Cognitive Sequelae of Intensive Treatment for Hematological Malignancies

Helena Harder

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De cognitieve gevolgen van intensieve behandeling voor hematologische maligniteiten

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Only the soul that loves is happy
(Goethe)

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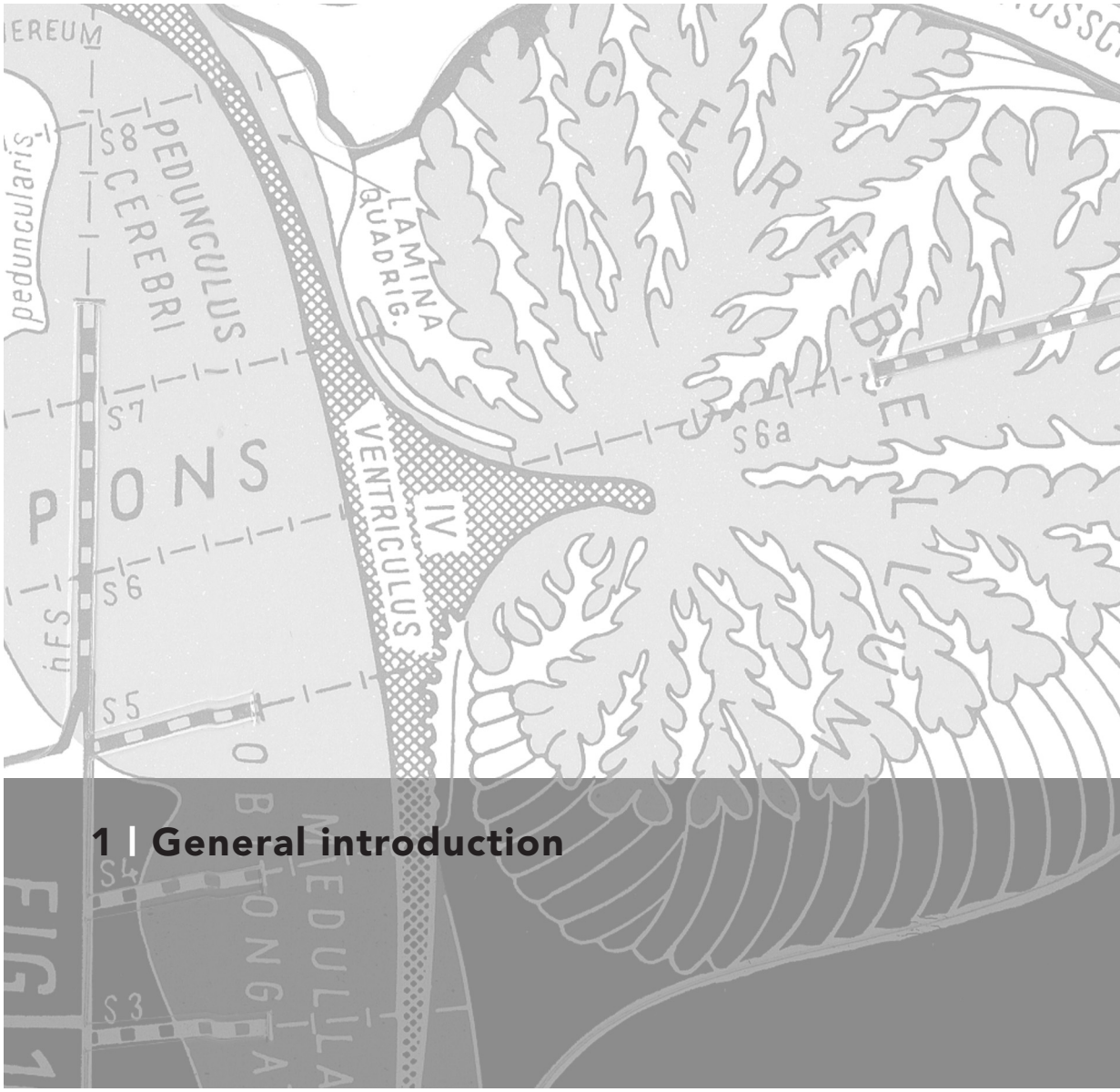

1 | General introduction

As newer and more intensive cancer therapies improve survival in patients with malignant diseases, issues relating to quality of life and cognitive functioning are becoming more prominent. Long-term survival depends on intensive and aggressive combined therapies for many malignancies, but this treatment can come at a price. For many years treatment modalities have been extensively investigated for their general and neurotoxic side-effects.[1-5] Though, far less is known about potential cognitive dysfunction associated with cancer therapy, and formal neuropsychological evaluation is rarely used as an outcome measure in clinical trials of anticancer agents.

Patients with cancer who are treated with systemic chemotherapy, cranial irradiation or combined modality treatment often report difficulties with memory, attention, new learning, and other higher cognitive processes.[6,7] These problems - commonly referred to as 'chemobrain' or 'chemofog' by long-term cancer survivors - only recently have been getting the attention they deserve. There is at present a growing awareness of potential cognitive side-effects of cancer treatment, but as yet, research in this field has not yielded conclusive data that could influence treatment decisions or development of new treatment strategies. In addition, still too many oncologists, and other clinicians and professionals are unaware of the impact of potential cognitive deficits on patients' daily functioning and quality of life. Conceivably, even minimal and subtle cognitive dysfunction may be profoundly disturbing to patients, especially when it involves the inability to maintain or advance professional careers, academic performance, or to take part in social or familial activities. Recovery to their baseline (or so called premorbid) state of function is therefore crucial for most patients undergoing cancer treatment.

The available literature on the potential cognitive side-effects of cancer and cancer treatment has expanded in the last decade.[8-11] The majority of these studies and review articles have focused on patients with breast cancer or brain tumors,[12-17] although patients with other cancer diagnoses are also at risk and require further investigation. The aim of this thesis is to study the cognitive sequelae of intensive or combined treatment regimens for hematological malignancies, focusing on patients treated with bone marrow or hematopoietic stem cell transplantation (HSCT), and patients who received treatment for primary central nervous system lymphoma (PCNSL).

The impetus for our investigations was derived from cognitive complaints that were frequently reported by cancer patients after their treatment during clinical consultations by their physician. As a result, several research projects have been initiated and undertaken by the Departments of Neuro-oncology, Hematology, Radiotherapy and Psychiatry of the Erasmus MC – Daniel den Hoed Cancer Center over the last eight years. The additional goals of these projects were to study the effect of cognitive impairment on general health-related quality of life (QOL), and to study its relation to subjective cognitive complaints and psychological functioning.

This thesis begins with an overview of potential neurotoxic complications observed after cancer treatment and its effect on cognitive functioning *(chapter 2)*. Two chapters with an extensive literature review on cognitive dysfunction in HSCT patients *(chapter 3)* and in PCNSL patients *(chapter 4)* follow. The next four chapters describe a series of investigations on the cognitive sequelae and quality of life (QOL) in patients treated with or undergoing HSCT. It starts with the results of a retrospective study in long-term survivors of HSCT in *chapter 5*. The preliminary findings of a pilot study with a one year follow-up in patients scheduled to undergo HSCT are presented in *chapter 6*. The next two chapters describe the pre-treatment baseline findings *(chapter 7)* and the follow-up results *(chapter 8)* of our large-scale longitudinal prospective study

in patients with hematological malignancies treated with HSCT, or with systemic chemotherapy and/or involved-field radiotherapy. *Chapter 9* presents the results of our neuropsychological study, including a neuroradiological evaluation, in PCNSL patients treated with combined modality treatment within a phase II trial of the European Organization for Research and Treatment. In *chapter 10* the main findings are summarized and discussed, followed by recommendations for future research.

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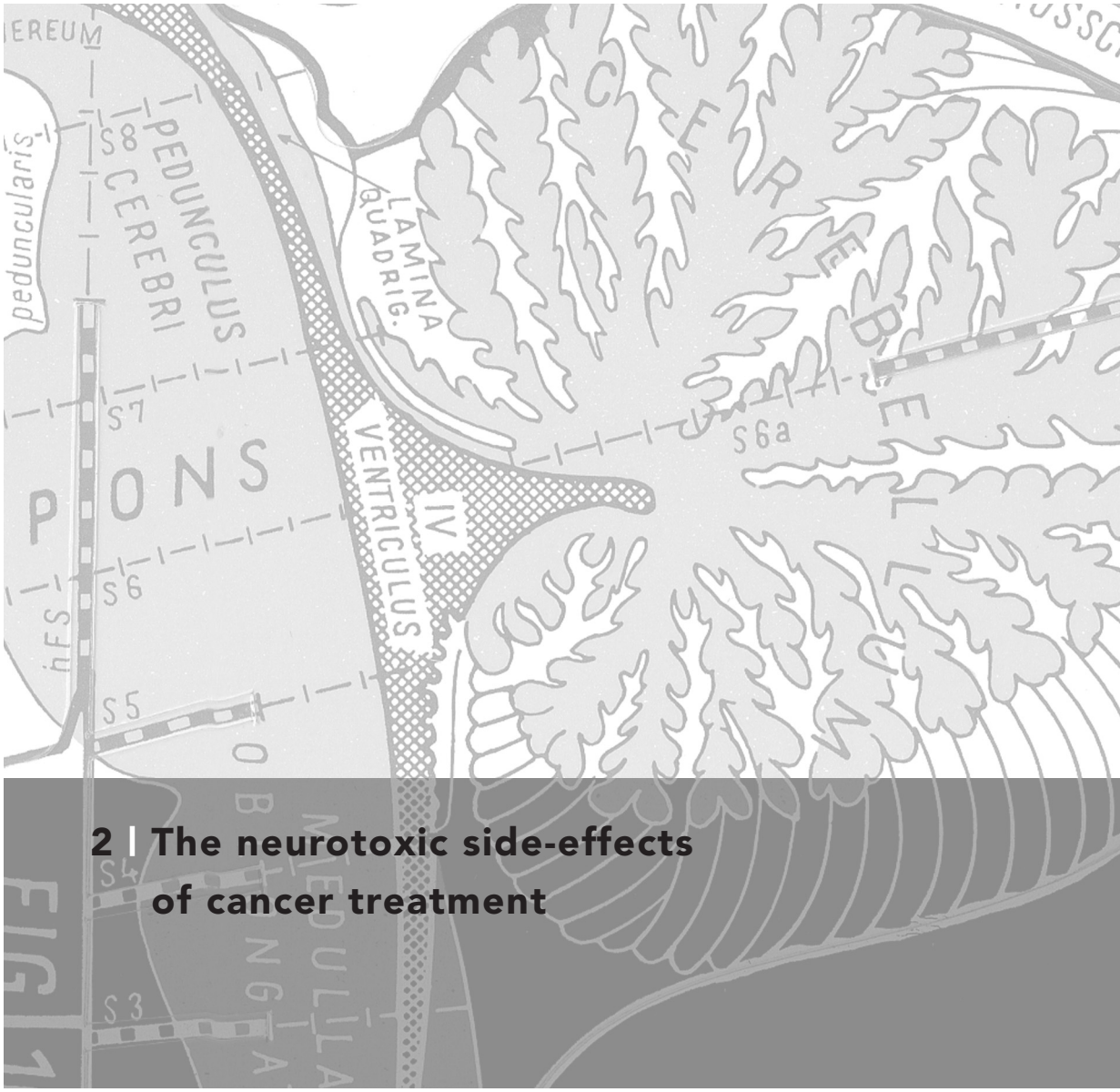

2 | The neurotoxic side-effects of cancer treatment

Neurotoxic complications of cancer therapy are an increasingly important concern in patient management. Because advances in cancer therapies have brought prolonged survival, toxicities with a delayed onset now become manifest when in the past patients did not survive long enough to be affected by them. In addition, improvement in systemic therapies and the use of local treatments to target specific tumor sites have resulted in an increased incidence of central nervous system (CNS) toxicity. For example, advances in supportive measures such as stem cell rescue technology, have enabled the possibility of high-dose chemotherapy. Although these supportive measures reduce systemic toxicity, they do not protect the CNS, and the same cytotoxic agent that at low doses cannot adequately cross the blood-brain barrier (BBB) may cause significant toxicity to the CNS when administrated in intensified doses. The main long-term CNS toxicities observed after cancer treatment are discussed in this chapter.

Radiotherapy and the nervous system

Radiotherapy plays a central role in cancer treatment as it continues to be the most widely used treatment for most cancers. Radiotherapy can produce a variety of adverse side-effects on the central and peripheral nervous system. Patients are exposed to radiotherapy-induced brain injury either directly when they receive cranial irradiation (CRT) for primary or metastatic brain tumors or as prophylactic treatment to prevent CNS cancers (eg, in small cell carcinoma of the lung and leukemia), or incidentally when treated for head, neck and pituitary tumors or other non-CNS tumors and nervous tissue is included within the radiation fields. The individual tolerance for radiation damage is quite variable and may be influenced by several factors; including volume (eg, whole brain or partial brain), total dose, dose per fraction, and duration of treatment.

Neurological complications associated with radiotherapy are usually classified according to the time of onset after radiotherapy and include acute, early-delayed (or sub-acute), and late-delayed (or delayed) complications.[1] Acute complications occur days to weeks after radiotherapy and usually involve constitutional symptoms such as headache, fatigue, and general malaise. Early-delayed injury arises one to six months after therapy, whereas late-delayed effects occur by more than six months after treatment and may be delayed for many years. Late-delayed complications differ from the former effects as the damage is in most cases irreversible and progressive.[2,3] Four major clinical syndromes have been described in relation to radiotherapy-induced CNS injury: encephalopathy, cranial neuropathy, myelopathy, and peripheral neuropathy. The two main late-delayed effects will be described in the next section.

The development of radiation-induced leukoencephalopathy or diffuse radiation injury is the most frequent complication in long-term survivors of CRT. Neuroimaging shows diffuse white matter lesions (with preservation of the gray matter) associated with cortical and subcortical atrophy, and ventricular enlargement. It may be clinically asymptomatic, but may also present with progressive cognitive impairment, ranging from mild dysfunction to severe dementia. Other clinical manifestations include gait abnormalities, fatigue, personality and emotional changes, apathy, and eventually ataxia, incontinence, and sometimes akinetic mutism. Improvement of clinical manifestations is rarely seen, and an ongoing deterioration is the rule. The incidence and potential risk of this radiotherapy-induced complication is directly related to several predisposing factors, including old age (ie, over 60 years), more than 2 Gy dose per fraction, higher total dose, greater volume of brain irradiated (ie, whole brain radiotherapy),

shorter overall treatment time, and concomitant or subsequent use of chemotherapy.[4]
In addition, CRT can cause focal areas of necrosis within six months of treatment.[5] Most areas develop within the white matter of the forebrain, and their occurrence is depending on the dosage delivered. It is infrequent after standard radiotherapy to a dosage of 60 to 65 Gy in fractions of 1.8 to 2.0 Gy, but it is more frequent after stereotactic radiosurgery and especially after interstitial brachytherapy. It is commonly referred to as delayed cranial irradiation necrosis or cerebral radionecrosis. Symptoms involve headache, personality change, focal neurological deficits (eg, dysphasia, hemiparesis) or seizures.[2] Patients may present with a clinical picture of a growing intracranial mass lesion that is indistinguishable from tumor recurrence on CT or MRI. It may however be entirely asymptomatic. The diagnosis can be established by brain biopsy, and surgery may be indicated in patients in whom signs and symptoms cannot be easily controlled with steroids.

Cognitive side-effects after radiotherapy to the brain have come increasingly into the focus of interest because of their influence on quality of life in long-term disease-free patients. Numerous reports have been published on cognitive decline following CRT for primary brain tumors or metastases, and following prophylaxis for leukemia and small cell carcinoma of the lung.[6-10] This research has shown distinctive patterns in the clinical presentation of CRT induced cognitive deficits. Most studies demonstrated deficits in memory functions (eg, memory retrieval), motor functions (eg, fine motor control, neurobehavioral slowing) and executive functions (eg, mental flexibility) during or after treatment, whereas other cognitive skills like visual-perceptual skills, language, and abstract reasoning remained relatively stable. In addition, there is evidence of more pronounced cognitive impairment after whole brain irradiation compared to focal irradiation.[11] Most studies showed that cognitive decline occurs more than one year after treatment, with a peak of cognitive dysfunction approximately 24 months after treatment.[12-14]
It is unknown whether this cognitive deterioration is entirely due to the therapeutic procedure. A recent study has shown that cognitive deterioration can actually predict tumor progression, and even may precede radiographic evidence of progression by more than 3 months.[15] Others have shown that there are substantial differences in cognitive performance between long-term survivors (patients who lived more than three years) and those who died between 20 and 36 months after treatment; patients who lived longer demonstrated significant better cognitive function.[16] So, even in patients with stable disease, the tumor itself may exert a significant negative impact on cognitive function, and this seems especially the case for aggressive brain tumors, such as high-grade gliomas. In sum, it appears that cognitive deterioration in tumor patients can be attributed to multiple causes: direct and indirect tumor effects as well as side-effects of the therapeutic procedure.

Chemotherapy and the nervous system

Chemotherapy regimens involve the use of antineoplastic agents administered orally, intravenously, intratumorally, or intrathecally (directly into the cerebral spinal fluid). Chemotherapy is associated with acute and rather persistent adverse effects on the nervous system which generally depend upon the dosage and type of drugs, the route of administration, and the presence of other treatment. The BBB plays a key role in the prevalence of neurotoxicity. It is a barrier system that protects the brain from harmful substances in the blood, while supplying

the brain with the required nutrients for proper function.[17] It strictly limits transport into the brain through both physical (tight junctions) and functional (transport proteins) barriers. It is the rate-limiting factor in the penetration of many compounds into the brain.
Many cytotoxic agents do not readily cross the BBB in conventional doses. Hence, most drugs do not cause significant CNS side effects. But, many drugs that if given in low dosage are not toxic to the CNS, may induce long-term neurotoxic complications if the BBB is disrupted, or when the drug is delivered intrathecally or in high doses. For example, a variety of neurological complications have been described for high-dose or intrathecal administration of cytosine arabinoside (ARA-C) or methotrexate (MTX), whereas these drugs are not toxic for the CNS if given in more 'standard' dosages.[18,19]

The neurotoxic potential of MTX, an antimetabolite used for chemotherapy of various malignant diseases, is more widely recognized than that of any other cytotoxic agents. MTX is poorly transported across the BBB, but significant concentrations can be achieved when the drug is administered intrathecally or intravenously in high doses. The major delayed complication of systemic high-dose MTX therapy is leukoencephalopathy manifested by symptoms similar as radiotherapy-induced leukoencephalopathy.[3,20] The course may progress to a permanent vegetative state or death, although the majority of patients experience partial or complete recovery when MTX is withdrawn. Leukoencephalopathy especially occurs if high-dose intravenous MTX is combined with radiotherapy to the brain, in particular when CRT is administered before or during MTX therapy. Aseptic meningitis is the most common acute manifestations of CNS toxicity from intrathecal MTX administration, but that treatment may also rarely give rise to an ascending and often fatal myelopathy.[21]
Ara-C is another frequently used drug for hematological malignancies that has little neurotoxicity when used systemically at conventional doses.[21] High-dose Ara-C may cause a usually reversible cerebellar syndrome.[22] It is also commonly used in intrathecal cancer treatment, which use may cause an aseptic meningitis and rarely an irreversible myelopathy and encephalopathy.

Many other agents used in the treatment of cancer may cause CNS toxicities, but these are usually transient (eg, high-dose ifosfamide, 5-FU, cyclosporine). Most research on potential side-effects of chemotherapy for solid tumors has been performed in patients receiving chemotherapy for breast cancer in the adjuvant setting. Relatively few literature data exist on possible late cognitive sequelae of chemotherapy, which is in part, due to small sample sizes of studies, relatively high rates of attrition in longitudinal studies, and the administration of several tests in a relatively small sample thereby increasing the risk of a Type I error.[23] The interpretation of data from cross-sectional study designs is troublesome because of inevitable differences between the chemotherapy treated groups and the control groups, comprising for instance differences in age, in use of hormonal therapy and in rates of (premature) menopause. Chemotherapy and hormonal therapy for breast cancer can induce premature menopause and induce long-term complaints of fatigue. Hormonal changes might affect the regulation of mood and anxiety as well as vigor, thereby in combination with factors underlying fatigue, affecting both objective and subjective measures of cognition.[24]
Although high rates of cognitive dysfunction have been found in breast cancer patients before the administration of chemotherapy, several cross-sectional studies using objective measures

for cognitive function found impairment in the groups treated with chemotherapy compared with control groups.[25-28] Since two recent longitudinal studies on cognition in breast cancer patients treated with adjuvant chemotherapy in the majority of women did not observe clear impairments , it is difficult to draw definitive conclusion.[25,29] Still, in both studies in a subset of women an association between chemotherapy and cognitive impairment appeared to be present. Meta-analyses of these studies showed small to moderate associations between chemotherapy and cognitive impairment, with a magnitude of impairment of –0,03 to –0.51 SD compared with matched controls.[23,30,31] In addition, the need for more longitudinal research was emphasized to the characteristics of chemotherapy-induced cognitive impairment and to determine the clinical significance of cognitive deficits in patients' daily-life functioning.

Effects of combined treatment and the nervous system

Multimodality treatment has become standard therapy for many cancer patients. However, a greater efficacy in treating disease is frequently associated with greater toxicity, and it is not surprising that neurotoxic effects of combined treatment are more profound than those of single modality treatment, and may even be synergistic especially if chemotherapy is combined with CRT.[22] The sequence of treatment is here of clinical relevance. When MTX and CRT are delivered sequentially, neurotoxicity appears to be less if chemotherapy is the initial treatment modality and a suitable time break is allowed between administration of chemotherapy and the start of radiotherapy. The administration of CRT prior to or concomitant with MTX, however, predisposes patients to a higher incidence of delayed leukoencephalopathy.[32] This seems in part due to a disturbance of the BBB by CRT, resulting in an increased penetration of drugs into the CNS. In children, the incidence and potential risk for the development of this delayed syndrome was found directly related to the total dose of CRT, systemic and intrathecal administration of MTX, and the sequence of their combined administration. Estimated incidence ranges from less than 1% to 45%, depending on the mode of therapy.[33]

Small cell lung cancer patients may be treated with prophylactic RT after a complete systemic response to chemotherapy is obtained. Despite the treatment of these patients with whole brain radiotherapy, the impact of delayed leukoencephalopathy seems limited. Remarkably, most studies have failed to demonstrate major effects on cognition in these patients.[34,35]

Effects of immunotherapy

In the last two decades there has been an increase in the use of biological therapies for cancer patients. One of these therapies involves immunotherapy with cytokines, also designated as biological response modifiers which is utilized for a number of malignancies, including hairy-cell leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, multiple myeloma, and melanoma.[36] Cytokines are regulatory molecules that allow communication among cells of the immune system. Immunotherapy focuses on the patients' immune system in an effort to enhance its ability to identify cancer cells and to support the organism's ability to destroy these cells. The most frequently used cytokines are interferon-alpha (IFN) and interleukin-2 (IL-2). Cytokine-induced changes in brain function are well documented. Cytokine receptors are found in many other organs, including the brain. Cytokine produced in the periphery can possibly cross the BBB and act directly in the CNS or can transmit signals to the CNS through visceral-neuronal and humoral pathways.

IFN therapy is characterized by a wide range of adverse effects. Almost all patients experience a 'flu-like' syndrome within hours after the first administration. Symptoms include fever, chills, and nausea, and generally abate after a few weeks of treatment. Other adverse effects reflect hematological, hepatic, renal, cardiovascular, pulmonary, and endocrine dysfunctions.[37] Severe neurological manifestations are uncommon despite the fact that IFN affects the CNS and the peripheral nervous system. Neurotoxicity tends to be dose-related and more common in older patients. Higher cumulative doses of IFN can cause headaches, confusion, lethargy, hallucinations, and seizures, and these symptoms are usually reversible. Furthermore, a growing number of studies have observed mood and cognitive changes after administration of prolonged IFN.[3,38,39] Changes include symptoms of depression, anxiety and fatigue and impairment of attention, memory, motor and executive functions.[40-43] Data show that these neuropsychiatric effects are suggestive of frontal-subcortical dysfunction, supported by EEG studies that showed notable slowing of frontal lobe waveforms in patients receiving high-doses of IFN.[44,45]
IL-2, a cytokine used to boost immune response in cancer therapy, has also been associated with neurotoxicity. Neurobehavioral complications are observed in 30 to 50% of patients that use IL-2. These symptoms usually include delusions, hallucinations, and depression. The cognitive changes associated with IL-2 are similar to those of IFN, and involve a triad of impaired memory, motor, and executive functioning in the context of preserved intellectual abilities.[46,47]

Effects of adjunctive medications

In addition to the neurotoxic effects of primary cancer treatment, adjuvant medications such as corticosteroids, other immunosuppressive agents, and anticonvulsants may also cause neurobehavioral symptoms. Corticosteroids are widely used in cancer therapy. They are a part of the anticancer therapy for a variety of tumors, including brain tumor (to control increased intracranial pressure) and hematological malignancies. In this latter patient group they are mainly used for their oncolytic effect. In patients treated with allogeneic HSCT, corticosteroids are administered for their immunosuppressive effects to control graft-versus-host disease. One of the most common neurological complications of corticosteroids is myopathy.[48] Cognitive and affective side effects are also common. Corticosteroids, amongst others, act at receptors in the hippocampus and can play a role in memory deficits after chemotherapy.[49] There is evidence of reduced hippocampal volume and declarative memory deficits after chronic corticosteroid exposure.[50] In addition, CNS infections may arise due to the immune suppressive action of corticosteroids.

Mechanisms of treatment-related neurotoxicity

Many parts of the precise pathogenesis of CNS complications associated with cancer treatment are still unknown. Complications may arise from direct toxic effects of treatment on the CNS, indirectly from metabolic abnormalities or cerebrovascular disorders induced by the treatment regimen, or from other additional factors. For radiation injury to the CNS two hypotheses have been proposed. The vascular hypothesis speculates radiation-induced vascular injury, accelerated atherosclerosis and mineralizing microangiopathy, resulting in vascular insufficiency and infarction. The glial hypothesis speculates radiation-induced ablation of glial precursors and resultant demyelinative necrosis.[1] In the more severe cases, obvious vascular damage and demyelination contribute to neurological deficits; these injuries may be amplified by an

extensive neural progenitor dysfunction that includes the more radioresistant glial and vascular progenitor cells.
The assumed underlying mechanisms for chemotherapy-induced neurotoxicity are similar to those of radiation-induced injury. Three mechanisms are commonly proposed: 1) direct neurotoxic injury to the cerebral parenchyma, including the microglia, oligodendrocytes, and neuronal axons, producing demyelination or altered water content; 2) secondary inflammatory response, an immunologic mechanism including allergic hypersensitivity and autoimmune vasculitis; and 3) microvascular injury leading to obstruction of small- and medium-sized blood vessels, spontaneous thrombosis, ischemia/infarction, and parenchymal necrosis.[51-53]

Other additional mechanisms involve altered neurotransmitter levels, particularly brain amines and metabolites, indirect chemical damage and oxidative damage, and indirect effects such anaemia or a reduction in hormone concentrations.[54-56] Last of all, CNS effects and subsequent cognitive impairment can also be increased by factors that normally confer increased vulnerability to cognitive dysfunction after any type of CNS injury, in particular older age.
Distinguishing treatment-induced toxicity from the numerous of other possible causes of the same symptoms is a difficult process, but also an important challenge in patient care and management. This may in particular be relevant in patients with CNS localizations of their malignancy. Therefore, the cause-and-effect issue remains a key subject when dealing with individual patients, in particular those with primary brain tumors.

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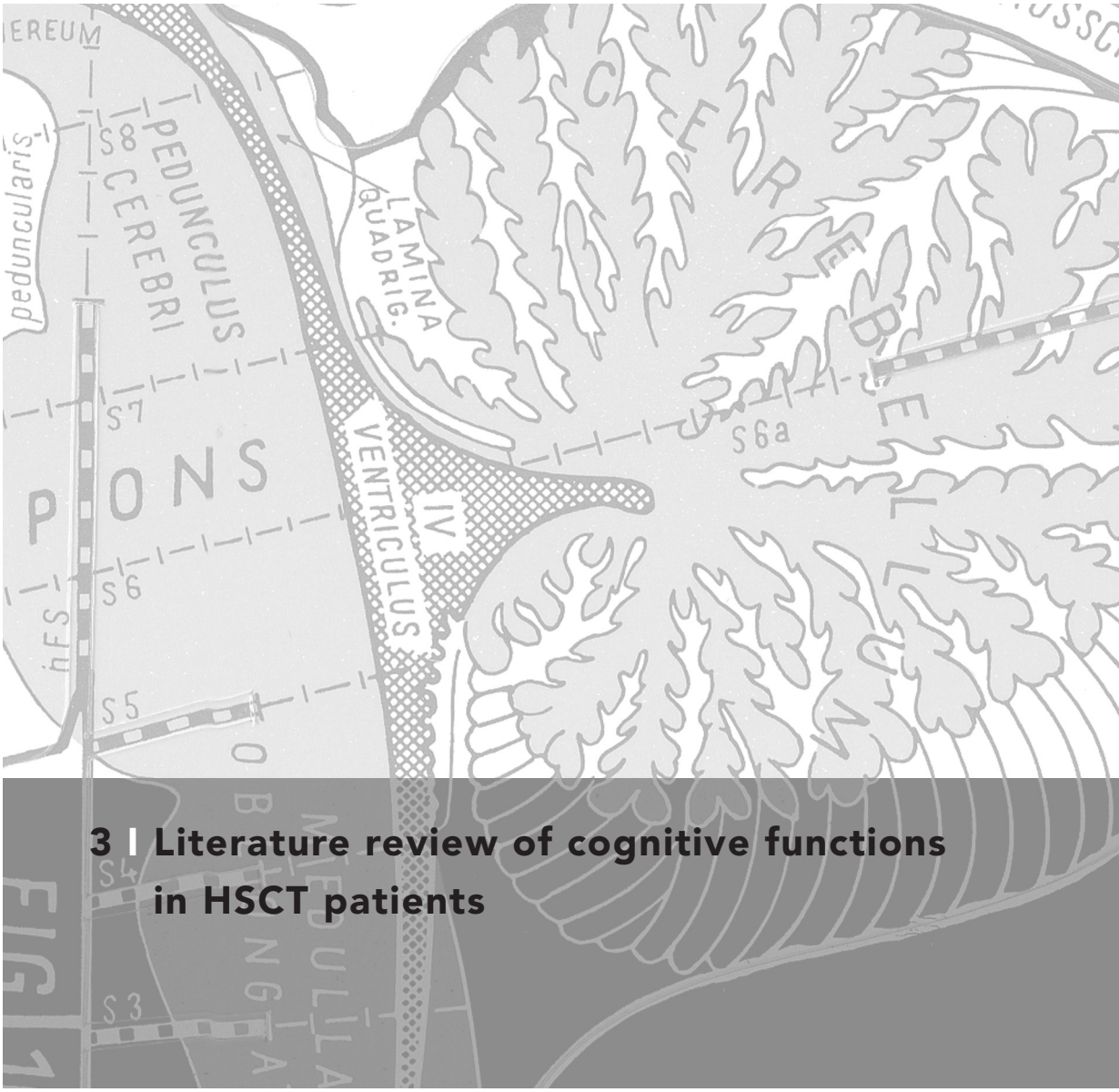

3 | Literature review of cognitive functions in HSCT patients

Bone marrow or hematopoietic stem cell transplantation (HSCT) can be defined as an intravenous infusion of hematopoietic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood. It is used as a procedure to re-establish hematopoietic and immune function in patients with damaged or defective bone marrow or immune systems. Significant advances in the development of HSCT were made in the late 1960s. These days, worldwide more than 45.000 patients annually receive HSCT, and this number continues to increase by 10-20% each year.[1,2]
HSCT is in particular a potentially curative treatment for hematological malignancies or disorders. High-dose chemotherapy and autologous stem cell rescue are considered standard therapies for relapsed Hodgkin disease and relapsed non-Hodgkin's lymphomas, and they are increasingly applied as part of initial therapy for patients with non-Hodgkin Lymphoma (NHL), multiple myeloma, and germ cell tumors. Allogeneic HSCT is potentially curative for acute and chronic leukemia, myleodysplastic syndromes, NHL, and multiple myeloma. Experimentally, HSCT is used for disorders such as multiple sclerosis, primary systemic amyloidosis, and primary brain tumors.[3-5]

The transplant procedure is generally divided in the following phases: conditioning, bone marrow or stem cell infusion, neutropenic phase, engraftment phase, and post engraftment period. The most common conditioning regimens include total body irradiation (TBI) and cyclophosphamide, or busulfan and cyclophosphamide. In allogeneic HSCT, bone marrow or stem cells from a HLA-matched or mismatched related donor, or an unrelated donor are utilized.
For many diseases, the curative potential of allogeneic HSCT is only in part due to the myeloablative conditioning regimen. A major therapeutic effect of allogeneic transplantation is related to an immune mediated graft-versus-malignancy effect (GVM), which is the alloreactive response of donor-immune cells against the host's tumor. Consequently, recipients of allografts have reduced rates of relapse compared to recipients of autografts.[6] Another type of HSCT is an autologous transplant, in which the patient's peripheral blood stem cells are harvested at an earlier timepoint in the course of the disease and reinfused following myeloablative therapy. No GVM effect ensues autologous HSCT, and, as a result the therapeutic efficacy exclusively results from the high-dose cytotoxic regimen.

Transplant-related complications
HSCT is associated with significant morbidity and mortality, which is evident throughout the course of treatment, beginning with induction therapy and continuing in the post-transplantation recovery phase. The severe toxicity of the preparative conditioning regimens, acute and chronic graft-versus-host-disease (GVHD), and infectious complications related to the immunodeficient state remain major obstacles of the HSCT procedure, especially in recipients of allografts. GVHD is the clinical manifestation of an immunological attack by donor lymphocytes on host tissues, and generally involves the skin, gastrointestinal tract, and the liver. By definition, acute GVHD occurs within the first 100 days of transplantation, and consists of a syndrome of dermatitis, enteritis, and hepatitis. The incidence and severity of acute GVHD varies and is directly correlated with HLA subtype mismatching and use of adequate prophylaxis. Chronic GVHD develops after day 100 and consists of an autoimmune-like syndrome directed towards multiple organs and organ systems. Chronic GVHD arises in 15-50% of patients who survive three months after transplantation, and commonly evolves as a transition from acute GVHD,

although it can occur de novo in 20-30% of patients. The primary cause of morbidity related to chronic GVHD is global immune dysfunction and organ malfunction. To prevent GVHD, patients receive a variety of immunosuppressive drugs, including cyclosporine, low-dose methotrexate (MTX), and corticosteroids. Many of these immunosuppressive drugs (in particular cyclosporine, tacrilomus, and corticosteroids) have neurological side-effects, mainly central nervous system (CNS) disorders, and they increase the risk of CNS infections.[7,8] Autologous HSCT has a lower frequency of complications, because it does not cause GVHD and does not require post-transplant immunosuppression. The risk of regimen-related toxicity and GVHD increases with advanced age, limiting standard HSCT to younger patients (below 60 years) who are in a good general condition. Reduced-intensity or nonmyeloablative conditioning regimens are alternative therapeutic options for elderly, and for patients who require a second transplant.[9]

Infectious complications arise during several stages of the transplant procedure. Especially during the first months after transplant patients are at high risk of fungal, bacterial and viral infections due to neutropenia and damage to mucosal barriers. But, even in the late engraftment period patients are at risk to develop infectious despite a slow recovery of immunity.

HSCT patients who survive the early phase after transplant and who remain disease-free are still at risk to develop late side-effects, even years after the HSCT procedure. Much of the research on late effects has focused on major medical events, in particular late deaths and secondary malignant diseases. Still, several non-malignant physical complications, as late ocular effects (eg, cataract), pulmonary late effects, liver complications (eg, hepatitis), musculoskeletal problems (eg, necrosis of bone, osteoporosis), and fertility problems may significantly impair the health-related quality of life (QOL) of long-term survivors.[10-12]

Neurological Complications of HSCT

The neurological and central nervous system (CNS) complications following HSCT not only affect survival,[13,14] they may also affect cognitive functioning of long term survivors. The nervous system is exposed to multiple sources of injury following HSCT, including the effects of pre-transplant conditioning, of immunodeficiency resulting from GVHD, and of immunosuppressive drugs.[8,15] Neurological complications following HSCT have been reported in up to 70% of patients.[16,17] Allogeneic HSCT has generally been reported to lead to more frequent neurological complications than autologous HSCT.[13]

Neurological complications predominantly involve encephalopathy, CNS infections, and cerebrovascular disorders.[18] Diffuse generalized encephalopathy may be a side-effect of drugs used in the conditioning regimen, like cytarabine, busulfan, ifosfamide, and cyclosporine.

It may also be the result of concurrent liver, lung and kidney dysfunction. Approximately 2% of HSCT recipients develop an infection of the CNS (eg, cerebral aspergillus, herpes zoster, toxoplasmosis).[19] The nature and severity of CNS infections are dependent on several factors, including donor histocompatibility, GVHD prophylaxis, concurrent viral infections, and presence of GVHD. Particularly, patients with persistent immunodeficiency (chronic GVHD, prolonged immunosuppressive drugs) are at continued and increased risk of infection.

Lastly, cerebral hemorrhages, including subarachnoid hemorrhage and subdural hematomas are relatively rare complications in HSCT patients.[20] The underlying disease may play a role in the development of these specific complications, as subarachnoid hemorrhages and subdural hematomas are more frequently observed in patients with relapsed leukemia or leukemic infiltration.

All these potential sources of CNS damage can affect cognitive functioning and pose significant problems for patients who attempt to resume their day-to-day lives after this intensive treatment. HSCT treatment has been extensively investigated for its physical toxic or acute neurological side-effects, but far less is known about late cognitive deficits related to HSCT. Several uncontrolled studies suggest that cognitive problems are not rare in HSCT patients, which would be an important concern of the QOL in this group of cancer patients.

This chapter reviews the results of studies on cognitive functioning in HSCT recipients. A bibliographic search of articles was conducted that included reports using formal neuropsychological evaluations, or self-report measures. The purpose of this review is to systematically assess and summarize what is known about cognitive functioning in patients prior to and following HSCT.

LITERATURE OVERVIEW OF COGNITIVE STUDIES

A systematic MEDLINE search was performed to identify key literature. Only articles published in English were included. Case-reports, pediatric studies, and studies which did not present their results in full detail were excluded. The electronic search was supplemented by a manual review of the bibliographies of the references retrieved. Articles were reviewed with respect to important psychometric issues related to cognitive functioning, including the cohort of patients, the neuropsychological measures utilized, the definition of cognitive impairment used, and observed cognitive dysfunction and, if presented, potential confounding factors related to cognitive functioning and implications for QOL.

The search identified 12 articles, seven of which have been published in the past decade, since 1989. Almost all studies were designed specifically to investigate cognitive functioning in HSCT patients before or following treatment. Two reports focused on the neurological effects of HSCT, including neuroradiological examination, and combined their evaluation with a neuropsychological assessment.[14,15] Three studies used either a relatively brief cognitive evaluation, a structured interview, or a self-reported measure to assess cognitive functioning.[15,21,22] In all other studies, formal neuropsychological testing was performed. Table 1 lists the neuropsychological instruments used to assess cognitive functioning.

The majority of studies concerned patients with a hematological malignancy, predominantly leukemia. In two studies the clinical diagnosis was not specified,[23,24] and two studies used a mixed group of hematological and breast cancer patients.[25,26] Seven studies reported solely on either autologous or allogeneic recipients. Sample sizes ranged from 14 to 65 patients in cross-sectional studies. In prospective studies, sample sizes ranged from 12 to 142 patients at baseline before HSCT conditioning, and from 11 to 54 patients at follow-up. One study included both pediatric and adult patients,[23] in all other studies, patients were between 16 and 63 years old. The review results are discussed by study design (see Table 2 and 3 for a detailed overview).

Table 1 Overview of neuropsychological measures

Attention and Executive Function	Memory
Trailmaking Test A and B	Buschke Selective Reminding Test
Ruff Two and Seven Test	Benton Visual Retention Test
Digit Span Test[b]	Verbal Learning Test
D2 Test	Non-Verbal Learning Test
Stroop Color Word Test	Hopkins Verbal Learning Test-revised
Wisconsin Card Sorting Test	Temporal Orientation Subtest
	Subtests Wechsler Memory Scale-revised[a]
Language	**Visuospatial Visual Function**
Controlled Oral Work Association	Block Design Test[b]
Verbal Fluency Test	Picture Completion Test[b]
	Fragmented Figures Recognition Test
Intelligence	**Psychomotor function**
Raven Standard Progressive Matrices	Grooved Pegboard Test
WAIS-R, short version	Finger Oscillation Test
Information Test[b]	Vienna Determination Test
Similarities Test[b]	Hand Dynamometer Test
National Adult Reading Test	Digit Symbol Test

[a] Visual Memory Span Test, Visual Reproduction, and Logical Memory; [b] Wechsler Adult Intelligence Scale

Results of prospective studies

Eight articles described the results of prospective longitudinal studies on cognitive functioning in HSCT patients.[14,22-25,27-29] The first study was carried out by Parth et al[23] to assess whether intensive chemoradiotherapy was related to cognitive deficits, and if improvement after recovery of treatment occurred. Serial neuropsychological assessment up to one year after treatment was performed in 11 patients and three controls. Between-group differences, in particular with regard to perceptual speed and reasoning, were found at all time points apart from one year after treatment. The authors concluded that slight changes in neuropsychological capacity were seen compared to controls, especially near the beginning of treatment.

Meyers et al followed a mixed group of 61 hematological patients scheduled to undergo HSCT.[22] Serial cognitive screening using the Dementia Rating Scale, was performed in 21 patients up to eight months following HSCT. Results showed that 20% of patients experienced mild cognitive dysfunction prior to HSCT, and nearly 40% had significant anxiety. Short-term memory deficits nearly doubled at follow-up. Pre-transplant emotional and cognitive functioning were important determinants of long-term outcome.

Ahles et al examined psychological and cognitive functioning in 54 patients with a hematological disorder or breast cancer undergoing autologous HSCT.[25] Serial evaluations before and following transplant, and at pre-discharge were available for 34 patients. No effect of prior

CNS treatment (eg, intrathecal chemotherapy and cranial irradiation) was found at baseline. The authors concluded that both groups demonstrated a general decline in cognitive performance over time.

The acute and delayed neurotoxic effects of low doses of hyperfractionated TBI (12 fractions of 1.2 Gy) in adults undergoing autologous HSCT were investigated in a series of studies of Wenz et al[24,27] and Peper et al.[28] The extent to which these three studies have an overlap of patients is unclear. Two of the three studies used small control groups of cancer patients who received radiotherapy on the pelvis, patients with renal insufficiency, and patients undergoing dental surgery. The first study examined 40 patients before and immediate after the first fraction of TBI.[24] Baseline results were within normal limits, and no decrease in functioning was observed. Attention functions improved as a result of practice effect of repeated testing. A long-term follow-up assessment at a median of 27 months following TBI was performed in 21 recurrence-free survivors, and revealed no deterioration of test results in intelligence, attention or memory.[27] The last study in the series compared three subgroups of patients, including a control group, and assessed 12 long-term survivors more than seven years after treatment. Patients underwent a neuropsychological, neurological, and neuroradiological examination. Results showed moderate brain atrophy in some survivors, and a mild decrease in memory function. The authors concluded that cognitive decline in individual patients was associated with CNS-treatment prior to HSCT, and that the incidence of long-term neurobehavioral toxicity was very low.

In the study of Sostak et al, patients treated with allogeneic HSCT were evaluated with neurological and neuroradiological examinations, and underwent a neuropsychological assessment.[14] Almost half of the 71 patients developed mild neurological abnormalities that primarily affected the peripheral nervous system with minor consequences for cognitive and neuroradiological outcome. Subclinical neurological abnormalities, cognitive deficits (mainly within the domain of executive function) and white matter lesions were detected in a small subgroup of patients following HSCT. The main risk factors related to these CNS changes were severe GVHD and prolonged immunosuppression.

Recently, Syrjala et al reported results of the first large-scale longitudinal study in recipients of allogeneic HSCT with serial assessments at 80 days and one year.[29] Complete follow-up was performed in 54 of the 142 patients who participated in the pre-transplant baseline assessment. Before transplant, patients performed comparable to normative data in all areas except motor dexterity, verbal fluency and verbal memory. A significant reduction in performance on all neuropsychological tests was found at 80 days, with improvement to pre-transplant levels at one year on all measures except grip strength and motor dexterity. Performance on tests of verbal fluency and verbal memory were significantly lower than normative data on all time points. Patients without pre-transplant chemotherapy (other than hydroxyurea) and patients without chronic GVHD medication at one year demonstrated a lower risk of cognitive impairment. The authors concluded that long-term cognitive deficits are only infrequently directly derived from HSCT.

Results of cross-sectional studies

Four studies used a cross-sectional design to examine cognitive functioning in HSCT patients. The time between transplant and the neuropsychological assessment ranged from 5 to 120 months in three studies,[15,21,26] while one study investigated pre-transplant cognitive functioning

only.[30] Andrykowski et al studied a cohort of 30 leukemia patients who received allogeneic transplant at a mean time of 47 months after HSCT using two standardized self-report measures.[21] Long-term impairments reported by HSCT survivors involved primarily slowed reaction time, reduced attention, and difficulties with problem-solving and reasoning. An increased dose of TBI was associated with increased cognitive dysfunction, even when controlling for psychological distress. In another study, Andrykowski et al demonstrated by formal neuropsychological testing that cognitive impairment was apparent before undergoing transplant in 56% of 55 HSCT candidates.[30] Performance in memory was most likely to be impaired, followed by performance in motor function, and complex attention function (eg, cognitive flexibility). Test performance was associated with specific disease and treatment factors: cranial irradiation and CNS involvement in conjunction with intrathecal chemotherapy were predictors of poor performance.

Other risk factors for cognitive impairment following HSCT were identified by Padovan et al.[15] Neurological, neuropsychological, and neuroradiological findings were examined seven to 120 months after transplantation. Cognitive functioning was evaluated in 46 long-term survivors by using a structured interview. Cognitive deficits, particularly reduced memory function, were reported by 37% of patients. Impairment was related to neurological abnormalities, long-term cyclosporine medication and age.

Very recently, Booth et al investigated the relationship between objective cognitive impairment and subjective cognitive complaints six months following HSCT.[26] The majority of the 65 patients was female, diagnosed with breast cancer, and had received autologous HSCT. Moderate to severe cognitive impairment was found in 28% of patients. Deficits in psychomotor speed and executive function were most profound. Impaired function was predominantly found in patients who were older, male, less educated, and had lower estimated intelligence. Subjective cognitive complaints reported by the patients failed to reflect their cognitive performance, as they were unrelated to overall cognitive functioning assessed with an extensive neuropsychological test battery. The authors concluded that patients who report cognitive deficits may not be the same as those who experience an actual decline following HSCT.

Table 2 Overview of prospective studies of cognitive functioning and HSCT

Parth *et al* 1989 [23]

Objective	*Design*	*Sample characteristics*	*Treatment*
To assess whether intensive chemoradio-therapy results in cognitive performance deficits and whether changes recover after treatment	Prospective design with assessment pre-HSCT, at discharge (50 days), at 100 days and at 1 year post-HSCT	Mixed sample HSCT patients (n=44) and healthy controls (n=42); medical diagnosis unknown Age 8-44 Serial NPA in 11 HSCT patients and 3 controls	CP (60 mg/kg for 2 days) followed by TBI (15 Gy in 6 fractions) Type of HSCT not specified

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Locally developed (computerized) test battery assessing information processing, memory, reasoning, spatial function, perceptual speed, fine motor skills and vigilance / -	Mean raw scores over time were compared to control group Cut-off for impairment not specified	Between-group differences on tasks before treatment: perceptual speed, spatial function and fine motor skills Between-group differences at discharge and 100 days, not at 1 year	Slight decrement on perceptual speed and reasoning in patient group at start of treatment

Meyers *et al* 1994 [22]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate cognitive and emotional functioning of patients scheduled to undergo HSCT	Prospective design with assessment pre-HSCT, after 2 weeks, at discharge (29 days) and at 8 months post-HSCT	Hematological patients (n=61), mainly leukemia; no CNS disease Age 19-63; mean 38	IFN pre-HSCT (n=22); HSCT conditioning regimens not specified Type of HSCT: autologous (n=19), MRD (n=25), MUD (n=17)

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
10 / IV,V,VI,VII	Impairment defined as total score was ≥ 2 SD below mean of healthy elderly subjects	20% mild impairment and 40% anxiety pre-HSCT; short-term memory deficits nearly doubled at follow-up; no problems on attention subtest at any time point; outcome unrelated to IFN, type of HSCT or age	Cognitive and emotional functioning pre-HSCT related to long-term outcome Depression increased at hospitalisation, and decreased at follow-up; anxiety decreased at follow-up and remained low

Ahles *et al* 1996 [25]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate psychological and neuropsychological functioning of autologous HSCT patients	Prospective design with assessment pre-HSCT, mid-treatment (1-3 days following reinfusion), 1-2 days before discharge	Mixed group of hematological (n=27) and breast cancer patients (n=27); Age mean 39; majority (78%) female Serial NPA in 34 patients	Various pre-treatment regimens, including CRT and/or IT-CT (n=11) Various HSCT induction regimens (CP, VP-16,BCNU,CA ,CY,CIS,TH) and TBI (n=5) ; all autologous HSCT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
4,6,11,12 / I (brief version), IV, VIII, IX	Between (patient) group comparisons of mean test scores	No effect of prior CNS treatment at baseline Decreased performance over time for both groups in higher order cognitive processing	Hematological patients showed more psychological distress at baseline Psychological status generally improved over time for both groups

Wenz *et al* 1999 [24]

Objective	*Design*	*Sample characteristics*	*Treatment*
To investigate acute CNS toxicity of low radiation doses in adults undergoing TBI	Prospective design with assessment 1 day before TBI and 1 hour after first dose of TBI	Patients in CR (n=58) diagnosis not specified; no CNS disease; mean age 43 ± 10; serial NPA in 40 patients Control group: cancer patients (no CNS disease) undergoing RT to pelvis (n=31), patients undergoing dental surgery (n=7); mean age 53 ± 15	Previous treatment not specified TBI (1.2 Gy in 1 fraction; total dose not specified); HD-CT (CP) after completion TBI All autologous HSCT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
9,14,15,16,17,18 / X	Comparison to normative data Test scores over time were compared within patient groups	TBI patients showed normal baseline results in intelligence and attention No decline in results after 1.2 Gy TBI Improvement in attention attributed to practice effects of repeated testing	TBI patients showed less positive feelings before start treatment No differences in mood states compared to control groups

Wenz *et al* 2000 [27]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate delayed CNS toxicity of TBI using neuropsychological testing of intelligence, attention and memory	Prospective design with assessment 1 day before TBI, 1 hour after first dose of 1.2 Gy TBI and after a median of 27 months (range 6-36)	Mixed group of hematological patients (n=58); no CNS disease Age 20-59; mean 43 Serial NPA in 21 patients	Various pre-treatment cytotoxic regimens HSCT regimen consisted of TBI (12 fractions of 1.2 Gy in 4 days) and CP followed by autologous HSCT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
9,14,16,17,18,19,20 / X	Comparison to normative data Test scores over time were compared for the patients tested at all time points (n=21)	Pre-HSCT results within normal limits apart from visual memory; improvement in all tests after first TBI dose; no deterioration at follow-up and significant improvement in attention and non verbal memory	Influence of practice effects (acute phase) and improvement in mood state (chronic phase) No effects of age at TBI, gender or length of follow-up

Peper *et al* 2000 [28]

Objective	*Design*	*Sample characteristics*	*Treatment*
To investigate neurobehavioral, neurological and neuroradiological effects of TBI in treatment of hematological malignancies	Cross-sectional study (I) with pre-TBI and post TBI group (I9-65 months post-TBI, mean 32) and prospective study (II) with mean long-term follow-up of 9 years after TBI (range 7-11)	Study I: Pre-TBI group (n=14) and post-TBI group (n=20); age 16-52, mean 36.5 and matched controls with renal insufficiencies (n=11; age 20-52, mean 38) Study II: survivors pre and post-TBI groups (n=12; age 23-59, mean 45)	Previous CNS treatment (n=4) HSCT induction regimen consisted of TBI (12 fractions of 1.2 Gy in 4 days) and CP followed by autologous HSCT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
3,4,5,6,9,21,22,23,24,25,26,27,28,29, 30,31 / VIII,X,XI	Comparison to normative data (z-score < -1.28 borderline or impaired) Between-group comparisons of mean test scores and comparison of mean test scores over time	Study I: scores within normative limits Post-TBI group showed subtle reduction (1 SD) in memory Cognitive decline associated with pre-TBI CRT or IT-CT	Study II: no clinical signs of dementia and stable intellectual abilities Slight increase in memory, verbal concept formation and attention Improved emotional state

Sostak *et al* 2003 [14]

Objective	*Design*	*Sample characteristics*	*Treatment*
To determine the risk and time course of neurologic sequelae after allogeneic HSCT to establish the risk profile	Prospective design with assessment 2 ± 4 months pre-HSCT and 14 ± 3 months after HSCT	Mixed group of hematological patients (n=71), mainly leukemia patients Age 17-58; mean 37 Serial NPA in 55 patients	Various pre-HSCT cytotoxic regimens: CNS treatment (n=11) Conditioning regimen consisted of CP combined with TBI (n=46) or Bu, VP-16, BCNU, MPD; IT-CT post HSCT (n=8)

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
5,8,9,13,25,30 / -	Comparison to normative data Impaired functioning defined as total score was 1 SD below mean; dementia defined as total score of structured interview was ≤ 32	Abnormal results in 58% pre- HSCT and 51% after HSCT (executive function) 17/32 HSCT improved post treatment, associated with female sex, shorter disease duration and stable disease stage at HSCT	5 deteriorated, 4 had neurological abnormalities Neurological outcome negatively affected by unrelated donor status, TBI, IT-MTX, disease duration, disease stage, aGVH and immunosuppression

Syrjala *et al* 2004 [29]

Objective	*Design*	*Sample characteristics*	*Treatment*
To examine neurocognitive changes over the first year in recipients of allogeneic HSCT	Prospective design with assessment pre-HSCT, at 80 days and 1 year after HSCT	Mixed group of hematological patients (n=142), mainly leukemia Age 22-61; mean 41 Serial NPA in 54 patients	Various pre-HSCT cytotoxic regimens CNS treatment (n=16), IFN (n=17) HSCT conditioning regimen: HD-CT alone (n=53) or combined with TBI (n=89) followed by allogeneic HSCT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,6,9,11,21,32,33,34 (6 tests administered at all time points) / -	Comparison to normative data Impairment was defined as test score ≥ 1 SD below normative mean Summary impairment scores were calculated based on the number of impaired tests	Pre-HSCT function comparable to norms except for motor dexterity, verbal fluency and verbal memory; reduction at 80 days on all tests with return to pre-HSCT levels at 1 year, except for motor dexterity and grip strength	Impairment pre-HSCT increased risk (6.3) at 1 year Lower risk in patients not treated with CT (or only hydroxyurea) pre-HSCT; cGVHD treatment increased risk of motor dexterity impairment at 1 year

Table 3 Overview of cross-sectional studies of cognitive functioning and HSCT

Andrykowski *et al* 1990 [21]

Objective	*Design*	*Sample characteristics*	*Treatment*
To investigate long-term cognitive dysfunction in adult survivors of allogeneic HSCT in relation to TBI dose	Retrospective design Time interval 12-96 months post-HSCT; mean 47 months	Chronic and acute leukaemia patients (n=30) Age 18-51; mean 34	HD-CT (CP, VP-16, BCNU, Ara-C, MPD) followed by TBI (5.5 to 14 Gy) 3 patients received HD-CT alone Type of HSCT: MRD 83%; haplo-identical partially MMR (17%)

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Measure of cognitive functioning based on self-report measures / -	Intercorrelations between subscales and total scores on subjective measures were compared to demographical, disease and treatment variables	Mild to moderate self-reported cognitive impairment independent of concurrent distress Increased dose of TBI was associated with increase in cognitive dysfunction	TBI-related cognitive impairment involved slowed reaction time, reduced attention and concentration, difficulties in reasoning and problem solving

Andrykowski *et al* 1992 [30]

Objective	*Design*	*Sample characteristics*	*Treatment*
To identify the nature, extent and correlates of neuropsychological impairment in HSCT patients before undergoing treatment	Cross-sectional assessment before HSCT treatment	Patients with hemato-logical disorders (n=55), including CNS disease (n=9) Most patients (n=42) had leukemia Age 19-53; mean 36	Pre-HSCT treatment consisted of chemotherapy alone (n=39) or combined with localized RT (n=7), CRT (n=8) or TBI (n=1); CNS treatment (n=9); CNS prophylaxis (n=27)

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,3,4,6,7,8,9 / I (brief version)	Summary z-scores were calculated Comparison to normative data Definite impaired ≥ 2 SD below norms; probable impairment ≥ 1.5 SD below norms	56% impaired (> 1.5 SD) on at least 2 of 11 test indices Memory most likely to be impaired (33%), attention least likely (6%) No relation with psychological distress	Impairment associated with CRT, HD Ara-C and IT-CT for CNS disease Risk impairment increased as disease and treatment risk factors increased

Padovan *et al* 1998 [15]

Objective	*Design*	*Sample characteristics*	*Treatment*
To assess neurological, neuropsychological and neuroradiological findings in long-term survivors of HSCT	Retrospective design Time interval 7-120 months post-HSCT, mean 34 months	Mixed group of hematological patients (n=66), mainly leukemia Age 19-59; mean 40 NPA in 46 patients	Various pre-treatment cytotoxic regimens, including IFN (n=15) HSCT regimens: CP followed by TBI (n=33); HD-CT (CP, BCNU) only (n=33); IT-CT (n=8) Type of HSCT: MRD (n=50), MUD (n=9), autologous (n=7)
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Cognitive functioning evaluated with structured interview (13), including items of orientation, memory and reasoning / -	Total scores compared to demographic, disease and treatment variables Total score ≤ 49 out of 55 defined as mild cognitive impairment; total score ≤ 32 cut off for dementia	Cognitive impairment in 17 patients, 3 (7%) fulfilled criteria dementia 16/17 mildly impaired patients had abnormal neurological functioning Deficits more frequent in cGVH evolving from aGVH	Impairment associated with long term CyA use (> 1 year) and age (> 40 years) Long-term CyA use, cGVH and steroids affected neurological status and MRI results

Booth-Jones *et al* 2005 [26]

Objective	*Design*	*Sample characteristics*	*Treatment*
To measure the prevalence of and relationship between subjective complaints and objective cognitive impairment following HSCT	Retrospective design Assessment 6 months (range 5-10) post-discharge from HSCT	Group of hematological (n=21) and breast cancer patients (n=44) Age 23-63, mean 47; majority (n=51) female	Treatment regimens not specified Autologous HSCT(n=52) and allogeneic HSCT (n=13)
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,5,6,8,9,11,25,28,29,34,35,36 / XII,XIII,XIV, XV	Comparison to normative data Summary z-scores were calculated by averaging test scores Mild impairment defined as score > 1 SD and < 1.5 SD below norms; moderate to severe impairment defined as score ≥ 1.5 SD below norms	51% mild impairment, 28% moderate-severe impairment ≥ 1 domain; most prevalent in psychomotor speed and executive function Negative influence of older age, male sex, low education and low IQ	Younger patients had more complaints (memory, attention and language) No relation cognitive complaints (total or domains) and objective cognitive functioning Objective and subjective cognitive complaints related to depression and fatigue

Abbreviations

NPA:neuropsychological assessment CT:chemotherapy HD-CT:high-dose chemotherapy IT-CT:intrathecal chemotherapy RT:radiotherapy CRT:cranial radiation TBI:total body irradiation CNS:central nervous system CP:cyclophosfamide Ara-C:cytosine arabinoside VP-16:etoposide MPD:methylprednisolone BCNU: 1,3-bis(2-chloroethyl)-1-nitrosournea BU:busulfan MTX:methotrexate CA:carmustine CY:cytarabine CIS:cisplatin TH:thiotepa MRD:matched related donor MMR:mismatched related donor MUD:matched unrelated donor IFN:interferon-alfa CyA:cyclosporine aGVH:acute graft versus host disease cGVH:chronic graft versus host disease

Neuropsychological tests

1:Grooved pegboard test 2:Finger oscillation test 3:Buschke selective reminding test 4:Benton visual retention test 5:Trailmaking test A 6:Trailmaking test B 7:Ruff two and seven test 8:Digit span test WAIS 9:Digit symbol test WAIS 10: Dementia rating scale 11: Controlled oral work association 12:Temporal orientation subtest 13:SIDAM 14:Standard progressive matrices, 15:WAIS-R short version 16: Zahlenverbindungstest (modified Trailmaking A) 17:D2 test 18:Complex stimulus reaction task (Vienna determination test) 19:Verbal learning test 20:Non-verbal learning test 21:Information test WAIS 22:Similarities test WAIS 23:Block design test WAIS 24:Picture completion test WAIS 25:Stroop colour word test 26:Digit span test WMS-R 27:Visual memory span test WMS-R 28:Logical memory WMS-R 29:Visual reproduction WMS-R 30:Verbal fluency test 31:Fragmented figures recognition test 32:Hand dynamometer test 33:Hopkins verbal learning test-revised 34:Wisconsin card sorting test 35:National adult reading test 36:Hopkins verbal learning test

Additional measures

I:Profile of mood states II:Psychological adjustment to illness scale III:Sickness impact profile IV:State-trait anxiety inventory V:Zung depression inventory VI:Internal-external locus of control scale VII:Norbeck social support questionnaire VIII:Beck depression inventory IX:Psychiatric diagnostic interview X:Eigenschaftwörterliste (assessment of mood state) XI:Freiburg personality inventory XII:Center for epidemiological studies depression scale XIII:Medical outcome SF-36 health survey measure XIV:Fatigue symptom inventory XV:Multiple abilities questionnaire

SUMMARY AND CONCLUSIONS

Cognitive outcome associated with HSCT was reported in 12 published studies involving a total of 720 patients, including a possible overlap of data in 162 patients.[24,27,28] Only three studies, however, compared HSCT patients to a control group of healthy controls[23] or other patient groups, including cancer patients treated with radiotherapy to the pelvis.[24,28] In no less than 10 trials out of the 12 studies summarized in Table 2 and 3 cognitive dysfunction was noted. The incidence of cognitive impairment (if indicated in the paper) before HSCT ranged from 20% to 58%; the incidence of impairment after transplant varied from 37% to 79%. Most studies showed significant differences to published test norms. In two reports, cognitive performance was within the normal range when compared with norms of healthy individuals, both before and after conditioning with low doses of TBI.[24,27] The results of the reviewed studies demonstrate that patients undergoing HSCT for hematological malignancies experience cognitive deficits that affect several cognitive domains.

Cognitive domains affected by HSCT

Although the available evidence suggests a fairly diffuse pattern of cognitive dysfunction following HSCT, some cognitive domains seem to be preferentially affected. Most published studies revealed deficits in motor, executive and memory function.[14,15,21,22,26,27,29,30] Other cognitive problems associated with HSCT involved poor performance in perceptual speed, reasoning, and problem solving.[21,23] One study reported a general cognitive decline after HSCT.[25] Cognitive impairment occurred in HSCT patients at different time points. Some studies demonstrated that cognitive impairment is evident before conditioning.[14,22,27,29,30] This is in line with research on cognitive functioning in patients who received standard systemic chemotherapy for lymphoma or breast cancer which observed cognitive dysfunction after standard-dose chemotherapy.[31-34]

Following transplant, most prospective reports indicated a mild to moderate decrease in functioning. One report revealed a transient reduction on all neuropsychological tests within three months after transplant, with return to pre-transplant levels at one year.[29] Only few studies observed an increase in test scores in the period immediately following HSCT. However, the authors suggested that this was related to practice effects of repeated testing, as the time between assessments was only a few days.[24,27,28]

Subjective cognitive impairment

Patients who received chemotherapy often report problems regarding their memory and concentration.[35,36] Only one study assessed subjective cognitive functioning in HSCT patients in addition to objective testing.[26] In this retrospective study, 50% of 65 patients reported up to 11 complaints, on a 48-item self-report questionnaire of subjective cognitive function in routine daily-life activities across six cognitive domains. The most common complaints were in the domains of remote memory, attention, and language. Younger patients made significantly more complaints. No correlation was found between objective and subjective cognitive functioning, which suggests that complaints about cognitive function after transplantation may be an indicator of emotional distress rather than factual cognitive deficits assessed by formal testing. Evidence of correlations between higher rates of complaints and respectively greater depressive symptomatology, more severe daily fatigue, and greater interference of fatigue, underline this assumption.

Assessment of confounding factors and QOL

Research examining psychological distress has reported that clinically significant levels of emotional distress are observed in roughly one-third of mixed oncology patients.[37-40] Undoubtedly, in HSCT patients these rates are higher as a result of the stressful situation before the initiation of treatment.[41,42] Emotional status can affect cognitive functioning, and may therefore contribute to the differences seen in cognitive functioning either before or following transplant. Seven of the reviewed studies used self-report questionnaires to assess psychological functioning and mood states, and have therefore controlled adequately for these potential confounding factors.[22,24-28,30] In short, their results on this issue vary from no relation between cognitive functioning and psychological distress at baseline and follow-up[30], to a strong association between pre-transplant anxiety and poorer cognitive performance at follow-up.[22] Most studies found a high prevalence of psychological distress before HSCT and during hospitalization, and decreased levels of distress at discharge.[22,25] Further results illustrate a general trend toward improved emotional functioning over time.[22,24,25,27] Lastly, differences in mood states between HSCT patients and control groups were not observed.[24]

Although assessment of potential confounding factors was performed in just over half of the studies, only one trial investigated the consequences of cognitive dysfunction on health-related QOL.[26] This study showed that cognitive performance was not associated with overall physical QOL, but a trend towards higher levels of performance and better mental QOL was observed. This area of research, and in particular the consequences of treatment-related cognitive dysfunction at QOL, requires further attention in future trials.

Risk factors of cognitive impairment following HSCT

Some of the studies under review performed a risk factor analysis to determine if demographic and/or disease-related factors were associated with cognitive functioning.[14,15,21,25,26,28-30] Although the data of this review suggest that some individual HSCT patients might be more vulnerable for cognitive problems than others, generally spoken, heterogeneous results were observed. With regard to demographical variables, relations between lower cognitive outcome and older age,[15,26] male gender,[14,26] low educational levels and low estimated intelligence scores IQ[26] were observed.

Analyses of disease- and treatment factors suggest that impairment prior to HSCT and diminished performance over time were associated with cranial irradiation and intrathecal chemotherapy for CNS disease.[28,30] This was not evident in all studies, Ahles et al[25] found no effect of prior CNS treatment on cognitive functioning at baseline. Other pre-transplant factors related to cognitive outcome were a history of previous chemotherapy, disease duration, and disease stage at the time of transplant. Syrjala et al found a lower risk of cognitive impairment in patients not treated with chemotherapy (or hydroxyurea only) before undergoing transplant compared to patients treated with chemotherapy or interferon.[29] In another study, patients with a prolonged disease duration (over 20 months) and patients with a progressive disease stage at transplant, demonstrated no improvement in functioning following HSCT, in contrast to patients with a short disease duration and a stable disease stage.[14]

Potential risk factors related to the HSCT conditioning regimen were total dose of TBI and GVHD factors. One study demonstrated that an increased dose of TBI was related to an increase in cognitive dysfunction.[21] In line with this report a series of studies found no significant evidence of cognitive impairment or cognitive changes after low radiation doses.[24,27,28] Lastly,

cognitive deficits were more frequently observed in patients with chronic GVHD evolving from acute GVHD[15], and in patients exposed to long-term chronic GVHD treatment like the use of cyclosporine for more than one year.[29]

Limitations of the studies under review

A number of methodological issues limit the applicability of available research. Many studies have used a small sample size, particularly following the transplant procedure. Small sample sizes are a common problem in HSCT research due to high morbidity and mortality rates, which consequently affects the power to permit conclusions. Only one study used a sufficient large group of HSCT patients at baseline and follow-up.[29] Yet, this recent report is lacking measures of psychological functions and QOL, therefore it does not control adequately for potential confounding factors.

In addition to small sample size, some patient samples were diverse in diagnosis or in HSCT treatment (eg, mixed group of allogeneic and autologous patients), and accordingly significant differences in treatment regimens were seen either before or during HSCT. Differences in treatment regimens may of course be associated with distinctive side-effects with a different impact on cognitive functioning. Given the more intensive treatment of and the different hematological diagnoses for which allogeneic transplant is used, it is possible that allograft patients will show a different cognitive outcome. Furthermore, two studies included a mixed group of patients with hematological malignancies and breast cancer.[25,26] Comparison with the other studies is difficult because of possible contributory effects of chemotherapy-induced menopause and the use of adjuvant hormonal therapy (eg, tamoxifen) in breast cancer patients.[43,44]

Cross study comparisons are also problematic because different studies used diverse criteria for cognitive impairment and measured patients at different time points. Some studies identified cognitive impaired patients as those who had an average score of at least one standard deviation below published norms, while others used deviated scores of at least two standard deviations below published norms as cut-off point. Differences in impairment rate across the reviewed studies may be partly due to these differing criteria. Additionally, there was a wide variance in the timing of the neuropsychological assessment in relation to previous treatment or HSCT. Most studies used uniform time points for their follow-up, but these time points ranged from one to 80 days following HSCT, with regular follow-ups till one year. In cross-sectional studies, patients were assessed between six months to approximately 10 years after completion of treatment. Straight forward conclusions about cognitive functioning remain therefore difficult.

Lastly, the lack of an appropriate control group is another major limitation in research on cognitive outcome of HSCT. The majority of studies used published norms rather than matched control groups, and only one study used a small control group of cancer patients who received less toxic treatment than HSCT. The use of control group of patients with hematological malignancies is essential for the interpretation of effects related to previous treatment before undergoing HSCT and the potential additional effects of HSCT conditioning regimens.

In conclusion, so far only a few studies with a relatively modest number of patients and several methodological biases have addressed the issue of possible cognitive dysfunction associated with HSCT. Results of this review suggest that HSCT causes cognitive deficits in a significant

number of patients. The existing studies indicate that the cognitive domains most affected by HSCT include motor and executive function, and memory. Several demographical and disease and treatment-related factors influence the prevalence and severity of cognitive outcome. Still, most studies have major methodological limitations which limit the conclusions that can be drawn.

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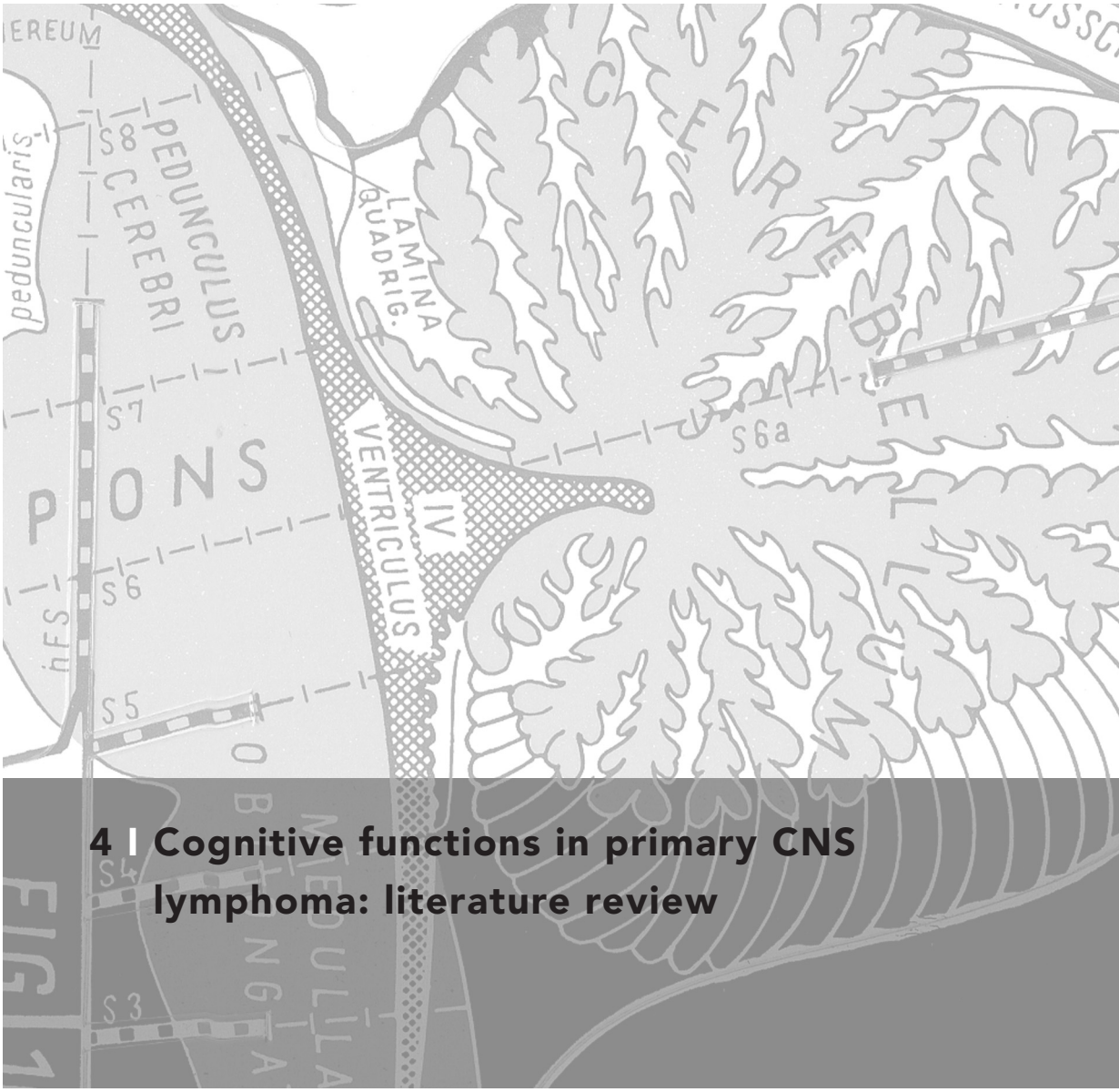

4 | Cognitive functions in primary CNS lymphoma: literature review

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's lymphoma (NHL) that appears solitary or multifocal within the brain, leptomeninges, spinal cord or eyes in the absence of systemic disease. Most PCNSLs are histologically high-grade and arise from B lymphocytes.[1] In the past, it was considered a rare disorder, accounting for 1-2% of all extra-nodal lymphomas and fewer than 5% of all cases of primary intracranial neoplasm.[2,3] Its incidence has been increasing steadily in the last three decades in both immunocompromised groups (eg, patients with acquired immunodeficiency syndrome and transplant recipients) and in the general population, in the latter for unknown reasons. PCNSL has been described at all ages, but it is more common in the elderly. Most cases arise in the sixth decade, with a median age of 55 years and male to female ratio of around 1.5.[4,5] The prognosis of PCNSL is still considered poor, despite new therapeutic approaches which improved outcome. In patients with severe immunodeficiency, treatment options and survival are heavily influenced by the underlying disease. Therefore, this review is restricted to immunocompetent patients with PCNSL.

Clinical features and treatment modalities

PCNSL is frequently a multifocal disease that involves deep brain structures (eg, supratentorial sites and periventricular location). Angiotropism and diffuse infiltrating growth are main characteristics of PCNSL. Primary symptoms may result from local mass effect due to raised intracranial pressure, from ocular involvement, or from focal deposits on cranial or spinal nerve roots. Initial symptoms include aspecific neurological deficits, seizures, mental status changes (including behavioural changes) and signs of increased intracranial pressure, like blurred vision, headache, vomiting and nausea. On MRI PCNSL lesions are usually homogeneously enhancing lesions, often localised near the ventricles. Despite the typical appearance of most lesions, MR findings are not specific. In about 10% of lesions no enhancement is present. Diagnosis is achieved by surgical resection or stereotactic biopsy techniques and by cerebrospinal fluid (CSF) cytology.

Due to the infiltrating growth pattern and the frequently multifocal presentation, local treatment is not curative. A resection does not contribute to disease control and after surgery only a median survival of 3 to 5 months is achieved. Although most PCNSL are sensitive to corticosteroid treatment, the disease usually recurs within months in patients receiving steroids only. Historically, treatment for this malignancy consisted of whole-brain radiotherapy (WBRT) in combination with corticosteroids. This therapy frequently produced a complete tumor response and ameliorated symptoms in most patients, but responses to WBRT are generally short-lived. The overall median survival of patients with PCNSL treated with initial WBRT is less than 18 months from the time of diagnosis, and the 5-year survival rate is less than 5%. A major improvement of the outcome of PCNSL patients was obtained by adding high-dose methotrexate (MTX) chemotherapy to WBRT.[6]

The benefits of chemotherapy in PCNSL were initially observed by studies evaluating treatment options for patients with recurrent disease after initial radiotherapy.[7] Standard systemic NHL regimens (in particular the CHOP regimen) have been unsuccessful for PCNSL, presumably because many of these drugs do not penetrate through an intact blood brain barrier (BBB).[8] The single most active and commonly used agent for PCNSL is MTX administered by intravenous systemic administration in high doses (> 3 g/m2).2 With this dosage, cytotoxic concentrations of MTX are achieved within the CNS even if the BBB is intact.[4] Currently, the treatment of choice is high-dose MTX-based chemotherapy alone or in combination with other agents as cytosine

arabinoside (Ara-C), cyclophosphamide, thiotepa, nitrosourea and procarbazine. Many physicians advocate the use of WBRT after treatment with high-dose intrathecal and systemic MTX-based chemotherapy, but others feel that this may contribute to late neurotoxicity. Whether intrathecal chemotherapy with MTX and/or ARA-C adds to the outcome is not clear, but it is often used.

Another therapeutic approach for PCNSL incorporates blood-brain barrier disruption (BBBD) chemotherapy. This approach aims at the delivery of chemotherapeutic agents past the BBB where potentially microscopic disease resides. Endothelial tight junctions of the BBB are disrupted by an intra-arterial infusion of hypertonic mannitol, allowing for increased drug penetration in the brain. BBBD is preceded by systemic cyclophosphamide and followed by intra-arterial MTX in combination with procarbazine and dexamethasone. This regimen is usually administered each month for about one year, and radiotherapy is not administered except at progression. Several reports confirm that this procedure results in high response rates and improved survival, with acceptable complication rates and low incidence of neurotoxicity.[9,10]

A recent development in the treatment of PCNSL is the use of intensified chemotherapy supported by autologous hematopoietic stem cell transplantation (HSCT). A number of preliminary trials have been carried out in either newly diagnosed PCNSL or relapsed disease.[11] Results are encouraging, but the role of HSCT as part of first line treatment needs further investigation.

Treatment-related neurotoxic complications

As the survival rates in PCNSL have improved, there is a need to address the potential long-term effects of therapy, in particular the risk of delayed neurotoxicity. Leukoencephalopathy is the main long-term treatment-related toxicity observed in PCNSL, and this often permanent and progressive.[12] The use of radiotherapy, intrathecal drug delivery, age over 60 years, and combined modality treatment (particularly when chemotherapy is administered after radiotherapy) are the major risk factors of delayed neurotoxicity.

Over 90% of the long-term survivors older than 60 years at the time of treatment with the combination of chemotherapy and WBRT will develop leukoencephalopathy, clinically characterized by behavioural changes, mental slowing, dementia, gait ataxia, and urinary incontinence.[13,14] Late-delayed complications usually appear 1-2 years after the completion of treatment, but in some patients symptoms and signs of leukoencephalopathy develop within months.[15,16] Mechanisms underlying delayed neurotoxicity are still poorly understood. Neuroimaging studies in PCNSL patients show diffuse white matter disease, cortical-subcortical atrophy, and often hydrocephalus.[16-19] Autopsy data reveal demyelination, axonal loss, gliosis, and thickening of the small vessels.[15,16] Vascular injury mediated by brain irradiation clearly is a component in the development of CNS damage in PCNSL patients. The tumor may also play a critical part, since even in complete responders residual parenchymal lesions ('scarring') may remain present.

In most clinical trials in PCNSL, treatment-related neurotoxicity is assessed clinically or based on global ratings, like performance status. Most of these methods lack sensitivity to detect cognitive dysfunction in patients, whereas objective and quantitative testing would reveal more subtle neurocognitive deficits and give a better picture about patients' functioning in daily life after completion of treatment.

This chapter presents a literature overview of studies that have addressed cognitive functions in adult PCNSL survivors. A bibliographic search of articles was conducted that included formal

neuropsychological evaluations or evaluations using mental status examinations. Case-reports, studies based on performance status or clinical observations, and studies which did not present their results in full detail were excluded. The criteria for inclusion of articles for this review were chosen with the aim to examine the full body of data available in the literature on assessment of cognitive functions in PCNSL survivors.

LITERATURE OVERVIEW OF COGNITIVE STUDIES IN PCNSL

A MEDLINE search of articles published in English, covering the period from January 1991 to December 2005, identified a total of 21 published studies including a brief communication of preliminary results. Table 1 lists a detailed chronological overview of data. The studies under review show a wide range of variance regarding patient selection, study design and psychometric methods. In the majority of these studies, cognitive functioning was assessed prospectively as a routine examination of treatment-related neurotoxicity within an ongoing clinical trial. Data of serial neuropsychological assessment is in some studies only available for small samples, ranging from seven to 32 patients. Few studies were specially designed to investigate disease-related cognitive impairment and changes in cognitive function associated with received treatment for PCNSL.[20-26] Seventeen studies used a prospective design and four studies used a retrospective design. The review results are discussed by treatment modality.

Results of studies with WBRT alone or with high-dose chemotherapy

Six studies have examined cognitive functioning in patients who received either WBRT alone or in combination with high-dose MTX-based chemotherapy administered before or after cranial irradiation (Table 1).[18,22,27-30] These studies included a total of 296 patients, although in three studies (226 patients) only a brief mental status evaluation was used.[27,28,30] Two studies did not report methods or test scores in full detail.[18,29]

Pels et al evaluated treatment-related neurotoxicity in different therapeutic modalities with WBRT in a consecutive group of 28 patients, of which half had a complete response to treatment.[18] The authors concluded that WBRT, either alone or combined with high-dose chemotherapy, was associated with cognitive deterioration. Three of thirteen patients who received chemotherapy alone showed white matter abnormalities in absence of cognitive decline. Pöttgen et al performed serial neuropsychological testing in only two of initially 14 patients.[29] Both patients were fully working, and one patient showed mild impairment in verbal memory, visual memory, and speed of information processing. Correa et al performed a detailed study on 14 PCNSL patients that included formal neuropsychological testing at baseline, a quality of life (QOL) assessment and comparison between different treatment modalities.[22] The authors concluded that WBRT alone or combined with high-dose chemotherapy was associated with more pronounced cognitive impairment than chemotherapy alone, regardless of time since treatment completion. Impairment was found in the following domains: attention and executive function, memory, psychomotor speed, and language. QOL assessment showed no differences according to treatment modality. Half of patients were either unemployed or worked at a lower capacity due to tumor or treatment-related effects.

Three studies reported on cognitive functions using the Mini Mental Status Examination (MMSE).[31] O'Neill et al assessed the consequences of survival in an intergroup phase II trial of

combined modality therapy for PCNSL.[27] Median MMSE score at study entry was above cut-off point (ie, ≥ 24 points), but nearly all patients who were alive more than one year after study entry had a demonstrable decline in cognitive function. Declines occurred before disease progression and in patients without evidence of disease progression. Of note, missing data (MMSE scores of only eight patients were available at one year) created difficulties in interpreting outcome. DeAngelis et al observed delayed neurotoxicity in 15% of 98 patients who received combined modality treatment.[28] Median baseline MMSE score was above cut-off point, but unfortunately follow-up scores were not reported. A recent study performed by Fisher et al evaluated whether a lower dose of hyperfractionated WBRT reduces neurotoxicity for PCNSL patients receiving combined modality treatment (patients received 45 Gy in 25 fractions or 36 Gy in 30 fractions).[30] Only complete responders to treatment and with baseline MMSE scores above ≥ 24 points were included in the analysis. A drop below the cut-off point was observed for some patients at eight months after pre-treatment baseline assessment, but no significant differences were found between patient groups.

Results of studies with high-dose chemotherapy alone

A total of seven studies evaluated cognitive functioning in PCNSL patients who only received high-dose, MTX-based chemotherapy (Table 1).[23,25,32-36] Baseline assessment was completed by a total of 190 patients, although some studies report on the results of the same patients.[23,25,35] Psychometric tests and/or test scores were not specified in three studies.[32,34,35]

Guha-Thakurta et al assessed 31 PCNSL survivors almost two years after diagnosis in a study with a retrospective design.[33] Patients were evaluated with two brief mental status examinations and QOL questionnaires. Results showed preserved cognition and memory with no evidence of leukoencephalopathy. Sandor et al conducted serial neuropsychological evaluations in a small group of 14 PCNSL patients and observed cognitive and motor decline subsequent to treatment in two of seven patients with serial measurements; both patients were over 65 years.[32] Schlegel et al found no evidence of treatment-related cognitive impairment in a study on 20 patients, with serial assessment on ten patients, eight of whom had a complete response.3[4] The test scores remained stable or improved at the last follow-up evaluation which was performed between 15 and 41 months post-treatment. Pels et al evaluated 22 patients with serial assessments after systemic and intraventricular chemotherapy with deferred radiotherapy.[35] They observed no cognitive decline in any patients who had either partial or complete response to therapy. Older patients had lower test scores, but overall cognitive performance post-treatment showed no significant differences between patients younger than 60 years and those older than 60 years. Fliessbach et al reported on ten patients with durable complete response who had serial measurements up to 96 months after treatment.[23] Cognitive impairment prior to treatment was found, with improved functioning at four months after treatment completion, in particular in attention and verbal memory. Patients who were not impaired at baseline remained stable at follow-up. At the last follow-up, a small decline was observed in written phonemic verbal fluency and memory. Neuropsychological test scores were impaired in patients who relapsed, or who received adjuvant WBRT or ocular radiotherapy. No influence of age was observed. In a recent study, Fliessbach et al assessed tumor and treatment-related effects on long-term cognition and QOL in survivors of PCNSL.[25] An overall improvement was observed in 21 of 23 patients, although scores remained in the low average range on tests of attention, executive function, and non-verbal memory. Diminished functioning

on QOL questionnaires was reported by 17% of patients. The authors suggested that cognitive deficits in PCNSL patients were caused primarily by tumor because no treatment-related cognitive decline was observed. Recently, Herrlinger et al performed cognitive evaluations in a small group of six PCNSL patients at least 48 months post-treatment.[36] All patients showed impaired attention and four patients had impaired memory. Moderate to marked restrictions with regard to QOL were found in four patients. The authors concluded that high-dose MTX with deferred radiotherapy had only moderate efficacy and was associated with significant neurotoxicity in long-term surviving patients.

Results of studies with BBBD chemotherapy

Seven studies measured cognitive outcome of BBBD chemotherapy in adults with PCNSL.[10,20,21,26,37-39] In each study, neuropsychological assessment was performed before the onset of chemotherapy, and follow-up evaluations were conducted at least one year after treatment completion. Three studies included subgroups of patients who received initial treatment with WBRT prior to BBBD chemotherapy,[10,37,38] and one study included patients who received previous chemotherapy.[20] A large number of patients appear in several of these studies which precludes an accurate calculation of the total number of patients assessed.[10,21,37]

The first study on cognitive functioning in PCNSL patients was performed by Neuwelt et al.[10] A small group of 12 patients who received WBRT and BBBD chemotherapy was followed before and one year after treatment. Stable or improved functioning compared to results of the baseline assessment was found in the majority of patients not treated with WBRT. At completion of treatment, most test scores were within the normal range. In contrast, nearly half of patients who received WBRT showed significant declines in overall cognitive functioning. Similar findings were reported by Dahlborg et al who followed the majority of these patients over time.[37] Stability or improvement in cognitive functioning following BBBD chemotherapy without WBRT was found in all age groups, including patients over 60 years. A decline in functioning was observed for some patients treated with WBRT. Two years later, Dahlborg et al reported on a mixed group of young adults with non-glial intracranial tumors, including seven young PCNSL patients (mean age was 24 years).[38] Test scores in PCNSL patients were mildly impaired at baseline, and remained stable or improved at follow-up. It remains unclear whether both studies show an overlap of data.

Four studies report data of the effects on cognition of administration of BBBD chemotherapy without prior or subsequent WBRT (yet again, some of these studies may report on the same patients). Crossen et al demonstrated significant impairment on mental flexibility, memory, and fine motor skills at baseline.[39] There was no evidence of treatment-related decline at follow-up. Patients either remained stable or improved significantly. Roman-Goldstein et al observed no change in overall cognitive functioning after treatment completion in a mixed group of patients with CNS tumors, including nine adults diagnosed with PCNSL.[20] However, performance on tests of attention and fine motor skills declined in one individual patient. McAllister et al demonstrated improvement in overall cognitive functioning at completion at treatment, while scores of verbal memory, mental flexibility and motor function remained stable.[21] Lastly, in a recent study, Neuwelt et al observed an improvement in overall cognitive functioning from baseline in a small group of 16 PCNSL patients.[26] Follow-up data of recurrence-free survivors two years after initial diagnosis showed, again, no significant declines in overall performance. The authors concluded that cognitive loss at baseline is associated with enhancement of tumor.

Results of studies with high-dose chemotherapy followed by HSCT

Only one study reported preliminary results of research on cognitive functions in 14 PCNSL patients who were assessed with a neuropsychological test battery and the MMSE, prior and subsequent to treatment with high-dose MTX-based induction chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue.[24] At baseline, impaired performance was found in attention and executive function, psychomotor speed, memory and language. Improvement was observed in seven patients available for post-induction follow-up, and was most profound in attention and executive function, and language. Cognitive performance remained stable at 18 months post-transplant. Of note, the sensitivity of the MMSE was too low to detect cognitive impairment in this patient population.

Table 1 Overview of studies on cognitive functions associated with PCNSL

Neuwelt *et al* 1991[10]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate the efficacy of BBBD chemotherapy in PCNSL patients	Prospective design Prior to BBBD chemotherapy, at completion of treatment at 1 year and at annual intervals post-treatment (ranged from 1 to 7 years)	PCNSL patients (n=30) with CR Group 1 (n=13): referred after PD; mean age 43 Group 2 (n=17): referred following diagnosis; mean age 54 Serial NPA in 12 patients	BBBD chemotherapy with CP, MTX, PC Group 1: received initial treatment with WBRT pre-BBBD Group 2: received subsequent WBRT post-BBBD for PD
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,3,4,5,6,7,8,9 / -	Comparison to published norms Summary z-scores were calculated by averaging test scores Mild impairment score ≥ 1 SD below norms; moderate impairment score ≥ 2 SD below norms	Preservation of cognitive functioning (stable or improved) in 6 patients without WBRT (n=7); z-scores -1.0 to .05; 1 patient declined and showed severe impairment)	Patients treated with WBRT (n=5) had average test results (z-scores -1.0 to .05); 1 patient (WBRT prior to BBBD) declined with evidence of radiation necrosis; 1 patient (WBRT post-BBBD) showed decline to lower normal limits

Crossen *et al* 1992[39]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate the risk of neurotoxicity in PCNSL survivors treated with BBBD chemotherapy	Prospective design with assessment prior to therapy and post-treatment (at 1-7 years, mean 2.6 years)	PCNSL patients (n=8) with CR after 1 year of BBBD Age 37-69, mean 56	BBBD chemotherapy with CP, MTX, PC No WBRT
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,3,4,5,6,7,8,9 / -	Comparison to published norms Changes in summary z-scores (average change in z-scores from baseline to follow-up) were reviewed Impairment defined as decline > 1 SD compared to baseline z-score	Summary z-scores at baseline -2.16 to .13; 4 patients showed overall cognitive impairment; at baseline significant impairment in mental flexibility, learning and memory and fine motor skills	Changes in summary z-scores -.60 to 1.53; 2 patients improved, 6 patients remained stable Follow-up assessment revealed stability of intelligence, learning and memory Absence of characteristics of dementia

Roman-Goldstein *et al* 1995[20]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate whether BBBD chemotherapy is associated with abnormalities diagnosed by MRI or detected by cognitive testing	Prospective design Prior to BBBD chemotherapy, at completion of treatment at 1 year and at yearly intervals	Mixed group of brain tumor patients with CR (n=15; age 6-66), including 9 adults with PCNSL (age 24-68)	Two BBBD chemotherapy regimens with CP, MTX, PC or VP-16 and CPL No WBRT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,3,4,6,7,8,9 / -	Comparison to published norms Summary test scores over time were compared for each individual patient Impairment or improvement defined as a 1 SD change from baseline performance	Summary z-scores (PCNSL) at baseline -2.15 to .62 (mean -.94); post-treatment change in z-scores -1.46 to 1.06 (mean -15) No evidence of global decline in cognitive functioning after treatment	Significant decline in attention and grip strength in 1 PCNSL patient 4/9 PCNSL patients showed new MRI changes; MRI changes not associated with decline in cognitive functioning

Dahlborg *et al* 1996[37]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate tumor response and survival in patients receiving MTX-based chemotherapy with BBBD with or without antecedent CRT	Prospective design Prior to BBBD chemotherapy, at completion of treatment at 1 year and at yearly intervals	PCNSL patients with CR (n=58; 30 previously reported[10] Group 1 (n=19): referred after PD; mean age 46; Group 2 (n=39): referred following diagnosis; mean age 52 Serial NPA in 23 patients	BBBD chemotherapy with CP, MTX, PC Group 1 received initial treatment with WBRT pre-BBBD; Group 2 received subsequent WBRT post-BBBD for PD only

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,3,4,6,7,8,9 / -	Comparison to published norms Summary z-scores were calculated by averaging test scores; mild impairment score ≥ 1 SD below norms; moderate impairment score ≥ 2 SD below norms; downward change in scores > 1 SD interpreted as decline	No cognitive decline in patients without WBRT (n=15) Summary z-scores decreased (from .86 to 1.07) in 3/8 WBRT patients	Stability or improvement in cognitive functioning following BBBD chemotherapy was seen in all age groups, including patients older than 60 years

Dahlborg *et al* 1998[38]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate tumor response and survival in children and young adults with non-glial intracranial tumors receiving carboplatin- or MTX-based chemotherapy with BBBD	Prospective design Prior to BBBD chemotherapy and post-treatment evaluation (time between baseline and post-treatment evaluation ranged from 12 to 60 months, mean 22 months)	Mixed group of patients (n=34) with non-glial intracranial tumors with CR; age 1-30, mean 18 (7 adult PCNSL patients; mean age 24) Serial NPA in 32 patients	Two BBBD chemotherapy regimens: CP, MTX with/without PC (replaced by VP-16 latter), or CPL, VP-16 (CP added latter) 10 patients initial WBRT, 18 CT Prior WBRT in 3 patients, 1 post-WBRT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Battery of neuro-psychological tests (measures not specified) assessing intelligence, concentration, short-term memory, visual perception and fine motor skills (motor dexterity and grip strength) / -	Comparison to published norms Summary z-scores were calculated by averaging test scores A change of 1 SD was interpreted as a change from baseline levels	7 patients scores > 1 SD below normative data at baseline; no distinctive pattern of global impairment; 1 patient declined at follow-up; individual test scores remained stable or improved	Overall data of paediatric and adult PCNSL patients (separation not possible) demonstrated complete and durable response (5/9 PCNSL patients) without cognitive loss

Sandor *et al* 1998[32]

Objective	*Design*	*Sample characteristics*	*Treatment*
To define the toxicity and efficacy of high-dose MTX-based chemotherapy regimen used as a single modality treatment of PCNSL and IOL	Prospective design with baseline assessment prior to treatment and regular follow-up evaluations after completion of treatment	Mixed group of PCNSL and IOL patients (n=14); age 34-69; CR in 11 patients	Serial NPA in 7 patients Chemotherapy with HD MTX, TH, VI and IT Ara-C and MTX Prior WBRT in 2 patients

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,3,4,10,11,12,13,14,15, 16,17,18 / I,II	Not specified	Individual test scores not available Test results of 5 patients who underwent serial NPA (n=7) remained stable; 2 showed severe cognitive and motor decline post-treatment	Severe clinical deterioration in 1 patient (not tested) who received MTX and WBRT All cognitive impaired patients (3/14) were > 65 years

Guha-Thakurta *et al* 1999[33]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate response, survival and QOL in patients with PCNSL who received high-dose MTX chemotherapy	Retrospective design; QOL assessed at a median of 22 months after diagnosis	PCNSL patients (n=31; CR in 20); age 35-87; median 63 QOL assessment only in patients with CR (n=11; age 45-78, median 56)	Chemotherapy with HD MTX (IV) Patient without initial CR received additional RT and/or other therapies

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
No neuropsychological tests / III,IV,V,VI,VII,VIII	Comparison to normative data	Mental status questionnaires indicated preserved cognition and memory No evidence of MTX-induced leukoencephalopathy	Psychosocial adjustment, well-being and stress coping abilities comparable to normative data; moderate rate of depression and anxiety

O'Neill *et al* 1999[27]

Objective	*Design*	*Sample characteristics*	*Treatment*
To assess the consequences of survival in a completed phase II trial of combined modality therapy	Prospective design with baseline assessment prior to study entry and regular (quarterly) follow-up evaluations after completion of treatment	PCNSL patients (n=53); median age 60 46 patients underwent cognitive evaluation at baseline, and 8 at 52 weeks	Chemotherapy with CP, VI and AD followed by WBRT, and HD Ara-C

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
No neuropsychological assessment /III	MMSE score < 24 used as a measure of dementia	Failure to obtain MMSE scores through study (13% at baseline and 66% at follow-up) Median MMSE at baseline above cut-off point (score = 26)	Long-term decline in cognitive function Decline may occur before PD or in occur in patients without evidence of PD

Pels *et al* 2000[18]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate the efficacy of chemotherapy in PCNSL and the frequency of treatment-related neurotoxicity in different therapeutic modalities	Prospective design with regular follow-up evaluations ranging from 1 to 95 months (intervals not specified)	Consecutive group of PCNSL patients (n=28); 14 with CR Age 27-74, mean 59	Various treatment regimens: WBRT alone; CT (systemic, IVT) alone; WBRT with HD MTX, Ara-C or Ara-C alone WBRT (alone or combined n=13); 1 patient received steroids only

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Standardized neuropsychological testing (tests not reported) / -	Not specified	Test results not reported 9 patients treated with WBRT alone or combined with CT showed cognitive decline at follow-up (1-95 months), while 2 patients who received CT alone declined at follow-up (10-38 months)	WMA and severe cognitive dysfunction in patients who received WBRT alone or combined with CT 3/13 patients treated with CT alone showed WMA without cognitive dysfunction

McAllister *et al* 2000[21]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate response, survival rate and cognitive outcome in patients who received MTX-based chemotherapy in conjunction with osmotic BBBD therapy for PCNSL	Prospective design with baseline assessment prior to treatment and regular follow-up evaluations from 6 months to 16 years after completion of treatment (mean 16.5 months)	PCNSL patients (n=74; 39 were previously reported[37] Age < 60 years n=36, ≥ 60 years n=38 Serial NPA in 23 patients	Two BBBD chemotherapy regimens: 1. MTX, PC, VP-16 or CP (n=44) 2. MTX, VP-16, CP (n=30) No WBRT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,3,4,6,7,8,9 / -	Comparison to published norms Summary z-scores were calculated by averaging test scores A core change of 1 SD was interpreted as a change from baseline levels	Summary z-scores improved in post-treatment assessment for all patients z-scores of verbal learning, memory, mental flexibility and motor tasks remained stable	2 patients showed cognitive decline at baseline and achieved z-scores within normal limits at follow-up

Schlegel *et al* 2001[34]

Objective	*Design*	*Sample characteristics*	*Treatment*
To evaluate response rate, response duration and toxicity after systemic and intraventricular chemotherapy in PCNSL	Prospective design with baseline and regular follow-up; NPA at therapy, at 4 months, 12 months and at 15 to 41 months	Consecutive group of PCNSL patients (n=20) Age 27-71, mean 59 Serial NPA in 10 patients (8 with CR)	Chemotherapy regimen consisted of MTX, Ara-C (systemic, IVT) and VI, IF, CP, VNS
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Detailed neuropsychological evaluation assessing attention, verbal and non-verbal memory, verbal fluency and visuoconstruction (measures not reported) / -	Comparison to normative data Global index score was calculated by averaging means of test scores (with 100 as a reference value for average cognitive function)	Preserved or improved cognitive function after therapy and during follow-up Median global index scores was 95 (range 89-107) at last follow-up	Severe cognitive dysfunction, possibly due to treatment, was seen in 1 patient (not tested) after additional ocular RT and combined CT for relaps

DeAngelis *et al* 2002[28]

Objective	*Design*	*Sample characteristics*	*Treatment*
To study the use of combination chemotherapy plus cranial irradiation in newly diagnosed patients with PCNSL	Prospective design with assessment prior to treatment and regular follow-up	Patients with PCNSL (n=98) Median age 56.5 (42% ≥ 60 years)	Systemic chemotherapy with MTX, VI, PC and IVT HD MTX followed by WBRT, followed by HD Ara-C; (WBRT n=82)
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
No neuropsychological assessment / III	MMSE score < 24 used as a measure of dementia	Delayed neurological toxicities (mainly leukoencephalopathy) after RT in 15% No influence of age	Baseline median MMSE score was 26.5 Follow-up data MMSE not reported

Fliessbach *et al* 2003[23]

Objective	*Design*	*Sample characteristics*	*Treatment*
To determine whether HD MTX-based chemotherapy results in cognitive impairment and/or changes detectable by MRI during long-term follow-up	Prospective design with baseline assessment prior to treatment, after completion of treatment at 4 months, 12 months and at most recent follow-up (ranging from 21 to 69 months, mean 43 months)	Consecutive group of PCNSL patients (n=20, some data published previously[34]) Age 27-67, median 60 Serial NPA in 10 patients with durable CR	Chemotherapy regimen consisted of MTX and Ara-C (systemic, IVT), VI, IF, CP, VNS

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
19,20,21,22,23 / -	Comparison to normative data Summary score was computed by averaging mean test scores (mean 100, range 90-110) Changes in performance were analyzed by calculating reliable change indices for each test score in every patient (compared with extent of changes expected to occur in healthy population)	Cognitive impairment in 5/8 patients prior to therapy; 3 scored within normal range at 4-months follow-up; improvement most profound in attention and verbal memory Patients with normal cognitive performance at baseline showed preserved or stable functioning at follow-up No influence of age	MRI revealed treatment-induced WMA in 4/10; changes not related to cognitive functioning 1 patient had WMA (with severe cognitive dysfunction) prior to therapy and showed progression with therapy

Pels *et al* 2003[35]

Objective	*Design*	*Sample characteristics*	*Treatment*
To address response rate, response duration, overall survival and toxicity in PCNSL after systemic and intraventricular chemotherapy with deferred radiotherapy	Prospective design with baseline assessment prior to treatment, after completion of treatment at 4 months, 12 months and one additional time point (ranging from 19 to 82 months, median 33 months)	PCNSL patients (n=65; 20 were previously reported[34] Age 27-75; median 62 Serial NPA in 22 patients; 15 had durable CR and were re-evaluated	Chemotherapy regimen consisted of MTX and Ara-C (systemic, IVT), VI, IF, CP, VNS

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
19,20,21,22,23	Not specified	Test results not reported No cognitive decline at serial testing No differences between patients older and younger than 60 years	2 patients showed cognitive decline (associated with leukoencephalopathy or WMA) due to tumor relapse or residual tumor

Pöttgen *et al* 2003[29]

Objective	*Design*	*Sample characteristics*	*Treatment*
To analyze long-term results following WBRT with sequential IT Ara-C with or without systemic Ara-C in PCNSL patients	Cross-sectional assessment after treatment completion (> 12 years post treatment in 2 tested patients)	PCNSL patients (n=14) Age 20-73; mean 54 Serial NPA in 2 patients	IT Ara-C (pre- and post-RT), WBRT with or without additional systemic Ara-C

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
3,4,11,13,22,24,25,26,27	Not specified	Test results not reported Mild impairment (34 percentile) in verbal learning and memory, visual reproduction and speed of information processing in 1 patient	Both patients fully working No signs of leuko-encephalopathy on MRI

Correa *et al* 2003[24]

Objective	*Design*	*Sample characteristics*	*Treatment*
To study cognitive functions in PCNSL patients treated with HD MTX and Ara-C followed by myeloablative chemotherapy with autologous stem cell rescue	Prospective design, baseline assessment at diagnosis and follow-up at completion of treatment, at 6, 12 and 18 months after treatment	Newly diagnosed PCNSL patients (n=14); Mean age 59 Serial NPA in 7 patients with long-term follow-up	Induction with HD MTX and Ara-C (IV) followed by BEAM chemotherapy and autologous stem cell rescue

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
Standardized battery of neuropsychological tests (measures not specified) assessing attention and executive function, psychomotor function, memory, language and visuoconstruction / III	Comparison to normative data Impairment defined as z-score of > 2 SD below mean of normative sample means	Performance in impaired range at baseline in all domains apart from visuoconstruction Improvement after treatment (n=7), in particularly in attention and executive function and language	Cognitive performance stable (ie, within 1 SD below normative mean) at long-term follow-up Baseline MMSE scores mildly reduced (mean 25); sensitivity MMSE too low to detect cognitive impairment

Correa *et al* 2004[22]

Objective	*Design*	*Sample characteristics*	*Treatment*
To assess cognitive functions and QOL in PCNSL survivors treated either with WBRT with or without MTX-based chemotherapy or with chemotherapy alone	Retrospective design with post-treatment baseline-evaluation and an 8-month follow-up evaluation Time interval of months after combined modality treatment and 18 months after CT alone	PCNSL patients with CR (n=28) Age 36-85; mean 60 Serial NPA in 14 patients	Various treatment regimens: HD MTX alone or with Ara-C (n=10), WBRT alone (n=1), WBRT and combined CT, including MTX, Ara-C, PC, VI and other agents (n=17)
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
3,4,17,25,28,29,30,31,32, 33,34 / I,V	Comparison to normative data Mild impairment defined as z-score between 1.4 - 1.9 SD below normative mean; moderate impairment as z-score ≥ 2 SD below normative mean Composite scores were calculated by averaging z-scores within cognitive domain	No cognitive decline at follow-up Patients treated with WBRT alone or combined with CT displayed more pronounced cognitive dysfunction, in attention, executive function, memory, psychomotor speed, and language (associated with extensive WMA)	Patients treated with CT alone had moderate impairment in psychomotor speed QOL-assessment showed no difference according to treatment modality 50% unemployed or worked at lower capacity due to tumor and treatment

Fisher *et al* 2005[30]

Objective	*Design*	*Sample characteristics*	*Treatment*
To determine whether hyper-fractionated WBRT reduces CNS morbidity without compromising survival for PCNSL patients receiving combined modality treatment	Prospective design with pre-treatment evaluation and regular follow-up evaluations (including pre-radiation and post-treatment)	PCNSL patients who received CT and RT (n=82) Only patients with CR to CT and baseline MMSE score ≥ 24 included (n=29; 20 WBRT, 9 HFX; age unknown	Systemic chemotherapy with MTX, VI and PC; IVT HD MTX followed by WBRT and HD Ara-C RT-dose modified through study: patients with CR had reduced dose
Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
No neuropsychological assessment / III	Cognitive decline (dementia) was defined as a drop of MMSE score below 24 in patients with a baseline score ≥ 24	Median baseline MMSE score was 26.5 At 8 months, mean MMSE scores improved; drop below cut-off in 8/20 WBRT and 2/9 HFX (not significant)	Significant between-group difference in MMSE scores ≥ 24 was found at 2 years (89% HFX vs. 70% WBRT) Leukoencephalopathy occurred at later stage in HFX group

Fliessbach *et al* 2005[25]

Objective	*Design*	*Sample characteristics*	*Treatment*
To assess the impact of the tumor itself and its treatment with HD MTX-based chemotherapy on long-term cognition and QOL in patients with PCNSL	Prospective design with assessments prior to treatment, 3 - 4 months after completion of treatment and at last available follow-up (ranging from 17 to 96 months after diagnosis, median 44 months)	PCNSL patients with CR (n=23) Age 28-68; mean 54 Serial NPA in 14 patients	Chemotherapy regimen consisted of MTX, Ara-C (systemic, IVT) and VI, IF, CP

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
3,4,8,19,21,22,23,25,35,36,37,38,39 / I,IX	Comparison to normative data Impairment within domains: mild z between -1.5 and -1.9; moderate z between -2 and -2.9; severe z ≥ -3 Overall: mild than mild/moderate impairment in 1 domain; moderate than mild/moderate impairment in > 1 domain or severe in 1 domain; severe as there was impairment in > 1 domain	83% impaired (at least I domain) prior to treatment, most in word fluency, attention and executive function and memory After completion of treatment 59% impaired; z-scores improved in 59% or remained stable; at long-term follow-up 48% impaired; 2 patients declined in motor speed and fluency	Overall cognitive functioning correlated to subjective cognitive and global functioning In 35% WMA (developed during treatment); associated with age, not with cognitive performance Overall, no long-term decline; impairment related to residual effects of tumor

Herrlinger *et al* 2005[36]

Objective	*Design*	*Sample characteristics*	*Treatment*
To explore the efficacy of HD MTX alone in PCNSL patients	Cross-sectional assessment after treatment completion (ranging from 55 to 69 months after treatment, mean 61.8 months)	PCNSL patients with CR (n=37) Serial NPA in 6 patients; age 56-63; mean 60	HD MTX (IV) and second-line therapy with either PCV or WBRT

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
2,26,40,41,42,43,44,45 / III,IX,X	Comparison to normative data Overall scores for attention and memory were calculated Reduced performance was defined as a score < 25th percentile of normative data	Mild to moderate cognitive impairment in all 6 patients, especially in attention and memory General cognitive functioning reduced in 2 patients	Deficits most pronounced in 2 patients with marked leukoencephalopathy Increased or stable MMSE Markedly affected QOL in 1 patient

Neuwelt *et al* 2005[26]

Objective	*Design*	*Sample characteristics*	*Treatment*
To examine the correlation between MRI changes in the brain and cognitive outcome after BBBD-enhanced chemotherapy for PCNSL	Prospective design with baseline assessment prior to treatment, at end of treatment and at yearly intervals (range 22-71 months, mean 40 months)	PCNSL patient with CR (n=16) Age 10-68; mean 47.7 (one child included) Serial NPA in 9 patients	BBBD chemotherapy regimen with MTX, VP-16 and CP No additional treatment

Neuropsychological tests / Additional measures	*Impairment definition*	*Remarks and Conclusion*	*Remarks and Conclusion*
1,2,6,7,8,9 / -	Comparison to published norms Summary z-scores were calculated by averaging test scores A z-score change of 1 SD was interpreted as a decline in cognitive functioning	Mean baseline summary z-score -1.1; improvement at end of treatment (mean z-score = -.35) No cognitive decline at long-term follow-up (range of change -.37 to .71)	Cognitive dysfunction prior to treatment correlated to abnormal signal intensity around enhanced tumor; no association after treatment Cognitive loss at baseline due to enhancing tumor

Abbreviations
NPA:neuropsychological assessment BBBD:blood brain barrier disruption PD:tumour progressive or recurrence CR:complete tumor response IOL:intraocular lymphoma MRI:magnetic resonance imaging CT:chemotherapy HD:high-dose IV:intravenous IT:intrathecal IVT:intraventricular RT:radiotherapy CRT:cranial radiation irradiation WBRT:whole brain radiotherapy HFX:hyperfractionated CNS:central nervous system WMA:white matter abnormalities/changes QOL:quality of life CP:cyclophosfamide MTX:methotrexate Ara-C:cytosine arabinoside PC:procarbazine CPL:carboplatin VP-16:etoposide TH:thiotepa VI:vincristine AD:Adriamycin IF:Ifosfamide VND:vindesine BEAM:carmustine, etoposide, cytarabine and melphalan PCV:procarbazine,lomustine,vincristine)

Neuropsychological tests
1:Wechsler adult intelligence test-revised 2:Wechsler memory scale-revised 3:Trailmaking test A 4:Trailmaking test B 5:Rey auditory verbal learning test 6:California verbal learning test 7:Rey complex figure test 8:Finger tapping test 9:Grip strength test 10:Mental control WMS 11:Logical memory WMS 12:Visual reproduction WMS 13: Paired association WMS 14:Peabody picture vocabulary test - revised 15:Wide range achievement test-revised 16:Raven standard progressive matrices test 17:Grooved pegboard test 18:Hand dynamometer test 19:Number connection test (analogous to Trailmaking A) 20:Controlled oral work association 21:Verbal learning and memory test (analogous to Rey auditory verbal learning test) 22:Benton visual retention test 23:Block design test WAIS 24:subtests WAIS measuring intellectual function 25:Digit span test WAIS 26:Divided attention test 27:Thurstone cognitive ability test 28:Brief test of attention 29:Stroop color word test 30:Phonemic verbal fluency test 31:Hopkins verbal learning test-revised 32:Boston naming test 33:Category fluency test 34:Clock drawing test 35:Short test for cerebral insufficiencies (symbol counting, interference inhibition) 36:Written phonemic fluency test 37:Corsi block tapping test 38:Semantic oral word association task 39:Reaction times test (Vienna determination test) 40:German leistungsprüfsystem-50+ test 41:Simple reaction time test 42:Aachen aphasia test 43:Bell's test 44:Letter cancellation task 45:Drawing geometrical figures and pictures

Additional measures
I:Beck depression inventory II:Spielberger inventory for anxiety III:Mini mental state examination (MMSE) IV:Short test of mental status V:Functional assessment of cancer therapy scale-brain subscale VI:Symptom questionnaire VII:Scale for social-adjustment by self-report VIII:Problem solving inventory IX:EORTC Quality of life questionnaire (EORTC QLQ C30) X:EORTC Brain cancer module

SUMMARY AND CONCLUSIONS

The reviewed studies on cognitive functioning in PCNSL show, despite a considerable heterogeneity, that patients treated for PCNSL suffer from a broad range of cognitive deficits. Cognitive domains most likely to be impaired include attention and executive function, memory, language, and psychomotor speed. The studies using additional QOL measures showed a moderate rate of depression and anxiety.[33] Diminished QOL was observed in a minority of evaluated patients, with no effect of treatment modality on overall QOL.[22,25,36]
The findings on cognitive outcome in PCNSL patients treated with combined modality therapy suggest more pronounced cognitive impairment than in patients treated with chemotherapy alone. The findings are consistent with the literature on treatment-related cognitive dysfunction in glioma patients who are usually treated with fractionated partial-brain radiotherapy, sometimes combined with systemic chemotherapy. These studies suggest that not all patients are equally affected and that cognitive impairment can occur at different time points. Deficits are fairly diffuse, but attention and executive functions, learning and retrieval of new information, and motor function are preferentially affected.[40-42] The adverse effects of the tumor itself on cognition should not be underestimated in brain tumor patients. Some studies show that in particular the brain tumor itself has a detrimental effect on cognitive functioning with only additional effects of cranial irradiation, if applied in high fraction doses (ie, 2 Gy or larger).[43]
The studies that reported the cognitive impact of treatment for PCNSL with high-dose MTX-based chemotherapy alone or with BBBD chemotherapy were mostly prospective. Several studies documented cognitive impairment at baseline (prior to all therapies) in the areas of attention, executive functions, memory, language, and psychomotor speed. Follow-up assessments after completion of treatment show, generally, either stable or improved cognitive performance. Only in a small number of patients a decline in memory, psychomotor speed, and word fluency was observed. These findings seem to be in line with previous research on the cognitive effects of systemic chemotherapy in patients with malignancies. Again, deficits are widespread with most apparent declines in memory, executive function, and motor function.[44-47] Though, a comparison between PCNSL patients and other patient groups is complicated due to the differences in chemotherapeutic regimens and the route of administration. For instance, many PCNSL patients will have received intrathecal or intraventricular chemotherapy.

There are several problems involved in interpreting the current findings and comparing the severity of cognitive dysfunction across reports. Several series show an overlap of data, and may be in fact redundant publications.[10,21,23,34,35,37] Extracting these cases, as an attempt not to duplicate data, is not possible. Another problem is the absence of precise and detailed information; in particular, the failure to present used psychometric measures, and numerical data of neuropsychological test scores. In addition, some studies used insensitive and invalid measures (eg, assessment with the MMSE only).[8,27,30,33]
Other problems concern the methodological shortcomings of the studies examined. There are considerable differences between the reviewed studies in selection of patient population, sample size, assessment time, selection of measures, and the definition of cognitive impairment. The composition of patient groups varies with regard to type of malignancy, disease status at the time of the assessment, and age. Three studies also enrolled patients with

other CNS tumors or with intraocular lymphoma.[20,32,38] Although most other studies included either newly diagnosed PCNSL patients, in some studies patients were included who received treatment for recurrent disease. Moreover, some studies included patients with only partial response to treatment, or even with disease progression. Inclusion of these patients obviously limits the ability to distinguish tumor from treatment effects on cognitive functioning.

There is also a wide variance in age of patients between the reviewed studies, in particular among studies evaluating cognitive functioning following BBBD chemotherapy. In these series, the patient age is substantially younger (with an average age of approximately 46 years) than that of the average PCNSL patient. High age (> 60 years) is clearly a very important risk factor for the development of leukoencephalopathy after high-dose MTX chemotherapy and WBRT. Three reports included a small subgroup of children from one year onwards.[20,26,38] This variance in age limits the generalization of results to the older population and this places the lower neurotoxicity rates in younger patients treated with BBBD in a different perspective.

Almost all of the reviewed studies are limited by their small sample size and by substantial differences in follow-up intervals. Apart from two studies using mental status evaluations,[28,30] all involved a relatively small number of patients (n < 35; not including the redundant or duplicate publications). The number of assessed patients ranged from eight to 65 patients at baseline, six to 32 patients at completion of treatment, and, in some cases, only three patients at long-term follow-up. Most published reports used a baseline assessment (prior to treatment), and at completion of treatment at four months and one year after treatment. The duration of long-term follow-up ranges from six months to 16 years after completion of treatment.[21,29] The small number of long-term survivors with a complete response and adequate testing, and the heterogeneous follow-up intervals, both limit the power to determine late sequelae of treatment.

Most studies were embedded in ongoing clinical trials evaluating therapeutic options for PCNSL, and almost all used an extensive neuropsychological test battery covering a wide range of cognitive domains. Noteworthy, four studies used self-report questionnaires of QOL and/or measures of potential confounding factors (eg, anxiety, depression, and fatigue) in combination with a neuropsychological assessment.[22,25,32,36] Additional use of QOL or psychological measures is an encouraging new trend in the more recent studies, which helps to determine the impact of possible cognitive impairment on QOL and daily-life functioning.

Lastly, the definition of cognitive impairment varies considerably across studies. Although some reports lack a specific definition of impairment, most compare patient data with published normative data. However, the criteria for impairment vary, as a general rule, from one to over two standard deviations below the mean of standardized normative data, causing significant difficulties in interpreting current findings.

In conclusion, all these limiting factors together preclude the assessment of the specific contributions of tumor and the delayed effects of treatment on cognitive functioning in PCNSL patients. Given the present state of literature on cognitive functioning in PCNSL, it appears that WBRT and combined modality therapy have a greater impact on cognitive functioning compared to chemotherapy alone. There is a need for further systematic and large-scale clinical studies using standardized methods of neuropsychological assessments and, preferably, a control group to determine if this can be solely attributed to the neurotoxic effects of treatment.

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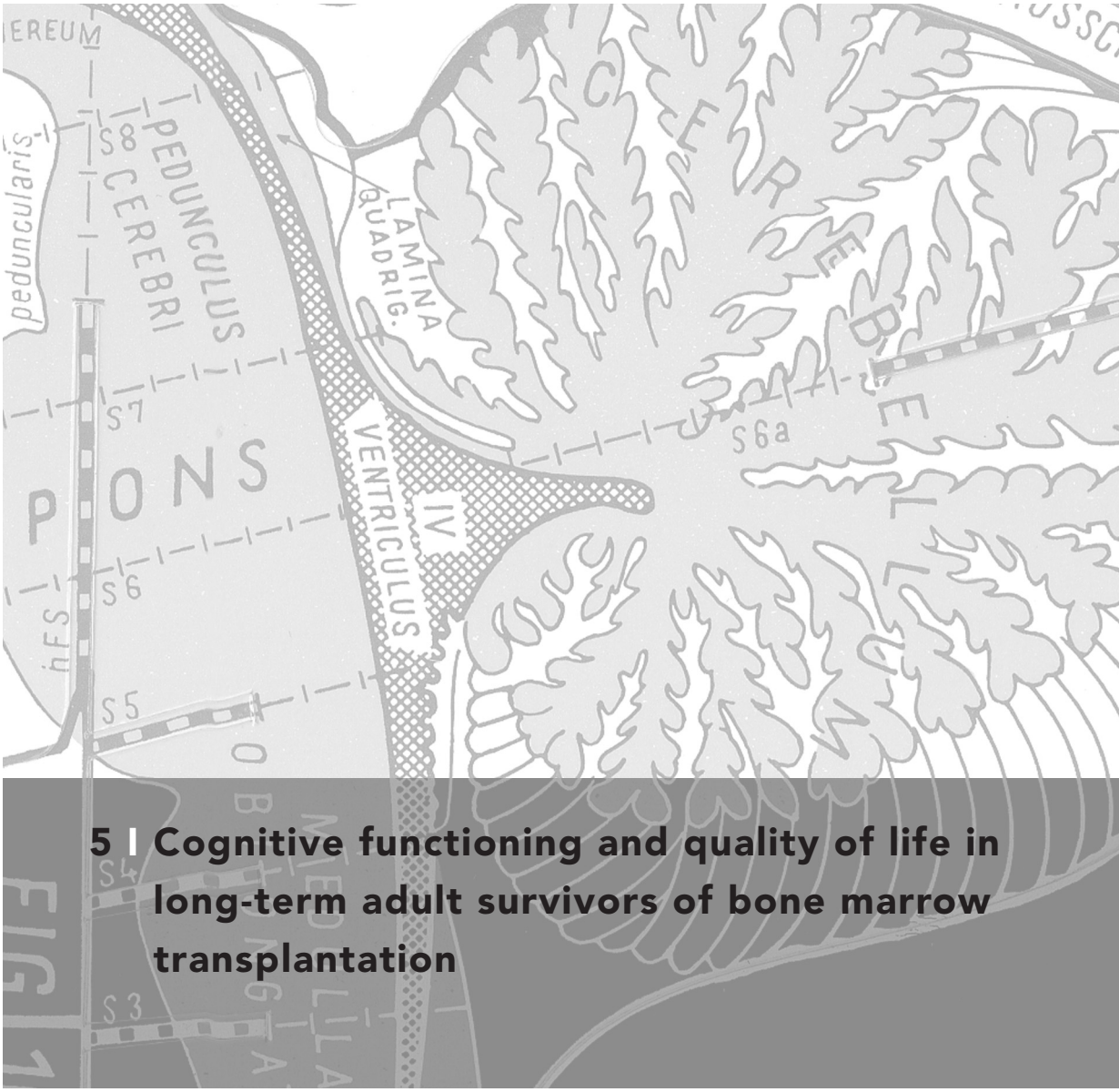

5 | Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation

H. Harder, JJ. Cornelissen, AR. Van Gool, HJ. Duivenvoorden, WMH. Eijkenboom, MJ. van den Bent
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ABSTRACT

Background: The late neurotoxic effects of bone marrow transplantation on cognitive functioning and quality of life were investigated in a consecutively treated cohort of long-term adult survivors.

Methods: Progression free patients treated with bone marrow transplantation or peripheral stem cell graft for a hematological malignancy at least 2 years before study participation were examined with a comprehensive battery of neuropsychological tests and questionnaires for quality of life and mood states. The results of the neuropsychological tests were compared to healthy population norms.

Results: Forty patients were included, 87.5% had undergone an allogeneic transplantation. All received total body irradiation up to 12 Gy (in 2 fractions). Assessment took place 22 to 82 months after BMT. Mild to moderate cognitive impairment was found in 24 patients (60%). Compared to healthy population norms, selective attention and executive function, information processing speed, verbal learning, and verbal and visual memory were most likely to be affected.

The mean score for the total patient group revealed that these patients scored significant lower on the information processing speed task compared to expected scores obtained from the normal population.

The main predictors for poor neuropsychological performance were fatigue, global health, and educational level. Other correlations with moderate to severe cognitive impairment were subjective cognitive complaints, physical functioning, social functioning, overall mood states and employment status.

Conclusions: These data indicate that bone marrow transplantation may lead to cognitive complaints and late cognitive deficits in adult long-term survivors. Cognitive functioning should therefore be used as an outcome parameter in bone marrow transplantation studies.

INTRODUCTION

Autologous or allogeneic bone marrow or stem cell transplantation (BMT) has become standard treatment for a variety of hematological malignancies. This treatment is curative for an increasing number of patients, and attention has turned to the long-term effects of BMT. Unfortunately, the BMT procedure carries still a considerable morbidity as a consequence of acute and delayed disease and treatment-related complications. Patients have a risk of developing neurological complications and delayed encephalopathies, which are associated with the BMT conditioning regimen.[1-7] The BMT conditioning regimen involves high-dose chemotherapy, often combined with total body irradiation (TBI). Both high-dose chemotherapy and radiation therapy to the brain are known causes for delayed central nervous system (CNS) toxicity.[8-11] Other potential severe treatment-related complications are opportunistic infections related to immunosuppression, extensive acute or chronic graft versus host disease (GVHD), side-effects of immunosuppressive therapy (cyclosporin, methotrexate or corticosteroids) or major organ failure. These may give rise to a variety of severe neurological complications, in particular (drug-induced) encephalopathies and opportunistic CNS infections.[6] Prior or post BMT intrathecal chemotherapy or whole brain irradiation as treatment or prophylaxis for CNS disease may also induce a delayed leukoencephalopathy.[12,13] The presence of this combination of many potential risk factors for late neurological sequelae makes the BMT procedure unique compared to other potentially neurotoxic forms of cancer treatment. The impact, however, of the mentioned risk factors on cognitive functioning in long-term survivors is not well documented. Neuropsychological studies in cancer patients treated with only one of the treatment forms used in the BMT conditioning regimen showed evidence of cognitive impairment.[14-18] The few previous reports on the specific neurocognitive side effects of BMT suggest that these patients are at risk to develop cognitive deficits.[5,19-26] Only five studies focused upon the late side effects but methodological shortcomings, such as lack of neuropsychological testing, small sample size or selection of patients, preclude reliable conclusions.[5,19,20,25,26] We have, therefore, assessed cognitive functioning and quality of life (QOL) in a consecutively treated cohort of long-term adult survivors of BMT. A minimum time interval of 2 years post treatment was used to elude influence of acute side effects of BMT.

MATERIALS AND METHODS

Patient selection

Patients treated with BMT for hematological malignancies 2 to 7 years before the time of this study were selected from the BMT database of the Department of Hematology. In this 5-year period a total of 141 patients were treated with a BMT conditioning regimen involving both high-dose chemotherapy and TBI. Of these, a cohort of 61 consecutive long-term survivors was identified.

Patients eligible for our study had to meet the following inclusion criteria: 1) no evidence of recurrent disease, 2) no previous neurological or psychiatric disorders, 3) no use of psychoactive drugs or medication known to affect cognitive functioning, 4) no history of, or current substance abuse, 5) basic proficiency of the Dutch language, 6) between 18 and 65 years of age.

Measures

Cognitive performance was assessed by a comprehensive battery of standardized neuropsychological tests. Prior to testing the patients were interviewed with regard to cognitive problems experienced in their daily-life routine. The extent of the problems was rated by the neuropsychologist on a 4-point Likert-type scale (0= no problems, 1= mild problems, 2= moderate problems, 3= severe problems.[27] In addition, a set of self-administered questionnaires was applied to collect data on quality of life and mood states. Ratings of a widely used mental status screening test, the Mini Mental State Examination (MMSE), and the Karnofsky performance status scale were obtained before the assessment.[28,29]

The neuropsychological evaluation consisted of eleven internationally used psychometric tests selected for validity and availability of normative data. The battery was designed to assess several cognitive functions: general intelligence and conceptual reasoning, verbal function, memory, attention functions and concentration, executive functions, visuospatial and visuoconstructive ability, psychomotor function, and speed of information processing.

The Groninger Intelligence Test, short form (GIT-V)

The GIT-V[30] measures actual general intelligence level. The test consists of three subtests for respectively spatial ability, abstract reasoning and arithmetic. The scores of the three subtests are transformed into an intelligence quotient (IQ) based on age and gender.

The National Adult Reading Test (NART)

The (NART)[31] estimates premorbid intelligence based on verbal ability. This is mea-sured by the ability to read aloud correctly a list of phonetically irregular words and accuracy of oral pronunciation is scored. Premorbid intelligence can be estimated by this test as vocabulary level and related verbal skills correlate with overall ability level.[32]

Wordfluency Test

The Wordfluency test[30] evaluates language processing by naming as many words as possible belonging to two word categories. The score is the sum of words produced in each trial.

California Verbal Learning Test (CVLT)

The CVLT[33] assesses verbal memory capacities. The test consists of five presentations with recall of a 16-word list, one presentation of a second 16-word list and recall, followed by a short-term free recall and cued recall of the first list. Retention is tested 20 minutes after learning by delayed free recall, delayed cued recall and recognition. The CVLT provides also information on learning strategies, and retroactive and proactive interference tendencies.

Rey Complex Figure Test (CFT)

The CFT[34] measures both visuospatial organization and visual memory. The patient is asked to copy a complex figure. Immediate recall is assessed 3 minutes after copying. Evaluation of the immediate recall is obtained by using scores based on a unit scoring system referring to specific details of the figure.

Digit Span of the Wechsler Adult Intelligence Scale

Digit span[35] assesses immediate recall and attention. The patient is asked to repeat successive series of digits in two conditions, forward and backward.

Trailmaking Test (TMT)

The TMT[36] measures psychomotor speed and attention. The test consists of small randomly printed consecutively numbered circles (part A) and consecutively numbered and lettered circles (part B). The patient has to draw lines to connect the circles, and in part B alternating between the two sequences is required. Slow performance on one or both parts of the test indicates cognitive deterioration.

Stroop Color Word Test (SCWT)

The SCWT[37] determines selective attention and executive functions. In part A and B, the time needed to complete reading 100 color names and naming 100 colored rectangles is recorded. Part C involves 100 color names in different printing ink than the color name; the speed at which the color of the printing ink is named is taken as the test variable. is recorded. The time taken to complete each part and the total number of failures are registered.

The Fingertapping Task

The Fingertapping task[32] measures the psychomotor speed. The patient is asked to press a marked button with the index finger of each hand separately as fast as possible for one minute. The number of hits in the first and second half (30 seconds) of the test and the number of total hits is recorded.

The Reaction Time Task

The Reaction time task[38] measures speed of information processing in two single stimuli tasks (visual and acoustic) and two complex binary choice tasks. The use of a rest button and reaction button enables breakdown into decision-making time and motor time. Decision time, motor time and the number of missing, incorrect or incomplete responses are scored.

Questionnaires of QOL and Mood States

QOL was measured with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.[39] This instrument includes five domains that assess functioning (physical, role, cognitive, emotional, social) by using multi-item scales, two domains assessing global health status and global QOL, and nine multi-item scales or single items assessing symptomatology. In conjunction with the EORTC QLQ-C30, we used the EORTC brain cancer module (BCM 20) to screen for neurological dysfunction.[40] The BCM 20 contains four multi-item scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and seven single items.

A questionnaire of mood states was administered to distinguish between cognitive deficits related to BMT treatment or to additional psychological distress. The brief version of the Profile of Mood States (POMS) was used as a summary measure.[41,42] The POMS has separate subscales for five dimensions of general psychological distress: depression, tension, anger, fatigue and vigor. In total there are thirty-two items to be scored on a 5-point Likert-type scale format, ranging from 0 to 4.

Procedure

The study was approved by the institutional ethics and scientific committee and written informed consent was obtained from all patients. The medical records of the patients were examined by a physician to record information regarding patients' current medical status (including current medication use) and history of disease and treatment (eg, cytotoxic treatment and complications of the BMT conditioning regimen). All psychometric tests were administered in the same order for all patients and scored by an experienced neuropsychologist. The assessment took approximately two and half-hours to complete.

Statistical Methods

The questionnaires were transformed into scores according to standard procedures. Before computing a total score for overall psychological distress, the total POMS score, the scores of the positive psychological distress subscale Vigor were transformed so they were in line with the scores of the negative psychological distress subscales. The total POMS score was computed by summing up the standard z-scores for each subscale and then dividing this score by the number of subscales. The total POMS score was considered aberrant when the score was 2 standard deviations ($z \leq -2.0$) below the mean of the healthy population norms.41 The raw data of each neuropsychological test (or test indices) were converted into standard scores (z-scores) and percentile scores by using age and gender corrected healthy population norms. Patients were classified according to the commonly accepted standard criteria of each test (ie, impaired either when test scores were 2 standard deviations ($z \leq -2.0$) below the mean of the standard scores ($z=0$) or below percentile 10). General intelligence was considered to be aberrant if the difference between the estimated premorbid intelligence quotient and the actual intelligence quotient was more than 20 points ($z \leq -2.0$), taking into account that the NART underestimates premorbid intelligence by 15 IQ points.31,43 A composite score for cognitive impairment was computed for each individual by counting all test indices on which the patient was impaired.

The mean score of each neuropsychological test was computed after transforming all test scores into percentile scores (to ease interpretation). In a normal population a percentile score of 50 means that the patient has an average test result; the standard deviation is 34. The differences between the distribution of the observed frequencies and the distribution of the expected frequencies were tested with a chi-square test (X^2 for trend). The distribution of the expected frequencies was calculated using the scores of the normal population as reference group.[30,32-38] The upper and lower cells were collapsed so that the percentage of cells with an expected count less than 5 did not exceed the limit of 20%.

Descriptive statistics were performed for all variables. Differences in individual test scores in various patients groups defined by demographic and disease and treatment-related parameters were analyzed by the Student's *t*-test. Relationships between overall cognitive performance, psychosocial functioning and subjective measures of cognitive complaints were analyzed using Pearson's correlation coefficients.

Multiple linear regression analysis was used to estimate the influence of disease and/or treatment related variables on cognitive impairment. The set of variables to enter the analysis were selected by the method of multiple regression; the composite score for cognitive impairment was used as the dependent variable. The standardized regression coefficient (ß) was used as a measure of relative importance.

Tests were two-sided and a *P*-value of 0.05 or less was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences (SPSS) Windows 9.0 software.

RESULTS

Demographic and clinical patient characteristics

Forty-two patients were eligible for study. Of these, forty patients (95%) provided written informed consent (one patient lived abroad temporary and one patient declined to participate). Ten patients were excluded because of recurrent disease or secondary malignancies and six patients because of the lack of basic proficiency of the Dutch language. Two patients were excluded due to long-term alcohol and/or drug abuse and one because of recurrent depressive episodes and use of psychotropic drugs. Demographic and clinical information is shown in Table 1. The two patients with aplastic anemia did not receive induction therapy prior to the BMT procedure. CNS prophylaxis was given to eleven patients prior to BMT (4-8 injections of intrathecal methotrexate or Ara-C), which was continued (2-3 injections) in five patients after the BMT procedure. One patient received low dose TBI (24 x 0.10 Gy) before undergoing the BMT conditioning regimen. Neurological complications prior to BMT were found in two patients: one patient had CNS disease and was treated with cranial radiotherapy (16 x 1.5 Gy), another patient had seizures related to intrathecal treatment.

All patients underwent conditioning with high-dose chemotherapy and TBI. High-dose chemotherapy consisted of cyclophosphamide, either alone (60 mg/kg of body weight per day for 2 days) or in combination with cytosine-arabinoside (1000 mg/m^2 per day for 2 days) or etoposide (350 mg/m^2 per day for 2 days). For the majority of patients high-dose chemotherapy was followed by 10 or 12 Gy of TBI, administered in 2 doses of either 5 or 6 Gy in 2 days. After the conditioning regimen most patients (87.5%) received bone marrow support from a related or unrelated donor.

Various regimens for prophylaxis of GVHD were utilized depending on the protocol and the compatibility of the donor. Thirty-four patients received cyclosporin (CyA) (mean 166.2 days, SD 116.5, range 42 to 507) and T-cell depletion of the donor graft was performed in thirty-three patients. Half of the patients received corticosteroids as immunosuppressive therapy (mean 139.8 days, SD 170.8, range 3 to 598). The median time interval between BMT and testing was 43 months.

Medical status and treatment-related neurological complications

After the BMT procedure complete remission was achieved in thirty-six patients. Four patients with multiple myeloma were in ongoing partial remission, of which three used a maintenance dose of interferon-alpha. Following BMT 69% of the allogeneic recipients experienced acute GVHD (grade I to III), and 29% developed mainly limited chronic GVHD (Table 2). Four patients had received treatment for recurrent disease (eg, donor buffy coat infusion or chemotherapy) and were again responding. All additional therapy was given at least one year before neuropsychological testing.

The severe neurological complications induced by the BMT-conditioning regimen are summarized in Table 2. A history of neurological complications such as encephalopathy, cerebrovascular events or cerebral infections was found in almost a fourth of this cohort. Fifteen patients underwent cranial MRI at the time of presence of clinical neurological signs. Abnormal neuroradiological findings (eg, white matter abnormalities or focal lesions) were present in seven patients. No current neuroradiological information was available at the time of neuropsychological evaluation.

Table 1 Patient characteristics (n=40)

	No. of patients	Mean (SD)	Range
Sex			
Male	24		
Female	16		
Age (years)		40.8 (10.3)	18 - 60
Age at BMT (years)		37.2 (10.4)	15 - 55
Time since BMT (months)		45.1 (17.3)	22 - 82
Estimated premorbid IQ		105.3 (10.0)	84 -126
Educational level			
Less than high school degree	3		
High school degree	14		
Vocational/trade school	10		
College/bachelors degree	7		
Graduate/professional degree	6		
Diagnosis			
Acute Lymphocytic Leukemia	8		
Acute Myelogenous Leukemia	10		
Chronic Myelogenous Leukemia	6		
Non-Hodgkin's Lymphoma	6		
Myelodysplastic Syndrome	4		
Multiple Myeloma	4		
Aplastic Anemia	2		
Intrathecal treatment			
Yes	11		
No	29		
Type of BMT			
Allogeneic MRD	26		
Allogeneic MUD	9		
Autologous	5		
Conditioning regimen			
CP	12		
Ara-C + CP	19		
VP-16+ CP	9		
TBI dose			
10 Gy (two fractions)	13		
12 Gy (two fractions)	25		
8.5 Gy (two fractions)	1		
8 Gy (one fraction)	1		

MRD = bone marrow transplantation; IQ = intelligence quotient MRD = matched related donor; MUD = matched unrelated donor
CP = cyclophosphamide; Ara-C = cytosine arabinoside; VP-16 = etoposide

Table 2 Treatment-related complications: GVHD and neurological disorders

Acute GVHD	No. of patients	Chronic GVHD	No. of patients
Grade I	12	Limited	9
Grade II	6	Extensive	1
Grade III	6		
Grade IV	-		
CyA encephalopathy	3		
Hypertensive encephalopathy	1		
Intracerebral hemorrhage	1		
Viral-meningo encephalitis	1		
Cerebral toxoplasmosis	1		
Pneumococcal meningitis and cerebral toxoplasmosis	1		
Unspecified cerebral lesion with seizures	1		

GVHD: graft versus host disease; CyA: cyclosporine

Clinical performance and cognitive screening

Mean performance status (KPS) was 89.8, (SD 10.0, range 70-100); twelve patients had a clinical performance below 90. The screening test of mental status revealed no abnormalities as all patients scored above the MMSE cut-off score of 23 points (mean 28.3, SD 1.1, range 26-30).

Subjective cognitive problems in daily life routine

The incidence of reported subjective cognitive problems interfering with daily life routine is shown in Table 3. Most patients reported no problems or only very mild problems. However, almost 28% experienced moderate to severe memory problems and 17.5% showed moderate problems in attentional functions. In most cases these patients experienced a decline in comparison to their level of cognitive functioning prior to BMT treatment.

Table 3 Subjective cognitive problems in daily life routine[a]

	Memory %	Attention %
No problems	37.5	50
Mild problems	35	32.5
Moderate problems	25	17.5
Severe problems	2.5	-

[a] Information based on a short pre-test interview and rated on a scale by the neuropsychologist

Table 4 Neuropsychological tests: percentage of impaired patients and mean test score

Cognitive Domain Neuropsychological Test	Impaired patients %	Mean test score (SD)[a]	P-value[b]
Intelligence			
Groninger Intelligence Test	5	71.43 (28.22)	.002
Language			
Wordfluency Test	0	74.95 (20.24)	.001
Memory			
California Verbal Learning Test	15		
- Total words		43.49 (30.97)	.48
- Learning speed		41.81 (31.06)	.43
- Consolidation		46.59 (29.13)	1.0
Rey Complex Figure Test-recall	20.5	50.26 (31.85)	.10
Attention and executive function			
Stroop Colour Word Test	23.1		
- Word card		46.54 (30.89)	.97
- Colour card		46.41 (29.33)	.88
- Colour-word card		40.90 (27.86)	.30
Digit Span	0	61.45 (23.38)	.01
Trailmaking Test A	0	63.91 (23.01)	.01
Trailmaking Test B	0	60.00 (24.19)	.01
Visuospatial organization			
Rey Complex Figure Test- copy	2.6	91.15 (20.50)	.001
Psychomotor speed			
Fingertapping Task	2.5		
- Dominant hand		50.40 (29.51)	.48
- Non-dominant hand		49.40 (29.83)	.08
Speed of information processing			
Reaction Time Task	32.5		
- Single choice task		11.20 (15.56)	.001
- Complex choice task		11.29 (20.65)	.001

[a] In percentiles (mean=50, SD=34)

[b] Compared to expected scores obtained from the reference group

Neuropsychological assessment

Only one patient could not perform all neuropsychological tests due to severe cataract. All other patients completed the battery of neuropsychological tests including the questionnaires. Table 4 presents the percentage of patients who performed in the impaired range of the eleven neuropsychological tests and the mean test score for the total patient group. The distribution of the composite score for cognitive impairment is summarized in Table 5. Sixty percent scored in the impaired range on at least 1 neuropsychological test. Five patients (12.5%) scored on 3 or more of the 11 tests they completed.

Compared to the normative data of each neuropsychological test the following domains of cognitive functioning were most frequently impaired: selective attention and executive function (SCWT;X^2=6.94,df=1,P=.008), information processing speed (Reaction time task;X^2=162.35,df =1,P<.001), visual memory (Rey CFT; X^2=4.44,df=1,P=.035) and verbal learning and memory (CVLT; X^2=25.64,df=1,P<.001). Verbal functions, intellectual functioning, motor speed, immediate verbal memory and perceptual organization were unaffected. However, when the distribution of the observed test scores were compared to the distribution of the expected test scores, only the scores on the test for information processing speed were far below from those obtained from the reference group (Table 4). The test scores on tests for verbal memory (CVLT) and selective attention (SCWT) were slightly lower but not significant. On several neuropsychological tests the test scores were higher than the expected scores, namely on the GIT-V, the Wordfluency Test, Digit Span, the Trailmaking A and the copy of the Rey CFT.
A multiple linear regression analysis (adjusted for age and gender) was carried out using a selected set of variables as covariates and the composite score for cognitive impairment as the dependent variable. Examination of the standardized regression coefficients (ß) for the individual variables indicated that the strongest predictors of the proportion of impaired tests were: fatigue rated with the EORTC QLQ-C30 (ß=.43;P=.03), global health of the EORTC QLQ-C30 (ß=.55;P=.004) and higher educational level (ß=.29;P=.04). Other potential predictor variables like age, the total POMS score, type of BMT, dose of TBI, use of CyA, use of T-cell depletion, use of corticosteroids, use of interferon-alpha, time since treatment, exposure to intrathecal treatment or treatment for recurrent disease, presence of acute or chronic GVHD, presence of pre treatment or post treatment CNS complications, and presence of MRI-confirmed abnormal neuroradiological findings did not account for the variance in the proportion of impaired tests.

Table 5 Overall cognitive status: composite score for cognitive impairment

	No. of patients (%)	
No test in impaired range	16	(40)
One test in impaired range	14	(35)
Two tests in impaired range [a]	5	(12.5)
Three tests in impaired range	3	(7.5)
Four tests in impaired range	2	(5)

[a] Including the patient who completed only six neuropsychological tests

QOL and mood states

The results of the questionnaires for QOL and psychological distress measured by the EORTC QLO C-30 and the brief POMS are listed in Table 6. Global QOL in this cohort of patients seems satisfactory (mean 82.5, SD 18.1). The cognitive function scale of the EORTC QLQ-C30 (Q20 and Q25) is of special interest in this study. The cognitive function scale was strongly correlated with the symptom fatigue (r=-.55;P<.001). The composite score for cognitive impairment was associated with several functional scales or items of the EORTC QLQ-C30: the physical function scale (r=-0.44;P=.005), the cognitive function scale (r=-0.58;P<.001), the social function scale (r=-0.38;P=.016) and the symptom fatigue (r=0.37;P=.02).

Table 6 Scores of the questionnaires of quality of life and mood states

	Mean (SD)	
EORTC QLQ C-30 a		
Functional scales		
Physical function	80.6	(18.4)
Role function	83.8	(22.2)
Cognitive function	74.2	(22.3)
Emotional function	79.2	(24.5)
Social function	72.9	(31.3)
Global health	80.0	(17.4)
Global quality of life	82.5	(18.1)
Symptom scales and/or items		
Fatigue	27.5	(18.7)
Nausea and vomiting	4.2	(11.2)
Pain	12.9	(18.3)
Dyspnea	14.2	(21.2)
Sleep disturbances	18.3	(22.6)
Appetite loss	5.8	(18.3)
Constipation	4.2	(17.2)
Diarrhea	4.2	(13.5)
Financial impact	15.0	(28.2)
EORTC BCM 20[a]		
Multi-item scales		
Future uncertainty	17.8	(19.2)
Visual disorder	11.9	(16.8)
Motor dysfunction	7.2	(10.5)
Communication deficit	17.2	(23.6)
Items		
Headaches	19.2	(23.7)
Seizures	0.8	(5.3)
Drowsiness	10.8	(15.8)
Bothered by hair loss	4.2	(11.2)
Bothered by itchy skin	29.2	(32.2)
Weakness of both legs	13.3	(21.2)
Trouble controlling bladder	5.0	(14.2)
POMS[b]		
Depression	4.3	(5.8)
Anger	8.4	(6.6)
Fatigue	6.1	(5.3)
Vigor	12.6	(3.5)
Tension	5.2	(4.9)

[a] EORTC QLQ C-30, EORTC BCM 20: scores range from 1 to 100; higher scores on the function scales represent a higher level of functioning; higher scores on the symptom scales and/or items represent more perceived symptoms

[b] POMS: scores range from 0 to 32 (depression), 0 to 28 (anger), 0 to 24 (fatigue and tension), and 0 to 20 (vigor); higher scores indicate greater current mood disturbances except for the subscale vigor

High levels of current distress (z ≤ -2.0 in comparison to healthy population norms) in one or more subscales of the brief POMS were found in 15 patients. Most of these patients (60%) had a high score on only one of the five subscales of the brief POMS, especially on the subscale anger. The total POMS score was aberrant in only three patients. The total POMS score was associated with the composite score for cognitive impairment (r=0.39;*P*=.02). Further analysis showed a substantial correlation between the composite score of cognitive impairment and the subscale fatigue (r=0.51;*P*<.001) and a weak correlation with the subscale tension (r=0.34; *P*=.03). Absence from work or school was in particular associated with the following factors: fatigue measured by the brief POMS (*r*=0.62;*P*<.001) and EORTC QLQ-C30 (*r*=0.46;*P*=.01), and physical functioning (*r*=-0.41;*P*=.021).

Attendance at work or at school either full-time or part-time was established in 47% of the patients who used to work or study prior to BMT. Forty percent of the patients were still on disability or sickness benefit. There was a relation between employment status and the incidence of subjective cognitive complaints measured by the EORTC QLQ-C30 (*r*= -0.57;*P*=.001), and self reported memory problems (*r*=0.53;*P*=.002), the composite score for cognitive impairment (*r*=0.42;*P*=.02) and the total POMS score (*r*=0.46;*P*=.003). More specific inspection of the data showed that.

DISCUSSION

Long-term survivors of BMT are at risk for cognitive impairment as a result of exposure to a number of potentially neurotoxic agents, including those used in conditioning regimen (eg, high-dose chemotherapy and TBI), as well as those used as prophylaxis or treatment of GVHD or immunosuppression. Likewise, intrathecal chemotherapy or whole brain irradiation, often used as prophylaxis or treatment for CNS disease involvement prior to the BMT conditioning regimen, are risk factors for the development of cognitive deficits. In our study we analyzed cognitive functioning in a consecutively treated sample of long-term adult survivors of mostly allogeneic BMT with a mean time interval between treatment and neuropsychological testing of more than 3 years. To our knowledge, this is the first study to examine long-term survivors of BMT, who attained a survival of at least 2 years, with both an extensive battery of neuropsychological tests and measures of QOL and mood states. As anticipated, we observed late cognitive sequelae in a significant percentage of patients. Most patients had only mild cognitive impairment, but five patients (12.5%) showed moderate to severe decreased performance on several neuropsychological measures compared to the normative data. Cognitive dysfunction in these patients was most profound in visual memory, verbal learning, and verbal short-term and long-term memory, attention or executive functions and speed of information processing. When comparing the distribution of observed and expected test scores, a few tests had a lower mean score than expected, but this was only significant for the speed of information processing task. Several neuropsychological tests showed a higher mean score compared to the reference group which is probably related to higher score on the intelligence test in this patient group. Measures of QOL and mood states revealed that the majority of patients reported satisfactory global QOL (median 83.3) and showed no signs of severe mood disturbances.

Only nine studies have been published regarding cognitive functioning in BMT patients five of which explored the neurocognitive status in long-term survivors a year or more after their treatment.[5,19-26] The first study in long-term survivors was performed by Parth et al.[19] In a

longitudinal design with a follow-up period up to a year post treatment, the cognitive and motor performance of 44 BMT patients was compared to the cognitive status of their relatives or donors. Cognitive changes in comparison to baseline levels and controls were most profound near the beginning of treatment and involved associative memory, perceptual speed and logical reasoning. These findings, however, reveal mainly the acute side effects of BMT treatment as the sample size at the last follow-up was reduced to just 11 patients.

Two retrospective studies with a similar time-interval between treatment and assessment to our current study found evidence for cognitive decrement.[5,20] Andrykowski et al [20] reported slowed cognitive processing, attention problems, and difficulties in reasoning in 30 allogeneic transplant patients and found an association with increased TBI dose. Reduced memory function after allogeneic BMT related to older age, a longer time-interval post BMT, chronic GvHD and long-term CyA use was found by Padovan et al.[5] However, both studies lack comprehensive neuropsychological testing as only subjective and unreliable measures (self-report questionnaires and a structured interview) were used. Therefore, the extent of cognitive problems could therefore be misjudged or underestimated.

Two recent studies showed only minor cognitive problems following autologous BMT which is contradictory to our findings.[25,26] Peper et al[25] used standardized neuropsychological tests in a small cross-sectional study of 20 survivors of autologous BMT at a mean time interval of 32 months after treatment. Only a slight reduction of memory function was found but these survivors were compared to control patients with renal insufficiencies in which cognitive dysfunctions are to be expected.[44,45] The same group found normal pretreatment results and improved test performance in a prospective evaluation of 58 autologous BMT patients with a mean follow-up of 27 months.[26] The improvement in cognitive functioning was explained by practice effects of the repeated measurements (before treatment, the first day of TBI and 6 to 36 months after TBI/BMT treatment), as well as by an increase of positive mood states. A possible explanation for the inconsistency between these studies and our findings is the difference in the type of BMT. In our study the majority of patients received allogeneic BMT, 26% of whom had an unrelated donor. The incidence of neurological complications varies among types of BMT with allogeneic BMT, in particular BMT with unrelated donors, carrying more treatment related morbidity than autologous BMT.[3-6] In our cohort of patients the neurotoxity and cognitive dysfunctions will have been more severe because of their exposure to acute and chronic GVHD and complications related to immunosuppression or immunosuppressive therapy.

Our data suggest correspondence between impaired cognitive function and educational level especially higher educational background. Parameters such as age, gender and level of education are known to influence cognitive functioning. Education level can in particular affect the level of performance on tasks involving verbal skills, stored information, and other school-related activities.[32] Although the normative data usually have corrections for age and gender, education–specific norms are not available for the majority of neuropsychological tests. Only a longitudinal study in which patients are followed in time and are tested before treatment will overcome this problem.

We also collected information regarding QOL and mood states. An important finding is that fatigue and global health are the main disease and treatment related predictors for cognitive impairment. Our results on QOL confirm earlier studies among long-term BMT survivors in, which, up to 10 years following treatment, a considerable percentage of patients still experience a wide range of lingering complaints.[46-48] Physical limitations or functional disability, pain, sexual problems, fatigue, sleep disturbances and social problems were the most common reported

complaints. Our findings show that both global QOL and fatigue were significantly associated with depressed mood measured by the brief POMS which shows that these lingering complaints have a great impact on patients' daily life in general. While it is still unknown whether the cohesion between fatigue, global health and cognitive impairment are possibly related to another unspecified factor, it may in the meantime be worthwhile to investigate whether intervention programs developed specifically to enhance QOL and to reduce fatigue and other late physical effects, help patients to re-establish their daily life routine after the BMT treatment. Our study is the first to evaluate late cognitive side-effects using an extensive neuropsychological test battery in combination with QOL and mood states measures in long-term survivors with a minimum survival of 2 years or more, it is preliminary and has some methodological limitations. The sample size is relatively small due to the low survival-rates and the limited number of disease-free survivors. Another limitation is that all patients in our study received a conditioning regimen with high-dose chemotherapy and TBI and therefore the effects directed to TBI only were not assessed. In addition, with this sample size we were unable to assess whether specific chemotherapeutic agents or dosages affect cognitive functioning. Similarly, the retrospective design and lack of pretreatment baseline assessment preclude definite conclusions about a change in cognitive functioning over time. The best way to evaluate the side effects of BMT treatment on cognitive functioning is through a longitudinal cohort study using a comprehensive neuropsychological test battery instead of a cognitive screening test or questionnaires only. Our results highlight the demand for systematic investigations on the late neurocognitive effects of BMT treatment. We have therefore started a prospective and longitudinal cross-sectional study to assess cognitive functioning and quality of life.

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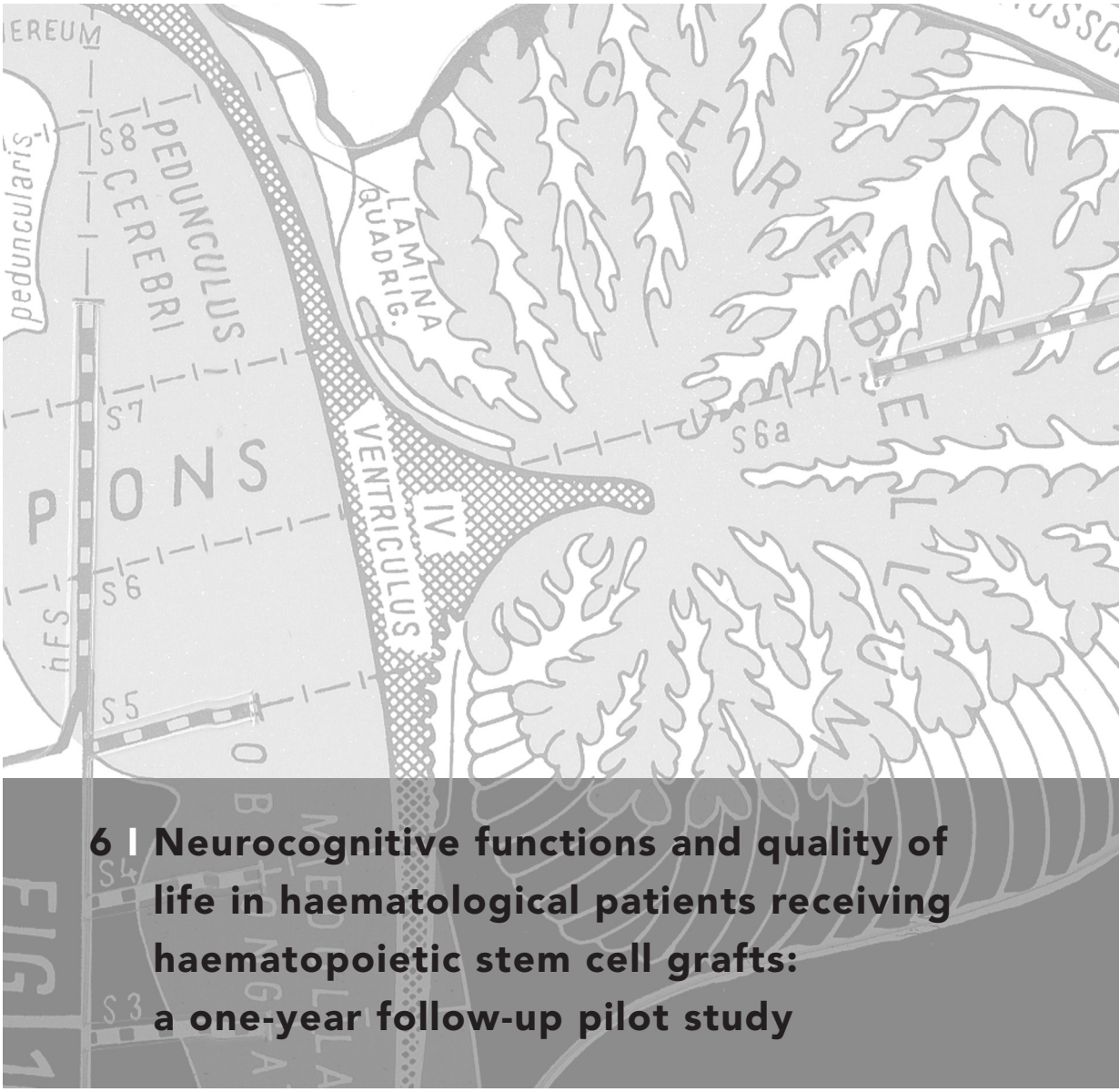

6 | Neurocognitive functions and quality of life in haematological patients receiving haematopoietic stem cell grafts: a one-year follow-up pilot study

H. Harder, HJ. Duivenvoorden, AR. Van Gool, JJ. Cornelissen, MJ. van den Bent
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ABSTRACT

Longitudinal data of neurocognitive functions and quality of life (QOL) were obtained for a cohort of 25 patients followed before transplant and through the first year after haematopoietic stem cell transplantation (SCT). A battery of neuropsychological tests and two self-report questionnaires were used to assess neurocognitive functions, QOL and psychological functioning. In comparison to normative data, up to one-fourth of the patients experienced impaired functioning on several cognitive domains before SCT. Random regression modelling revealed a slight improvement in the mean group scores of memory tasks over time, especially for younger patients. Impairment in neurocognitive functions was positively related to depression and anger at baseline, and to the emotional functioning scale at follow-up. These preliminary results emphasise the significance of a pre-treatment assessment and the need of a large baseline sample in future longitudinal studies to overcome the expected dropout-rate of more than 50%.

INTRODUCTION

Progress in haematopoietic stem cell transplantation (SCT) procedures and supportive care following bone marrow and peripheral blood stem cell transplantation has resulted in higher survival rates. As a consequence, the impact of SCT on neurocognitive functions and quality of life (QOL) is receiving more attention. Research into the neurocognitive consequences of SCT is critical as SCT-recipients are exposed to several potential sources of neurotoxic damage. The pre-transplant treatment schedules followed by intensive conditioning regimens with high-dose chemotherapy and total body irradiation (TBI), together with frequent infections, neurological complications and long-term use of graft versus host disease (GVHD) prophylactics may well affect the central nervous system and lead to long-term cognitive impairment.

Previous research indeed suggested that SCT recipients develop cognitive deficits, even years after treatment. Recently, we reported that more than half of 40 long-term survivors experienced mild to moderate cognitive impairment and less than half were back at work at a mean time of almost four years after SCT.[1] Like the few other reports in long-term SCT survivors this study was performed without an assessment prior to SCT.[2-4] Therefore, one cannot conclude that post-transplant cognitive impairments are directly attributable to the transplantation rather than other factors. Study designs with a pre-treatment baseline evaluation will differentiate between effects of previous treatment and the intensive SCT conditioning regimens or post-treatment complications, and monitor the influence of behavioural factors and psychological adjustment. However, longitudinal neurocognitive studies in SCT patients are problematic especially in areas of feasibility and statistical analysis. Mortality and morbidity rates are high caused by the toxicity of conditioning regimens, relapse, and acute or delayed treatment-related complications. Consequently, it takes many years to obtain data from a sufficient number of long-term survivors. The longitudinal studies performed so far investigated cognitive functions mainly in the periods before and immediately after hospitalisation for SCT.[5-8] Reports with longer follow-up included both children and adults, used subjective psychometric methods or had widely varying time-intervals between the assessments.[9-11]

The aim of the current pilot-study was to describe changes in cognitive functioning in the first year after SCT in a group of 25 patients, and to assess the feasibility of longitudinal research of objective neurocognitive functions and QOL methods in SCT patients.

METHODS

Patients

A total of 25 recipients of haematopoietic stem cell grafts were enrolled in the study and were tested before hospitalisation. Patients eligible for the study had to be over age 17 years, have sufficient knowledge of the Dutch language, and provided written informed consent. The study excluded patients with a history or presence of psychiatric or neurological disorders, and substance abuse. For follow-up, only patients without relapse or severe medical problems were included. The pre-transplant medical and demographic characteristics are summarised in Table 1. Most patients (20/25) had received prior systemic chemotherapy and the last cycle of chemotherapy was given at a median of 1.8 (range 1-14) months before baseline. Additional

(non-cranial) radiotherapy before SCT had been given to three patients. Two patients received intrathecal MTX chemotherapy. One patient had a subdural haematoma prior to SCT and used anti-epileptic drugs. The study was approved by the ethical committee of our hospital.

Table 1 Pre-transplant medical and demographic characteristics (n = 25)

Male / Female, no.	16 / 9
Median age in years (range)	47 (18-56)
Median premorbid IQ[a] (range)	104 (81-126)
Median educational level[b] (range)	3 (1-5)
Median KPS score[c] (range)	90 (70-100)
Diagnosis, no.	
ALL	1
AML	2
CLL	2
MM	7
MDS	2
HD	3
NHL	4
SAA	4
Disease status[d], no.	
Low risk	15
High risk	10
Chemotherapy treatment history, no.	
No previous treatment	5
1 course of chemotherapy	10
> 1 course of chemotherapy	10

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CML = chronic myeloid leukaemia; MM = multiple myeloma; MDS = myelodysplastic syndrome; HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; SAA = severe aplastic anaemia;
[a] NART intelligence quotient; [b] level 1 '< high school degree', level 2 'high school degree', level 3 'vocational/trade school', level 4 'college/bachelors degree', level 5 'graduate/professional degree'; [c] Karnofsky Performance Score; [d] Low risk = first remission, High risk = one or more relapses and second remission

Materials

Neurocognitive functions The standardised neuropsychological test battery and procedures have been described in detail elsewhere.[1] In short, four cognitive domains were examined with the following tests: Intelligence & Complex Tasks: short form of the Groninger Intelligence Test[12], National Adult Reading test[13], copy of the Rey Complex Figure Test[14,15]; Memory: Digit Span of the Wechsler Adult Intelligence Scale[16], California Verbal Learning Test[17], immediate recall of the Rey Complex Figure Test[14,15]; Attention & Executive Functions: Stroop Colour Word Test[18], Trailmaking A and B[19], Wordfluency Test[12]; Psychomotor Functions & Speed: Finger-tapping Test[20], Reaction Time Test.[21] To help to control for practice effects, alternate versions were used for the memory tests. Healthy populations norms, adjusted for age and sex, are available for all tests. Before every neuropsychological assessment the Karnofsky Performance

Score was rated.[22] Additionally, the patients were interviewed by the neuropsychologist about subjective cognitive complaints (memory and concentration) experienced in their daily life activities.

QOL and psychological functioning Patients completed two standardised self-report questionnaires. QOL was assessed with the EORTC QLQ-C30.[23] Psychological functioning was measured with the Dutch version of the short Profile of Mood States (POMS) with the following subscales: depression, tension, anger, fatigue and vigour.[24]

Data Analyses

The neuropsychological tests were scored according to standard procedures. Corrected test indices scores of more than two standard deviations ($z <= -2.0$) below population norms ($z = 0$) or below percentile 10 were classified as impaired.[1] For the evaluation of neurocognitive functions over time, the raw scores for each patient were transformed into T-scores based on the performance at baseline (mean=50 and sd=10). The measure for that given time point was T=50 + (10(x-m)/sd) in which *x* is the individual score, and *m* and *sd* are respectively the corresponding group mean and standard deviation for the baseline score. For each of the four cognitive domains, a mean cognitive domain index was calculated by using the sum of all T-scores divided by the number of test indices in that domain.

The large number of missing observations due to relapse or morbidity and mortality precluded the use of traditional statistical approaches for longitudinal designs (eg, end-point analysis and ANOVA models). Therefore, Random Regression Modelling (RRM) analyses were conducted, using the mean cognitive domain indices, to assess changes in neurocognitive functions over time.[25-27] The RRM approach allows for missing observations, time-varying covariables (psychological functioning) and invariant covariables (sex, age and education), and assessments at different end points. RRM estimates both average time trends and individual time trends. The individual time trend curves are based on available data for each patient, augmented by information from data from all other patients in the sample. The general model assumes that the individual response of each patient can be described by a line with intercept (baseline response) and slope (change rate) that is specific to the individual. Spearman's correlation techniques were used to identify and evaluate potential determinants for treatment and performance on neuropsychological testing. Nonparametric tests (Mann-Whitney U-test) were used to compare different groups of individuals. The probability level for statistical significance was set at 0.05 (two-tailed). All analyses were performed using the Statistical Package for Social Sciences (SPSS), version 10.1 and the SAS System version 8.2.

RESULTS

Clinical Outcomes

SCT was cancelled in two patients because of relapse, and two patients were not approached for follow-up because SCT was delayed severely due to medical complications. Table 2 presents a summary of the SCT treatment characteristics for the remaining 21 patients. Pre-treatment baseline testing was completed at a median of 23 (range 6-107) days before initiation of SCT-conditioning. Most patients (16/21) had an allogeneic transplant, while five patients received autologous stem cells, both following ablative high-dose chemotherapy. The majority of

patients (18/21) received CY (60 mg/kg once daily iv for 2 days) as a conditioning regimen followed by TBI up to a total dose of 12 Gy. Six patients experienced acute GVHD. Chronic GVHD was not observed. Severe complications immediately after SCT occurred in two patients (meningo-encephalitis and toxic pneumonitis). Twelve patients were included in the follow-up evaluation at 6 months and nine at 12 months. Failure to complete the 6-months follow-up evaluation was due to death (n = 3), long-term hospitalisation (n = 4; these patients were hospitalised because of severe post-SCT complications and died before the last assessment) and refusal (n = 2). Missing at the 12-months follow-up was caused by death (n = 1), long-term hospitalisation (not related to SCT; n = 1) and relapse (n = 1).

Table 2 SCT characteristics (n = 21)

Type of SCT, no.	
Autologous SCT	5
Related donor SCT	15
Unrelated donor SCT	1
Conditioning regimen, no.	
CY / TBI	18
BU / CY	1
CBV	2
TBI dose , no.	
2 x 5 Gy	6
2 x 6 Gy	12

CY = cyclophosphamide (60 mg/kg once daily iv. on days 1 & 2); BU = Busulphan (4 mg/kg p.o. in divided doses daily for 4 days); CBV = (BCNU 300 mg/m^2 once daily iv. on day 1, cyclophosphamide 1500 mg/m^2 once daily on days 2-5, VP16 125 mg/m^2 twice daily iv. on days 2-4)

Pre-Transplant Neurocognitive Functions Compared to Normative Data

Table 3 presents the mean scores of the neuropsychological tests and the percentages of impaired scores compared to normative data at baseline and follow-up evaluations. Baseline scores were examined for the entire patient sample (n = 25). Impaired test results were observed in the domains Intelligence & Complex Tasks, Attention & Executive Functions and Psychomotor Functions & Speed. The dropouts at 6 and 12 months did not differ from the non-dropouts on any of the neuropsychological tests at baseline.

Neurocognitive functions during the first year after SCT

The performance of the RRM models is shown in Table 4. To examine the degree to which neurocognitive functions varied across time and to explore the interaction of additional covariables, the RRM analysis strategy was as follows. First of all, time trend was entered in all models as linear and quadratic terms. Linear terms were introduced as random in half of the models and, in addition, psychological functioning (POMS) was introduced in half of the models. In all models the error variance was declared unstructured and the following variables were entered as covariables: premorbid intelligence, sex, age and education. The results of the RRM analysis are summarised in Table 5. The overall time effect was significant for the domain Memory, which reflects improvement in test performance over time. Additionally, a negative effect of age was

Table 3 Means (SD) and percentages of impaired test scores for the neuropsychological tests over the three time points

Cognitive Domain Neuropsychological test	Baseline (n = 25)		6-months FU (n = 12)		12-months FU (n = 9)	
Intelligence & Complex Tasks						
Short-GIT (score 0-66)	35.6 (7.4)	4%			37.7 (6.5)	-
CFT-copy (score 0-36)	35.4 (1.0)	-	35.1 (1.1)	-	35.3 (0.9)	-
Memory						
Digits (score 0-24)	12.6 (4.0)	-	12.6 (3.7)	-	13.8 (4.9)	-
CVLT (score 0-75)	55.0 (8.3)	-	59.9 (6.2)	-	58.3 (7.2)	11%
CFT-recall (score 0-36)	23.5 (5.4)	-	27.9 (5.7)	-	27.0 (4.8)	-
Attention &						
Executive Functions						
Stroop-Colour	93.7 (21.8)	24%	95.8 (27.7)	25%	91.6 (16.0)	22%
Word Card (sec)						
TMT-A (sec)	39.1 (15.6)	8%	33.2 (10.8)	-	27.6 (6.1)	-
TMT-B (sec)	74.9 (19.1)	8%	68.1 (20.6)	-	71.0 (29.6)	11%
Wordfluency (in 1 min)	21.4 (4.2)	-	20.1 (3.4)	-	22.7 (3.3)	-
Psychomotor Functions						
& Speed						
Tapping-dominant (in 1 min)	343.6 (48.3)	8%	350.2 (32.4)	-	344.2 (34.3)	-
Tapping-nondominant (in 1 min)	297.1 (47.1)	12%	302.3 (52.1)	-	293.8 (54.9)	11%
Single Motor Speed (msec)	166.6 (47.8)	12%	161.7 (32.0)	8%	145.0 (33.2)	-
Complex Motor Speed (msec)	166.8 (51.9)	12%	158.5 (36.0)	-	160.0 (52.0)	-
Single Decision Time (msec)	344.9 (37.5)	24%	341.1 (25.6)	8%	353.3 (34.7)	22%
Complex Decision Time (msec)	521.8 (65.3)	8%	498.8 (62.6)	-	490.1 (93.5)	-

Percentage of impaired test scores in italics; standard deviation values in parentheses; SD = standard deviation; FU = follow-up evaluation; GIT = Groninger Intelligence Test; CFT = Rey Complex Figure Test; CVLT = California Verbal learning Test; TMT = Trailmaking Test; sec = seconds; min = minutes; msec = milliseconds

observed, suggesting that the change in test performance on memory tasks varied by age (ie. older patients showed less improvement). For the other three cognitive domains, there was no evidence of any significant change over time or effects of the covariables.

Subjective cognitive problems, psychological functioning and QOL

At baseline the majority of patients (20/25) reported no subjective cognitive complaints (i.e. memory and concentration problems). At the first follow-up, six patients reported light to moderate cognitive problems (memory and concentration) and at the last assessment three out of nine patients complained about memory problems. The differences in the scores of subjective cognitive complaints over time were not significant. The percentage of impaired test results correlated positively with the subjective concentration problems at the one-year follow-up (r = .85, P = < .004), and no correlations were found at 6-months or at baseline.

Analysis of the QLQ-C30 revealed that patients who only performed the baseline assessment had lower scores on the emotional functioning scale of the QLQ-C30 (mean scores respectively

Table 4 Fit statistics for the four most plausible RRM models

RRM Models	-2 res LL	AICC	BIC
Intelligence & Complex Tasks			
Model 1	216.9	226.7	229.8
Model 2	219.1	223.6	225.6
Model 3	217.2	227.1	230.1
Model 4	218.9	223.4	225.4
Memory			
Model 1	260.2	264.5	266.6
Model 2	263.8	267.8	270.2
Model 3	260.8	265.1	267.2
Model 4	265.0	269.3	271.4
Attention & Executive Functions			
Model 1	267.8	276.9	280.6
Model 2	269.3	273.7	275.8
Model 3	264.2	270.9	273.8
Model 4	266.6	270.9	273.0
Psychomotor Functions & Speed			
Model 1	257.9	267.0	270.7
Model 2	259.9	264.2	266.3
Model 3	259.5	268.7	272.4
Model 4	261.5	265.9	268.0

-2 res LL = -2 restricted Log Likelihood; BIC = Bayesian Information Criterion (smaller is better) (Schwarz, 1978); AICC = small sample corrected Akaike Information Criterion Corrected (Hurvich & Tsai, 1995)

71 and 85, $P = .05$; adjusted for sex and age). No other differences between dropouts and non-dropouts were found. Similar RRM analysis strategies as described for the neurocognitive performance were applied for further examination of the QLQ-C30 and the short-POMS. No effects were found for the short-POMS or the QLQ-C30 symptoms scales or symptom items. A time effect was found for the emotional functioning scale ($P = < .005$), indicating an improvement at follow-up assessments. For global QOL, an effect of education was observed ($P = .01$); higher educational level was associated with higher global QOL. Differences in scores between sexes were observed for global health at the first follow-up assessment (females had higher scores, $P = .04$). At baseline, none of the QLQ-C30 scores correlated with neurocognitive functioning (although 'emotional functioning' reached an almost significant level; $r = -.34$, $P = .10$). The subscales depression and anger of the short-POMS associated positively with neurocognitive functions at baseline (respectively $r = .40$, $P = .05$; $r = .47$, $P = .02$). At both follow-up assessments, a negative correlation was observed between neurocognitive functions and 'emotional functioning' of the QLQ-C30 (6-months evaluation $r = -.60$, $P = .04$; 12-months evaluation $r = -.75$, $P = .02$), indicating that patients with more disturbed emotional functioning had more impaired test results.

Table 5 Neurocognitive functions after SCT: modelling trends over time and effects of covariables

Effect	Estimate	SE	t-value	*P*-value
Intelligence & Complex Tasks				
Overall Time Effect	1.927	0.987	1.95	0.09
Premorbid IQ	0.025	0.205	0.12	0.91
Sex	0.370	3.578	0.10	0.92
Age	0.125	0.152	0.82	0.44
Education	9.094	4.481	2.03	0.08
Memory				
Overall Time Effect	11.284	4.629	2.44	0.03
Premorbid IQ	0.166	0.140	1.18	0.25
Sex	- 3.812	2.453	- 1.55	0.14
Age	- 0.373	0.104	- 3.57	< 0.002
Education	3.825	3.077	1.24	0.23
Attention & Executive Functions				
Overall Time Effect	- 0.441	4.228	- 0.10	0.92
Premorbid IQ	0.098	0.177	0.51	0.61
Sex	2.538	3.076	0.83	0.42
Age	- 0.061	0.131	- 0.47	0.65
Education	4.566	3.845	1.19	0.25
Psychomotor Functions & Speed				
Overall Time Effect	5.184	4.247	1.22	0.24
Premorbid IQ	- 0.198	0.138	- 1.43	0.17
Sex	- 2.144	2.412	- 0.89	0.39
Age	0.120	0.103	1.16	0.26
Education	4.897	3.030	1.62	0.12

SE = standard error

DISCUSSION

The present prospective and longitudinal pilot-study assessed neurocognitive functions and QOL in 25 adult SCT recipients. Patients were evaluated in a prospective design and tested with a comprehensive battery of neuropsychological tests and questionnaires of QOL and psychological functioning at six and twelve months after baseline. All patients completed the test battery.

The use of repeated evaluations enabled individual changes in neurocognitive functions and QOL-related issues to be examined over time. During the first six months an attrition rate of 52% was observed caused by relapse before SCT, pre-treatment medical problems (pulmonary or cardiac) and severe SCT treatment-related morbidity or mortality. Only two patients declined to participate at the follow-up evaluations. The attrition rate increased to 64% at the last follow-up evaluation one year after baseline. High percentages of dropouts are well known in longitudinal studies of SCT patients as a result of the significant treatment-related morbidity or mortality in the first months after SCT. Therefore, systematic measurements of neurocognitive functions and QOL have proven difficult. We analysed our data with RRM, an adequate statistical technique in handling missing data, in which the analysis is not limited to survivors only or to those patients who were available for testing. Our data revealed that at the baseline assessment, cognitive deficits were mainly found in 'Attention & Executive Function' in comparison to age-adjusted healthy population norms. Almost one-fourth of the patients had impaired scores on the Stroop Colour Word Test, a measure for mental control, response flexibility and perceptual interference.[20] The percentage of impairment on this test remained stable throughout the first year and associated strongly with subjective concentration problems at the last follow-up. RRM analysis revealed no statistical differences in mean group scores before and during follow-up up to one year after SCT for most cognitive domains. Only performance on memory tests improved slightly across time, in particular for younger patients. The influence of practice effects in performance on memory tasks cannot be completely ruled out despite the use of alternate versions. Because of the regular follow-up assessments, patients get familiar with the test procedures what may improve the test outcome.

During the first year post-SCT, only minor statistical changes were found in QOL and psychological functioning. The level of psychological distress (depression and anger) affected neurocognitive performance at baseline but not at follow-up, which is in line with results from previous reports.[6,8,10] They showed that mood disturbances at baseline, probably as a response to the forthcoming SCT treatment, were followed by declining stress levels after hospitalisation. Our findings show that before SCT many patients have impaired test results in several domains of neurocognitive functions. This confirms other studies that focused on cognitive functioning in the first year after SCT treatment.[5,6,10,11] However, unlike some studies no significant decline in neurocognitive functions was observed during the first year after SCT.[6,7] The methodological differences (ie, differences in methods and duration of follow-up) probably contribute to the variability in results, but alternative explanations for these contradictory results should be considered. First of all, the effects of additional factors (eg, age and education) on decline or improvement of neurocognitive functions were not reported because of limitations in addressing group differences due to the small sample size. It is more likely that these effects may be detected in al larger sample of patients and play a possible role in the rate and patterns of cognitive changes. Furthermore, a potential selection bias needs to be considered given the

high attrition rate, partly caused by the fact that patients with a relapse or severe medical problems were excluded from further follow-up for ethical reasons. The current sample of patients may not be representative for all SCT patients and, consequently, the neurocognitive problems experienced by some patients could be underestimated. Therefore, our results should be interpreted in the context of common limitations of pilot studies and replication of the findings in a larger sample is essential.

In conclusion, this pilot-study predominantly demonstrated the feasibility and relevance of a prospective longitudinal design in studying neurocognitive functions in SCT patients. It also emphasises the importance of a pre-treatment assessment as observed post-SCT cognitive deficits may be due to impairment found before the SCT procedure. Furthermore, the results implicate that, based on an expected dropout of at least 50% and the extensive battery of neuropsychological tests, a sample size of approximately 100 patients at baseline is needed in future research to obtain sufficient power. A study evaluating the neurocognitive functions in a larger sample of SCT patients in comparison to other haematological cancer patients is currently ongoing.

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7 | Assessment of pre-treatment cognitive performance in adult bone marrow or haematopoietic stem cell transplantation patients: a comparative study.

H. Harder, AR. Van Gool, JJ. Cornelissen, HJ. Duivenvoorden, W.M.H. Eijkenboom, R.M.Y. Barge, MJ. van den Bent.
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ABSTRACT

The aim of this study was to examine cognitive performance in patients prior to bone marrow or haematopoietic stem cell transplantation (SCT) and in haematological patients who received non-myeloablative cancer therapies. A consecutive sample of 101 SCT patients and 82 haematological patients completed a neuropsychological test battery and 5 questionnaires assessing subjective cognitive complaints, psychological functioning, health-related quality of life (HRQOL), and fatigue. Results were compared with normative data. Percentages of cognitive impaired patients were equally divided between groups. Most deficits were observed in visual memory, visuospatial and constructional ability and psychomotor functions. The SCT group showed a higher rate of anxiety cases and reported lower cognitive functioning, emotional functioning and social functioning. Results of neuropschychological testing were not associated with outcome of the questionnaires. This study showed impaired cognitive performance prior to SCT. Haematological patients treated with non-myeloablative cancer therapies proved to be a reliable reference group for longitudinal studies.

INTRODUCTION

With more effective anticancer treatment, late side effects of treatment are an increasing source of concern. This also holds for cognitive dysfunction. The most consistent cognitive deficits in patients treated for advanced malignancies outside the central nervous system (CNS) involve executive function, verbal memory and motor skills.[1] Even though most of these cognitive changes are mild or subtle, they can affect many aspects of patients' lives and have serious consequences for health-related quality of life (HRQOL), family role functions, and employment status or vocational training.

Bone marrow or haematopoietic stem cell transplantation (SCT) in adults with haematological malignancies is a potential cause of cognitive dysfunction.[2-12] SCT patients are exposed to a variety of profound neurotoxic influences during a prolonged period of time. First of all, most patients faced intensive treatment schedules before undergoing SCT, like high-dose systemic chemotherapy, intrathecal chemotherapy or relapse therapies.[13,14] This is followed by the induction phase of SCT, which involves high-dose myeloablative chemotherapy with or without total body irradiation (TBI).[15] Finally post-engraftment, many patients need long-term immunosuppression with steroids or cyclosporin, they are at risk of opportunistic infections caused by immunosuppression, and they experience acute or chronic graft versus host disease (GVHD).[16] All these factors put SCT patients at an increased risk of CNS damage and result in possible long-term cognitive deficits. In a retrospective study on cognitive functioning in adult survivors of SCT, we observed that a significant proportion of patients experienced ongoing cognitive problems several years after SCT treatment.[11]

The curative intent of SCT underscores the importance of evaluating long-term cognitive performance in these patients. Better insight and understanding of the cognitive consequences of SCT can be obtained by using a longitudinal repeated measurement design with a pre-SCT assessment. A pre-treatment measurement is of pivotal importance because it allows for differentiating between observed deficits due to the SCT procedure, the ensuing treatment and complications on the one hand, and deficits induced by the disease itself, pre-SCT treatment or confounding factors as psychological distress on the other hand. Previous prospective reports showed cognitive deficits prior to SCT treatment in up 60% of patients.[4,5,12] Although, most of these studies used measures of psychological functioning, all failed to incorporate an appropriate reference group, which is necessary to draw conclusions about the underlying causes of the observed effects. However, there are inherent difficulties in selecting a reference group. Differences in pre-SCT treatment schedules, in particular in the intensity of chemotherapy, may cause varying degrees of cognitive deficits prior to SCT. In the present study, we therefore assessed cognitive performance, psychological functioning, fatigue and HRQOL in SCT patients prior to SCT and in a group of patients with haematological malignancies who were treated with systemic chemotherapy and/or involved-field radiotherapy. The objectives were to study pre-SCT cognitive functioning in a sufficiently large sample of SCT patients and its relation to potential confounding factors, and to investigate if a group of patients with haematological malignancies treated with non-myeloablative cancer therapies can be used as a clinically relevant reference group in future longitudinal studies.

PATIENTS AND METHODS

Patient accrual and study procedure

SCT study participants and patients of the reference group were recruited from the outpatient clinics of the Departments of Haematology and Radiotherapy of the Erasmus Medical Center (n=169) and the Department of Haematology of the Leiden University Medical Center (n=14). Inclusion criteria were: completion of (pre-SCT) treatment for a haematological malignancy, age 16 to 65 years, and fluent in Dutch. Patients were excluded in case of previous or current neurological or psychiatric disorders with known impact on cognitive and/or motor functions, and in case of previous or current substance abuse. Patient accrual started in June 1999 and lasted through December 2001. All patients were asked by their physician to take part in the study. An appointment for assessment of the patient was scheduled before starting SCT induction regimens. The institutional ethics committee for each participating center approved the research protocol and all patients provided written informed consent. Medical data were collected from the patients' records. Performance status was assessed using the Karnofsky performance status scale (KPS).17

Assessment of cognitive performance

A comprehensive test-battery was designed to assess four cognitive domains: *Memory and learning*: the Dutch version of the California verbal learning test,[18] the Rey complex figure test and recognition trial,[19] the Benton visual retention test;[20] *Attention and executive Functions*: Category wordfluency;[21] Digit span,[22] the abbreviated Stroop colour-word test,[23,24] Trails A and B,[25] the D2 test;[26] *Visuospatial and constructional ability*: the Rey complex figure test-copy trial,[19] Block design;[22] *Psychomotor functions*: Digit symbol,[22] Finger tapping;[27] the Reaction time test[28]. In addition, the Dutch version of the National Adult Rea-ding test[29] was used to estimate the premorbid intelligence level. All tests were selected with regard to available normative data and their sensitivity to measure specific cognitive deficits. The tests were administered in the same order to each patient and the assessment took approximately 2 h to complete.

Assessment of subjective cognitive functioning

The Dutch version of the Cognitive Failure Questionnaire (CFQ) was administered to measure the frequency of everyday cognitive failures in memory, attention, action and perception.[30] It has 25 items with a 5-point scale from 0 (never) to 4 (very often). Raw scores were transformed and a total CFQ-score was computed by summing the item scores. The total CFQ scores range from 0 to 100, with higher scores indicating more cognitive failures. Additionally, all patients (except for those who reported no cognitive failures) indicated if they experienced an increase in cognitive failures in the last year, if they were hindered, worried and annoyed about the cognitive failures.

Assessment of psychosocial functioning, fatigue and HRQOL

The Hospital Anxiety and Depression Scale (HADS), comprising 14 items, was used to screen for anxiety and depression.[31] A cut-off level of >10 points for both subscales was used to identify potential clinical cases.[32] The severity of psychological reactions to disease and treatment was evaluated with the Impact of Event Scale (IES).[33] The IES relates to specific events associated

with stress disorders and is based on a list of comments composed of commonly reported experience of intrusion (7 items) and avoidance (8 items). Patients have to indicate how frequently these comments applied to them during the past week on a 4-point scale with scores ranging from 0 (not at all) to 5 (often). Separate scores of intrusion of disease, intrusion of treatment, avoidance of disease and avoidance of treatment were computed, ranging from 0 to 35 for the intrusion scales and from 0 to 40 for the avoidance scales with higher scores indicating more complaints.

The Multi-dimensional Fatigue Inventory (MFI) was used to measure fatigue.[34] The MFI has five subscales assessing general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. The subscale scores range from 4 to 20 with higher scores representing more symptoms.

HRQOL was measured with the EORTC QLQ-C30.[35] This instrument incorporates functional and symptom scales, symptom items and two scales to assess health and global QOL. All scores were transformed ranging from 0 to 100.[36] The Leukaemia-BMT module (QLQ-LEU-BMT) was added to evaluate somatic symptoms associated with SCT.[37]

Data analyses

The neuropsychological test scores were compared to normative data adjusted for age and gender. Raw test scores were converted into standard (*z*-scores) scores. Patients were classified as cognitive impaired when scores were more than 1.5 standard deviation (SD) below the mean of the standard scores on at least 4 subtests.[27] A measure of overall cognitive performance was derived for each individual patient by summing the number of impaired test scores divided by the number of completed tests and multiplied by 100. Descriptive statistics were used to summarise the demographic and clinical characteristics, neuropsychological test scores and questionnaires responses. Because of a large number of categorical potential confounding variables, a multivariate confounder score (using gender, diagnosis, relapse, chemotherapy, and radiotherapy) was calculated for each patient to reduce a bias in test results.[38] Differences between groups in raw neuropsychological test scores and the scores of the questionnaires were tested by univariate analysis of covariance (ANCOVA) with the multivariate confounder score as a covariate. Between-group differences in other variables were evaluated using Students' *t*-tests for independent samples (two-sided) or chi-square tests. Pearson's' correlation coefficients were calculated to assess the relations between various variables, test scores and measure of overall cognitive performance. A 0.05 level of statistical significance was used in all statistical procedures. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) Windows 11.0 software.

RESULTS

Patients characteristics

Of the 151 patients scheduled for SCT, 135 (89%) met the inclusion criteria. In the reference group, 99 (83%) of the 119 consecutive patients were eligible for study. Main reasons for exclusion in both groups were: age over 65, language difficulties, and concomitant neurological disorders. Thirty-three (24%) SCT patients and 17 (17%) patients of the reference group refused to participate. The primary reported reason for refusal in the SCT group was the burden of an

Table 1 Demographic and clinical patients characteristics

	SCT group (n=101)		Reference group (n=82)		*P*-value
Gender, n (%)					0.02
Male	62	(61)	37	(45)	
Female	39	(39)	45	(55)	
Age in years, mean (SD)	42.0	(12.1)	39.2	(13.1)	0.14
Premorbid IQ level, mean (SD)[a]	104.6	(10.7)	102.9	(10.7)	0.28
KPS, mean (SD)[b]	83.7	(8.4)	85.2	(8.4)	0.20
Educational level, n (%)					0.90
Less than high school	5	(5)	4	(5)	
High school	0	(30)	24	(29)	
Vocational/trade school	37	(36)	31	(38)	
College/bachelor degree	19	(19)	18	(22)	
University degree	10	(10)	5	(6)	
Civil status, n (%)					0.70
Married / living with partner	77	(76)	59	(72)	
Single, divorced, widowed	24	(24)	23	(28)	
Premorbid employment status, n (%)					0.78
Full-time work	51	(50)	43	(52)	
Part-time work	25	(25)	21	(26)	
Housewife or student	18	(18)	12	(14)	
Disability benefits	1	(1)	3	(4)	
Pension	6	(6)	3	(4)	
Current employment status, n (%)					0.51
Full-time work	2	(2)	5	(6)	
Part-time work	6	(6)	8	(10)	
Housewife or student	18	(18)	14	(17)	
Disability benefits	16	(16)	7	(8)	
Pension	7	(7)	4	(5)	
Sick-leave	52	(51)	44	(54)	
Primary Diagnosis, n (%)					<.001
Acute myelogenous leukaemia	19	(19)	1	(1)	
Acute lymphocytic leukaemia	8	(8)	0		
Chronic myelogenous leukaemia	16	(16)	1	(1)	
Chronic lymphocytic leukaemia	1	(1)	1	(1)	
Non-Hodgkin lymphoma	30	(29)	28	(34)	
Hodgkin's disease	4	(4)	49	(60)	
Multiple myeloma	17	(17)	2	(3)	
Myelodysplastic syndrome	3	(3)	0		
Other[c]	3	(3)	0		

Table 1 Continued

Relapse, n (%)					<.001
No	58	(57)	74	(90)	
Yes, first relapse	30	(30)	6	(7)	
Yes, > 1 relapse	13	(13)	2	(3)	
Chemotherapy, n (%)					<.001
No previous chemotherapy	2	(2)	8	(10)	
1 course of chemotherapy	47	(47)	71	(86)	
>1 course of chemotherapy	52	(51)	3	(4)	
Intrathecal chemotherapy, n (%)					0.007
Yes	11	(11)	1	(1)	
No	90	(89)	81	(99)	
Radiotherapy (non-CNS), n (%)					<.001
Yes	19	(19)	60	(73)	
No	82	(81)	22	(27)	
Time since diagnosis (yr), mean (SD)	1.6	(2.9)	1.1	(2.1)	0.16
Time since treatment (m), mean (SD)	2.7	(4.0)	2.0	(2.1)	0.15

SCT = bone marrow or haematopoietic stem cell transplantation

[a] Derived from the Dutch National Adult Reading Test, [b] KPS = Karnofsky Performance Score, [c] Other = Aplastic anaemia, Amyloidosis, Waldenstrom's macroglobulinemia

additional assessment along with many other medical examinations before long-term hospitalisation for SCT. In the reference group the main reported reason for refusal was that patients wished not to be confronted with their disease after the end of treatment. One SCT patient was unable to complete the assessment and was excluded from the study. All remaining 101 SCT patients completed the pre-treatment assessment prior to the start of SCT induction phase. Mean time between the assessment and start of SCT treatment was 21 days (SD = 23.0). Thirty-five (34%) SCT patients were scheduled for autologous SCT, 42 (42%) for an allogeneic related donor transplant and 24 (24%) for an unrelated donor transplant. The patients' characteristics are described in Table 1. Gender was not equally distributed (P = 0.03) when comparing both groups.

Two SCT patients received no treatment prior to transplant. All other patients (98%) received chemotherapy according to standard treatment protocols and 19 (19%) had additional (non-cranial) radiotherapy. In the reference group, chemotherapy had been given to 74 (90%) patients. Radiotherapy (mantle field and mediastinal fields) subsequent to chemotherapy was administered to 52 (63%) patients. Eight (10%) patients of the reference group received radiotherapy as primary treatment. Intrathecal chemotherapy was given to 11 (11%) SCT patients as opposed to 1 (1%) patient of the reference group (P = 0.01). Forty-three percent of SCT patients had been treated for a relapse in contrast to 10% in the reference group (P = <.001). There was no between-group difference in time interval between last treatment and the neuropsychological assessment.

Table 2 Neuropsychological results: raw means ± SD by group (adjusted means[a]) and percentage of impaired patients

	SCT group (n=101)			Reference group (n=82)			*P*-value [b]
Memory and learning							
Verbal learning							
CVLT, total score list A	54.3 ± 9.9	(53.9)	8%	54.7± 9.9	(55.3)	11%	0.46
Verbal memory							
CVLT, short-delay free recall	11.4 ± 2.6	(11.6)	11%	11.9 ± 2.6	(11.7)	14%	0.91
CVLT, consolidation	2.0 ± 2.8	(12.1)	8%	12.2 ± 2.6	(12.1)	10%	0.10
CVLT, recognition	14.9 ± 1.4	(15.0)	8%	15.1 ± 1.1	(15.0)	4%	0.10
CVLT, false-positives	.9 ± 1.6	(0.9)	0%	9 ± 1.4	(0.9)	0%	0.91
Visual memory							
RCFT, short-delay recall	20.9 ± 6.2	(21.1)	15%	21.9 ± 5.9	(21.7)	13%	0.58
RCFT, long-delay recall	20.9 ± 6.3	(21.2)	18%	22.1 ± 5.7	(21.8)	15%	0.63
RCFT, recognition	20.2 ± 2.0	(20.2)	17%	20.5 ± 2.1	(20.5)	16%	0.42
BVRT, no. correct	7.4 ± 1.7	(7.4)	2%	7.6 ± 1.6	(7.6)	1%	0.52
BVRT, no. wrong	3.5 ± 2.7	(3.6)	11%	3.2 ± 2.4	(3.2)	5%	0.44
Attention and executive functions							
Category wordfluency	20.5 ± 4.5	(20.3)	1%	20.5 ± 4.1	(20.7)	0%	0.68
Digit span, total score	12.9 ± 3.6	(12.8)	1%	13.0 ± 3.3	(13.1)	1%	0.65
Stroop colour-word card, total time	90.8 ± 35.9	(89.0)	11%	89.7 ± 19.8	(91.9)	13%	0.61
Trails A, total time	33.8 ± 13.9	(35.0)	4%	30.9 ±11.7	(29.4)	2%	0.03
Trails B, total time	72.2 ± 28.3	(71.9)	1%	66.4 ± 27.4	(66.8)	2%	0.35
D2 test, total score GZ	409.6 ± 76.8	(405.6)	3%	417.8 ± 77.9	(422.7)	2%	0.25
D2 test, total score F%	4.2 ± 3.7	(4.4)	0%	4.3 ± 3.2	(4.1)	0%	0.57
D2 test, total score KL	155.1 ± 34.4	(152.2)	10%	161.7 ± 40.8	(165.2)	10%	0.07
Visuospatial and constructional ability							
RCFT, total score copy	34.0 ± 2.9	(34.0)	20%	34.4 ± 1.9	(34.3)	16%	0.59
Block design, total score	18.8 ± 6.2	(18.9)	0%	19.7 ± 5.6	(19.3)	0%	0.57
Psychomotor functions							
Digit symbol, total score	54.2 ± 11.3	(54.3)	1%	56.7 ± 10.8	(56.6)	0%	0.29
FT, total score dominant hand	353.6 ± 51.1	(352.0)	13%	352.9 ± 46.3	(354.8)	16%	0.76
FT, total score non-dominant hand	305.6 ± 51.7	(305.6)	21%	302.9 ± 49.7	(302.9)	18%	0.78
RTT, decision time single stimuli	322.8 ± 39.1	(323.9)	6%	320.3 ± 42.1	(319.0)	7%	0.54
RTT, motor time single stimuli	146.5 ± 41.2	(150.8)	16%	144.3 ± 39.9	(139.2)	10%	0.15
RTT, decision time complex stimuli	515.4 ± 82.0	(515.8)	17%	509.5 ± 94.5	(509.0)	22%	0.70
RTT, motor time complex stimuli	150.1 ± 50.8	(152.2)	20%	148.2 ± 44.7	(145.7)	12%	0.49
RTT, error score	1.7 ± 2.4	(1.9)	11%	1.4 ± 1.5	(1.2)	7%	0.08

Percentage of impaired patients in *italics*

n/a = not available, CVLT = California verbal learning test, RCFT = Rey complex figure test and recognition trial, BVRT = Benton visual retention test, GZ = total number of identified targets , F% = percentage of errors and omissions, KL = accuracy score , FT = Finger tapping, RTT = Reaction time test

SCT = bone marrow or haematopoietic stem cell transplantation

[a] raw mean test scores adjusted for confounding factors

[b] adjusted *P*-values

Table 3 Subjective cognitive complaints: mean scores ± SD[a] of the Cognitive Failure Questionnaire

	SCT group (n=101)			Reference group (n=82)		*P*-value
CFQ						
Total score	26.2 ± 12.6		(26.6)	28.0 ± 14.1 (27.6)		0.69[b]
CFQ score-distribution[c], n (%)						0.13
Very low score	14	(14)		9	(11)	
Low score	20	(20)		19	(23)	
Average score	57	(56)		36	(44)	
High score	7	(7)		15	(18)	
Very high score	3	(3)		3	(4)	
Increase in cognitive failures[d]						0.46
No increase	49	(51)		31	(40)	
Little increase	31	(32)		33	(42)	
Moderate increase	11	(12)		9	(12)	
Quite an increase	4	(4)		5	(6)	
Very strong increase	1	(1)		0		
Hindered by cognitive failures[d]						0.30
No hindrance	33	(34)		23	(30)	
Little hindrance	41	(43)		30	(38)	
Moderate hindrance	20	(21)		19	(24)	
Quite some hindrance	2	(2)		6	(8)	
Very much hindrance	0			0		
Worried by cognitive failures[d]						0.39
No worries	55	(57)		38	(49)	
Little worries	26	(27)		20	(26)	
Moderate worries	13	(14)		16	(20)	
Quite a lot worries	2	(2)		4	(5)	
Very much worries	0			0		
Annoyed about cognitive failures[d]						0.15
No annoyance	42	(44)		31	(40)	
Little annoyance	41	(43)		25	(32)	
Moderate annoyance	8	(8)		14	(18)	
Quite a lot annoyance	5	(5)		7	(9)	
Very much annoyance	0			1	(1)	

SCT = bone marrow or haematopoietic stem cell transplantation, CFQ = Cognitive Failure Questionnaire

[a] mean scores adjusted for confounding factors

[b] *P* = 0.69 (adjusted p-value of an ANCOVA)

[c] CFQ scores compared to normative data

[d] 96 SCT patients and 78 control patients completed these additional questions

Cognitive performance

Comparisons of the assessment prior to SCT showed minor group differences on neuropsychological tests (Table 2). The SCT group was slower on the Trails A than the reference group (P = 0.03). No differences between groups were found in percentages of impaired patients (compared to normative data). Most deficits were seen in visual memory, visuospatial and constructional ability, and psychomotor functions. The measure of overall cognitive performance was not significantly different between groups (respectively 9.2 in the SCT group and 8.3 in the reference group; P = 0.47) No differences were observed between groups in the percentages of impaired test scores per cognitive domain. Twelve percent of the SCT patients and 8.5 percent of the patients in the reference group had impaired scores on more than 20% (ie, > 5 of the 26 subtests) of the neuropsychological tests. No associations were found between cognitive performance and treatment parameters.

Subjective cognitive functioning

Results of the CFQ are shown in Table 3. Comparisons of the mean CFQ scores with published norms indicated that total scores fell within normal limits (ie, very low, low or average score) for the majority of SCT patients and the reference group (respectively 90% and 78%). There was no difference in the total score between groups. The percentages of patients reporting an increase in cognitive failures or who were hindered, worried or annoyed about their cognitive failures were small. The distributions of these scores were not different between groups.

Psychological functioning, fatigue and HRQOL

Table 4 shows the results of the questionnaires of psychological functioning and fatigue. No differences in mean scores of anxiety and depression of the HADS were found between groups. The number of anxiety cases (ie, scale score > 10) was higher in the SCT group, but no differences were found in the number of depression cases between groups. In both groups, no correlations were observed between the HADS and cognitive performance. No differences between groups were found in mean subscale scores of the IES and the MFI. The scores of the IES and the MFI were not associated with cognitive performance.

Analysis of the EORTC QLQ-C30 and the QLQ-LEU-BMT revealed that the SCT patients had lower scores (ie, lower level of functioning) on cognitive functioning, emotional functioning and social functioning compared to the patients of the reference group (Table 5). Higher scores (ie, more complaints) for the reference group were found on the symptom item dyspnoea. On the QLQ-LEU-BMT, the SCT patients reported higher scores on chills, fever, weight loss, mouth sores and functional status. The HRQOL scores were not related to cognitive performance.

Table 4 Psychological functioning: Means ± SD (adjusted means) of the Hospital Anxiety and Depression Scale, the Impact of Event Scale, and the Multi-dimensional Fatigue Inventory

	SCT group (n=101)		Reference group (n=82)		*P*-value [b]
HADS[a]					
Anxiety	5.5 ± 4.0	(5.5)	4.7 ± 3.5	(4.7)	0.30
Depression	3.7 ± 3.4	(3.6)	3.7 ± 3.5	(3.8)	0.77
Anxiety > 10, n (%)	14	(13.9)	3	(3.7)	0.02
Depression >10, n (%)	5	(5.0)	7	(8.5)	0.34
IES[a]					
Intrusion disease	11.0 ± 7.5	(10.9)	9.4 ± 6.7	(9.5)	0.90
Intrusion treatment	7.8 ± 6.9	(8.3)	8.5 ± 6.7	(7.9)	0.79
Avoidance disease	10.6 ± 8.9	(10.5)	7.4 ± 7.3	(7.5)	0.06
Avoidance treatment	8.3 ± 8.4	(8.8)	6.7 ± 7.3	(6.0)	0.06
MFI[a]					
General fatigue	11.0 ± 4.7	(11.1)	12.1 ± 4.4	(12.0)	0.34
Physical fatigue	11.2 ± 5.0	(11.3)	12.2 ± 5.1	(12.0)	0.48
Reduced activity	10.5 ± 5.0	(10.6)	11.1 ± 5.0	(11.0)	0.71
Reduced motivation	8.0 ± 3.9	(7.6)	8.4 ± 4.1	(8.8)	0.14
Mental fatigue	9.6 ± 4.6	(9.7)	9.8 ± 4.3	(9.7)	0.94

SCT = bone marrow or haematopoietic stem cell transplantation, HADS = Hospital anxiety and depression scale, IES = Impact of event scale, MFI = Multi-dimensional fatigue inventory

[a] mean scores adjusted for confounding factors

[b] adjusted P-values

Table 5 EORTC QOL questionnaire and Leukemia-BMT module: means ± SD (adjusted means[a])

	SCT group (n=101)		Reference group (n=82)		*P*-value [b]
QLQ-C30 functioning scales[c]					
Physical functioning	74.3 ± 23.2	(74.4)	77.1 ± 19.7	(77.1)	0.53
Role functioning	62.4 ± 31.1	(61.6)	69.5 ± 26.2	(70.4)	0.12
Cognitive functioning	76.5 ± 10.0	(75.0)	83.5 ± 17.6	(83.6)	0.02
Emotional functioning	70.2 ± 28.3	(68.9)	79.4 ± 18.8	(81.4)	0.009
Social functioning	69.2 ± 29.8	(68.0)	76.8 ± 23.4	(78.3)	0.05
Global health	66.7 ± 23.0	(65.5)	66.5 ± 18.8	(67.8)	0.58
Global quality of life	71.0 ± 21.5	(70.6)	72.4 ± 21.2	(72.9)	0.58
QLQ-C30 symptom scales and items[d]					
Fatigue	31.9 ± 25.5	(34.4)	38.3 ± 25.4	(35.4)	0.82
Nausea/vomiting	5.1 ± 13.1	(5.0)	7.3 ± 16.2	(7.5)	0.39
Pain	16.8 ± 25.2	(18.7)	13.8 ± 20.3	(11.5)	0.10
Dyspnoea	15.3 ± 20.8	(13.0)	21.9 ± 25.8	(24.8)	0.009
Sleep disturbances	20.7 ± 28.3	(23.3)	19.9 ± 28.1	(16.8)	0.23
Appetite loss	7.0 ± 17.3	(7.5)	9.3 ± 19.1	(8.8)	0.71
Constipation	4.7 ± 14.3	(4.5)	3.3 ± 10.0	(3.5)	0.69
Diarrhoea	10.4 ± 18.8	(8.3)	5.7 ± 15.5	(8.3)	1.0
Financial impact	14.5 ± 25.7	(14.4)	9.8 ± 20.6	(9.8)	0.31
QLQ-LEU-BMT symptom scales and items[d]					
Chills	17.5 ± 24.0	(18.1)	9.9 ± 17.0	(9.1)	0.03
Itchy skin	22.3 ± 30.7	(20.5)	20.6 ± 30.7	(23.0)	0.65
Dry skin	29.7 ± 28.4	(29.0)	28.4 ± 25.9	(29.5)	0.93
Stiff joints	24.9 ± 27.0	(21.9)	20.2 ± 24.0	(22.6)	0.89
Feeling cold	24.0 ± 26.8	(25.3)	21.4 ± 28.5	(20.2)	0.34
Flushes	10.4 ± 20.0	(9.6)	10.7 ± 21.6	(11.8)	0.59
Headache	12.8 ± 19.5	(13.5)	13.2 ± 19.5	(12.3)	0.76
Hearing loss	6.1 ± 18.7	(6.3)	3.3 ± 10.0	(3.0)	0.26
Pain during sex	7.1 ± 17.4	(7.8)	6.2 ± 16.8	(5.3)	0.44
Fever	15.2 ± 25.8	(16.1)	4.9 ± 13.0	(3.8)	0.003
Infection	15.5 ± 24.9	(16.2)	9.5 ± 18.4	(8.6)	0.08
Weight loss	10.4 ± 19.4	(12.4)	6.6 ± 17.0	(4.2)	0.02
Abdominal pain	11.5 ± 21.9	(12.1)	12.8 ± 20.1	(12.0)	0.98
Mouth sores	11.8 ± 23.5	(12.4)	3.3 ± 12.5	(2.5)	0.009
Pain during urination	1.0 ± 5.7	(1.7)	2.1 ± 8.1	(1.2)	0.73
Blood in urine	1.3 ± 8.1	(1.5)	0.4 ± 3.7	(.3)	0.36
Sensory loss	18.0 ± 22.5	(17.9)	13.2 ± 19.7	(13.3)	0.26
Functional status	4.4 ± 12.0	(4.7)	0.6 ± 3.2	(.2)	0.01

SCT = bone marrow or haematopoietic stem cell transplantation, QLQ-C30 = EORTC QOL que-stionnaire, QLQ-LEU-BMT = Leukemia-BMT module
[a] mean scores adjusted for confounding factors
[b] adjusted P-values
[c] scores on functioning scales range from 0 to 100 with a higher score indicating better functioning
[d] scores on the symptoms scales and items range from 0 to 100 with higher scores meaning more bothered by complaints

DISCUSSION

This comparative study constitutes the largest published sample of SCT patients evaluated with a comprehensive battery of neuropsychological tests prior to SCT treatment and is the first to compare the results to a reference group of haematological patients. It revealed that up to around 20% of SCT patients showed deficits in visual memory, visuospatial and constructional ability, and psychomotor functions before undergoing SCT treatment. No significant correlations were found between patients' subjective estimations of cognitive performance in daily-life functioning and the results of objective neuropsychological testing.

Our findings are in line with 3 other reports despite differences in design and methods.[4,5,12] Andrykowski and colleagues found cognitive impairment in 56% of 55 SCT candidates.[4] Meyers and colleagues observed cognitive dysfunction in 20% of 61 SCT candidates by using a self-reporting instrument to identify cognitive problems.[5] Recently, Sostak and colleagues found abnormal results in a neuropsychological examination in 58% of 71 allogeneic SCT patients.[12]

To date, research has centred on cognitive functions in SCT patients only. By using a reference group, we were able to examine differences in cognitive functioning prior to SCT between SCT candidates and haematological patients treated with chemotherapy, radiotherapy, or a combination of these. Our results showed no between-group differences in degree or patterns of cognitive impairment. Patients in the reference group scored slightly higher in only one out of 26 neuropsychological subtests. Using a different threshold for statistical significance (P = 0.01) to correct for multiple testing would not have altered our findings. In both groups correlations between cognitive performance and specific treatment parameters were lacking. Therefore, the observed cognitive dysfunctions in our patients can possibly be attributed to the undergone treatment (ie, chemotherapy, radiotherapy, and adjuvant drugs), the underlying disease or a combination of these factors.

Between 90% and 98% of all patients in our study were treated with at least one course of systemic chemotherapy at an average time interval of 2 - 3 months before the neuropsychological assessment. Most cytotoxic agents, although some more than others, are known to affect both the CNS and the peripheral nerves.[39] A variety of treatment induced neurological complications have been described, including peripheral neuropathies, leukoencephalopathies, and cerebellar symptoms.[40] In some instances, these complications are persistent and involve structural changes in the brain, in particular white matter lesions (mainly in the subcortical areas), brain atrophy and ventricular dilation.

Support for the hypothesis that systemic chemotherapy has a negative impact on cognitive functioning comes from research comparing systemic chemotherapy with local therapy (ie, surgery and local radiotherapy) in breast cancer and lymphoma patients.[41] Patients in chemotherapy groups showed more cognitive impairment compared with those treated with local therapy only. In contrast, we observed no significant differences between patients treated with systemic chemotherapy or local radiotherapy only. Furthermore, there was an absence of significant differences between patients treated with one course of chemotherapy or those who received multiple courses. The similarities of the cognitive dysfunctions found in our patient groups suggest that differences in treatment intensity between groups play no prevailing role in the development of cognitive impairment. Thus, it is unlikely that chemotherapy-related neurotoxicity is the only cause of the observed cognitive deficits in our patient population.

Besides chemotherapy, other factors could be involved in the aetiology of cancer-related

cognitive impairment. Systemic chemotherapy is often given in combination with adjuvant drugs (eg, corticosteroids) or other treatment modalities. High doses of exogenous corticosteroids might well affect CNS structure and functioning. Reduced hippocampal volume and memory deficits in patients receiving chronic corticosteroid therapy have been reported previously.[42] Similarly, synergistic effects of combined treatment have been noted to play a role in impaired cognitive functioning of primary CNS lymphoma patients.[43] Lastly, cytokines released from the tumour issue or exogenous cytokines used in immunotherapy (eg, interferon alpha), could affect CNS functioning and have a sizeable effect on cognitive performance.[44] Further research on the identification of specific cytotoxic agents, combined effects of drugs and other additional factors responsible for CNS damage is required and should increase the understanding of the specific mechanisms involved in the development of cognitive deficits after cancer treatment.

This assessment of psychological functioning, HRQOL and fatigue prior to SCT confirms earlier findings that anxiety, depression, sleep disturbances, or fatigue are common complaints in patients before undergoing SCT.[4-6] The number of anxiety cases in our sample of SCT patients was indeed substantial higher than in the reference group and we also observed distinct differences between the two groups on a number of HRQOL functioning scales and symptom items. The between-group differences in the symptom items suggest a relationship with adverse effects of previous treatment, either radiotherapy with mantle and mediastinal fields or pre-SCT chemotherapy schedules. Of particular importance is the finding that none of the between-group differences in psychological functioning or HRQOL affected cognitive performance. A contributing effect of psychological distress, related to either the disease itself or its treatment, on cognitive performance in our patient groups, is probably not significant.

The present findings indicated that physicians or health care practitioners preparing patients for the transplantation and its complications should be aware of a wide range of cognitive and emotional problems associated with treatment prior to SCT. More importantly, they should be sensitive to further functional declines in these particular areas. For the moment, greater effort should be directed to translate the outcome of the assessments into the development of educational interventions, and perhaps cognitive rehabilitation programs. Preventive rehabilitation programs, in particular, could minimise further functional loss, facilitate recovery after SCT treatment, and thereby retard the patient's well being and enhance HRQOL.

In conclusion, this study has provided additional information about pre-transplant cognitive performance in SCT patients and its relation to confounding factors, in part by being the first to specifically evaluate this in comparison to a reference group. The results confirm that cognitive performance is impaired prior to SCT treatment. Also, they showed that cognitive impairment was not associated with confounding psychological factors, nor that it was different to patients treated with conventional cancer therapies. More research is needed to identify whether these observed effects are reversible or persist over time, and to investigate if SCT patients develop further deterioration after additional SCT treatment. A longitudinal study in SCT patients is now being undertaken to explore these critical issues. Our data emphasise that prospective longitudinal designs using a similar reference group of patients with haematological malignancies are required for future trials on the cognitive impact of SCT.

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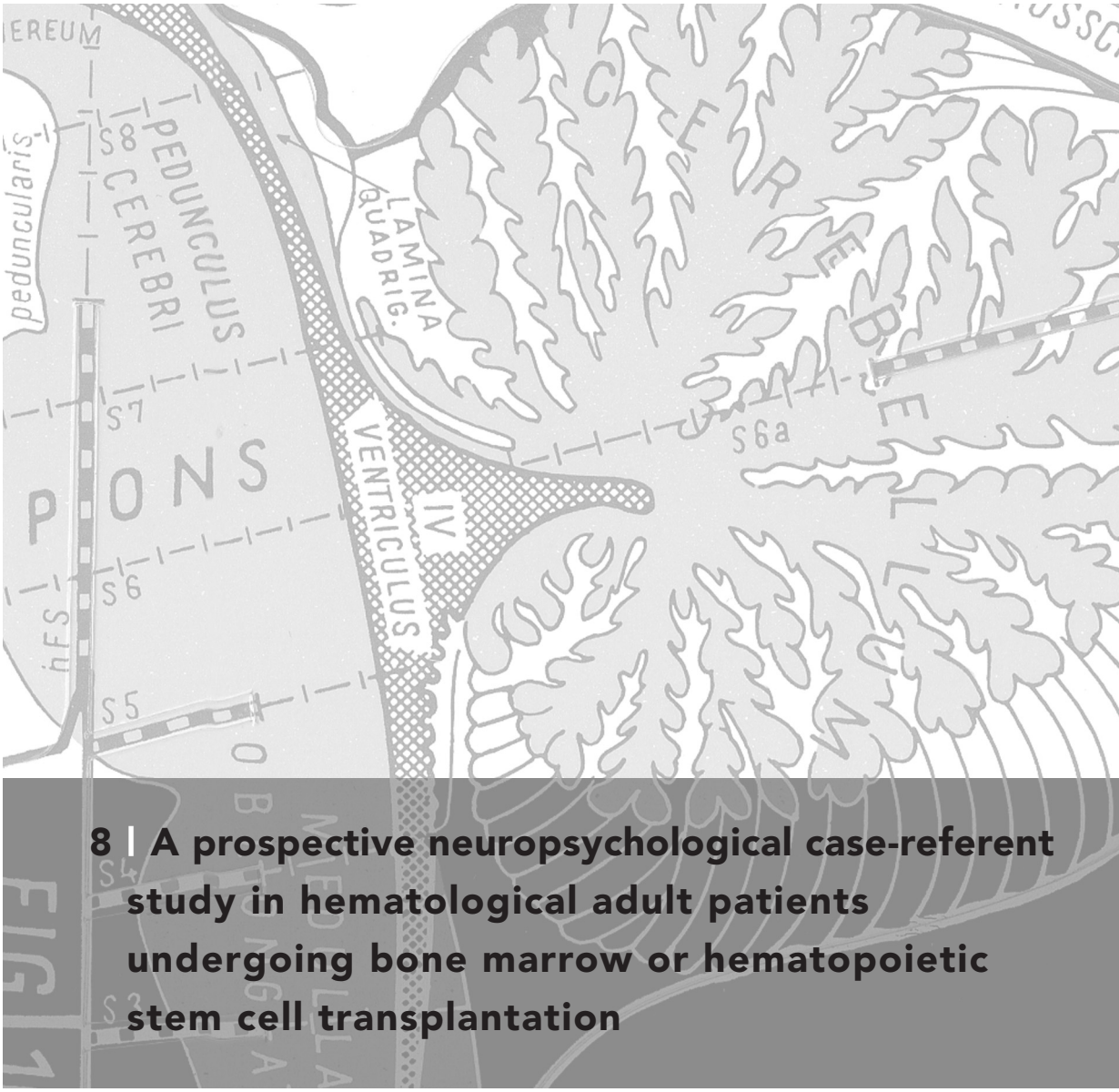


8 | A prospective neuropsychological case-referent study in hematological adult patients undergoing bone marrow or hematopoietic stem cell transplantation

H. Harder, AR. Van Gool, HJ. Duivenvoorden, JJ. Cornelissen, WMH. Eijkenboom, RMY. Barge, MJ. van den Bent.

(Submitted)

ABSTRACT

Previous research demonstrates poor cognitive performance prior to and following bone marrow or hematopoietic stem cell transplantation (HSCT). This prospective study examined latent cognitive changes in 101 adult patients undergoing HSCT in comparison to 82 hematological reference patients treated with systemic chemotherapy and/or radiotherapy. Serial extensive neuropsychological testing was performed at baseline before HSCT and after 8 and 20 months. Additional measures included questionnaires of subjective cognitive function, health-related quality of life, fatigue and psychological function. Baseline assessment showed no between-group differences and indicated mild impairment in visual memory, visuospatial function, and psychomotor function in both patient groups. Follow-up showed no significant changes over time for the entire sample. Performance in attention and executive function (P = .01) and psychomotor function (P = .03) over time was reduced in HSCT patients, which was in part related to total body irradiation. Female gender and older age negatively affected outcome, while education had a positive effect. Results indicate that mild cognitive impairment is apparent in a subset of patients before transplant. HSCT has only a limited adverse effect on tasks measuring attention and executive function, and psychomotor function when compared to a disease-specific reference group.

INTRODUCTION

Bone marrow or hematopoietic stem cell transplantation (HSCT) is an accepted therapeutic option for various malignant hematological disorders. Improved patient selection and development of new treatment regimens and transplant techniques have expanded its use. HSCT is preceded by high-dose cytotoxic treatment with or without total body irradiation (TBI) to eradicate the malignant disease and suppress the immune system to allow engraftment of donor or autologous stem cells or bone marrow.[1] Complications related to HSCT treatment are generally due to toxicity associated with the myeloablative chemoradiotherapy, the period of profound immunodeficiency, and graft-versus-host disease (GVHD).[2-4] As many of these complications are now better controlled, delayed central nervous system (CNS) toxicity might become a relevant long-term side-effect in HSCT. Indeed, several studies using cross sectional retrospective designs have given evidence of poor cognitive performance following HSCT.[5-9]
Recently, two prospective longitudinal studies reported on cognitive functions up to 14 months after allogeneic HSCT.[10,11] Sostak et al found impaired function in half of patients evaluated with a brief neuropsychological assessment at baseline and at 14 months after HSCT.[10] A decline of cognitive function after HSCT treatment was most apparent in executive function. Risk factors for cognitive decline included acute GVHD, prolonged immunosuppression and metabolic disturbances. Syrjala et al found a generalized cognitive decline at 80 days, with recovery to pre-transplant levels at one year after HSCT in most cognitive domains, except for motor dexterity and grip strength.[11] Chemotherapy prior to HSCT and drug treatment for GVHD at one year were associated with impairment.
Longitudinal research on cognitive changes is difficult due to a high attrition rate, and because administration of the neuropsychological assessment is time-intensive and requires specialized training. Most longitudinal studies have focused on the impact of HSCT before and during hospitalization and, consequently, have a limited duration of follow up.[12-15] Perhaps even more importantly, there are at present no longitudinal data documenting cognitive changes following HSCT in comparison to a disease-specific reference group. Concurrent neuropsychological evaluation in reference patients is important for discerning cognitive changes related to disease and/or previous treatment from effects related to HSCT and its complications.
To establish if HSCT is associated with cognitive decline over time, we conducted a prospective longitudinal study to examine patterns of neuropsychological changes over 20 months in adult hematological patients undergoing HSCT in comparison with a reference group with hematological disorders. The primary objective was to assess the effect of HSCT on neuropsychological function in comparison to standard treatment regimens. The relationship between neuropsychological function and subjective cognitive complaints, health-related quality of life (HRQL), fatigue, psychological functioning, treatment-related variables, and work attendance were measured as secondary end points.

PATIENTS, MATERIALS, AND METHODS

Patients and procedure

Serial neuropsychological assessments were carried out in a consecutive group of hematological patients before undergoing HSCT (time 1 [T1]), and at intervals of 8 months (time

2 [T2]) and 20 months (time 3 [T3]) after baseline. Reference patients (REF) were assessed at similar time points. Patients were accrued from the Erasmus Medical Center (Rotterdam, the Netherlands) and Leiden University Medical Center (Leiden, the Netherlands). Eligible patients (HSCT, REF) were between 16 and 65 years of age, diagnosed with a hematological disorder and had completed (pretransplant) treatment, fluent in Dutch, and without overt psychopathology, neurological disorders or substance abuse. The study protocol was reviewed and approved by the institutional ethics and research committees. Written informed consent was obtained before study participation.

Study measures

Demographical and clinical information. Information was extracted from chart review and the transplant-database and reviewed at baseline and prior to follow up.

Neuropsychological function. A comprehensive battery of neuropsychological tests was designed to assess a wide range of functions. Tests were selected on availability of normative data and sensitivity to detect cognitive impairment. The following cognitive domains were assessed: *Verbal memory*: California verbal learning test[16] (CVLT); *Visual memory*: Rey complex figure test and recognition trial[17] (RCFT), Benton visual retention test[18] (BVRT); *Attention and executive function*: Category wordfluency[19] (CF), WAIS Digit span[20] (WD), Trailmaking A and B[21] (TMTA, TMTB), abbreviated Stroop color-word test[22] (SCWT), D2-test[23] (D2); *Visuospatial function*: RCFT-copy trial,[17] WAIS Block design[20] (WBD); *Psychomotor function*: WAIS Digit symbol[20] (WDS), Finger tapping[24] (FT), Reaction time test[25] (RTT). Premorbid intelligence was estimated with the National Adult Reading test[26]. Alternate forms were used when possible to minimize practice effects.

Subjective Cognitive Functioning. The Cognitive Failure Questionnaire (CFQ)[27] was used to assess the frequency of everyday cognitive failures.

HRQL. Measures included the EORTC QLQ-C30[28] and the MRC/EORTC QLO Leukemia-BMT module (QLQ-LEU).[28]

Fatigue. The Multi-dimensional Fatigue Inventory (MFI)[29] was used to address general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation.

Psychological Functioning. Measures included the Hospital Anxiety and Depression Scale (HADS)[30] and the Impact of Event Scale (IES).[31] A dichotomized index was used for the HADS to define potential cases of anxiety and depression based on a cutoff score of > 10.[32]

Statistical analysis

Raw neuropsychological test scores were compared to normative data adjusted for age and gender and converted into standardized scores (*z* scores; mean = 0, standard deviation [SD] = 1.0) to facilitate comparisons among measures. Cognitive impairment was defined as a test score of 2.0 SD below the mean of healthy controls. Composite test scores were calculated for each cognitive domain by adding *z* scores for each subtest and dividing the sum by the number of subtests. A measure of overall neuropsychological function was computed based on the number of impaired subtests.

Descriptive statistics were generated for demographic and clinical characteristics and study measures. Because of a large number of categorical potential confounding demographic and clinical variables, a multivariate confounder score (using gender, diagnosis, relapse, pretransplant treatment) was calculated to reduce the potential bias in test results.[33] Between

group differences for continuous variables were evaluated using Students' *t*-tests for independent samples (two-sided). Similarly, X^2-analysis was used to compare distributions of categorical variables. Group differences in neuropsychological function were tested by univariate analysis of covariance (ANCOVA) with the multivariate confounder score as a covariate. To determine changes in neuropsychological function over time, random regression models (RRM) analyses were conducted for all cognitive domains.[34,35] The RRM approach allows for missing observations, time-varying covariables, invariant covariables and assessments at unequal end-points. RRM estimates both average time trends and individual time trends. The individual time trend curves are based on available data for each patient, augmented by information from data from the entire sample. The approach allows for modeling changes of variances in neuropsychological function and changes in correlations between neuropsychological function and covariables. Pearson's correlation techniques were used in survivors to evaluate associations between measures and treatment-related variables. The two-sided probability level for statistical significance was set at 0.05 for primary end points and at 0.01 for secondary end points. Analyses were performed using the Statistical Package for Social Sciences (version 10.1) and RRM models were implemented using PROC MIXED (SAS System, version 8.2).

RESULTS

Patients and treatment

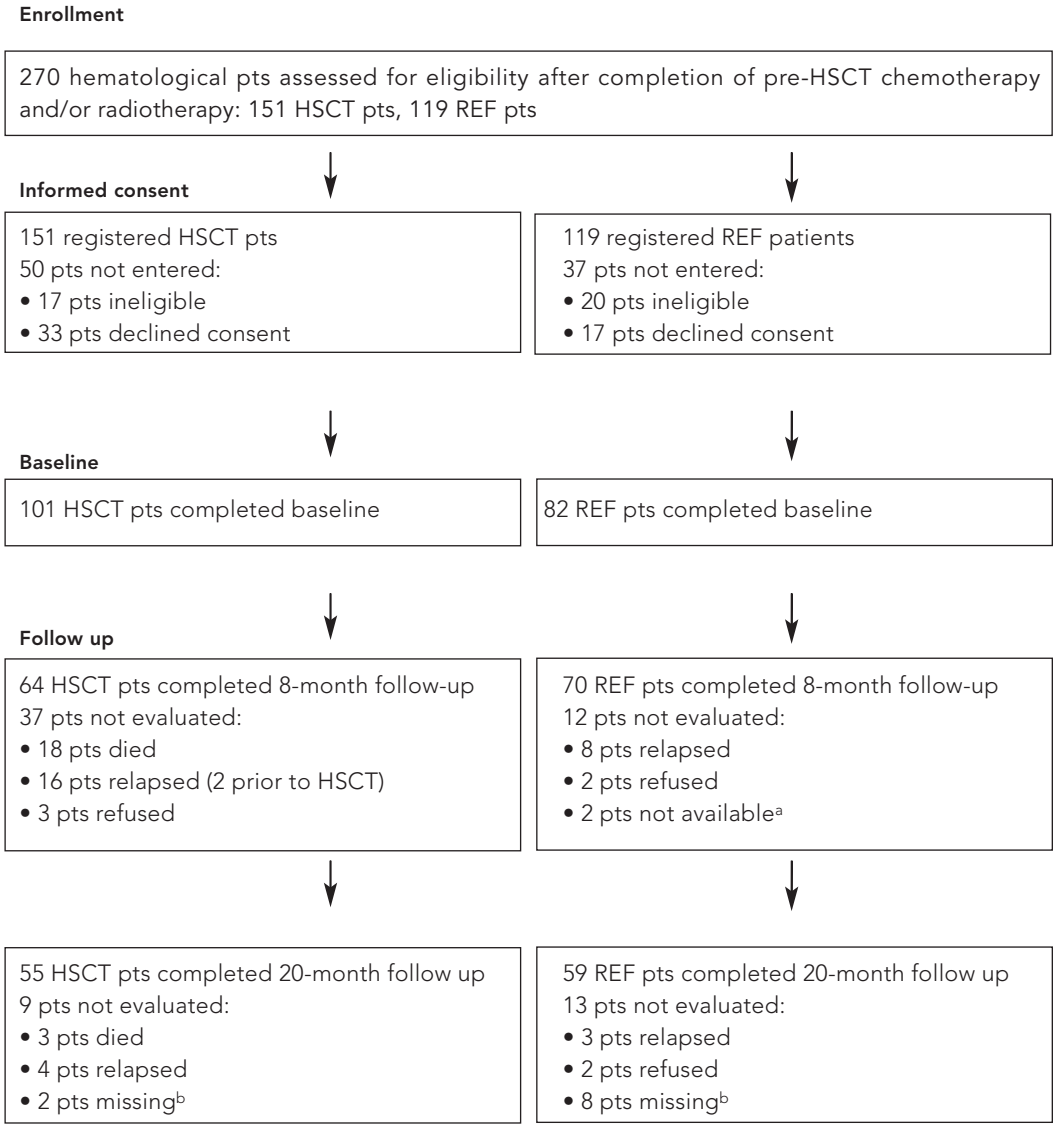
Figure 1 summarizes the flow of patients through the study. Fifty-four percent of HSCT patients completed the neuropsychological assessment at each time point opposed to 72% of REF patients. Table 1 lists the demographic and clinical characteristics. Various HSCT conditioning regimens were used. The most common regimen was high-dose cyclophosphamide followed by TBI (74%). GVHD prophylaxis consisted of cyclosporine-A and T-cell depletion of the donor graft. GVHD ratios were considered for allogeneic HSCT recipients who underwent follow up assessment. Four patients (11%) developed acute GVHD (grade III-IV). Chronic GVHD was observed in 41% (15 of 37) and 27% (9 of 34) of patients at T2 and T3 respectively, of which 24% (9 of 37) and 12% (4 of 34) had extensive disease. Most patients with chronic GVHD (90%) received immunosuppressive medication at follow up. Seventeen HSCT patients died of transplant-related complications and six HSCT patients died of recurrent disease.

Neuropsychological function at baseline

The results of the baseline assessment were reported in detail previously.[36] In short, mean z scores of all neuropsychological tests were classified as non-impaired for both groups (Table 2). Between group differences in mean z scores were not observed. Evidence of impairment on ≤ 3 tests was found in 53 (53%) HSCT and 40 (49%) REF patients, while 14 (14%) HSCT and 7 (9%) REF patients were impaired on ≥ 4 tests ($P = .33$). In both groups, impairment was most frequently seen in visual memory, visuospatial function and psychomotor function. No difference was found in overall neuropsychological function between groups ($P = .26$).

Changes in neuropsychological function over time

Mean *z* scores in the HSCT group were significantly lower at follow up for several measures of attention and executive function, and psychomotor function (Table 2). Mean *z* scores of verbal



[a] Two patients were not available for T2 because of work commitments;
[b] ten patients could not be evaluated at T3 because of end of the study.

Figure 1 Flow of patients through the study

Table 1 Demographic and clinical characteristics for the HSCT patients and the reference patients

Characteristic	HSCT (n=101)		REF (n=82)		*P*-value
Gender, no. (%)					.02
Male	62	(61)	37	(45)	
Female	39	(39)	45	(55)	
Age					.14
Mean, y (SD)	42.0	(12.1)	39.2	(13.1)	
Performance status[a]					.20
Mean (SD)	83.7	(8.4)	85.2	(8.4)	
Estimated IQ					.28
Mean (SD)	104.6	(10.7)	102.9	(10.7)	
Diagnosis, no. (%)					<.001
Lymphoma	30	(29)	28	(35)	
Hodgkin's disease	4	(4)	49	(60)	
Acute Leukemia	27	(27)	1	(1)	
Chronic Leukemia	17	(17)	2	(2)	
Multiple myeloma	17	(17)	2	(2)	
Myelodysplasia	3	(3)	0	(0)	
Other[b]	3	(3)	0	(0)	
Relapse, no. (%)	43	(43)	8	(10)	<.001
Pretransplant treatment, no. (%)					
Chemotherapy only	84	(84)	22	(27)	<.001
Chemotherapy and radiation therapy	15	(14)	52	(63)	<.001
Radiation therapy only	0	(0)	8	(10)	.001
No previous treatment	2	(2)	0	(0)	.20
Intrathecal chemotherapy, no. (%)	11	(11)	1	(1)	.007
HSCT conditioning regimen[c]**, no. (%)**			NA		
Cyclophosphamide and TBI[d]	73	(74)			
Cyclophosphamide and Busulphan	6	(6)			
BEAC[e]	10	(10)			
BEAM[f]	7	(7)			
Other[g]	3	(3)			
Type of transplant, no. (%)			NA		
Autologous	34	(34)			
Allogeneic related	41	(42)			
Allogeneic unrelated	24	(24)			

SD = standard deviation; IQ = intelligence quotient; NA = not applicable; TBI = total body irradiation

[a] Karnofsky Performance Score

[b] Aplastic anemia, Amyloidosis, Waldenstrom's macroglobulinemia

[c] 2 HSCT patients died before transplant (n=99)

[d] TBI dose: 5 Gy or 6 Gy daily for 2 days, or 9 Gy for 1 day

[e] BEAC, Busulphan (300 mg/m2 for 1 day, Etoposide 100 mg/m2 twice per day for 4 days, Ara-C 100 mg/m2 twice per day for 4 days, f Cyclophosphamide 15 mg/kg per day for 4 days)

[f] BEAM, Busulphan (300 mg/m2 for 1 day, Etoposide 125 mg/m2 twice per day for 4 days, Ara-C 100 mg/m2 twice per day for 4 days Melfalan 140 mg/ m2 for 1 day)

[g] CBV , Busulphan (300 mg/m2 for 1 day), Cyclophosfamide (1500 mg/m2 per day for 4 days) and Etoposide (250 mg/m2 per day for 3 days); Fludarabine (30 mg/m2 per day for 6 days), Methotrexate (10 mg/m2 per day for 3 days); induction with 3 cycles of VAD (Vincristine 0.4 mg; Doxorubicine 9 mg/m2, Dexamethasone 40 mg) followed by high-dose Melphalan (100 mg/m2 per day for 2 days)

Table 2 Neuropsychological test scores (*z*-scores) and percentages of impaired test scores over time

Measures	Baseline				8-month follow up				20-month follow up			
	HSCT (n=101)		REF (n=82)		HSCT (n=64)		REF (n=70)		HSCT (n=55)		REF (n=59)	
	M (SD)	%	M (SD)	%	M (SD)	%	M (SD)	%	M (SD)	%	M (SD)	%
Verbal memory												
CVLTT	0.12 (1.0)	5	-0.06 (1.0)	6	-0.00 (0.0)	5	0.04 (1.0)	3	0.45 (1.0)	4	0.42 (0.9)	2
CVLTSD	0.04 (1.2)	5	-0.14 (1.1)	5	-0.06 (1.0)	6	0.10 (1.0)	3	0.19 (1.0)	0	-0.14 (1.2)	5
CVLTLD	-0.12 (1.0	4	-0.19 (0.9)	7	0.02 (0.9)	0	0.16 (1.0)	3	0.04 (1.0)	0	-0.19 (0.9)	7
CVLTC	0.01 (1.1)	4	-0.11 (1.1)	6	-0.15 (1.1)	3	-0.10 (1.0)	3	0.18 (1.0)	4	0.12 (1.1)	5
CVLTR	-0.02 (1.0)	6	0.12 (0.8)	2	0.50 (0.9)*	0	0.13 (0.9)*	0	0.15 (0.8)	2	-0.04 (1.0)	9
Nonverbal memory												
RCFTSD	0.00 (1.3)	10	0.09 (1.2)	6	0.84 (1.2)	2	0.57 (1.4)	4	0.86 (1.2)	4	1.03 (1.3)	3
RCFTLD	-0.03 (1.3)	15	0.09 (1.2)	6	0.72 (1.2)	3	0.49 (1.5)	6	0.82 (1.2)	4	0.95 (1.3)	3
RCFTR	-0.35 (1.1)	10	-0.19 (1.1)	10	-0.09 (1.2)	6	0.15 (1.0)	3	0.10 (1.3)	6	0.36 (1.0)	5
BVRTC	-0.06 (0.7)	2	0.01 (0.7)	1	0.00 (0.7)	0	0.02 (0.7)	3	0.00 (0.8)	4	0.12 (0.6)	0
BVRTE	0.00 (1.0)	8	0.10 (0.8)	2	0.03 (0.8)	2	0.05 (0.9)	6	0.02 (1.0)	10	0.20 (0.8)	2
Attention/executive function												
CF	0.61 (0.8)	0	0.65 (0.7)	0	0.70 (0.8)	0	0.76 (0.8)	0	0.78 (0.8)	0	0.68 (0.7)	0
WD	0.74 (1.0)	1	0.75 (0.9)	1	0.75 (1.0)	1	0.83 (1.0)	1	0.91 (1.1)	0	0.96 (1.1)	0
TMTA	0.47 (1.3)	4	0.81 (1.4)	2	0.48 (0.9)**	0	1.07 (1.3)**	1	0.87 (1.4)*	2	1.51 (1.3)*	0
TMTB	0.64 (1.2)	1	0.84 (1.3)	2	0.64 (1.3)*	3	1.13 (1.3)*	1	0.57 (1.5)**	6	1.35 (1.4)**	2
SCWT	0.14 (1.1)	0	-0.01 (1.0)	1	0.10 (1.2)*	3	0.59 (1.5)*	4	0.51 (1.6)	9	0.82 (1.2)	0
D2GZ	0.35 (1.0)	0	0.56 (1.0)	2	0.48 (1.0)*	0	0.91 (1.1)*	0	0.71 (1.1)	2	1.05 (1.2)	0
D2F	1.12 (1.4)	0	0.91 (1.3)	0	1.12 (1.3)	0	1.13 (1.6)	6	1.33 (1.4)	2	1.56 (1.3)	0
D2KL	0.42 (1.7)	10	0.60 (1.8)	10	0.79 (1.6)	5	1.23 (1.7)	4	1.21 (1.6)	4	1.47 (1.8)	5
Visuospatial function												
RCFTC	0.56 (2.0)	9	0.83 (1.8)	4	0.45 (1.7)	5	0.36 (1.9)	9	0.10 (1.6)	7	0.04 (1.5)	7
WBD	1.20 (1.0)	0	1.20 (0.8)	0	1.55 (1.0)	0	1.49 (0.9)	0	1.54 (1.0)	0	1.62 (0.9)	0
Psychomotor function												
WDS	1.02 (0.9)	0	1.10 (0.8)	0	1.04 (1.0)*	0	1.37 (0.8) *	0	0.91 (1.1)	0	1.43 (0.9)	0
FTD	-0.22 (1.3)	9	-0.14 (1.2)	6	-0.47 (1.3)	14	-0.31 (1.2)	9	-0.56 (1.4)	13	-0.22 (1.2)	7
FTND	-0.47 (1.4)	15	-0.45 (1.3)	13	-0.83 (1.4)	21	-0.56 (1.2)	17	-1.06 (1.4)*	18	-0.47 (1.2)*	7
RTTSDT	-0.17 (0.9)	3	-0.24 (1.0)	5	-0.37 (0.9)	10	-0.34 (1.0)	7	-0.84 (2.4)	17	-0.56 (1.1)	10
RTTSMT	-0.39 (1.3)	11	-0.31 (1.1)	7	-0.39 (1.4)	7	-0.23 (1.0)	6	-0.70 (3.8)	11	-0.13 (1.0)	3
RTTCDT	-0.36 (1.3)	10	-0.38 (1.5)	12	-0.60 (1.3)	8	-0.44 (1.1)	10	-0.64 (1.3)	19	-0.53 (1.3)	14
RTTCMT	-0.64 (1.5)	13	-0.41 (1.1)	7	-0.67 (1.5)	14	-0.38 (1.0)	6	-0.70 (2.2)	15	-0.29 (1.0)	7
RTTE	-0.31 (2.0)	11	-0.03 (1.3)	7	-0.00 (1.2)	6	0.14 (1.0)	4	-0.29 (1.2)**	11	0.22 (0.8)**	2

*P < .05; ** P < .01 for between groups differences

CVLTT, California Verbal Learning Test, total score; CVLTSD, California Verbal Learning Test, short delay recall; CVLTLD, California Verbal Learning Test, long delay recall; CVLTC, California Verbal Learning Test, consolidation; CVLTR, California Verbal Learning Test, recognition; RCFTSD, Rey Complex Figure Test and Recognition Trial, short delay recall; RCFTLD, Rey Complex Figure Test and Recognition Trial, long delay recall; RCFTR, Rey Complex Figure Test and Recognition Trial, recognition; BVRTC, Benton Visual Retention Test, correct score; BVRTE, Benton Visual Retention Test, error score; CF, Category Fluency; WD, WAIS Digit span; TMTA , Trailmaking A; TMTB, Trailmaking B; SCWT, abbreviated Stroop Color Word Test, color-word card; D2GZ, D2 Test, total score; D2F, D2 Test, error score; D2KL, D2 Test, concentration score; RCFTC, Rey Complex Figure Test and Recognition Trial, copy trial; WBD, WAIS Block design; WDS, WAIS Digit symbol; FTD, Fingertapping dominant; FTND, Fingertapping nondominant; RTTSDT, Reaction time test–single decision time; RTTSMT, Reaction time test–single motor time; RTTCDT, Reaction time test–complex decision time; RTTCMT, Reaction time test–complex motor time; RTTE, Reaction time test, error score

memory recognition were higher in the HSCT group at T2, indicating an improvement in long-term word retrieval during a recognition procedure when compared a free recall procedure. Four RRM models were generated to evaluate changes in neuropsychological function over time. Composite scores of the cognitive domains were entered as dependent variables. Time trend was entered as linear and quadratic time (time^2) terms. Error variance was declared unstructured and age, gender and education were entered as covariables. Interaction terms (time x group, time x gender, time x age, time x dropouts, time^2 x dropouts, group x dropouts) were considered as random, and only maintained when the models significantly improved. Based on fit statistics, the model that included covariables and interaction terms was selected for interpretation. Intercepts represent neuropsychological function at baseline and slopes characterize change in neuropsychological function over time. Linear time terms assume a constant rate of change over time, while quadratic time terms reflect curvature in the slope of the function. For all cognitive domains, linear and quadratic time terms were not significant, suggesting no changes in functioning over time for the entire sample. Interactions between time and group showed significant negative slopes for attention and executive function (P = .01) and for psychomotor function (P = .03), indicating a mild time-dependent decline in functioning over time for the HSCT group compared to the REF group (Table 3). An interaction between time and age was also observed for attention and executive function (P = .01), suggesting poorer functioning over time for older patients for the entire group. An interaction between group and dropouts was seen in visuospatial function (P = .04) suggesting that improvement within the domain was related to attrition of patients. Significant negative slopes were also observed for older age in verbal and visual memory, attention and executive function and visuospatial function and for female gender in visual memory, visuospatial function and psychomotor function. Lastly, positive effects of education were observed for all cognitive domains.

Subjective cognitive complaints and neuropsychological function

No significant differences in mean scores of subjective cognitive complaints (CFQ) were observed between groups at any time point (Table 4). Overall neuropsychological function was associated with subjective cognitive complaints at T2 in the HSCT group (r = .26; P = .04) and at all time points in the REF group (r = .29, P =.009; r = .25, P =.04; r = .34, P = .009).

Effects of health-related quality of life, fatigue and psychological function

Poorer emotional function and functional status (respectively P = .05 and P < .01) and more symptoms of fever and mouth sores were reported by HSCT patients at baseline (P < .01; data not tabulated). At follow up, HSCT patients had lower scores on several functioning scales (physical, role and social functioning, global health and quality of life) and more symptoms compared to REF patients. In the HSCT group, overall neuropsychological function was associated with global health at T3 (r = -.41; P = .002). Overall neuropsychological function in the REF group was related to physical function at baseline and T3 (respectively r = -.30; P < .01 and r = -.27; P = .04) and to cognitive functioning at all time points (r = -.22, p = .05; r = -.32, P = .007; r = -.38, P = .003).

Similar levels of fatigue were reported by HSCT and REF patients at baseline (data not tabulated). Physical fatigue levels were higher in HSCT patients at follow up (P < .05). Reduced motivation in HSCT patients was associated with overall neuropsychological function at baseline. Overall

Table 3 Estimated intercepts and slopes of time X group effects of the cognitive domains

Domain	Intercept		Slope		*P*-value
	Estimate	SE	Estimate	SE	
Verbal memory	49.03	4.35	-0.57	0.60	.35
Visual memory	59.32	4.00	0.09	0.56	.87
Attention/executive function	54.03	3.42	-0.98	0.37	.01
Visuospatial function	62.03	4.78	-0.41	0.61	.50
Psychomotor function	56.58	3.15	-1.31	0.58	.03

Intercepts represent neuropsychological function at baseline (estimate in T-scores with a mean of 50 and standard deviation of 10), and slopes characterize change in neuropsychological function over time. SE indicates standard error

Table 4 Overview of subjective cognitive complaints over time

Measures	Baseline				8-month follow up				20-month follow up			
	HSCT (n=101)		REF (n=82)		HSCT (n=64)		REF (n=70)		HSCT (n=55)		REF (n=59)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)
Total raw score[a]	26.2	(12.9)	28.0	(14.1)	27.4	(14.3)	30.5	(16.6)	28.4	(15.3)	30.2	(16.4)
Increase in cognitive failures[b]	.7	(.9)	.9	(.9)	.9	(1.0)	1.1	(1.1)	1.1	(1.0)	1.2	(1.3)
Hindered by cognitive failures[b]	.9	(.8)	1.1	(.9)	.9	(.8)	1.1	(1.0)	1.0	(.9)	1.3	(1.0)
Worried by cognitive failures[b]	.6	(.8)	.8	(.9)	.6	(.8)*	1.0	(1.0)*	.7	(.9)	1.0	(1.0)
Annoyed by cognitive failures[b]	.8	(.8)	1.0	(1.0)	.7	(.9)**	1.3	(1.2)**	.8	(.9)*	1.2	(1.0)*

*$P < .05$; ** $P < .01$

[a] Mean raw total scores (range, 0 to 100) are indicated. Higher scores indicate more subjective cognitive complaints.

[b] Mean raw scores (range, 0 to 4) are indicated. Higher scores indicate more problems.

neuropsychological function was associated with mental fatigue at follow up in REF patients (r = .24, P = .04; r = .32, P = .02).

No significant differences between groups were found in mean scores of anxiety and depression or in the number of depression cases as defined by the HADS at any time point. At baseline, the number of anxiety cases was higher in the HSCT group than in the REF group (14% v 4%; P = .02). Impairment levels in both groups were higher in patients defined as anxiety cases at baseline (HSCT $P < .01$; REF P = .05). Overall neuropsychological function in HSCT patients was associated with anxiety at baseline (r = .21; P = .04) and T3 (r = .32; P = .02), and to depression (r = .28; P = .04) at T3.

HSCT patients reported feelings of avoidance of disease (IES) more frequently than REF patients at baseline. At baseline, overall neuropsychological function was associated with avoidance of disease in the HSCT group (r = .23; P = .02) and with intrusion of treatment (r = .23; Ps = .04) in the REF group. Overall neuropsychological function at follow up was associated with intrusion in the HSCT group (r = .30, P = .02; r = .31, P = .01) and avoidance in the REF group (r = .30, P = .01; r = .29; P = .02).

Effects of treatment-related factors

TBI had a negative effect on psychomotor function at T3 (P = .02), while the effect on overall neuropsychological function reached a trend level significance (P = .07). Overall neuropsychological function at follow up was not affected by any other treatment-related factors, like pretransplant treatment (intrathecal chemotherapy), type of HSCT (autologous *v* allogeneic transplantation, related *v* unrelated donor status), HSCT conditioning regimen (myeloablative *v* non-myeloablative), acute GVHD, chronic GVHD, prolonged immunosuppressive therapy and infections (acute or long term).

Occupational status and neuropsychological function

Most HSCT patients (86%) and REF patients (79%) were not working or studying at baseline (P = .24). Occupational status was not associated with HRQL, fatigue or psychological function in HSCT patients. At follow up, work attendance was lower in HSCT patients (respectively 14% *v* 50%, P < .001; 40% *v* 66%, P = .008). A positive association between overall neuropsychological function and work attendance was found in REF patients (P = .01). HSCT patients who resumed their activities at follow up reported better cognitive function on the QLQ-C30 (T2, P = .05; T3, P = .005). No associations between occupational status and subjective cognitive complaints measured by the CFQ were observed at any time point in either group.

DISCUSSION

The present study is one of the few prospective reports on neuropsychological function in HSCT patients using a pretreatment baseline assessment and the first to compare performance over time to a disease-specific reference group. Our data demonstrate that neuropsychological function prior to HSCT was similar in both patient groups. Before HSCT, subsets of patients show cognitive deficits in visual memory, visuospatial function, and psychomotor function. No significant changes were observed compared to baseline function during a follow up period of 20 months. Only mild differences in performance over time were seen within two cognitive domains in comparison to the reference group. HSCT patients showed poorer performance on attention and executive function, and psychomotor function. Regarding the covariate adjustment used in the RRM analysis, function over time decline was significantly influenced by sociodemographic factors, and older patients and females were found to be especially at risk. In contrast, a higher educational level had a positive effect on performance in all cognitive domains.

These findings are in accordance with previous reports.[5,8-11] In our retrospective study in long-term survivors of HSCT, late cognitive deficits more than two years following HSCT were found in attention and executive function, information processing speed, and memory. Current data lack evidence of significant impairment in memory function, which may be explained by slight differences in measures and normative data and patients groups. Also, and again contrary to previous studies, we found no evidence for recovery to pretransplant levels at follow up as function over time remained stable.[10,11]

In the present study, objective and subjective measures of neuropsychological function were only weakly associated in HSCT patients. Recently, Booth-Jones et al did not find a relationship between patients' subjective estimation of function in every day life and objective cognitive

impairment following HSCT, but both subjective and objective cognitive function were related to depression and fatigue.[9] Further analysis of our results showed that patients who complained about cognitive problems, indeed achieved more cognitive test scores within the impaired range. It is important to note, however, that some test instruments may be insufficiently sensitive to detect mild deficits, which may result in an underestimation of subtle differences in function. Moreover, subjective self-reported questionnaires and neuropsychological test batteries might not be measuring the same function, as questionnaires may not necessarily relate directly to cognitive problems encountered by patients in everyday lives. Consequently, studies evaluating cognitive function in HSCT patients should not be based on questionnaires only.

The physical and emotional effects of the HSCT procedure play an important role in the general well-being in patients before and after undergoing transplant.[37,38] Previous studies on neuropsychological function in HSCT patients found that HRQL factors may contribute to observed cognitive deficits or to changes over time.[8,9] Main predictors of cognitive impairment after HSCT in our previous retrospective study were global health and fatigue. Our current results show weak correlations between HRQL factors and objective neuropsychological function, despite significant between group differences on several HRQL functioning scales and symptoms at all time points. In addition, in the present study no effect was found of fatigue at follow up. The inconsistency between these results could be related to differences in the duration of follow up because mean time between HSCT and the assessment in our retrospective study was almost four years.

The current study provides evidence that affective status has only a minor impact on neuropsychological function before and after HSCT. Because of the intensive nature of the transplant procedure, HSCT patients experience high levels of emotional distress. In the present study, more anxiety cases were found in the HSCT group together with more feelings of avoidance of disease at baseline. However, only a weak association between depression and neuropsychological function was observed at follow up, and in REF patients, similar levels of correlations were observed. The observed differences in neuropsychological function between HSCT and REF patients can therefore not be solely explained by psychological factors.

TBI for conditioning contributed to poorer psychomotor function at follow up which is consistent with previous findings.[5,10] No other treatment-related factors were found to relate to impairment. In future studies, risk factors for cognitive impairment may need to be further identified by MRI techniques.

Several factors may have confounded this study. First, we did not observe our patients from diagnosis onwards and before the start of any treatment. Subject attrition is another common problem in longitudinal studies in HSCT patients, but our data were collected from a sufficiently large sample of HSCT patients. Attrition was related to death and recurrent disease, and refusal after consenting to the baseline assessment was less than five percent in both patient groups. It is therefore unlikely that attrition affected our study significantly.

In conclusion, this first longitudinal study on HSCT with a disease-specific reference group shows the absence of significant treatment-related changes in neuropsychological function up to 20 months after treatment. Neuropsychological function remained stable and is, in general, comparable to functioning in hematological patients not treated with HSCT. The observed differences in performance are subtle, and domain specific because they are limited to attention and executive function, and to psychomotor function. Further long-term follow up of

this patient cohort is essential as it may show changes in functioning within these particular domains. At this point in time, however, it seems legitimate to consider HSCT as a treatment with no significant additional effect on neuropsychological functioning compared to the standard therapies for hematological malignancies.

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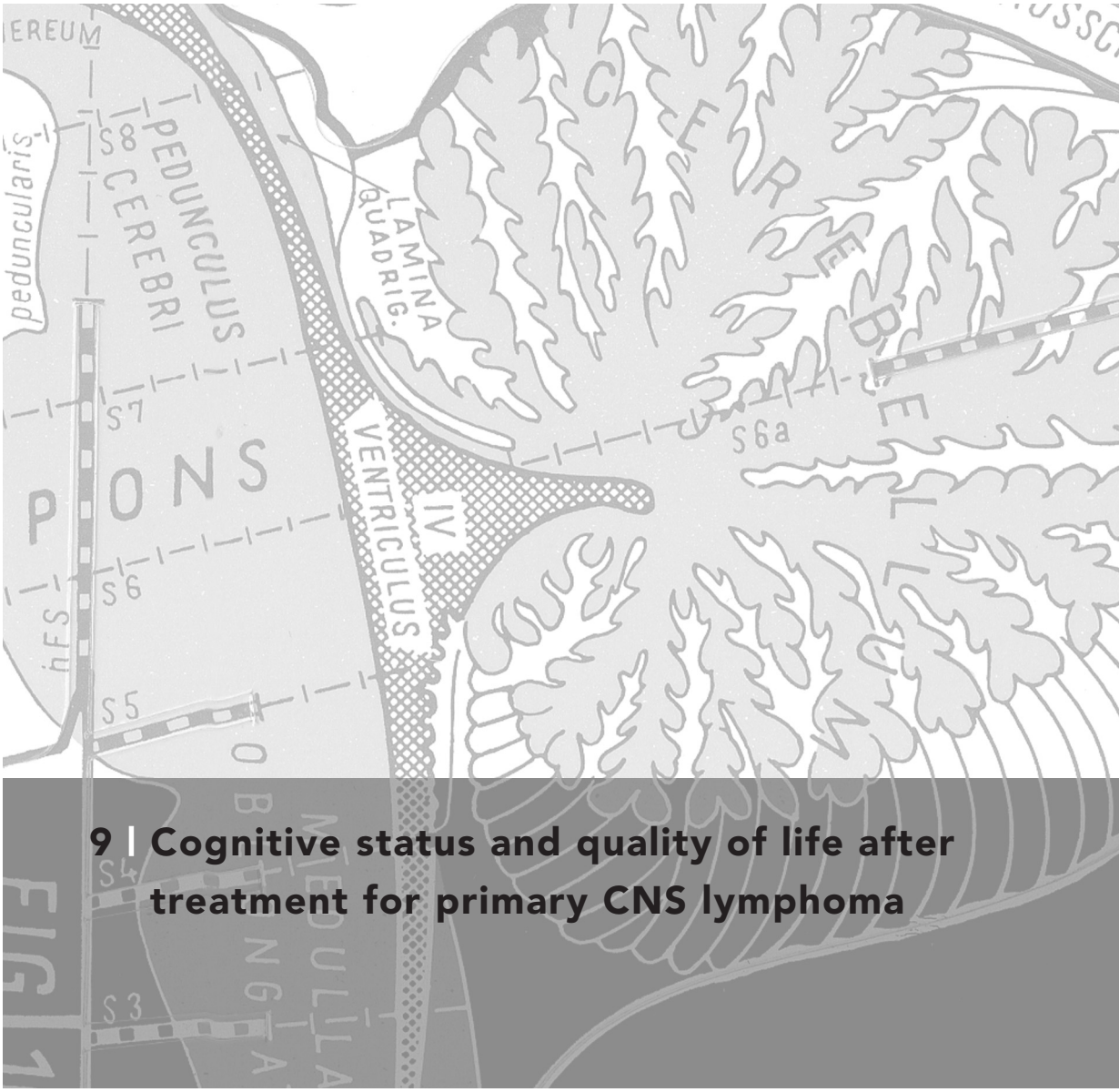

9 | Cognitive status and quality of life after treatment for primary CNS lymphoma

H. Harder, H. Holtel, JEC. Bromberg, P. Poortmans, H. Haaxma-Reiche, HC. Kluin-Nelemans, J. Menten, MJ. van den Bent.
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ABSTRACT

Objective: To evaluate the cognitive status and quality of life (QOL) in a cohort of 19 consecutive patients treated in a prospective European Organization for Research and Treatment of Cancer study (20962) for primary CNS lymphoma (PCNSL). All patients were in complete remission after combined-modality treatment with intravenous and intrathecal high-dose methotrexate (MTX)-based chemotherapy followed by whole brain radiotherapy (WBRT).
Methods: An extensive neuropsychological assessment, including QOL measures, was conducted in 19 patients with PCNSL. The results were compared to matched controls with systemic hematological malignancies treated with systemic chemotherapy or non-CNS radiotherapy. In addition, a neuroradiological evaluation was carried out in 18 patients with PCNSL.
Results: Cognitive impairment was found in 12 patients with PCNSL (63%), despite a complete tumor response. Four patients (21%) showed severe cognitive deficits, and the percentage of impaired test-indices correlated with age. In comparison, only two controls (11%) showed cognitive dysfunction ($p = .002$). Forty-two percent of the patients with PCNSL, in contrast to 81% of the controls resumed work. White matter abnormalities were observed in 14 patients with PCNSL, and 14 had cortical atrophy. Cortical atrophy correlated with cognitive functioning, age and, Karnofsky performance score. Group differences in cognitive status and QOL could not be explained by anxiety, depression, or fatigue.
Conclusions: Combined-modality treatment for PCNSL is associated with cognitive impairment even in patients aged < 60.

Treatment protocols for primary CNS lymphoma (PCNSL) have changed over the past years. Intensified therapeutic regimens, particularly those with high-dose methotrexate (MTX)-based chemotherapy followed by whole brain radiotherapy (WBRT) have resulted in long-term remissions and improved survival rates.[1] Consequently, late neurotoxicity has become a serious problem with important implications for cognitive functions and quality of life (QOL). The reported incidence of late neurotoxicity in PCNSL patients varies from 5% to 32%, and is more common in patients aged > 60 years.[2-4] However, most studies have addressed late neurotoxicity with clinical data, sometimes in combination with radiological findings.[5,6] A well-conducted study assessing cognitive status and QOL in patients in complete response to combined-modality treatment is lacking, and the incidence of late neurotoxicity is probably underestimated. The objective of the current study was to evaluate systemically cognitive status and QOL in PCNSL patients in complete remission to combined-modality treatment. The results were compared to controls and neuroradiological data.

METHODS

Patients

From July 1997 to March 2002, a phase II trial to confirm the feasibility of high-dose MTX-based chemotherapy followed by WBRT in non-AIDS related PCNSL was carried out by the European Organization for Research and Treatment of Cancer (EORTC). Patients received two cycles of MBVP chemotherapy (Methylprednisolone 60 mg/m^2 PO day 1-5, MTX 3 g/m^2 IV days 1 and 15, Teniposide 100 mg/m^2 IV day 2-3, BCNU 100 mg/m^2 IV day 4) and two intrathecal injections of chemotherapy (MTX 15 mg, Cytarabine 40 mg and Hydrocortisone 25 mg, days 1 and 15). WBRT was given at a total dose of 39 to 40 Gy. Inclusion criteria were: aged 16 to 65 years, Karnofsky performance score (KPS) 40 to 100, neurological function status 0 to 3, histological or cytological proven non-Hodgkin Lymphoma (NHL) of the CNS including the leptomeninges and the spinal cord and at least one measurable lesion for response evaluation. Fifty-two patients were included.[7] To be eligible for the neuropsychological evaluation, patients had to meet the following supplementary criteria: treated for intracranial tumor localization only, at least 6 months post treatment and in complete remission, no presence or history of drug abuse or psychiatric or neurological disorders, and fluent in Dutch. The medical ethics committee approved the study and written informed consent was obtained from all patients.

The results were compared to the results of controls selected from a database of an ongoing longitudinal cognitive study among patients with a hematological malignancy. The control patients were treated at a single institution for Hodgkin disease or systemic Non-Hodgkin Lymphoma (NHL) with systemic chemotherapy or radiotherapy, or both. Patients were matched for sex, age, education, and time since the end of treatment.

Measures

Neuropsychological evaluation. All patients underwent a formal neuropsychological assessment using standardized psychometric testing procedures. The neuropsychological test battery (12 tests, 18 test indices) measured a broad range of cognitive domains and is described in detail elsewhere.[8] Normative data were available for all tests. The assessment took place in the hospital where the patient was treated or at home.

Assessment of Quality of Life. The EORTC QLQ-C30 (QLQ-C30) was used to measure subjective health-related QOL.[9] It evaluates five functioning scales (physical, role, cognitive, emotional, social), global health status, global QOL, and several QOL symptom scales or items. In addition, the EORTC Brain Cancer Module (BCM20) was used to assess neurological functioning.[10] Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI), which has five scales: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity.[11] Current mood was evaluated using the Hospital Anxiety and Depression Scale (HADS).[12] The recommended cut-off score for cancer populations (total score >10) was used as an indication for increased levels of anxiety or depression.[13]

Clinical data and evaluation of neuroradiological data. Data on medical status, tumor characteristics, and treatment history were derived from the EORTC Data Center in Brussels. The pretreatment and the last follow-up brain scans (MRI or CT) were obtained from the treating specialist. The presence of white matter abnormalities (WMA) and cortical atrophy was scored blind to clinical and neuropsychological data. The WMA were separately evaluated in the anterior and posterior white matter on three subsequent MRI/CT slices according to a semi-quantitative method.[14] The changes were scored on a 3 - point grading system for each region: grade 0 'no lesions'; grade 1 'multiple focal lesions restricted to the region adjoining the ventricles'; grade 2 'multiple confluent lesions scattered throughout the white matter'. The overall atrophy score ranged from 0 (no atrophy) to 2 (moderate-severe atrophy).

Data analysis

The raw scores of the neuropsychological tests were converted to standard (*z*-scores) or percentile scores, depending on normative data. Based on a commonly accepted categorization of cognitive performance levels, standard scores < 2 SD below average or percentile scores < 10 were classified as impaired.[15] Subsequently, for each individual the total number and the percentage of impaired test-indices were calculated (for the statistical analyses the percentage was used because not all patients completed the neuropsychological test battery). The severity of cognitive impairment was defined as follows: mild to moderate impairment: ≥ 4 test-indices in the impaired range; severe impairment: > 6 test-indices in the impaired range. Non-parametric analyses (Mann-Whitney *U* tests for independent samples, Spearman's rho test) were used because of small samples. For all statistical analyses with the neuropsychological tests, a Bonferroni alpha adjustment (*P*=. 01) was used because of multiple testing.

RESULTS

Patients and treatment

Twenty-five of the 38 patients who had been treated in the Netherlands and Belgium were still alive. Six patients were ineligible (two had recurrent disease, two had tumor localization in the spinal cord only, one suffered from severe psychiatric problems, and one was lost to follow up), leaving 19 patients. All patients agreed to participate in the study. Patient characteristics and main clinical features are summarized in the table 1. Median age was 44 years (range 24 to 63), only two patients were > 60. In two patients the second cycle of MBVP was omitted because of insufficient tumor response. Eighteen patients received intrathecal chemotherapy. All patients were treated with WBRT, and most received 39 to 40 Gy in 22 to 26 fractions. In the control

group, six patients were treated with systemic chemotherapy or involved-field radiotherapy only. Thirteen patients received radiotherapy up to 42 Gy in 15 to 28 fractions after systemic chemotherapy.

Table 1 Patient characteristics

	PCNSL		Controls	
Male/female	15/4		15/4	
Mean ± SD age, y	44 ± 12		45 ± 12	
Education level, no. (%)				
High school degree or less	5	(26)	4	(21)
Vocational/trade school	6	(32)	8	(42)
College/bachelor degree	4	(21)	4	(21)
Graduate/professional degree	4	(21)	3	(16)
Mean ± SD time since treatment, mo	23 ± 14		16 ± 7	
Mean ± SD pre-treatment KPS	75 ± 19		NA	
Mean ± SD KPS[a]	87 ± 8		94 ± 6	
Diagnosis, no. (%)				
PCNSL	19	(100)		
Hodgkin disease			8	(42)
NHL			11	(58)
Extension CNS lesion, no. (%)				
Single mass lesion	13	(68)		
Multifocal lesion	6	(32)		
Pre RT meningeal infiltration, no. (%)[b]				
Negative	13	(68)		
Positive	2	(11)		
Not done	4	(21)		
Tumor lateralization, no. (%)				
Left-sided	6	(32)		
Right-sided	6	(32)		
Bilateral	6	(32)		
Central	1	(5)		
Tumor Localization no. (%)				
Frontal	3	(16)		
Temporal	3	(16)		
Parietal	1	(5)		
Occipital	1	(5)		
Cerebellum	1	(5)		
Other[c]	10	(53)		

Table 1 (continued)

Chemotherapy, no. (%)[d]				
MBVP	19	(100)		
ABVD			5	(31)
CHOP			4	(25)
MOPP/ABV			3	(19)
BEACOPP			2	(13)
LEUKERAN			1	(6)
Other			1	(6)
Radiotherapy, no. (%)				
WBRT 39-40 Gy	17	(89)		
WBRT 45-50 Gy	2	(11)		
IF-RT 30 Gy			1	(6)
IF-RT 36-42 Gy			15	(94)

KPS = Karnofsky performance score; NA = not available; PCNSL = primary CNS lymphoma; NHL = non-Hodgkin lymphoma; WBRT = whole brain radiotherapy; IF-RT = involved-field radiotherapy

[a] *P*-value is .005

[b] Lymphoma cells identified in cerebrospinal fluid

[c] Other = deep lesions (basal ganglia and thalamus, n=4) and tumor lesion(s) in: frontal regions and corpus callosum (n=1), septum pellucidum (n=1), 3rd ventricle (n=1), foramina of Monroe and 4th ventricle (n=1), frontal and deep regions (n=1), and temporal and frontal areas and basal ganglia (n=1)

[d] MBVP (methylprednisolone, methotrexate, teniposide, carmustine); CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone or dexamethasone); ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); MOPP/ABV (chloormethine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine); BEACOPP (doxorubicin, cyclophosphamide, procarbazine, prednisone, etoposide, bleomycin, vincristine); LEUKERAN (chlorambucil); other= CVP (cyclophosphamide, vincristine, prednisone), DHAP (dexamethasone, cisplatine, cytarabine) and EMP (etoposide, mitoxantrone, prednisone)

Neuropsychological assessment

Two patients with PCNSL did not complete the neuropsychological test battery (due to insufficient knowledge of the Dutch vocabulary and a disease-induced hemi-paresis). Almost two-third (63%) showed mild to moderate impairment (Table 2). Four patients (21%) were severely impaired. In contrast, only 11% of the controls showed mild to moderate cognitive impairment and none were severely impaired. Compared to the controls, the patients with PCNSL had lower scores on some or all of the neuropsychological tests of the following domains: verbal and nonverbal memory (California Verbal Learning Test, Rey Complex Figure Test), attention (Digit Symbol, Trailmaking A), executive function (Trailmaking B), and motor speed (Fingertapping Task and motor times of the Reaction Time Test). For the patients with PCNSL cognitive impairment was positively correlated with age (r=. 56; P=. 013).

Impaired cognitive status was not related to work-attendance. Eight patients with PCNSL (42%) attended work. Four of them worked on a lower level, and 2 worked less than before diagnosis. Additionally, 10 patients were on disability benefits of which four were slowly re-entering the workplace. One patient retired early, but required intensive nursing care due to severe physical disabilities and cognitive deficits. Out of the 16 controls working before diagnosis, 13 (81%) resumed work. Only three controls were on disability benefits.

Table 2 Neuropsychological data: mean (SD) raw scores and percentile-scores, including percentage of impaired patients

	PCNSL		Controls		*P*-value[a]
Intelligence					
GIT IQ	99 (16) / 50 (29)	0%	NA		-
Verbal Ability					
Word Fluency	19 (5) / 53 (28)	0%	22 (4) / 72 (16)	0%	.06
Memory					
Digit Span	11 (3) / 54 (27)	0%	13 (3) / 73 (23)	0%	.04
California Verbal Learning Test		37%		5%	
Total learning	41 (15) / 24 (25)		58 (7) / 67 (21)		<.001
Immediate free recall[b]	7 (4) / 62 (33)		12 (2) / 56 (32)		<.001
Delayed free recall[b]	8 (5) / 63 (24)		13 (2) / 42 (33)		.001
Recognition	14 (1) / 68 (25)		15 (1) / 64 (27)		.05
Rey Complex Figure Test-recall[c,d]	17 (7) / 28 (31)	17%	24 (7) / 71 (36)	11%	.004
Visual Reproduction I[c]	30 (7) / 46 (27)	0%	NA	-	
Visual Reproduction II[c]	23 (12) / 40 (37)	11%	NA	-	
Attention					
Digit Symbol[c]	39 (15) / 43 (31)	11%	58 (9) / 88 (12)	0%	<.001
Trailmaking A[e]	52 (33) / 39 (30)	21%	25 (8) / 85 (14)	0%	<.001
Stroop Color Word Test I[e]	20 (5) / 37 (31)	32%	18 (4) / 62 (30)	5%	.07
Stroop Color Word Test II[e]	27 (7) / 32 (32)	44%	22 (4) / 60 (31)	11%	.02
Executive functions					
Trailmaking B[e]	122 (75) / 38 (22)	26%	62 (24) / 78 (19)	0%	.007
Stroop Color Word Test III[e]	46 (20) / 35 (29)	37%	33 (8) / 67 (30)	11%	.04
Visuoconstructive abiliy					
Rey Complex Figure Test-copy[c]	33 (2) / 60 (23)	39%	34 (2) / 67 (27)	32%	.33
Motor Speed					
Fingertapping Test dominant[f]	286 (67) / 10 (16)	47%	351 (46) / 36 (32)	16%	.002
Fingertapping Test non-dominant[f]	245 (59) / 8 (13)	58%	310 (40) / 32 (28)	5%	.001
Single Motor time[g]	192 (55) / 15 (24)	37%	130 (38) / 54 (28)	11%	.001
Complex Motor time[g]	204 (75) / 17 (23)	47%	136 (37) / 44 (22)	11%	.003
Speed of information processing					
Single Decision time[g]	358 (50) / 31 (25)	27%	327 (52) / 38 (27)	16%	.03
Complex Decision time[g]	559 (113) / 31 (34)	32%	527 (77) / 33 (24)	11%	.31
Error rate	2 (2) / 43 (35)	11%	.7 (1) / 67 (15)	0%	.05

SD in parentheses
Percentile-scores: in a normal population a percentile score of 50 (SD=34) is an average score
GIT IQ = Intelligence quotient of the abbreviated Groninger Intelligence Test; NA = not available
[a] *P*-value for mean raw test scores
[b] percentile-scores are based on the differences between free recall and cued recall
[c] n =18 for PCNSL patients
[d] the 3-minute Immediate Recall score
[e] scores in sec
[f] total number of hits in 1 minute
[g] scores in msec

Table 3 QLQ-C30 and BCM20; mean ± SD

	PCNSL	Controls	*P*-value
QLQ C30			
Functioning scales			
Physical functioning	82 ± 27	92 ± 17	.25
Role functioning	63 ± 33	80 ± 25	.10
Cognitive functioning	62 ± 28	81 ± 21	.04
Emotional functioning	64 ± 27	82 ± 15	.03
Social functioning	70 ± 32	88 ± 21	.03
Global health	68 ± 17	78 ± 16	.05
Global quality of life	67 ± 24	80 ± 17	.07
Symptom scales and items			
Fatigue	35 ± 25	22 ± 21	.13
Nausea/vomiting	4 ± 9	2 ± 5	.29
Pain	16 ± 20	6 ± 12	.06
Dyspnea	2 ± 8	16 ± 20	.01
Sleep disturbances	33 ± 35	19 ± 26	.22
Appetite loss	9 ± 19	0	.04
Constipation	9 ± 16	2 ± 8	.08
Diarrhea	4 ± 14	2 ± 8	.16
Financial impact	16 ± 30	11 ± 19	.84
BCM20			
Symptom scales			
Future uncertainty	28 ± 22		
Visual disorder	17 ± 22		
Motor dysfunction	13 ± 16		
deficit	17 ± 18		
Items			
Headaches	14 ± 26		
Seizures	5 ± 23		
Drowsiness	18 ± 23		
Bothered by hair loss	4 ± 11		
Bothered by itching skin	16 ± 28		
Weakness of both legs	9 ± 19		
Trouble controlling bladder	9 ± 22		

Scores range from 0 to 100. Functioning scales, global health and global QOL: higher scores denote better function. Symptom scales and items: higher scores denote higher symptom levels

Evaluation of neuroradiological data

Brain scans were available for review in 18 patients with PCNSL. WMA were observed in 14 patients (78%). Fourteen patients had cortical atrophy, of which six (33%) severely. One patient had a mild atrophy before the start of treatment. Twelve patients (67%) showed WMA and cortical atrophy. Cortical atrophy was associated with cognitive impairment (r=. 60, P =. 008), age (r=. 50; P=. 035), and KPS (r=-. 66, P =. 003). WMA and cortical atrophy were not related to tumor size before treatment, extent of the lesion, total dose of WBRT, or time since the end of treatment.

QOL assessment

Nine patients with PCNSL (47%) reported well to excellent QOL ('global QOL' score > 5; Table 3). However, they had significant lower scores than the controls on the following QOL functioning scales: 'cognitive functioning', 'emotional functioning', 'social functioning' and 'global health'. The scores of 'cognitive functioning' and 'global QOL' were not related to cognitive performance. Patients who attended work had higher scores on the 'global QOL' scale.

Two patients with PCNSL scored above the cut-off point on the anxiety and the depression scale of the HADS (Table 4). Differences between groups on the MFI were not found. The scores on the HADS and the MFI were not related to cognitive performance. The patients with PCNSL, who resumed work, had lower scores on 'general fatigue' and 'reduced activity' of the MFI.

Table 4 MFI and HADS; mean ± SD and percentage of impaired patients

	PCNSL	Controls	*P*-value
MFI			
General Fatigue	11 ± 5	11 ± 5	.86
Physical Fatigue	11 ± 5	9 ± 5	.45
Reduced Activity	11 ± 5	8 ± 5	.06
Reduced Motivation	9 ± 5	7± 3	.22
Mental Fatigue	12 ± 5	10 ± 5	.11
HADS[a]			
Anxiety	7 ± 5	5 ± 3	.16
% > 10	(22)	(5)	.14
Depression	6 ± 4	3 ± 3	.08
% > 10	(11)	(0)	.14

Percentages range from 4 to 20; higher scores indicate more symptoms
HADS: scores range from 0 to 21; higher scores denote more complaints

DISCUSSION

Our cohort of patients represents a relatively young group of patients compared to other PCNSL series.[16] Nevertheless, the expected better outcome that younger patients tend to have, was not reflected in our study and only less than half of the patients resumed work. The incidence of white matter abnormalities and cortical atrophy in our study is similar to earlier findings.[5] Cerebral damage from chemotherapy or cranial radiation usually affects the white matter tracts devoted to higher cortical function.[17] Especially tasks that involve psychomotor speed, attention and concentration, memory and learning abilities, and executive functions appear to be affected by white matter abnormalities.[18] The observed differences between our patient groups on these particular cognitive tasks cannot be explained by confounding factors related to the psychological effects of the diagnosis or treatment of cancer because the controls were also treated with systemic chemotherapy or radiotherapy or both.

There are several possible causes for the observed cognitive deficits and the neuroradiological changes in these patients with PCNSL. The first is the neurotoxic effect of combined-modality treatment with intravenous and intrathecal MTX-based chemotherapy before WBRT. Each treatment modality independently is potential neurotoxic, but once combined the risk to develop neurological and cognitive deficits increases in more than an additive way.[19,20] Apart from treatment side effects, the cognitive deficits could also be attributed to cerebral scarring as a result of prior tumor infiltration of the brain. Most studies on cognitive functioning in brain tumor patients addressed patients with gliomas who suffer from significant residual tumor. In those patients, treatment with cranial irradiation and chemotherapy is related to cognitive deficits, but coexistence of residual tumor, influence of surgery and tumor lateralization make interpretation difficult.[21-24] In our study the effects of residual tumor are negligible because all patients had a complete tumor response without evidence of tumor activity. However, due to the absence of a pre-treatment evaluation, the effect of other tumor characterizations (eg, site and number of lesions) on cognitive functioning cannot be ruled out.

Our findings are in contrast with previous studies investigating cognitive functioning in patients with PCNSL with standardized psychometric methods.[25-32] All evaluated patients treated with chemotherapy alone, which was associated with a low risk of late neurotoxicity. Cognitive impairment was only found in those patients who received cranial radiotherapy as first-line treatment or in a later stage for refractory disease.[25,28,31]

Our results indicate that the difficult balance between prolongation of disease-free survival and the risk of increased neurotoxicity needs to be carefully monitored. Assessment of cognitive status and QOL should be considered as endpoints in new clinical trials, and future trials should particularly aim at reducing these side effects. Further follow-up of our cohort of patients is needed to show whether the prolonged and complete remissions are lasting over time and, in particular, whether a possible progressive cognitive decline can be detected.

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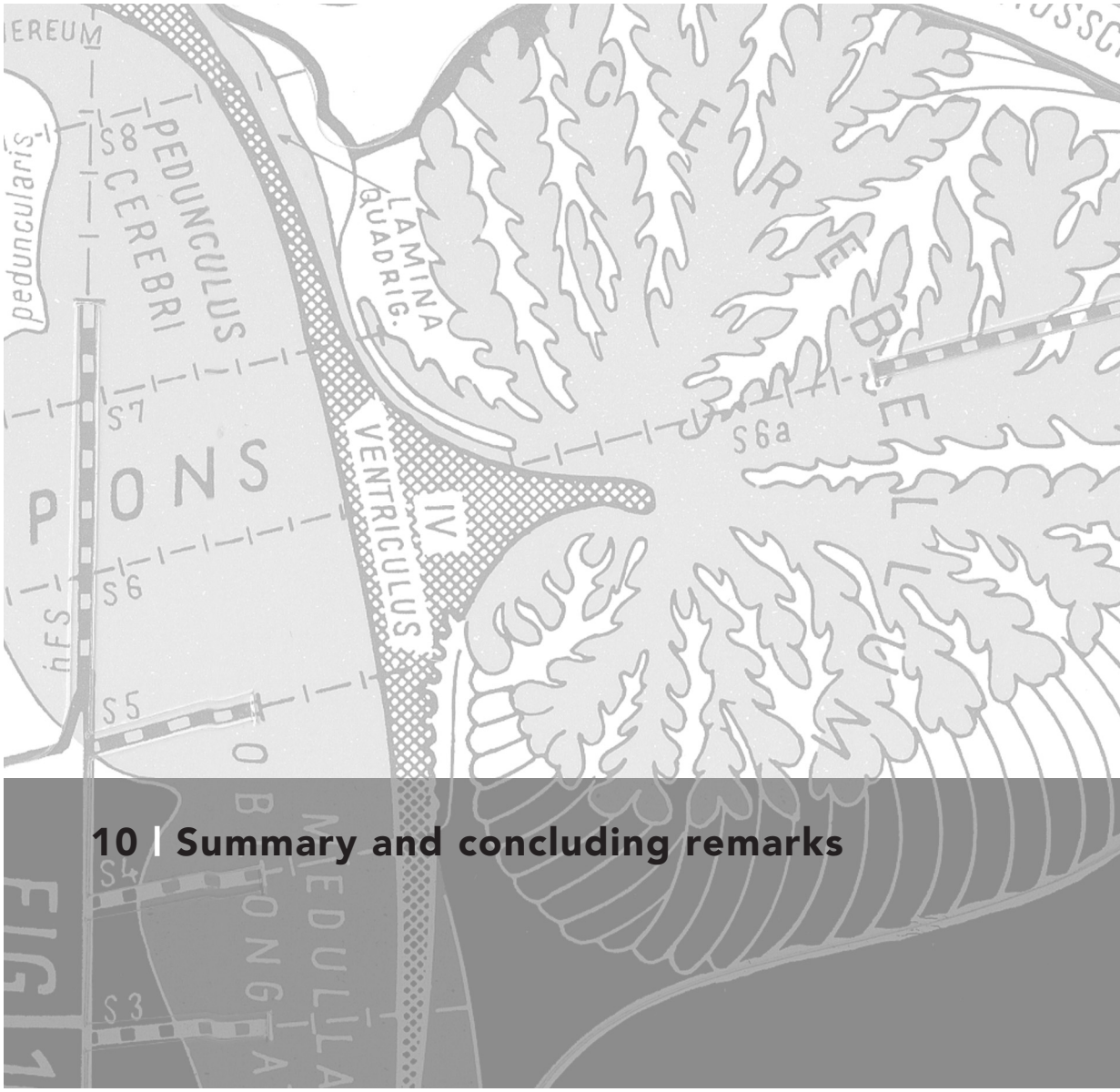

10 | Summary and concluding remarks

With more active treatments becoming available, cancer is increasingly becoming a more chronic illness. The side-effects of cancer treatment, including potential neurotoxic effects are a major concern. The number of long-term cancer survivors will further increase in the near future, as will the number of survivors with cognitive and neurobehavioral impairment. Both chemotherapy and cranial irradiation may induce cognitive impairment.[1] Research on cognitive functioning following cancer treatment started in the early 1980s,[2] but still there is a paucity of systematic prospective, longitudinal and large-scale studies using objective psychometric measures. Up till recently, most clinical trials investigating new treatment approaches focused on survival, time to tumor progression, physical side-effects and its impact on quality of life (QOL), rather than on potential cognitive side-effects.

This thesis reports on the cognitive sequelae of intensive treatment for hematological malignancies. The central aim of this thesis was to examine the prevalence and the characteristics of cognitive impairment in patients treated with or undergoing bone marrow or hematopoietic stem cell transplantation (HSCT), and in patients treated for primary central nervous system lymphoma (PCNSL). Additional goals were to study the relationship between cognitive functioning and subjective cognitive complaints, general QOL-related issues, and psychological functioning. This chapter presents and discusses the main findings, the limitations of the studies and recommendations for future research.

SUMMARY

In **chapter 2** the toxic effects of cancer treatment on the central nervous system (CNS), including the putative underlying mechanisms and its effect on cognitive functioning, were described. Severe delayed treatment-induced neurological complications are radiation necrosis, and delayed leukoencephalopathy which is characterized by neurological abnormalities and progressive cognitive decline. The incidence and risk of chemotherapy- and radiotherapy-induced neurotoxicity depends on the capillary permeability of the blood-brain barrier (BBB), the dosage and route of administration of antineoplastic agents, total dose and fraction dose, and volume of the brain irradiated, and administration of other treatment modalities. Immunotherapy with cytokines and adjunctive medications like corticosteroids and immunosuppressive agents may also induce neurotoxic effects. The pathogenesis of neurotoxicity is an unknown and complex process of direct and indirect effects on neurons and glial cells that leads to disruption of genetic, metabolic or neurotransmitter-related processes, to secondary inflammatory or autoimmune responses, and to cerebrovascular damage, particularly in the capillary microvasculature and the capillary permeability of the BBB.

Chapter 3 focused on the available literature data on cognitive dysfunction in HSCT patients. Results of this review suggest that cognitive dysfunction in HSCT patients includes diffuse impairment of motor function, executive function, and memory prior to and following the transplant procedure. The reported prevalence of cognitive impairment varies from 20 to 58% prior to HSCT and 37 to 79% after completion of treatment; this large range is in part explained by the use of different criteria for cognitive impairment. Risk factors for poorer cognitive outcome include demographical factors (ie, old age, male gender, low educational level, low estimated premorbid intelligence) and disease and/or treatment-related factors (ie, cranial irradiation, history of previous chemotherapy, intrathecal treatment, disease duration and

disease stage at transplant, total dose of total body irradiation (TBI), and graft-versus-host-disease). Methodological limitations, including small sample size, diversity in patient selection and lack of an appropriate reference group, greatly limit the interpretation of currently available results.

Chapter 4 presented a literature review of cognitive dysfunction associated with PCNSL and its treatment with whole brain radiotherapy, high-dose chemotherapy, combined modality therapy, and blood-brain barrier disruption chemotherapy. Most neuropsychological studies on PCNSL are prospective and embedded in clinical trials. A broad range of cognitive deficits is observed, including deficits in attention, executive functions, memory, language (eg, naming), and psychomotor speed. Cognitive impairment is usually already apparent before treatment. PCNSL patients treated with combined modality therapy demonstrate generally more pronounced cognitive impairment than those who received chemotherapy alone. Treatment with chemotherapy alone is associated with either stable or improved cognitive performance after completion of treatment. Further large-scale systematic clinical and neuropsychological studies are needed.

The results of a retrospective study in adult long-term survivors of HSCT were described in **chapter 5**. We evaluated a cohort of 40 progression-free patients with hematological malignancies who received HSCT at least two years before study participation. The induction regimen consisted of high-dose chemotherapy and TBI, followed by an allogeneic transplant for most patients. Mild to moderate cognitive impairment was found in 60% of patients compared to normative data. Impairment involved deficits in selective attention, executive function, information processing speed, and verbal and visual memory. Performance on tasks of information processing speed was significantly lower when compared to expected scores of a healthy population ($p = .001$). Fatigue, global health, and educational level accounted for the variance in impaired test scores. A brief mental status evaluation (the Mini-Mental Status Examination)[3] revealed no abnormalities. The findings emphasized the importance of including cognitive functioning as an outcome parameter in HSCT trials.

In **chapter 6**, the results of a pilot study on changes in cognitive functioning in HSCT candidates during the first year following transplant were presented. Less than half of the 25 patients included in the pre-treatment baseline assessment were evaluated at follow-up. Attrition was caused by death and relapse (both before and after transplant), and to severe post-HSCT complications. Cognitive impairment prior to HSCT was observed in up to 24% of patients, predominantly in selective attention and information processing speed. Random regression modeling revealed a slight improvement in mean group scores of memory tasks over time, particularly for younger patients, which may be related to practice effects. Emotional functioning improved over time. Depression and anger affected performance at baseline, and emotional functioning was correlated with cognitive performance at follow-up. We concluded that future research requires a pre-treatment assessment together with a sufficient large sample of patients to overcome an expected drop-out of at least 50%.

We examined cognitive performance in HSCT candidates prior to transplant in comparison to a reference group of patients with hematological malignancies who received conventional non-myeloablative cancer therapy in **chapter 7**. The baseline results of this prospective comparative study in a large-scale and representative cohort of 101 HSCT patients and 82 reference patients indicated that up to 20% of HSCT candidates experienced cognitive impairment before undergoing HSCT. Deficits were observed in visual memory, visuospatial and constructional

ability, and psychomotor functions. There were no differences in degree or pattern of cognitive impairment between groups. We also observed no associations between cognitive performance and treatment parameters. In the transplant group, a higher rate of anxiety cases was observed, and levels of subjective cognitive functioning, emotional functioning, and social functioning were significantly lower. However, this was not related to cognitive performance.

The same cohort of patients was assessed at eight months and 20 months after baseline to investigate whether cognitive functioning would change over time and may be affected by the transplant procedure. The results of this study were described in **chapter 8**. As predicted in our pilot-study, only 54% of the HSCT patients completed follow-up in contrast to 72% of the reference patients. Random regression modeling indicated that there were no significant changes in cognitive functioning over time. However, performance on several measures of attention and executive function (p = .01), and psychomotor function (p = .03) in the HSCT group was reduced when compared to the reference group. This was partly related to TBI. Further analyses demonstrated adverse effects of female gender and older age on cognitive functioning. Moreover, physical fatigue levels were significantly higher in HSCT patients at follow-up, and weak correlations were found between cognitive functioning, and global health and psychological functioning. Work attendance in the transplant group was considerably lower in comparison to the reference group. So far, almost two years after transplant, HSCT has no significant additional effect on cognitive functioning. These results may suggest that cytotoxic treatment before HSCT may play a prevailing role in the development of treatment-related cognitive impairment. We recommended further long-term follow-up to evaluate whether cognitive functioning, particularly within the domains of attention and executive function, and psychomotor function improves, stabilizes or progresses over time.

In **chapter 9**, we presented the results of a study on cognitive functioning in a relatively young cohort (median age was 44 years) of disease-free survivors of PCNSL who were treated in a prospective European Organization for Research and Treatment of Cancer study (EORTC 20962). All 19 patients received intravenous and intrathecal high-dose MTX-based chemotherapy followed by consolidating whole brain radiotherapy. The results were compared with matched control subjects with systemic hematological malignancies and were related to neuroradiological findings. Mild to moderate cognitive impairment was observed in 63% of PCNSL patients in comparison to 11% of control subjects (p = .002). Impairment predominantly involved verbal and visual memory, attention, executive function, and motor speed. We found that impairment rate was positively correlated with older age. Group differences could not be explained by confounding factors like psychological functioning or fatigue. Evaluation of neuroradiological findings revealed white matter abnormalities and cortical atrophy in 78% of patients. Cortical atrophy was associated with a higher rate of cognitive impairment, older age and lower performance status. We concluded that combined modality treatment for PCNSL is associated with cognitive impairment, even in patients under 60 years.

CONCLUDING REMARKS

Discussion of main findings

In line with other studies on the cognitive side-effects of cancer treatment,[4] we found evidence for cognitive impairment in a number of patients who received intensive treatment for

hematological malignancies. Our studies revealed that particularly patients with CNS tumors experience cognitive impairment, whereas in hematological patients with non-CNS cancer only a subgroup of patients displayed cognitive dysfunction.

In our first cross-sectional study on cognitive dysfunction associated with HSCT, we observed mild to moderate cognitive deficits in 60% of long-term survivors,[5] particularly in information processing speed. Two prospective trials showed that some of these cognitive problems predate the transplantation procedure.[6,7] The data from our ensuing prospective study indeed indicated that approximately a quarter of patients experience cognitive deficits before undergoing transplant. However, neuropsychological assessments following transplant demonstrated no significant change in cognitive functioning compared to the baseline evaluation. Moreover, when compared to reference patients who had not received HSCT, only mild differences in attention and executive function, and psychomotor function were detected.[8]

Based on literature data, and in view of the results of our first cross-sectional study, we had anticipated coming across a higher rate of cognitive deficits after HSCT and more profound changes in cognitive functioning over time. HSCT patients undergo an intensive preparative conditioning regimen with high-dose chemotherapy and often TBI, and they are submitted to long-term use of immunosuppressive drugs and treatment-related complications like GVHD and infectious diseases due to the immunodeficient state. In comparison to patients of the reference group, therefore, they are not only exposed to additional anti-cancer treatment but also to more potential risks of CNS toxicity as a result of severe post-transplant complications.

A possible explanation for this lower than expected prevalence of cognitive dysfunction could be that the patients in our large-scale longitudinal study were assessed at an earlier time point following HSCT than the patients in the retrospective study. The last neuropsychological assessment in the longitudinal study took place at a mean time of 19 months after transplant, while in the retrospective study patients were assessed between 22 and 82 months after HSCT. It is well-known that some adverse effects of cytotoxic agents or other treatment modalities may take substantial time to evolve (chapter 2). They can appear years after actual exposure and cause CNS toxicity and cognitive dysfunction. Together with late effects of HSCT including a greater number of health problems and persistent fatigue,[9] this may have contributed to differences in impairment rates.

An alternative hypothesis is that the discrepancy in post-HSCT cognitive functioning is related to differences in HSCT conditioning regimens and treatment group assignment. In our retrospective study, all patients were treated with high-dose chemotherapy followed with TBI, whereas in the longitudinal study almost 25% of patients received no TBI. The majority of the included patients was recruited from a single cancer center and received similar pre-HSCT conditioning regimens. However, the conditioning regimens have changed slightly over the last years, and more patients received non-myeloablative treatment regimens followed by an autologous graft. These treatment regimens could be associated with lower risks of neurotoxicity and consequently a less profound impact on cognitive functioning. However, this remains speculative as our data revealed no differences in cognitive performance between patients with autologous grafts and allogeneic grafts.

In addition, the results of our large-scale longitudinal study suggest that treatment prior to transplant may play an important role in the development of cognitive sequelae because almost two years after baseline, no significant changes in functioning could be detected.

Our study in PCNSL patients is one of the first investigations on the cognitive side-effects of combined modality treatment in a large clinical trial.[10] We used an extensive neuropsychological test battery to investigate long-term effects of treatment. In contrast to the HSCT studies, we encountered a significant number of cognitive problems in a relatively young group of PCNSL survivors. Our data suggest that combined modality treatment but also the disease itself is associated with substantial cognitive impairment and has a negative impact on daily-life functioning as less than half of these young patients resumed work. The immediate priority for future research in PCNSL patients is to confirm these observed effects in the setting of large, well-designed longitudinal studies. Such a study is currently underway.

In our studies we could not find consistent associations between subjective cognitive functioning or complaints and actual performance assessed by objective neuropsychological testing. This may be in part related to the diverse use of measures of subjective cognitive functioning. In our retrospective study and pilot study in HSCT patients, the extent of subjective cognitive problems was rated by the neuropsychologist during a short interview before testing. This is a common procedure in a clinical practice, and inter-rating problems were avoided by using the same neuropsychologist for all assessments. In the other studies, patients were asked to fill in a questionnaire to measure the frequency of everyday cognitive failures in memory, attention, action and perception.[11,12] Both instruments could measure different concepts, leading to inconsistent findings.
Additional suggestions for the lack of association between subjective and objective cognitive measures might be that patients misjudge their actual performance state (eg, patients with brain tumors often have diminished appreciation of their cognitive problems as a result of their impairment), or that patients somehow adapt to cognitive deficits and problems, or cope differently with them. In addition, long-term survivors may get used to a new way of life, which makes fewer demands on their cognitive abilities, so that a decline in cognitive function as assessed by formal objective neuropsychological testing is not an issue for these patients in their daily life. This seems a plausible explanation, because large numbers of survivors do not regain their premorbid role function, as many have not (yet) fully returned to their professional careers or academic performance, or are unable to take part abundantly in social or familial activities. Another explanation for the lack of association between subjective and objective cognitive measures might be found in the concept of response-shift, in which individuals, in the course of time, change their internal standards by which they judge their quality of life. For example, a cancer survivor might judge the same cognitive deficits after his illness differently – in this case, less bothersome - as he would have done before. Having survived, the survivor may be inclined to attach less value to - and to underreport - his cognitive complaints because other concepts (eg, being alive, family bonds) have become more important.

An important area of research that remains to be investigated is the identification of specific cytotoxic agents, treatment regimens or combinations of therapeutic modalities that may have caused the cognitive deficits. Our studies do not provide an answer to this cause-and-effect issue. Our PCNSL study presents however a first step towards unraveling potential causes of treatment-related cognitive dysfunction. We compared overall cognitive functioning with evidence of neuroradiological abnormalities manifested on MRI. In the majority of patients, white matter abnormalities and/or cortical atrophy were found. Only one of these patients had

signs of a mild atrophy before the start of treatment, suggesting a direct relationship between treatment and cognitive impairment. However, the aim to unveil the structural, metabolic, and functional consequences of cancer therapies goes beyond the field of clinical neuropsychological research and beyond the scope of the thesis.

Limitations and methodological considerations

The studies presented in this thesis have some methodological limitations. First of all, there is a possibility of selection bias in the HSCT studies despite the use of similar in- and exclusion criteria. In contrast to our retrospective study, about 20% of patients declined to participate to the longitudinal HSCT study. In the light of a fully scheduled and intensive pre-transplant check-up-scheme and distance to the hospital, this was not unexpected. Our patient groups may therefore not resemble the entire patient population which may have contributed to the disparities in the results.

A limitation of the longitudinal study is that outcome differences in our studies could be attributable to pre-existing group disparities rather than treatment effects. Given the fact that we did not observe differences between HSCT candidates and reference patients in our baseline assessment, this does not seem likely. In addition, using patients as their own controls by measuring cognitive function before and at various times after HSCT, was an important advantage of the longitudinal study. As such, pre-treatment baseline testing showing group equality and the use of an appropriate reference group is the next best alternative to a true random assignment. However, a 'true' baseline time-point prior to the start of the disease is impossible, as patients cannot be identified before their cancer diagnosis. Assessing hematological patients immediately after being diagnosed with a malignancy (and often life-threatening disease) before the start of any treatment is, regardless of ethical considerations associated with major supplementary difficulties. One is that the psychological effect of a recent cancer diagnosis would most likely result in a lower, rather than higher true baseline measurement of cognitive functioning.

Lastly, the assessment of cognitive impairment in the studies presented in this thesis involved a comparison between patients' test scores on measures of cognitive skills and published normative data. This is a common approach in clinical neuropsychology.[13,14] Test performance scores for a group of healthy individuals (ie, without cancer) comprise a valid control for the purpose of the studies, especially because patients diagnosed with non-CNS cancer are not commonly believed to experience overt neurological dysfunction and related cognitive impairment. So, their performance should be in a similar range to that of healthy controls with a comparable demographical background, in terms of age, gender and possibly educational level. The use of normative data has the advantage that it represents a larger sample than a control group recruited for a study, and it gives a more accurate and valid estimate of a so-called true score for the control group with which the study cohort is compared. Nonetheless, there are two problems with this method of comparison. Firstly, each neuropsychological test has its own set of published test norms; consequently there is a wide variance within normative test data, including differences in sample sizes and selection of healthy controls. This may lead to inconsistency in interpreting results. The other reason for critique is its failure to control for potential differences in emotional well-being and psychological distress that may accompany being diagnosed with a medical illness, in particular cancer. Thus, a similar affected reference group is desirable to control for this potentially confounding influence. We used therefore a

reference group of patients with hematological malignancies in the longitudinal study and the PCNSL study. Moreover, in each trial our neuropsychological assessment was supplemented with measures of psychological functioning, QOL and fatigue, to investigate the correlation between emotional and psychological distress and cognitive functioning.

Implications for clinical practice

Despite a growing recognition that cancer and its treatment may be associated with cognitive impairment, and that cognitive evaluations are valuable for patient care, there is still a shortage of practical contributions, like directions to provide better information, and to guide treatment decisions and therapeutic interventions.

Cognitive complaints should not be dismissed as being 'all in your head' or minimized as insubstantial. This is especially relevant given the lack of concordance between objective and subjective measures of cognitive functioning in existing literature and in our studies. Regardless of the level of cognitive difficulty experienced by cancer patients, it is essential for professionals to bear in mind that even minor cognitive deficits can have an impact on QOL. It is also important to identify the effects of the cognitive deficits in terms of everyday living. Neuropsychological expertise should be readily available in oncology clinics, and patients should be referred for a comprehensive evaluation if necessary.

Nurses and nurse practitioners, but also mental health professionals as psychologists and psychiatrists working in clinical settings, may play an important role in informing patients not only about their diagnoses and treatment, but also about potential side–effects and cognitive dysfunction interfering with daily-life routine, and assist in coping with them. For some patients the knowledge that cognitive dysfunction following treatment is not unique and the reassurance that deficits may possibly dissolve over time, is sufficient. In other cases, a neuropsychological assessment may be necessary to assess the extent of problems and monitor changes over time.

Final considerations and future perspectives

It is crucial for oncologists and other health professionals to recognize the cognitive sequelae of cancer and cancer treatment, and to intervene to minimize long-term effects. This issue has been underestimated in the past given that most studies focused on survival rates, adequate disease control or the physical side-effects of treatment. Though, it is also fair to mention that, particularly in the last five years, this area of research has received increased attention, and that the psychometric quality of the studies undertaken has improved immensely. Yet, there are still issues that need further investigation.

Despite our HSCT study, longitudinal data on the persistence of the observed deficits remain very scarce. It is world-wide recognized that patients' recovery from HSCT is a lengthy process that takes much longer than one year. Further long-term follow-up of our HSCT survivors and reference patients is necessary to investigate whether the observed deficits persist over time. As negative side-effects of HSCT on cognition are confirmed in future longitudinal studies, arguments should be made for a routine incorporation of objective cognitive measures as part of the neurotoxicity evaluation in clinical trials, simultaneously methods of intervention and preventing should be developed. Incorporating cognitive testing as a primary end point in clinical trials will help to determine the risks versus benefits of different treatment approaches.

Future research in PCNSL patients should focus on prospective and longitudinal studies to investigate the extent and changes associated with the different treatment regimens for this

malignancy. Age-related co-morbidity in PCNSL patients and the contribution of the disease itself (eg, the microscopally diffuse lesions, the angiopathic growth pattern and the wide spread infiltration) in cognitive decline, need further attention. Difficulties within this area of research are the low incidence of the disease and the absence of a standard neuropsychological test battery that could be included in clinical trials. A test battery that is useful in clinical trials should have the following characteristics: it should be brief, to reduce patient and clinical burden; standardized and simple to administer; have good psychometric properties (eg, good validity, reliability and populations norms); and, include tests that measure cognitive effects of the tumor and of treatment.[15]
It is promising that very recently guidelines for the assessment of cognitive functions in PCNSL patients have been developed in cooperation with the International PCNSL Collaborative Group, and that a standardized and core battery of neuropsychological and QOL measures for prospective clinical trials will be introduced internationally in the near future.[16] Incorporation of formal and systematic cognitive evaluations in PCNSL studies will increase our understanding of treatment-related toxicity in this population.

In conclusion, the consistent findings of cognitive impairment in the studies discussed in this thesis suggest a measurable and sustained effect of intensive treatment regimens for hematological malignancies on cognitive functioning, although all studies had multiple confounding factors as noted in each chapter. The relationship between intensive treatment schedules and cognitive functioning is complicated. There are a number of factors which may influence cognitive performance and it is difficult to establish which of these factors play a central role. The present findings point out that treatment-related cognitive changes are not universal among cancer patients. Some patients are able to tolerate therapy with no obvious impairments, while others will develop significant toxicities that seriously compromise their QOL and prevent them from social and occupational roles. The challenge to date has been to convincingly demonstrate the existence of this subgroup of cancer patients through methodologically sound longitudinal neuropsychological studies. This thesis highlighted some aspects of a complex puzzle; nevertheless many pieces are still missing.

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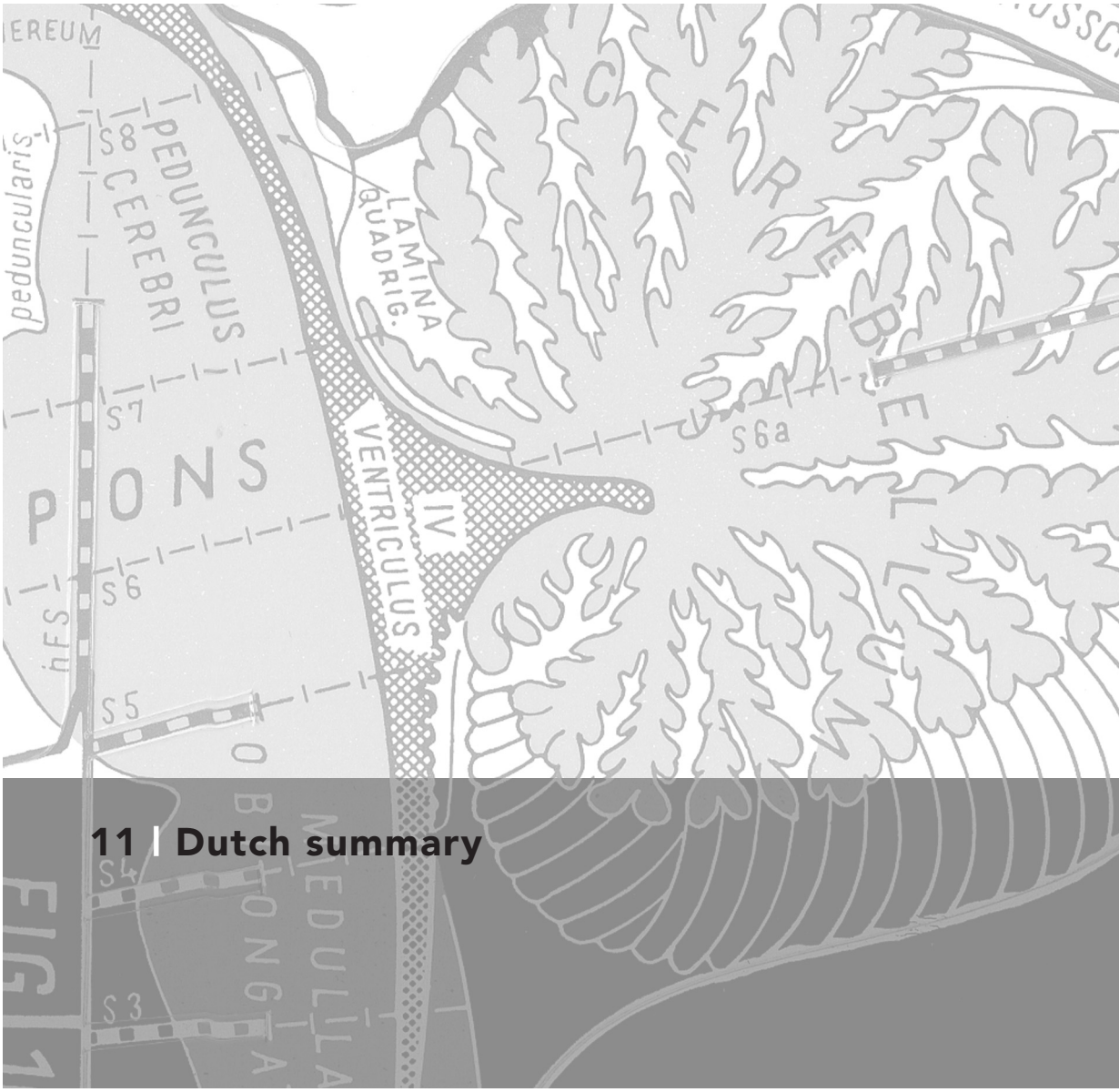

11 | Dutch summary

Door intensievere behandelingen wordt de diagnose kanker in toenemende mate een chronische aandoening. De betekenis van bijwerkingen van kankerbehandelingen op de lange termijn, waaronder neurotoxiciteit, wordt daardoor een belangrijker probleem. Naar verwachting zal het aantal overlevenden dat succesvol behandeld is voor kanker toenemen en daarmee ook het aantal patiënten dat te maken heeft met cognitieve en gedragsmatige beperkingen. Chemotherapie en radiotherapie op de hersenen kan leiden tot cognitieve beperkingen.[1] Onderzoek naar cognitieve functies na kankerbehandeling vindt zijn oorsprong in het begin van de jaren 80.[2] Er is echter nog steeds een tekort aan systematische, prospectieve en longitudinale studies waarin gebruik is gemaakt van grote steekproeven en objectieve psychometrische methoden. Tot voor kort richtten de meeste klinische studies zich op de overlevingsduur, de tijd tot progressie van de ziekte, de fysieke bijwerkingen of de gevolgen voor de kwaliteit van leven; de mogelijke cognitieve bijwerkingen van kankerbehandeling zijn onderbelicht gebleven.
In dit proefschrift worden de cognitieve gevolgen van intensieve behandeling voor hematologische maligniteiten besproken. De nadruk ligt op de prevalentie en de kenmerken van cognitieve beperkingen van patiënten die behandeld zijn met een beenmerg- of stamceltransplantatie (HSCT) en patiënten met een primair centraal zenuwstelsel lymfoom (PCNSL). Daarnaast wordt de relatie tussen cognitieve functies en subjectieve cognitieve klachten, kwaliteit van leven en psychologisch functioneren belicht. Dit hoofdstuk beschrijft de belangrijkste bevindingen van de studies uit dit proefschrift, de methodologische overwegingen en aanbevelingen voor vervolgonderzoek.

Hoofdstuk 2 geeft een overzicht van de bijwerkingen (toxiciteit) van kankerbehandelingen op het centraal zenuwstelsel (CNS), waaronder de mogelijke oorzaken en de gevolgen van deze bijwerkingen op cognitieve functies. Ernstige 'late' neurologische complicaties die samenhangen met de behandeling zijn radiatienecrosis en leukencefalopathie; beide worden gekenmerkt door neurologische afwijkingen en progressieve cognitieve achteruitgang. De incidentie en het risico van neurotoxiciteit is afhankelijk van een aantal factoren, zoals de doorlaatbaarheid van de bloed-hersenbarriére (BBB) voor chemotherapeutica, de dosis en de wijze van toediening van chemotherapeutica, de totale dosis en fractiedosis van de radiotherapie, de omvang van het bestralingsveld en andere aanvullende behandelingen die gelijktijdig worden gegeven. Immunotherapie met cytokines en behandeling met bepaalde medicamenten zoals corticosteroiden of middelen tegen immuunsuppressie, kunnen ook leiden tot neurotoxiteit. De onderliggende pathogenese van neurotoxiciteit is een onbegrepen en complex proces. Het is een aaneenschakeling van directe en indirecte effecten op neuronen en gliacellen waarbij waarschijnlijk sprake is van een verstoring in genetische, metabolische en neurotransmitterprocessen, van secundaire inflammatie of auto-immunologische reacties en van cerebrovasculaire beschadigingen, vooral in de capillaire microvasculatuur en de doorlaatbaarheid van de BBB.
Hoofdstuk 3 beschrijft een literatuuronderzoek naar cognitieve disfuncties bij HSCT patiënten. Deze bestaan vooral uit diffuse afwijkingen in de motorische functies, de executieve functies en het geheugen, zowel voorafgaand aan de transplantatie als na afloop van de behandeling. De gerapporteerde prevalentie loopt uiteen van 20%-78% voor de behandeling en van 37%-79% na de transplantatie. Deze discrepantie kan ondermeer verklaard worden door verschillen in de definitie van cognitief disfunctioneren. Risicofactoren voor een slechtere uitkomst zijn demo-

grafische factoren (resp. hogere leeftijd, mannelijk geslacht, lager opleidingsniveau en lagere premorbide intelligentie) en factoren gerelateerd aan ziekte en/of behandeling (resp. schedelbestraling, chemotherapie vóór de transplantatie, intrathecale behandeling, duur en stadium van de ziekte bij transplantatie, dosis van de totale lichaamsbestraling [TBI] en graft-versus-host-ziekte). De methodologische tekortkomingen van de studies (resp. relatief kleine steekproeven, diversiteit in patiëntenselectie en het ontbreken van een controlegroep) beperken de interpretatie van de huidige onderzoeksresultaten.

In **hoofdstuk 4** wordt een literatuuroverzicht gegeven van de studies op het gebied van het cognitief functioneren na behandeling voor PCNSL met totale schedelbestraling, hoge-dosis-chemotherapie, combinatiebehandeling (chemo- en radiotherapie) of intra-arteriële chemotherapie met verstoring van de BBB. Het merendeel van de neuropsychologische studies is prospectief en veelal opgenomen in een klinische studie. De geobjectiveerde cognitieve beperkingen bestaan uit stoornissen in de aandacht, de executieve functies, het geheugen, de taal (benoemen) en de psychomotorische snelheid. Vaak is al voor de behandeling sprake van cognitieve beperkingen. Patiënten die een combinatiebehandeling hebben ondergaan lijken meer nadrukkelijke stoornissen te vertonen, terwijl bij chemotherapie sprake is van een stabiel of verbeterd functioneren na afloop van de behandeling. Meer grootschalig en systematisch klinisch en neuropsychologisch onderzoek is wenselijk.

De resultaten van een retrospectieve studie bij langdurige overlevenden van HSCT worden weergegeven in **hoofdstuk 5**. We onderzochten een cohort van 40 ziektevrije patiënten met hematologische maligniteiten die minstens twee jaar voorafgaand aan de studie waren behandeld met HSCT. De inductie bestond uit hoge-dosis-chemotherapie en TBI waarna de meeste patiënten een allogeen transplantaat kregen toegediend. In vergelijking met normgegevens werden milde tot matige cognitieve beperkingen geobjectiveerd bij 60% van de patiënten. Deze bestonden uit stoornissen in de selectieve aandacht, de executieve functies, de snelheid van informatieverwerking en het verbale en visuele geheugen. De snelheid van informatieverwerking was significant lager vergeleken met verwachte scores van een gezonde normpopulatie ($p = .001$). Vermoeidheid, algehele gezondheid en opleidingsniveau droegen bij aan de spreiding van de afwijkende scores. Een korte cognitieve screening test (de Mini-Mental State Examination)[3] liet geen afwijkingen zien. Onze bevindingen benadrukken de waarde van het gebruiken van cognitieve functies als een uitkomst-variabele in HSCT studies.

In **hoofdstuk 6** staan de resultaten beschreven van een pilotstudie naar mogelijke veranderingen in de cognitieve functies van HSCT patiënten gedurende het eerste jaar na de transplantatie. Minder dan de helft van een groep van 25 patiënten die geïncludeerd waren voor de baselinemeting, kon deelnemen aan het vervolgonderzoek. Uitval werd veroorzaakt door overlijden, progressie van de ziekte (voor en na HSCT) en ernstige complicaties na de transplantatie. Bij 24% werden cognitieve beperkingen geobjectiveerd voorafgaand aan de transplantatie, voornamelijk in de selectieve aandacht en de snelheid van de informatieverwerking. Random regression modeling (RRM) analyse liet een kleine verbetering zien in de gemiddelde groepscores van de geheugentaken, vooral bij jongere patienten. Dit kan samenhangen met leereffecten. Er was sprake van een verbetering van het emotioneel functioneren in de loop van de tijd. Depressie en woede beïnvloedden de cognitieve prestaties van de baselinemeting. Het emotioneel functioneren had invloed op de prestaties bij het vervolgonderzoek. We concludeerden dat een baselinemeting voorafgaand aan HSCT noodzakelijk is, evenals een voldoende grote onderzoeksgroep vanwege de 50% uitval.

We vergeleken de cognitieve functies van HSCT patiënten voor de transplantatie met die van een referentiegroep van patiënten met hematologische maligniteiten die een standaard (niet-myeloablatieve) behandeling ondergingen in **hoofdstuk 7**. De resultaten van de baselinemeting van deze prospectieve en vergelijkende studie met een groot en representatief cohort van 101 HSCT patiënten en 82 referentie-patiënten gaven weer dat bijna 20% van de HSCT patiënten cognitieve beperkingen ondervindt voorafgaand aan de transplantatie. Deze bestaan uit stoornissen in het visuele geheugen, de visuospatiële- en constructieve vaardigheden en de psychomotorische functies. Tussen beide groepen bestonden geen verschillen met betrekking tot de ernst en de aard van de cognitieve beperkingen. Ook vonden we geen verband tussen de cognitieve functies en behandelingsfactoren. In de transplantatiegroep was sprake van een hoger percentage patiënten dat geclassificeerd kon worden als een patiënt met een angststoornis. Daarnaast was sprake van een significant lager niveau van subjectief-cognitief, emotioneel en sociaal functioneren in deze groep. Deze bevindingen waren niet gerelateerd aan de cognitieve prestaties.

We onderzochten of de cognitieve functies in deze patiëntengroepen veranderden in de loop van tijd met vervolgonderzoek na 8 en 20 maanden. De resultaten van deze studie worden beschreven in **hoofdstuk 8**. Zoals voorspelt in de pilotstudie, was slechts 54% van de HSCT patiënten in staat om aan het vervolgonderzoek deel te nemen in tegenstelling tot 72% van de referentie-patiënten. Bij RRM analyse was geen sprake van significante veranderingen in de cognitieve functies in de loop van de tijd. Echter, de prestaties op tests voor de aandacht en executieve functies en de psychomotorische functies waren lager in de HSCT groep (resp. $p = .01$, $p = .03$). Dit werd gedeeltelijk verklaard door TBI. De analyse wees uit dat vrouwelijke en oudere patiënten lagere resultaten behaalden. Bij de vragenlijsten was sprake van meer fysieke vermoeidheidsklachten in de HSCT groep en een matig verband tussen de cognitieve functies en globale gezondheid en psychologisch functioneren. Het percentage patiënten dat weer deelnam aan het arbeidsproces was lager in de HSCT groep. Er lijkt echter anderhalf jaar na de transplantatie geen sprake van aanzienlijke bijkomende negatieve effecten van HSCT op de cognitieve functies. Onze resultaten suggereren dat vooral de cytotoxische behandeling voor de transplantatie een belangrijke rol lijkt te spelen in de ontwikkeling van behandeling-geïnduceerde cognitieve beperkingen. We benadrukten dat nader onderzoek in dit cohort op de lange termijn geïndiceerd is om te onderzoeken of de cognitieve functies, in het bijzonder de aandacht en executieve functies en de psychomotorische functies, zullen verbeteren, stabiliseren of verminderen.

In **hoofdstuk 9** zijn de resultaten beschreven van een studie naar de cognitieve functies van een relatief jonge (mediane leeftijd is 44 jaar) groep ziektevrije patiënten die behandeld waren voor PCNSL in een prospectieve 'European Organization for Research and Treatment of Cancer' studie (EORTC studie 20962). Alle 19 patiënten kregen intraveneuze en intrathecale hogedosis-chemotherapie (MTX), gevolgd door totale schedelbestraling. De resultaten werden vergeleken met controlepersonen (geselecteerd op leeftijd, geslacht en duur na behandeling) met systemische hematologische maligniteiten en met neuroradiologische bevindingen. Bij 63% van de patiënten werden milde tot matige cognitieve beperkingen gevonden, terwijl dit percentage in de controlegroep slechts 11% was ($p = .002$). Deze beperkingen bevonden zich vooral op het gebied van het verbale en visuele geheugen, de aandacht en executieve functies en de motorische snelheid. Er was een positieve correlatie tussen de ernst van de stoornissen en oudere leeftijd. De verschillen tussen beide patiëntengroepen konden niet verklaard worden

door 'storende' factoren, zoals het psychologisch functioneren en vermoeidheid. Bij 78% van de patiënten was sprake van witte stof afwijkingen en corticale atrofie. De aanwezigheid van corticale atrofie correleerde met een hoger percentage cognitieve afwijkingen, oudere leeftijd en een lagere performance status. Uit onze studie kan geconcludeerd worden dat PCNSL patiënten die behandeld zijn met deze combinatiebehandeling cognitieve beperkingen hebben, zelfs indien deze patiënten jonger zijn dan 60 jaar.

CONCLUSIES

Discussie van de belangrijkste bevindingen

In onze studies vonden we aanwijzingen voor cognitieve beperkingen bij een deel van de patiënten die een intensieve behandeling ondergaan voor hematologische maligniteiten. Deze bevindingen komen overeen met eerdere onderzoeksresultaten.[4] Cognitieve beperkingen werden vooral gevonden bij patiënten met een tumorlokalisatie in het CNS, en slechts in een deel van de patiënten met andere hematologische maligniteiten.

In een cross-sectionele studie naar cognitief disfunctioneren bij HSCT patiënten bleek 60% milde tot matige cognitieve beperkingen te hebben, in het bijzonder met betrekking tot de snelheid van informatieverwerking.[5] De resultaten van twee prospectieve studie wezen uit dat een aantal van deze problemen al voor de transplantatie aanwezig zijn; ongeveer een kwart van de patiënten heeft cognitieve beperkingen voor de behandeling.[6,7] Neuropsychologisch onderzoek na de transplantatie liet geen significante veranderingen zien ten opzichte van de baselinemeting en er was sprake van kleine verschillen in vergelijking met patiënten die geen transplantatie hadden ondergaan met betrekking tot de aandacht, de executieve functies en de psychomotorische functies.[8]

Op basis van literatuurgegevens en de cross-sectionele studie hadden we een groter aantal cognitieve problemen verwacht na de transplantatie, evenals veranderingen in de cognitieve functies door de tijd heen. HSCT patiënten ondergaan een intensieve behandeling met hoge-dosis-chemotherapie en vaak ook TBI. Daarnaast is deze patiëntengroep onderhevig aan langdurig gebruik van medicatie voor immunosuppressie en complicaties die samenhangen met de behandeling, zoals graft-versus-host-ziekte en infectieziekten die ontstaan door immunodeficiëntie. De patiënten hebben naast een aanvullende kankerbehandeling ook meer risico's op neurotoxiciteit vooral door ernstige complicaties na de transplantatie.

Een mogelijke verklaring voor deze lagere prevalentie van cognitieve disfuncties is dat de patiënten in de longitudinale studie op een eerder tijdstip na de transplantatie werden onderzocht dan de patiënten in de cross-sectionele studie. Het laatste neuropsychologisch onderzoek werd gemiddeld 19 maanden na de transplantatie afgenomen terwijl de patiënten van de retrospectieve studie tussen 22 en 82 maanden na de behandeling werden onderzocht. Het is algemeen bekend dat de nadelige effecten van kankerbehandeling zich soms pas in de loop van de tijd ontwikkelen. De bijwerkingen kunnen jaren na de feitelijke blootstelling ontstaan waardoor neurotoxiciteit en cognitieve disfuncties optreden. Samen met de late effecten van de transplantatie, zoals een groot aantal gezondheidsproblemen en aanhoudende vermoeidheid,[9] kan dit hebben bijgedragen aan verschillen tussen de studies.

Ook kan deze discrepantie zijn ontstaan door verschillen in de transplantatie-inductie schema's en indicatiestelling. Alle patiënten in onze cross-sectionele studie kregen hoge-dosis-

chemotherapie en TBI, terwijl in onze longitudinale studie bijna een kwart van de patiënten niet werd behandeld met TBI. De meerderheid van de patiënten was afkomstig van één oncologisch behandelcentrum en kregen vergelijkbare inductieschema's. De inductie behandeling is in de afgelopen jaren enigszins gewijzigd met een lager risico op neurotoxiciteit en mogelijk minder invloed op de cognitieve functies. Deze verklaring blijft echter speculatief, zo werden er geen aanwijzingen gevonden voor verschil in functioneren bij autologe en allogene transplantatie-patiënten. Daarnaast suggereren de resultaten van de longitudinale studie dat de behandeling voorafgaand aan de transplantatie mogelijk een belangrijke rol speelt in de ontwikkeling van cognitieve beperkingen aangezien bijna twee jaar na de baselinemeting geen significante veranderingen werden gevonden.

Onze PCNSL-studie is één van de eerste onderzoeken naar de cognitieve gevolgen van een combinatiebehandeling uit een klinische trial.[10] We gebruikten een uitgebreide neuropsychologische testbatterij om de lange-termijn effecten te onderzoeken. In tegenstelling tot de transplantatie studies bleek sprake van een fors aantal cognitieve problemen bij patiënten met een relatief jonge leeftijd. Onze bevindingen wijzen uit dat de combinatiebehandeling en de ziekte zelf leidt tot substantiële cognitieve beperkingen die een negatieve invloed hebben op het alledaags functioneren omdat minder dan de helft van de patiënten was teruggekeerd in het arbeidsproces. Een aandachtspunt voor verder onderzoek op dit gebied is de bovenstaande bevindingen te verifiëren in een grootschalige en longitudinale studie. Momenteel is er een internationale studie in voorbereiding.

Er bleek in onze HSCT-studies geen consistent verband te zijn tussen het subjectief cognitief funcioneren (cognitieve klachten) en de prestaties van het neuropsychologisch onderzoek. Dit kan samenhangen met de verschillende meetinstrumenten die gebruikt werden om deze klachten te meten. In de cross-sectionele studie en de pilotstudie werd de aanwezigheid en ernst van de klachten gemeten door de neuropsycholoog tijdens een korte anamnese voor het onderzoek. Dit is een algemene procedure in de klinische praktijk en mogelijke problemen werden voorkomen door alle onderzoeken af te laten nemen door één individu. In de andere studies werden patiënten gevraagd om een vragenlijst in te vullen waarmee de frequentie van alledaagse cognitieve beperkingen over geheugen, aandacht, uitvoering en perceptie werd gemeten.[11,12] Beide instrumenten kunnen verschillende concepten meten en de aanleiding zijn voor inconsistente bevindingen.
Een andere verklaring voor het ontbreken van een verband tussen de subjectieve en de objectieve meetinstrumenten kan zijn dat patiënten hun eigen prestaties niet goed kunnen beoordelen (patiënten met een hersentumor kunnen bijvoorbeeld een beperkt ziekte-inzicht hebben door de hersenbeschadiging), zich aanpassen aan de beperkingen, of er op een andere wijze mee om leren gaan. Ook is het mogelijk dat patiënten zich aanpassen aan een 'nieuwe manier van leven' en minder een beroep doen op hun cognitieve mogelijkheden waardoor een achteruitgang in functioneren niet meer van belang is. Dit lijkt plausibel omdat een groot deel van de patiënten niet meer kan terugkeren op het premorbide niveau of volledig kan deelnemen aan beroepsmatige, opleidings- of sociale activiteiten. Daarnaast speelt mogelijk een zogenaamde 'response-shift' een rol omdat patiënten de standaard waarmee ze de kwaliteit van leven beoordelen in de loop van de tijd veranderen. Zo kan bijvoorbeeld iemand die behandeld is voor kanker anders (minder belastend) tegen cognitieve beperkingen aankijken.

De patiënt kan zich min of meer gedwongen voelen om minder waarde te hechten aan en minder te klagen over cognitieve klachten omdat andere concepten (zoals 'nog in leven zijn', familiecontacten) een belangrijkere plaats hebben ingenomen.

Een belangrijk punt voor verder onderzoek is het vaststellen van de specifieke cytotoxische middelen, behandelingsmethoden en combinaties van behandelingen die verantwoordelijk zijn voor het ontstaan van de cognitieve beperkingen. Onze studies leveren geen antwoord op dit oorzaak-en-gevolg-vraagstuk. De PCNSL studie is een eerste stap naar de zoektocht naar eventuele oorzaken. Het cognitief functioneren werd vergeleken met neuroradiologische afwijkingen op de MRI. Witte stof afwijkingen en/of corticale atrofie werden gevonden in de meerderheid van de patiëntengroep. Bij slechts één van de patiënten was sprake van een milde atrofie voor de behandeling; dit suggereert dat er een directe relatie bestaat tussen de behandeling en de geobjectiveerde cognitieve beperkingen. Tumor effecten valen echter niet uit te sluiten. Onderzoek naar de structurele, metabolische en functionele gevolgen van kankerbehandelingen gaat echter verder dan de klinische neuropsychologie en voorbij aan het doel van dit proefschrift.

Beperkingen en methodologische overwegingen

De studies die in dit proefschrift zijn beschreven hebben een aantal methodologische beperkingen. Allereerst is in de HSCT-studies mogelijk sprake van een selectie-bias ondanks het gebruik van inclusie- en exclusiecriteria. In de longitudinale studie weigerden ongeveer 20% van de patiënten om deel te nemen aan de studie. Dit is niet onverwacht gezien het intensieve behandelingsschema voorafgaand aan de transplantatie. Het is daardoor mogelijk dat de patiëntengroepen uit de studies niet vergelijkbaar zijn met de totale patiëntenpopulatie.

Een beperking van de longitudinale studie is dat discrepanties in de resultaten kunnen samenhangen met verschillen die reeds bestonden voor de behandeling, en niet met effecten van de behandeling. De invloed van deze vorm van test-bias lijkt echter klein gezien het feit dat er geen verschillen werden gevonden tussen de patiëntgroepen bij de baselinemeting. Ook fungeerden de patiënten als eigen controlepatiënt doordat het cognitief functioneren door de tijd heen werd gemeten op verschillende meetmomenten. Een baselinemeting voor de behandeling en het gebruik van een referentiegroep zijn een goed alternatief voor randomisatie. Een 'echte' baselinemeting voor de aanvang van de ziekte is echter niet mogelijk. Het afnemen van een neuropsychologisch onderzoek vlak nadat men op de hoogte is van een maligne aandoening (en veelal levensbedreigende ziekte) en voor aanvang van de behandeling, gaat naast allerlei ethische bezwaren samen met andere methodologische beperkingen. Eén hiervan is dat het psychologische effect kort na het vernemen van een maligne diagnose zeer waarschijnlijk resulteert in lagere testresultaten.

Onderzoek naar cognitieve functies in dit proefschrift werd uitgevoerd door de testresultaten van patiënten te vergelijken met normscores. Dit is een gebruikelijke benadering in de klinische neuropsychologie.[13,14] De prestaties van gezonde personen kunnen dienen als een controle, temeer omdat bij patiënten zonder tumorlokalisatie in het CNS geen neurologische disfuncties, - en hieraan gerelateerde cognitieve beperkingen - worden gevonden. Het gebruik van testnormen heeft ook het voordeel dat gebruik gemaakt kan worden van een grotere steekproef. Hierdoor kan een accurate schatting worden gemaakt van de prestaties van de controlegroep waarmee de patiëntengroep wordt vergeleken. Er zijn echter een tweetal

nadelen aan het gebruik testnormen. Elke neuropsychologische test heeft veelal afzonderlijke normscores waardoor variatie bestaat in de steekproefgrootte en de selectie van de proefpersonen. Hierdoor kan sprake zijn van inconsistentie in de interpretatie van de resultaten. Daarnaast kan bij het gebruik van testnormen niet gecontroleerd worden voor verschillen ten aanzien van emotioneel en psychologisch disfunctioneren waarmee een medische aandoening vooral kanker, vaak gepaard gaat. Om hiervoor te controleren is het gebruik van een vergelijkbare groep patiënten wenselijk. In de longitudinale HSCT studie en in de PCNSL studie werd derhalve gebruik gemaakt van een referentiegroep met patiënten met hematologische maligniteiten. Daarnaast werden in elke studie instrumenten opgenomen om het psychologisch functioneren, de kwaliteit van leven en vermoeidheid te meten om het verband tussen de verschillende functies vast te stellen.

Implicaties voor de klinische praktijk

Ondanks de erkenning dat kanker en kankerbehandeling kunnen samengaan met cognitieve beperkingen en dat cognitieve evaluaties belangrijk zijn voor de patiëntenzorg, is er nog steeds een tekort aan praktische bijdragen zoals bijvoorbeeld instructies voor betere patiëntenvoorlichting, begeleiding van beslissingen voor de behandeling en therapeutische interventies.
Cognitieve klachten van patiënten dienen serieus genomen te worden vooral omdat een verband tussen objectieve en subjectieve cognitieve meetinstrumenten ontbreekt. Onafhankelijk van de ernst van mogelijke stoornissen bij kankerpatiënten, is het essentieel dat men begrijpt dat zelfs milde cognitieve beperkingen invloed kunnen hebben op de kwaliteit van leven. Ook is het belangrijk om de effecten van cognitieve beperkingen op het alledaags functioneren te onderzoeken. Expertise op neuropsychologisch gebied dient aanwezig te zijn in oncologische behandelcentra en patiënten zouden indien nodig doorgestuurd moeten worden voor een uitgebreid testonderzoek.
Diverse medewerkers uit de klinische setting (verpleegkundigen, verpleegkundig-specialisten, psychologen en psychiaters) hebben een invloedrijke rol in de voorlichting van patiënten, niet alleen ten aanzien van de diagnose en behandeling, maar ook over mogelijke bijwerkingen en cognitieve beperkingen die kunnen interfereren met de dagelijkse routine. Tevens spelen ze een rol in het leren omgaan met eventuele beperkingen. Voor sommige patiënten voldoet de kennis dat cognitieve beperkingen na de behandeling kunnen voor komen en dat de stoornissen mogelijk kunnen verminderen in de loop van de tijd. Voor andere patiënten kan een neuropsychologisch onderzoek noodzakelijk zijn om de omvang van de beperkingen te meten en veranderingen in de tijd te volgen.

Beschouwing en toekomstperspectieven

Het is cruciaal dat oncologen en andere medewerkers uit de kliniek de cognitieve gevolgen van kanker en kankerbehandeling herkennen en ingrijpen om de lange termijn gevolgen te minimaliseren. In het verleden is dit onderschat en hebben de meeste studies zich op overlevingsduur, controle van de ziekte en de fysieke bijwerkingen gericht. Vooral de laatste vijf jaar is de belangstelling voor dit onderzoeksgebied toegenomen en is de psychometrische kwaliteit van de ondernomen studies sterk verbeterd. Desondanks zijn er een aantal aandachtspunten voor verder onderzoek.
Longitudinale gegevens over de persistentie van de geobjectiveerde cognitieve beperkingen blijft beperkt. Men erkent dat de herstelperiode na HSCT een langdurig proces is dat langer

dan een jaar kan duren. Vervolgonderzoek is noodzakelijk om te bepalen of de geobjectiveerde cognitieve beperkingen blijven bestaan in de loop van de tijd. Indien bij vervolgonderzoek aanwijzingen worden gevonden voor persisterende stoornissen dan is het belangrijk om objectieve cognitieve meetinstrumenten op te nemen als een onderdeel van de evaluatie naar toxiciteit in klinische trials. Ook dienen dan interventie en preventiemogelijkheden te worden overwogen. Neuropsychologisch onderzoek in klinische trials kan een bijdrage leveren in het onderzoek naar de voor- en nadelen van verschillende behandelingsmethoden.
Vervolgonderzoek bij PCNSL patiënten dient zich te richten op prospectieve en longitudinale studies die de aard en veranderingen bestuderen van de verschillende behandelingsmethoden voor deze aandoening. De leeftijdsafhankelijke co-morbiditeit en de bijdrage van de ziekte zelf (die kan resulteren in parenchym schade) aan de cognitieve achteruitgang dient meer aandacht te krijgen. Problemen binnen dit onderzoeksgebied zijn de lage incidentie van de ziekte en het ontbreken van een standaard neuropsychologische testbatterij. Zo'n testbatterij dient aan de volgende eisen te voldoen: kort, voor patiënt en medewerker van de kliniek; goede psychometrische eigenschappen (validiteit, betrouwbaarheid en normatieve data); en inclusie van tests die de effecten van de tumor en de behandeling te meten.[15]
Het is veelbelovend dat zeer recent richtlijnen voor onderzoek naar cognitieve functies bij PCNSL patiënten zijn ontwikkeld in samenwerking met 'the International PCNSL Collaborative Group' en dat een gestandaardiseerde kernbatterij van neuropsychologische tests en kwaliteit van leven meetinstrumenten wordt geïntroduceerd in de nabije toekomst.[16] Het opnemen van formele en systematische evaluaties in PCNSL studies zal de kennis van de toxiciteit van de behandeling voor deze aandoening doen toenemen.

Concluderend, de consistente bevindingen voor de aanwezigheid van cognitieve beperkingen in de studies die in dit proefschrift zijn beschreven suggereren een meetbare en aanhoudende invloed van intensieve behandelingen voor hematologische maligniteiten op het cognitief functioneren, ondanks de verschillende beperkende factoren die in elk hoofdstuk zijn aangegeven. Het verband tussen intensieve behandeling en de cognitieve functies blijft gecompliceerd. Er zijn verschillende factoren van invloed op de cognitieve functies en het is bijna onmogelijk om te bepalen welke factor de meest centrale rol speelt. De huidige bevindingen geven aan dat cognitieve veranderingen na een kankerbehandeling niet universeel zijn. Sommige patiënten zijn in staat een behandeling te doorstaan zonder aantoonbare stoornissen, terwijl anderen neurotoxiteit ontwikkelen die de kwaliteit van leven aanzienlijk beperkt en hen weerhoudt om sociale en beroepsmatige activiteiten te ondernemen. Tot op heden was het een uitdaging om het bestaan van deze subgroep van patiënten te bewijzen met behulp van goede methodologische en longitudinale studies. Dit proefschrift heeft een aantal aspecten van de complexe puzzel belicht, echter er zijn nog veel stukken die onvindbaar blijven.

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De volgende in de rij is mijn promoter Martin van den Bent. Martin, ik weet dat vooral jij opgelucht zal zijn dat het werk (ondanks een vermeende IT-kloof) dan toch écht af is. Door de jaren heen heb je een goede balans kunnen vinden tussen enerzijds aanhoudend begrip en steun voor het onderzoek en schrijfwerk en anderzijds enig 'pushwerk', wat toch echt nodig was voor de productie van dit boekwerk. Je was een uitstekende leerschool voor het opdoen van kennis op neuro-oncologisch gebied en vooral ook bij het schrijven en publiceren van manuscripten, waarbij het aantal versies door de jaren heen aardig gereduceerd is. Daarnaast is je wens (de ontwikkeling van een verkorte neuropsychologische testbatterij) dan toch, indirect, uitgekomen. In mijn ogen is het alleen maar een voordeel dat het allemaal wat langer heeft moeten duren omdat je nu in eigen persoon mijn promotor kunt zijn. Datzelfde geldt ook voor mijn co-promotor Arthur Van Gool die door zijn promotie nu plaats heeft kunnen nemen in de grote commissie. Arthur, je kwam trouw even polsen hoe de zaken ervoor stonden als ik weer eens in het ziekenhuis was en toonde je altijd bereid om je snel door mijn bergen papier heen te werken. Daarnaast heb ik met alle plezier over de jaren heen diverse klinisch diagnostische 'consulten' voor jou mogen verrichtten. Ik hoop dat voor jullie beiden na mijn definitieve vertrek uit de Daniel, de betrokkenheid en belangstelling voor onderzoek naar de cognitieve gevolgen van kankerbehandeling zal blijven voortbestaan.
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Zonder de test-assistenten die bij het onderzoek betrokken waren (Daniëlle Smeets, Hester Holtel en Gwendolien Graumans) had ik, logistiek gezien, de ruim 500 neuropsychologische onderzoeken nooit kunnen afnemen. Wij hebben in de Daniel en door heel Nederland heen (van Leeuwarden, Alkmaar, Goes tot den Bosch) een berg data weten te verzamelen. In het bijzonder wil ik Hester Holtel bedanken die voor haar afstudeerproject alle PNCSL patiënten van de EORTC studie heeft onderzocht, zelfs in België.
De medewerksters van het secretariaat van de afdeling Neuro-oncologie, Ria van Straten, Erica Kroos en Marieke van Walsum hebben mijn werkzaamheden aanzienlijk weten te verlichten door hun hulp bij de coördinatie van alle afspraken als ik afwezig was als in deeltijd-werkende-moeder. Zeker de laatste twee jaar wanneer ik niet daadwerkelijk op de afdeling aanwezig was bleek jullie inzet onmisbaar. Vooral Ria heeft mij, met haar kennis van allerlei zaken in het

ziekenhuis veel diensten mogen bewijzen, van een handleiding voor de fax tot zelfs het boeken van de promotiedatum; daar kan geen fles rosé tegen op. Ook de andere collega's van de afdeling wil ik bedanken voor de diverse lunch- en taartbijeenkomsten die het soms werk even deden vergeten.
Mijn (inmiddels oud-) collega's van de afdeling Neuropsychologie van GGZ-Delfland in Delft hebben de afgelopen twee jaar veel belangstelling en waardering getoond voor mijn inzet voor dit boekwerk. Het was naast al het schrijfwerk goed om ook met 'echt' klinisch werk bezig te zijn bij een bijzondere patiëntendoelgroep (en Meike, zoals beloofd, bedankt voor het lenen van 'het hoofd' dat een prominente plaats heeft gekregen).
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Last, but not least natuurlijk mijn eigen familie. Lieve Naomi en Rowan, 'het boek is uit'. Eindelijk is er alle tijd om jullie eindeloos voor te lezen, samen te voetballen, koekjes te bakken of er gewoon voor jullie te zijn. Dear Nick, this book was just one of the reasons for our stay in the Netherlands. We have had a hectic but fruitful and very good time. Thanks for your endless support throughout the years and for now: let our adventure begin!

CURRICULUM VITAE

Helena Harder werd op 11 december 1965 geboren in Smallingerland. In 1983 behaalde zij haar HAVO-diploma aan het Corderius College in Amersfoort en begon ze de opleiding Jeugdwelzijnswerk aan de Windesheim Academie in Zwolle. Na deze HBO-opleiding begon ze in 1987 aan de studie Pedagogiek aan de Universiteit van Utrecht. Via de propedeuse Algemene Sociale Wetenschappen stapte ze na één jaar over naar de studie Psychologie. In 1991 begon ze aan de praktijkstage op de afdeling Neuropsychologie van het Leids Universitair Medisch Centrum in Leiden. In 1993 en 1994 deed ze tijdens haar studie werkervaring op als testpsycholoog bij Centrum Maliebaan, een centrum voor verslavingszorg in Utrecht. In 1995 behaalde ze haar doctoraal-examen binnen de vakgroep Psychonomie met als afstudeerrichting Cognitieve Functiestoornissen.
Van 1996 tot 2004 was ze werkzaam als neuropsycholoog/onderzoeker op de afdeling Neurooncologie van het Erasmus MC-Daniel den Hoed Oncologisch Centrum in Rotterdam. Ze was hier betrokken bij verschillende onderzoeksprojecten naar cognitief functioneren en kankerbehandeling. In de periode 1999 tot 2003 werd de data verzameld voor de studies die beschreven zijn in dit proefschrift. Dit onderzoek werd gefinancieerd door de Nederlandse Kankerbestrijding. Hiernaast was ze van 1997 tot medio 1999 werkzaam als testpsycholoog bij Centrum Maliebaan in Utrecht waar ze haar ervaring met psychodiagnostische werkzaamheden kon uitbreiden. Vanaf medio 2004 werkte ze in de psychiatrie, als neuropsycholoog op de afdeling Neuropsychologie van GGZ-Delfland in Delft. In augustus 2006 is ze met haar man en gezin voor een aantal jaren naar Kathmandu in Nepal vertrokken.


CP
CORPUS PINEALE
BER CINEREUM
Fossa inter-peduncularis
PEDUNCULUS CEREBRI
S8
S7
S6
S6a
PONS
LAMINA QUADRIG.
VENTRICULUS IV
CEREBELLUM
S5
S4
S3
S2
MEDULLA OBLONGATA
FIG. 10
ENDHAKEN
V
C
RA