPC transplantation after each course) was to achieve good-quality remission and hopefully to increase long-term survival in these patients.

Because experience with the multiple autotransplantation procedures was still limited in 1993, a working party (consisting of physicians, nurses, a psychologist and a psychiatrist) was formed to monitor all patients participating in this protocol. During screening it was noted by nurses that some patients who completed the intensive treatment experienced memory and concentration problems. Since the emerging problems were marked, it was decided to assess the cognitive functioning of patients participating in the triple CTC protocol in a more systematic manner using a neuropsychological examination.

Initial neuropsychological study

The cognitive functioning of patients participating in the triple CTC protocol was assessed by means of a standardized neuropsychological examination to investigate whether the reported complaints of the patients with regard to their cognitive functioning could be validated by neuropsychological data.[3]

Neuropsychology is an applied science concerned with the behavioral expression of brain dysfunction. It is a component of quality of life research but differs on a number of aspects. In mainstream quality of life research, patients are asked about their symptoms or complaints in a retrospective manner. For example, questions such as "Have you had difficulty in concentrating on things, like reading a newspaper or watching television?" can be answered with the response options: "not at all", "a little", "quite a bit" or "very much". In this way a checklist addressing several functions and symptoms can be completed.[4] Although patient self-report data on cognitive function are integral to quality of life assessment measures in oncology, it is unclear whether self-reported complaints reflect objective cognitive dysfunction. Neuropsychological examination focuses on an objective or direct assessment of cognitive functions rather than on the patient's opinion about these functions.[5]

A neuropsychological examination typically consists of a battery of tests that addresses the major dimensions of cognitive behavior such as memory, attention, verbal function, speed of information processing, visuoconstructive function, motor function and frontal function. Each of these functions is assessed by one or more specific tests and, to cover all functions, a battery of tests is needed often taking 2 to 3 hours to complete. For most tests normative data are available, enabling the patient's test results to be compared with those of healthy persons matched for age, gender and level of education. The performance of patients is usually expressed in relation to the norms of the healthy group.

A battery of tests covering a broad range of functions was used in this study, because no specific hypotheses could yet be formulated about the nature of the potential deficits. The choice of test battery was limited by the availability of tests in all modalities that were sufficiently well standardized or frequently used to provide reliable standards for comparison purposes. Verbal functioning, memory, attention/concentration, speed of information processing and mental flexibility were examined using 8 separate tests (Rey auditory verbal memory test [6,7]; Story recall for the Rivermead behavioral Memory Test [8]; Benton Visual Retention Test [9]; Trailmaking A and B [10]; Digit symbol of the Wechsler Adult Intelligence Scale [11]; Stroop Color Word Test [12,13]; Word fluency from the S.A.N. test [14]; and the Dutch adult reading test [15]). In addition, all patients had an extensive interview about potential cognitive problems experienced in their daily life.

Eligible for the neuropsychological study were patients participating in the triple CTC protocol who completed any previous treatment at least 3 months before the start of the high-dose regimen, who used no medication known to affect cognitive functioning, who were clinically free of brain metastases at the time of the testing and who had no reported history of neurological or psychiatric signs or symptoms which could in itself lead to deviant test performance. Patients were tested prior to and three months after the intensive treatment.

The study sample comprised 8 consecutive non-selected patients diagnosed with breast cancer (n=3), germ cell cancer (n=3) or ovarian cancer (n=2). All patients had metastatic disease and were previously treated with chemotherapy. The mean age of the group was 34.1 (range 29-49) years. Four patients were tested prior to and after completion of the high-dose treatment. For one patient only a baseline evaluation (i.e. prior to the intensive regimen) was obtained, and 3 patients were only tested after the high-dose treatment. In all cases, testing took place at a minimum of three months post therapy.

Six patients reported that they experienced cognitive problems in daily life: mainly forgetting details of recent and past events, and/or lack of sustained attention. In five of these patients, the neuropsychological examination revealed mild to moderate cognitive disturbances compared with the healthy controls. The test results showed impairments in a broad range of functioning, including deficits in the reproduction of newly acquired verbal information, a heightened susceptibility to interference, and a decreased rate of information processing.

Three patients in whom a pre- and posttest was performed stated that cognitive problems in daily life had increased following the CTC treatment. These observations were partly confirmed by an increase in the extent of cognitive impairment on a number of neuropsychological tests, whereas on some tests an improvement was observed.

The results of the feasibility study clearly show that the potential relations between cognitive impairment and cytotoxic treatment need to be addressed more comprehensively. Six of the 8 patients reported cognitive problems in their daily life activities and the neuropsychological examination showed substantial impairment in some of these patients.

Several circumstances hampered the recognition of a relation between test results and the actual treatment given. As stated previously, the patients participating in this study were treated for metastatic disease and all had received chemotherapy previously. The initial purpose of the neuropsychological study was to assess the cognitive functioning of the patients prior to and after completion of the intensive treatment. This prospective design was specifically chosen to obtain insight in the extent to which impairment could be attributed to the intensive regimen, and to overcome difficulties in interpreting the findings due to the previous exposure to cytotoxic drugs. However, as often happens in studies with very ill patients, in only half of the group it was possible to obtain both a pre-test and a post-test. Therefore, determination of the presence and of the etiology of possible cognitive sequelae of cytotoxic agents was confounded by the difficulty of excluding previous or metastatic-related impairment. In addition, the potential influence of confounding factors such as depression, anxiety and fatigue on the cognitive deficits found could not be excluded sufficiently in this study.

Adjuvant treatment of breast cancer as a model for the study of cognitive deficits after chemotherapy

At the time of completion of this study, a trial was in progress in the Netherlands Cancer Institute to investigate the curative potential of intensive adjuvant chemotherapy in women treated for high-risk breast cancer (stage II and III, involving ≥4 tumor-positive axillary lymph nodes with no evidence of distant metastases). [16] The availability of patients with breast cancer randomized to undergo either high-dose adjuvant chemotherapy or standard-dose adjuvant chemotherapy, provided the opportunity to obtain more insight into the potential side-effects of chemotherapy on cognitive functioning. Firstly, some confounding factors can be eliminated in the adjuvant setting where the impact of active disease processes and transient pharmacological effects can be excluded, because these patients are clinically free of disease and have not been treated with systemic therapy. Additionally, breast cancer was considered to be a good model for the study of long-term side-effects, as patient populations are large and a relatively long period of disease-free survival is expected, giving this study significant clinical relevance.

Aim and outline of this thesis

The main theme of this thesis is the study of cognitive deficits following adjuvant chemotherapy for breast cancer, focussing on the prevalence of the deficits, their characteristics and their determinants.

First, chapter 2 presents an overview of research on the neuropsychological functioning of cancer patients after treatment with cytotoxic agents. Attention is paid to the separate measures used for the assessment of cognitive functioning and the methods applied for the determination of cognitive impairment in the different studies.

Chapter 3 discusses the anti-neoplastic agents used in the treatment of patients with breast cancer participating in our neuropsychological studies, and the potential toxic side-effects on the central nervous system.

Chapters 4 and 5 describe the neuropsychological studies on the cognitive status of breast cancer patients treated with various cytotoxic regimens as part of an adjuvant therapy strategy. The patients in these studies were tested two years after completion of treatment. The pattern of deficits found is discussed, and the relation between the impairment and anxiety, depression, fatigue and self-reported cognitive problems is evaluated.

Chapter 6 presents the results of a neurophysiological study (including quantitative electroencephalography and event-related potentials) conducted in a non-selected subgroup of breast cancer patients treated with adjuvant chemotherapy. The relation between neurophysiological data and neuropsychological test results was investigated. Furthermore, a brief description is given of the relevant literature on this topic.

To obtain more insight in the long-term neuropsychological sequelae following chemotherapy, chapter 7 presents a study designed to re-evaluate the cognitive status of patients who participated in the previous neuropsychological investigations. Patients who were still free of disease four years after completion of therapy, were included in this study.

Chapter 8 presents a summary of the different studies and some critical considerations related to the studies. Comments that were beyond the scope of the empirical studies are presented and related to recent literature and to ongoing research on this topic in the Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital. Finally, a Dutch summary is presented of the results of this work.

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