Care for consequences in children treated for leukemia or brain tumor
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CHAPTER 1

GENERAL INTRODUCTION
Introduction

This thesis focuses on survivors of a childhood brain tumor or childhood leukemia. The overall survival rate of children who are treated for cancer, including a brain tumor [1] or leukemia [2], has increased substantially as a result of ever-improving treatment strategies. The survival rates for brain tumor subtypes vary considerably. The 5-year survival rate for medulloblastoma has increased to 80-85%; however, little progress has been made in treating high-grade glioma or infants with malignant tumors (the survival rate is 30%) [1]. At present the overall 5-year survival rate for children diagnosed with acute lymphoblastic leukemia (ALL) is 80-90% [2]. As a consequence of the tumor and their multimodal treatment, childhood brain tumor survivors (CBTS) and ALL survivors are at considerable risk for a variety of physical, neurocognitive and/or psychosocial long-term consequences, which materialize especially after cranial radiation therapy (CRT) [3]. These long-term consequences consist of late effects resulting from cancer and its treatment, have a negative impact on daily life and emphasize the need for aftercare. This thesis includes exploratory studies of the scope of long-term consequences for CBTS and ALL survivors, years after treatment. This introductory section describes the medical aspects of brain tumors and ALL, the diversity of late effects and the need for follow-up care and aftercare. The scope of this thesis is outlined in the last paragraph of this introduction.

Medical aspects of brain tumors and ALL

Diagnosis and treatment

In the Netherlands, approximately 600 children are diagnosed with cancer each year, of whom approximately 110 are diagnosed with a brain tumor and 140 are diagnosed with ALL [4].

Brain tumors

Childhood brain tumors are very diverse and can roughly be categorized into low-grade tumors (e.g., low-grade glioma, craniopharyngeoma), and high-grade tumors (e.g., medulloblastoma, ependymoma, high-grade glioma) which behave more aggressively. About 30% of the brain tumors are low-grade tumors [5]. Over the past few decades improved neurosurgical techniques, improvements in chemotherapy schedules and radiation therapy and better diagnostic techniques have all attributed to increased survival rates [1]. Brain tumor treatment most often consists of either neurosurgery only, neurosurgery followed by adjuvant CRT and/or various chemotherapeutic agents or chemotherapy only. Low-grade brain tumors are more often treated with surgery only, while high-grade brain tumors are mostly treated with adjuvant therapy. In the case of some low-grade tumors a wait-and-see strategy is followed subject to strict imaging control. Children with cancer are treated
according to well-defined treatment protocols, partly developed as clinical trials in international cooperation and research. The variation in treatment of childhood brain tumors depends on the tumor histology, the location, the stage of the disease and a patient’s age [1].

**ALL**

Before 1990 children with ALL were treated with CRT in addition to systemic chemotherapy to prevent recurrence of the disease in or from the central nervous system (CNS). Prophylactic intrathecal chemotherapy and high-dose methotrexate (MTX) have replaced CRT in the Netherlands since 1990 since it became evident that CRT was associated with neurocognitive late effects [6, 7]. The knowledge deriving from this irradiated patient group is still important with respect to children with a brain tumor.

**Different stages during cancer treatment**

The cancer treatment comprises different stages: The diagnosis and acute stage, treatment, early after treatment and survivorship, and each stage has its own characteristics and related emotions [8].

**Diagnosis, acute stage and during treatment**

The diagnostic stage and start of treatment are very stressful and the medical procedures cause children and their parents pain and distress. When a child is diagnosed with cancer, its family faces a multitude of stressors, including the most feared stressor: potential death of the child. The child, its family and its social environment need to find a way to deal with this new situation. While neurosurgery causes acute severe stress, radiotherapy and chemotherapy do not only affect cancer cells but also normal cells, which can result in temporary side effects during treatment and/or remaining long-term effects after treatment [9, 10]. These long-term effects are addressed in paragraph 3. Temporary side effects such as sickness (nausea, vomiting) and hair loss can occur within days or months after the start of treatment. The low blood counts and reduced immunity resulting from therapy can cause additional health problems with sometimes life threatening situations. During treatment most children and parents adjust well to the situation, despite the enormous daily impact of the disease. Psychosocial care is provided to increase the ability to cope with the disease and its treatment. The treatment of a childhood malignancy can take years, and can result in exhaustion in all family members.

**Early after treatment and survivorship**

At the end of a successful treatment, patients need to make a transition back to ‘normal’ life. At this stage, families often start to realize the emotional and physically exhausting impact of the treatment. Feelings of grief over all loss and the fear of
relapse are frequently evoked emotions [11]. Regular medical aftercare is needed in order to provide specific aftercare for treatment effects and also to be able to identify disease recurrence at an early stage. Psychosocial aftercare care is also needed to identify difficulties with emotional functioning and to refer patients to specialized care if needed. In the case of learning difficulties referral to neuropsychological aftercare services is necessary. Five years after diagnosis, cancer patients are considered “survivors”. While only a small risk of recurrence remains, the long-term consequences of the tumor and its treatment require ongoing attention, which is the specific focus of this thesis.

Long-term consequences of brain tumors and ALL and their treatment

Unfortunately, the increase in childhood cancer survival rates has come at a “cost”. As a consequence of the tumor and its treatment, CBTS run a considerable risk for a variety of late effects. ALL survivors treated with CRT also run the risk for late effects. Contemporary professional literature outlines difficulties in physical functioning [3, 12], neurocognitive functioning [6, 7, 13-15] and psychosocial functioning [16-20]. These late effects can have severe negative effects on survivors’ functioning in daily life [21].

The impact of treatment

How medical parameters affect these late effects is as yet unclear. CRT, applied to both patients with a brain tumor or ALL, is associated with an increased risk of endocrine, neurological, psychosocial and neurocognitive late effects, as well as fatigue and secondary malignancies [3, 22]. Meanwhile, it has become clear that survivors of a low-grade brain tumor, often treated with surgery only, also suffer from considerable long-term consequences of their tumor and their treatment [23-25]. Not only ALL survivors treated with CRT but also ALL survivors treated with prophylactic chemotherapy seem to be at risk for long-term consequences, especially more subtle neurocognitive late effects [7, 26-28].

Physical late effects

Of the long-term survivors of childhood cancer, 62-75% have chronic health problems and 25% of them suffer considerably from these conditions [3, 12]. Loss of energy and cancer-related fatigue have a negative impact on daily life [29]. Survivors are at high risk of suffering from long-term neurological (e.g. epilepsy, neuropathy, motor and coordination dysfunction and posterior fossa syndrome) and neurosensory impairments (vision, hearing and pain), which hamper the ability to function in normal everyday life [30]. Endocrine side effects occur in about 70% of irradiated survivors of CNS tumors,
because the radiation field often includes the hypothalamic/pituitary region which results in endocrinopathies [26]. Pituitary hormone deficiencies, such as growth hormone deficiency (GHD) resulting in growth failure (in about 80% of the CBTS) and hypothyroidism (in 20-30% of the CBTS after CRT and in 60-80% of the CBTS after CRT and chemotherapy) are frequently seen, and require hormone substitution [26]. Other endocrinological consequences include gonadotropin deficiency, precocious puberty, diabetes insipidus, and obesity. After a suprasellar tumor, patients can also suffer from the hypothalamic obesity syndrome [30]. Furthermore, many survivors live with permanent changes in physical appearance and body image. Scars, hair loss, short stature and sometimes notable changes to the skull bone structure are frequently seen after CRT [30]. Finally patients are at risk for a secondary malignancy following treatment, especially after CRT [31].

**Neurocognitive late effects and White matter damage**

*Neurocognitive late effects*

CBTS, especially those treated with CRT, and ALL survivors treated with CRT are at elevated risk for neurocognitive late effects [26]. A decline in intellectual acuity has been documented frequently and can be explained by a slow acquisition rate of knowledge rather than a regression in acquired skills [14, 32, 33]. This results in an increasing gap between survivors and peers. Underlying basic cognitive skills, such as the speed of information processing, attention and working memory are important for the normal acquisition of new skills and knowledge [13, 34]. The basic cognitive skills of the majority of CBTS appear to be damaged, which results in learning disabilities, such as learning disadvantages in spelling, reading and mathematics [6, 7, 32, 35, 36] for which special education services are frequently needed [37]. Neurocognitive late effects also seem to have a negative impact on the emotional and social development of survivors, such as the development of self-esteem (e.g., about learning results), feeling different from peers, and being less socially competent than peers [38].

Several documented risk factors increase neurocognitive late effects, for instance commencing treatment at a younger age, being female, and treatment with CRT [6, 39].

In the past decade several studies have revealed that survivors of low-grade brain tumors who are treated with surgery only can also suffer considerably from late effects and run an elevated risk for poor neurocognitive and adaptive outcomes. Difficulties with information processing speed, visual spatial skills, sustained attention, memory and executive function have been documented in these survivors [23, 40]. In ALL survivors treated with prophylactic chemotherapy, subtle neurocognitive late effects such as subtle problem with attention, complex fine motor skills and non-verbal memory have also been documented [6, 7, 27, 41-43].
White matter damage
The neurocognitive late effects described above seem to be related to white matter damage caused by CRT, chemotherapeutic agents, and other factors such as CSF obstruction, and hydrocephalus [44-46]. White matter is important for the speed of information processing because it facilitates the rate of transmission of electrical signals along axons [47]. Damage to white matter has been linked to neurocognitive late effects, especially after CRT [7]. White matter damage may be caused by either a failure of ‘normal’ maturation and myelination of the brain at an age-appropriate rate, or by damage to already existing white matter tracts. White matter damage has also been documented in ALL survivors [27, 48]. By using magnetic resonance imaging (MRI) techniques, including diffusion tensor imaging (DTI) to visualize white matter, the understanding of white matter damage and the pathophysiology of neurocognitive late effects is improving.

Psychological and social late effects
Many long-term survivors function relatively well, although symptoms of overall distress and impaired quality of life about physical functioning have been found [49, 50]. In general, no psychopathology as referred to in the Diagnostic Statistical Manual (DSM), such as depression or anxiety disorders, was found in the CBTS documented in various reviews [18, 51, 52, 53]. Despite exposure to major challenges and medical traumas, this positive and relatively adequate functioning of survivors could be indicative of their resilience and strength to cope with cancer [54, 55].
In CBTS, limited opportunities in achieving the normal milestones of young adulthood, including graduating from college, being financially independent and getting married, have been documented [19, 20, 56]. In order to study survivors’ own perceptions of their physical, psychological and social functioning and late effects, health-related quality of life (HRQOL) is measured using patient-reported outcomes. Contradictory results are found among CBTS, varying from low [24, 57-61], to good or equal HRQOL with only lower physical HRQOL, compared with peers [62-64].

What is needed for survivors at risk for long-term consequences?
In general, participation at school and normal peer contact are important for normal childhood and adolescent development. The existence of different late effects can, however, have a negative impact on children’s development and require specialized aftercare.
This thesis focuses on interventions for neurocognitive late effects.
Specialized aftercare
To be able to detect late effects (physical, neurocognitive and psychosocial) early and to refer patients to specialized aftercare, regular follow-up care is necessary. Improvement in survival rates results in a growing group of CBTS and an increased demand for structured aftercare in which respect multidisciplinary follow-up programs are desirable [17, 39, 65, 66]. For each domain of late effects, several aftercare options are available, for instance physiotherapy or medication for physical problems, educational support for learning disabilities and psychological counseling for psychosocial problems.

The need for aftercare for CBTS treated with adjuvant therapy (CRT and chemotherapy) seems obvious. However, children treated with surgery only (most often for low-grade tumors) are assumed to run a minimal risk for late effects [40]. As such, they often do not participate in routine and comprehensive follow-up programs. It is unknown whether professional care providers identify their need for aftercare on time and whether existing options for aftercare are initiated on time.

Interventions for neurocognitive late effects
In recent years, the object of several studies has shifted from documenting neurocognitive late effects to describing potential interventions to remediate these effects [6, 7, 14, 32, 46]. Because of the severity and the impact of cognitive late effects on learning abilities, there is a high need for effective interventions.

To date, only a few intervention programs have been developed to remediate cognitive functioning, such as Butler and Mulhern’s Attention Process Training and the Attention and Memory Training of Hooft et al. [67, 68]. Although some improvement in parent-rated attention and academic skills [67], and in attention and memory tests results [68] have been observed, intensity and compliance have been reported to be a concern, and sustainability of the effects remains to be studied. The high need for interventions and comparable neurocognitive problems makes researchers focus on cognitive interventions in other pediatric populations with neurocognitive problems, for instance children with Attention Deficit Hyperactivity Disorder (ADHD) or traumatic brain injury (TBI) as well. In studying interventions for neurocognitive late effects several options can be considered, such as neurocognitive rehabilitation [6, 7, 35] and pharmacological interventions [69, 70, 71]. Neurocognitive rehabilitation in the form of neurofeedback is of increasing interest in children with ADHD [72, 73]. Neurofeedback training (NFT) is based on operant conditioning in which self-regulation of brain activity is taught [73]. Although CBTS differ from children with ADHD, CBTS seem to have comparable inattention symptoms and pharmacological intervention improves attention functioning in CBTS [74, 75]. As such, the effectiveness of NFT could be hypothesized in CBTS as well. A pharmacological approach may be the use of growth hormone (GH) treatment, often used in patients with growth hormone deficiency (GHD) in order to improve
growth. Patients with GHD can experience several cognitive problems [76 -78]. Some studies suggest that GH replacement therapy can have beneficial effects for the cognitive functioning of GHD adults [79-81]. The presence of many binding sites of GH and insulin-like growth factor I (IGF-I), a serum marker for GH status, in the hippocampus could explain this beneficial effect. The hippocampus is a brain structure that is important for learning and memory functions. Since many patients treated with CRT have pituitary hormone deficiencies, such as GHD, GH treatment could benefit not only growth but also neurocognitive late effects in cancer survivors [26].

Background and aims

Background
Surviving childhood cancer, especially a brain tumor, often comes with a high risk for a variety of moderate to severe physical, neurocognitive and psychosocial late effects. Based on professional literature and clinical experience, CBTS who were treated with adjuvant therapy seem to be at greatest risk. However, survivors treated with surgery only also seem to experience several late effects, although these late effects tend to be more subtle compared with other survivors. Aftercare facilities for these patients are often not as comprehensive as the aftercare provided to patients treated with adjuvant therapy [25].

Aims
This thesis addresses the long-term consequences for CBTS from different points of view. The subsequent chapters describe the perceived late effects and need for aftercare from parents’ and children’s points of view and finally white matter damage as a pathophysiological substitute for neurocognitive decline. Lastly, we examine two interventions in survivors aimed at reducing neurocognitive late effects.

Participants
Participants in the studies described in Chapters 2-5 were recruited from a patient cohort of survivors who were treated between 1991 and 2006 at the Emma Children’s Hospital AMC. Of the 160 children found in our database, 57 met the inclusion criteria of the different studies described in this thesis. The other 103 were not eligible (e.g., deceased, were lost to follow-up care or had a secondary malignancy other than a brain tumor).
Inclusion criteria were (1) treated for a brain tumor diagnosed between 0 and 18 years of age (2) current age of the survivor is between 4-20 years of age, (3) complete remission or stable residual tumor, (4) at least one year after the end of treatment, and (5) able to complete a questionnaire in Dutch. Children and parents in this group of CBTS were asked to participate in different studies depending on the aim and the
The young adult survivors of childhood leukemia referred to in Chapter 6 were selected from a group of 56 patients treated between 1972 and 1990 at the Oncology Departments of the VU University Medical Center and the Academic Medical Center in Amsterdam. Participants had to have reduced bone mineral density and/or low IGF-I scores to be included in this study.

Table 1: Overview of the CBTS and ALL participants in the different studies

<table>
<thead>
<tr>
<th>Chapter</th>
<th>N</th>
<th>Criteria: age at study</th>
<th>Criteria: time since EoT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2: Aftercare</td>
<td>42 CBTS</td>
<td>4-20 yrs</td>
<td>1 yrs</td>
</tr>
<tr>
<td>3: HRQOL</td>
<td>34 CBTS *</td>
<td>8-18 yrs</td>
<td>1 yrs</td>
</tr>
<tr>
<td>4: WMFA</td>
<td>6 CBTS **</td>
<td>8-16 yrs</td>
<td>2 yrs</td>
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<td></td>
<td>11 ALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: NFT</td>
<td>9 CBTS ***</td>
<td>8-20 yrs</td>
<td>2 yrs</td>
</tr>
<tr>
<td>6: GH</td>
<td>13 ALL</td>
<td>&gt;20 yrs</td>
<td>No criteria</td>
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EoT: End of treatment; HRQOL: Health related Quality of life; WMFA: White matter fractional anisotropy; NFT: Neurofeedback training; GH: growth hormone; CBTS: Childhood brain tumor survivors; ALL: acute lymphoblastic leukemia; yrs: years

* n=34 from chapter 2; ** n=5 from chapter 2, n=3 from chapter 5, n=1 new; ***n=9 from chapter 2, n=3 from chapter 4

Outline of this thesis

Chapter 2: Late effects of CBTS are described from a parent’s perspective and the need for aftercare for these late effects is studied. This chapter describes the aftercare process in terms of timing of the care, type of referrer and needs for improvement. The need for aftercare for survivors who were treated with surgery only versus survivors who were treated with surgery plus adjuvant therapy is compared.

Chapter 3: The HRQOL of CBTS is described in mean scores and percentages at risk. Differences in HRQOL between survivors who were treated with surgery only and survivors who were treated with surgery plus adjuvant therapy are examined.

Chapter 4: White matter damage is studied by measuring the white matter fractional anisotropy (WMFA) of CBTS using the Diffusion Tensor Imaging technique on a 3.0-T MRI, in comparison with a control group of ALL patients treated with MTX for CNS prophylaxis and healthy subjects. The relationship between WMFA and information processing speed and motor speed is examined.
Chapter 5: The feasibility of neurofeedback training (NFT) as a potential intervention for neurocognitive late effects is examined in a pilot study of nine CBTS. Pre- and post NFT assessment consist of neurocognitive tests and psychosocial questionnaires. Parents and participants are interviewed to evaluate their experience with NFT and perceived changes in daily life.

Chapter 6: In this chapter the effects of two years of growth hormone (GH) replacement therapy as an intervention for reduced bone mineral density and/or low IGF-I scores is studied for its neurocognitive effects in a group of young adult ALL survivors most treated with CRT as CNS prophylaxis.

Finally, a general discussion reflects on the main findings of the studies and future perspectives and the implications for the Dutch pediatric neuro-oncology practice are addressed.
References


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