Chapter 8

Summary and General Discussion

The aim of this study was to determine neurocognitive function after childhood cancer. With the rise of the survival rate of childhood cancer, late effects of treatment are becoming increasingly apparent, including deleterious effects on neurocognitive function. Recent research demonstrates that cognitive problems are among the late effects reported most frequently by survivors.[1] Children who have received therapy toxic to the developing brain or who have survived cancers involving the central nervous system (CNS) have the highest risk of developing long-term neurocognitive sequelae. Adverse outcomes are observed most frequently in survivors in survivors of a brain tumor and in survivors of acute lymphoblastic leukemia (ALL), treatment of which includes CNS-directed therapy.[2]

Our study focused on the long-term neurocognitive effects of CNS-directed chemotherapy and of neurosurgery. Our study did not concentrate on the effects treatment with cranial irradiation, as the deleterious effects of this treatment modality on neurocognitive function in children have been well documented previously, and there are efforts to reduce its use as much as possible. Our focus was on the childhood cancers with the highest incidence: ALL and brain tumors. The largest part of our study concerned neurocognitive sequelae of CNS-directed chemotherapy in children with ALL, and the relationship of neurocognitive outcome with psychosocial functioning. A smaller section of our study involved long-term neurocognitive outcome after cerebellar tumors, treated with neurosurgery without additional radio- or chemotherapy. Our study focused on basic neuropsychological functions, underlying higher order cognitive ability.

Chapter 1 and ***2*** comprise the introduction, aims, design and outline of the study.

In ***Chapter 3*** the effects of CNS-directed chemotherapy on attentional function were analyzed in survivors of childhood ALL. We compared the performance of children with ALL treated with chemotherapy only, at least one year after end of treatment, with two control groups: children with a Wilms tumor, treated with non-CNS chemotherapy, and healthy controls. Within the ALL group, a distinction was made between standard treatment, for standard risk ALL, and intensified treatment, for higher risk ALL. Neurocognitive deficits were found in survivors of ALL, while the performance of survivors of a Wilms tumor was similar to controls. We found neurocognitive deficits to be mainly restricted to children who received intensified treatment. Children with ALL treated according to standard protocols showed worse performance than controls on only one task, assessing attentional flexibility. Children who received intensified treatment showed more extensive deficits. These deficits were in the domains of sustained attention, attentional

flexibility and visuomotor control and fall under the common denominator of executive function deficits.
Compared to standard protocols, intensified treatment was most notably characterized by higher dose systemic methotrexate, which has neurotoxic properties and is known to be potentially damaging to the central nervous system. Other risk factors that we identified in children with ALL were a young age at diagnosis and female sex.

In ***Chapter 4***, we studied in detail the various levels of visuomotor control in survivors of childhood ALL. Results were compared with children who had survived a Wilms tumor, siblings and with healthy school children controls. We found that higher order visuomotor control deficits were present in survivors of ALL. Results of children with a Wilms tumor and siblings did not differ from controls. Risk factors for worse performance in the ALL group were female sex and a shorter time since diagnosis. A non-significant trend was found for young age at diagnosis. Neurological examination of the children revealed no major neurological signs, indicating visuomotor performance is a marker of more subtle neurological impairment. This is in accordance with the notion of visuomotor skills as sensitive indicators of cerebral damage.[3,4] The relationship between motor performance and neurocognitive function, especially attention and other aspects of executive functioning, has been established in studies on normal and delayed development.[5] We suggest that the visuomotor problems in children with ALL may be related to abnormalities in the development of cerebellar-frontal brain systems due to treatment with methotrexate. This hypothesis has recently been supported by the results of a study by Mahone et al.[6], who found perceptual and motor timing deficits comparable to individuals with cerebello-frontal abnormalities in children with ALL treated with chemotherapy only. Cerebral white matter changes,[7-9] neuronal damage[10-12] and neurotransmitter abnormalities[13] have been described in children treated with chemotherapy. These mechanisms could be responsible for damage to these neural networks.

In ***Chapter 5***, Behavioral functioning and school performance in children with ALL and children with a Wilms tumor were compared to siblings and school children controls. Behavioral and educational limitations were found in the survivors of ALL, but not in the Wilms tumor or in the sibling group. There was a higher incidence of parent- and teacher reported problem behavior for children with ALL compared with controls. Parent-rated problem behavior was mainly attributable to internalizing problems and attention problems. There was an association between parent-reported attention problems and teacher-reported behavior problems. Weaker overall academic performance was observed in

survivors of ALL compared with controls. Poorer attentional function, as detected with neuropsychological tests (chapter 3) was associated with weaker mathematics performance. Treatment intensity was a risk factor for behavioral problems and weaker mathematics performance. Our results corroborate previous reports of an association between mathematics weaknesses and cognitive deficits in children with ALL.[14-16] Our findings of weaker school performance in the children with ALL must be viewed in the context that the great majority of these children are able to function in normal schools. Our observations indicate subtle but nevertheless significant problems of failing to quite realize innate potential regarding cognitive, educational and behavioral functioning in children with ALL. Although siblings have previously been reported to experience emotional distress and behavioral problems past the time of treatment of the cancer patient,[17] we could not confirm the presence of longer-term behavioral- or educational problems in this group.

In ***Chapter 6***, we compared performance on neuropsychological tasks between eleven survivors of a cerebellar tumor, treated with neurosurgery only, with healthy controls. We found executive function deficits in the survivors of a cerebellar tumor, characterized by slower information processing, increased variability of response times and decreased inhibition. The group of children with a cerebellar tumor that we studied is small compared to the ALL group in the previous chapters, but puts the findings in the children with ALL in perspective. As we have hypothesized that disturbance of cerebellar-frontal networks play a role in the emerge of neurocognitive deficits in children with ALL, it is of interest that the children with a cerebellar tumor show certain similarities in neurocognitive profile, regarding executive functioning. However, the children with a cerebellar tumor show more extensive deficits, and the effect sizes of the comparisons with the control group are larger for the children with a cerebellar tumor than for the children with ALL.

In ***Chapter 7***, a review is presented of studies of neurocognitive outcome after chemotherapy only for childhood ALL. The review includes 38 studies published until July 2007, and includes our studies from chapter 3 and 4. The review focused solely onstudies that included a chemotherapy-only group and a comparison group of healty children or patients who did not receive CNS-directed treatment. The conclusion was that survivors of childhood ALL treated with chemotherapy only experience subtle long-term neurocognitive deficits. The deficits mainly involve basic neuropsychological processes of attention and executive functioning, while global intellectual function is relatively preserved. Young age at diagnosis and female sex emerge as risk factors for poorer neurocognitive outcome.

RELATIONSHIP BETWEEN TREATMENT INTENSITY AND NEUROCOGNITIVE OUTCOME

In children with ALL treated with chemotherapy only, we found attentional dysfunction to be mainly restricted to the children who received intensified treatment for high risk disease. From our findings, methotrexate emerges as an important neurotoxic agent linked to neurocognitive sequelae. Compared to standard treatment, the cumulative systemic methotrexate dose was the only treatment factor that was significantly higher in intensified treatment for childhood ALL. Treatment of childhood ALL involves intravenous as well as intrathecal methotrexate. At the employed doses, intravenous methotrexate penetrates though the blood-brain barrier. To our knowledge, dose-related differences in task performance in patients with ALL receiving chemotherapy only have not previously been reported. Our study on visuomotor performance has been, to our knowledge, the first to report a direct relation between methotrexate dose and visuomotor task performance in survivors of ALL treated with chemotherapy only. This reached statistical significance only in girls.

In a recent study by Carey et al.[18], difficulties in working memory and nonverbal skills during ALL treatment were also related to higher intravenous methotrexate dose, as well as shorter infusion rate of methotrexate. In contrast to our findings, Spiegler et al.[19] reported no difference in outcome between treatment entailing high dose or very high dose methotrexate. However, as the treatment protocols in this study entailed an intravenous methotrexate dose that was higher than the high risk group in our study, even in the lowest risk group, and as there was no control group, it can not be excluded that perhaps subtle deficits were present even in the lowest methotrexate group in this study. More research on the relationship of methotrexate dose with neurocognitive outcome is warranted.

PATIENT-RELATED RISK FACTORS FOR NEUROCOGNITIVE DEFICITS

Age at diagnosis

We have found a young age at diagnosis to be related to poorer performance by survivors of childhood ALL on several measures of attention, information processing and visuomotor control. There is a expanding body of literature demonstrating young age at diagnosis to be a risk factor for cognitive dysfunction in survivors of childhood ALL and brain tumors.[20-29] The association has been explained as a greater vulnerability of less mature brain structures to neurotoxic insult.[30] It is becoming apparent that this applies not only to children treated with cranial irradiation, but also to children who received chemotherapy only.

Sex

In survivors of childhood ALL, we have found female sex to be a risk factor for

worse performance on attentional tasks and higher order visuomotor control. That females are more vulnerable to neurocognitive sequelae is becoming increasingly evident.[20,22,31,32] There is no definite explanation for this. It has been hypothesized that gender differences in brain maturation may underlie varying vulnerabilities between girls and boys. Increase in white matter during childhood has been demonstrated to be smaller in girls than in boys,[33] which could make girls more vulnerable to neurotoxic effects of chemotherapy. Female survivors of childhood cancer are not only at higher risk of long-term neurocognitive deficits, but have a higher risk in general for chronic health conditions relative to males.[34] A recent review of late effects of cancer therapy on health status showed that besides cognitive effects, female sex is a risk factor for cardiac, skeletal and endocrine problems.[35] The underlying causes of this female predisposition to toxic effects of cancer therapy remain to be elucidated. Theories based on hormonal differences between the sexes, or sex-based differences in DNA-repair enzymes are not (yet) supported by evidence.

STUDY DESIGN: THE INCLUSION OF COMPARISON GROUPS

The inclusion of several comparison groups permitted us to relate the results of the children with ALL who received CNS-directed treatment to children with a Wilms tumor, who experienced cancer but received no CNS-directed treatment, and to a sibling control group, who did not experience cancer, but did experience the emotional distress of a family member with the disease. This makes the hypothesis that neurotoxic effects of CNS-directed chemotherapy, rather than the experience of childhood cancer or the associated emotional distress, is a factor in the emergence of the cognitive, behavioral and educational problems in children with ALL more convincing. The inclusion of a large group of normal controls offered the advantage of not having to rely solely on population norms for comparison: performance within the population norm does not mean that there is no decline in neuropsychological function in the individual.

CLINICAL IMPLICATIONS

The computerized tests from the Amsterdam Neuropsychological Tests (ANT), we have used are very sensitive to deficits in attention and information processing.[36,37] We found subtle, but statistically significant deficits in children with ALL, treated with chemotherapy only. That these deficits also have clinical relevance is demonstrated in chapter 5: There is a correlation between attention deficits in survivors of ALL and behavioral and academic limitations. Children who underwent intensified treatment were at highest risk for negative neurocognitive as well as behavioral and academic outcome. The limitations found are generally subtle, but nevertheless, clinically significant. Regarding school

performance, the survivors of ALL were underperforming compared to their peers. They were 4 times as likely to have repeated a grade, compared with controls. However, the rate of children who needed special education services in our study is low and compares favorably with previously published rates of children with ALL treated with cranial irradiation.[38-43]

We have found executive function deficits in the children with cerebellar tumors treated with neurosurgery only. Although classically considered to be involved in motor coordination, a role of the cerebellum in cognitive development has become apparent in recent decades.[44] Our results are supported by recent studies that provide evidence for a role of the cerebellum in executive functioning.[45] It is becoming clear that even in the children with low-grade cerebellar tumors, who have high survival rates and are treated with neurosurgery only, long-term neurocognitive problems are often present. Further study of behavioral and educational functioning in children after resection of a cerebellar tumor without additional radio- or chemotherapy is certainly warranted. Long-term follow-up of cognitive and psychosocial functioning appears indicated for these children.[46]

In children with a Wilms tumor, treated with non-CNS chemotherapy, we did not find evidence of neurocognitive deficits, an increase of behavioral problems or a decrease of school performance. Also, siblings of cancer patients did not show increased rates of behavior or school problems.

RECOMMENDATIONS FOR THE FUTURE

Prospective studies

Most studies concerning neurocognitive outcome after childhood cancer, including our study, are cross-sectional. Longitudinal follow-up of childhood cancer patients, preferably starting at the time of diagnosis would provide more insight in the degree of possible neurocognitive decline, the effects of the various elements of therapy, and long-term course of neurocognitive problems in survivors of childhood cancer.

Identification of neurocognitive deficits in survivors of childhood cancer

A recent report form the Children's Oncology Group recently provided "Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer".[47] This group recommends that all childhood cancer survivors at risk for neurocognitive difficulties should have a baseline evaluation at the time of entry into long-term follow-up, even in the absence of any overt manifestation of CNS injury. In our opinion, neuropsychological testing may even be advisable at the start of treatment. It has been demonstrated that

testing shortly after diagnosis is feasible. In children with recently diagnosed ALL, results of testing shortly after diagnosis indicated no adverse effect of illness and psychological factors on IQ and neuropsychological functioning.[48] Based on the results of our study this neuropsychological testing would be advisable for children with brain tumors and for children with ALL. In children with ALL, this would be especially important for children with high risk disease, who will undergo intensified treatment. Baseline evaluation would help determine whether a child's functioning at a later time represents a decline. Further testing after baseline could be advised for example at one year after end of treatment or, in each case, when cognitive complaints, difficulties in school performance or in behavior arise.

Intervention strategies

The feasibility of using cognitive remediation for survivors of childhood cancer who have impairments has been tested: the Cognitive Remediation Program (CRP), developed by Copeland and Butler, comprises techniques from several disciplines: brain injury rehabilitation, special education/ educational psychology, and clinical psychology.[49,50] Pilot data have shown that participation in the program can result in improvement on a sustained attention task.[51] In the Netherlands, a training has been developed targeting children with cancer, for training attention and memory, the Amsterdam Training of Attention and Memory for children (ATAG-k).[52] As yet, no data on effectiveness of this training have been published. Further research is required to demonstrate efficacy of cognitive training programs for survivors of childhood cancer, and to give a better understanding of where additional development is still needed.[53]

Pharmacological intervention for neurocognitive late effects in survivors of childhood cancer has also received interest recently. As some symptoms in survivors of childhood ALL and brain tumors show correspondence with children with attention deficit hyperactivity disorder (ADHD), it has been suggested that these survivors might benefit from stimulant medication. Thompson et al.[54] reported improvement on measures of sustained attention from use of methylphenidate in learning-impaired survivors of childhood ALL and brain tumors in a randomized, double-blind, placebo-controlled clinical trial. Mulhern et al. found significant improvement with methylphenidate compared to placebo on behavior rating scales among survivors of childhood ALL and brain tumors, as reported by teachers and parents.[55] Although these studies show some promise for short-term management of attention problems, and do not report worse adverse side effects than known from children with ADHD, evidence for long-term efficacy and safety of stimulant use in children who survived cancer remains to be established.

Study of outcome in adults surviving childhood cancer

What surviving childhood cancer entails for adults, their vocational achievement and quality of life, is an area of research to be explored. Information on the quality of life in adulthood after surviving childhood cancer is starting to become available in recent years. There are indications that quality of life of adult childhood cancer survivors is comparable to general population,[56,57] but also a lower quality of life has been reported.[58] It appears that there are subgroups that do report lower quality of life.[59,60] Further study of the quality of life of the survivors who received CNS-directed treatment is certainly warranted.

Study of neuropathological mechanisms

A great deal of work remains to done to identify the exact neuropathological mechanisms that account for neurocognitive sequelae of treatment. Especially the long-term effects of central nervous system chemotherapy on the developing brain in children with ALL are not fully understood. Direct effects of treatment on intra-cranial endothelial cells and brain white matter, as well as immunological mechanisms could be involved in the pathogenesis of central nervous system damage.[30,61,62] Also, changes in cerebral blood flow and glucose metabolism have been reported.[63] Reports on structural brain abnormalities in survivors of ALL, treated with chemotherapy only have not been consistent. So far, abnormalities detected by conventional imaging studies have not been found to correlate with neurocognitive function in children treated with chemotherapy only.[64-68] However, using quantative MRI methods, evidence has been provided of atypical white matter development in children with ALL, treated with chemotherapy only.[69,70] Advanced brain imaging techniques, such as functional MRI and diffusion tensor imaging (DTI), that assess neural networks in the brain, are now showing promise in shedding light on the nature of neural changes after treatment.[71,72] DTI can be employed to measure functional connectivity in the brain. DTI measures have been shown to correlate better with cognition than conventional MRI measures, specifically with tests of executive function.[73] This technique shows promise in detecting treatment-induced neurotoxicity in survivors of childhood cancer.[74,75] This field of research may also help to elucidate the neuropathological correlates of specific cognitive deficits and the reason why females seem to more vulnerable to central neurotoxicity of chemotherapy.

Design of future treatment protocols for ALL

The dose-related effects of chemotherapy on neurocognitive function that we report, emphasize the need to consider reducing doses of neurotoxic chemotherapy as much as possible in the design of future treatment protocols for ALL. As we found intensified treatment to be a risk factor for neurocognitive, academic

and behavioral sequelae, our results are an extra motivation for being very judicious in defining criteria for risk group assignment. Especially in girls and in young children, who are most vulnerable to neurotoxic effects of treatment.

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