Chapter 1

General Introduction

CHILDHOOD CANCER

The chance of a child developing cancer before the age of 18 is around 1 in 400 in the general population. In The Netherlands, around 500 new cases of childhood cancer are diagnosed each year. Leukemia and brain tumors are the most common types of childhood cancer. Leukemia accounts for around 30% of cases, with acute lymphoblastic leukemia (ALL) showing the highest incidence (75% of the leukemias). Brain tumors comprise around 20% of new cases of childhood malignancy.[1,2]

CHILDHOOD CANCER SURVIVAL

Four decades since the beginning of multimodality treatment for childhood cancer survival rates have risen substantially. During the twentieth century, 5-year survival figures have increased from around 25% in children diagnosed in the 1960s to around 75% in children diagnosed in the 1990s. The introduction of combination chemotherapy in the late 1960s and early 1970s greatly improved chances of survival, and since that time the results of clinical trials have led to further progress in the treatment of pediatric malignancies. The centralization of specialized care has further helped to ensure that the majority of children with cancer today receive the currently best treatment. The survival trends for ALL have been most striking, improving from around 5 percent in the early 1970s to over 80% for the children diagnosed between 1991 and 1996.[3] In other common diagnostic groups large advances have also been made, for example in non-Hodgkin lymphoma and Wilms tumor, with recent 5-year survival rates reported to be around 85% [4] and 90%,[5,6] respectively. Improvement of survival of childhood brain tumors has been less pronounced – current 5-year survival rates for all central nervous system (CNS) tumors are around 65%. Between childhood brain tumor subtypes, however, prognosis varies considerably. Astrocytomas have the most favorable 5-year survival rate, around 77%.[7] These data are current for the developed countries only. In resource-poor countries the cure rate is often still lower than 35%. The great majority of 5-year survivors may be regarded as cured, with around a 10% risk of death from recurrent primary tumor, a second malignancy, or death of a treatment-related cause during the ensuing years.[8,9] As a consequence of the increased survival, the number of childhood cancer survivors in the population is steadily increasing.

CHILDHOOD CANCER TREATMENT

Most children are treated in a standardized way, according to treatment protocols which are part of clinical trials. In the Netherlands, the Dutch Childhood Leukemia Study group (DCLSG), later the Dutch Childhood Oncology Group (DCOG), has developed treatment protocols. International pediatric co-operative

groups include the International Berlin Frankfurt Muenster (I-BFM) study group, the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (COG). Surgery, radiation and chemotherapy are the treatment modalities available to treat cancer in children. Often, multimodal treatment is employed in children. For many solid tumors, surgery is the primary and most effective treatment. For larger tumors, radiation or chemotherapy is often used before surgery to reduce the size of the tumor, make surgery safer for the patient, and lessen any physical or functional defects. For hematologic malignancies, combined chemotherapy treatment is the most important option.

LATE EFFECTS OF CHILDHOOD CANCER TREATMENT

Cancer therapy can affect not only cancer cells but also other rapidly dividing normal cells, such as those in the gastrointestinal tract, bone marrow, hair follicles, reproductive system and nervous system. Because of this, unwanted side effects of the treatment can and often do occur. It has become clear that damage to organ systems due to cancer treatment in children may not become clinically evident for many years. It is also becoming apparent that survivors of childhood cancer have a high rate of illness owing to chronic health conditions.[10] Special late effects clinics have been established in childhood cancer centers to monitor these long-term effects in childhood and into adulthood.[11]

NEUROTOXICITY OF CHILDHOOD CANCER TREATMENT

Cranial irradiation has been associated with cognitive decline in children with brain tumors and children with leukemia.[12,13] Children with ALL receive CNS-directed treatment to prevent recurrence of the disease in the cerebromeningeal space. Intellectual dysfunction typically occurs gradually after radiotherapy and tends to be progressive in nature.[14] In children with ALL, evidence of a detrimental effect of prophylactic cranial irradiation on neurocognitive function[15-17] has led to the development of chemotherapy-only protocols, using CNS-directed chemotherapy, with the same rate of treatment success.[18-22] However, many chemotherapeutic agents also have central neurotoxic properties.

The major chemotherapeutic agents used in childhood cancer that have central neurotoxic properties are:

Methotrexate

Methotrexate is an anti-metabolite. The main action of methotrexate is interference with RNA and DNA synthesis by the inhibition of the enzyme dihydrofolate reductase.[23] Clinically, methotrexate associated neurotoxicity is related to seizures and stroke-like episodes in the acute and subacute phase, and with

cognitive impairment in the chronic or late phase.[24] Demyelinisation,[25] cerebrovascular damage,[26] damage to astrocytes,[27] impaired synthesis of neurotransmitters[28] and production of excitotoxic amino acids[29,30] are all processes that have been suggested to occur as a consequence of methotrexate administration. Radiographically, white matter changes have been documented during treatment of children with ALL with methotrexate.[31-33]

Cytarabine

Cytarabine is an anti-metabolite, a synthetic pyrimidine analogue which affects DNA synthesis by competitive inhibition of DNA polymerase. It is used both systemically and intrathecally in the treatment of children with ALL. Regarding neurotoxic effects, clinically it has been associated mainly with acute cerebellar dysfunction,[34,35] with aseptic meningitis, myelopathy in rare cases, and with acute peripheral polyneuropathy.[36]

Corticosteroids

Historically, prednisone has been the corticosteroid used most often in the treatment of ALL but more recently, dexamethasone has gained use because of greater bioavailability,[37] superior anti-leukemic activity in vitro[38,39] and enhanced CNS penetration.[40] A connection between corticosteroid use and cognitive function has been suggested, with a special vulnerability of the hippocampus and the frontal lobes for its effects.[41] While acute behavioral effects of exogenous corticosteroids have been documented in adults as well as in children,[42-44] little is known about the long-term effects of corticosteroids, especially in the developing child. It has been suggested that especially dexamethasone may be associated with long-term cognitive effects in children with ALL.[45]

Vincristine

Vincristine is a vinca-alkaloid, inhibiting cell proliferation by binding to tubulin and disrupting the function of mitotic spindle microtubules.[46] The neurotoxic effects of vincristine are probably caused by interference with axonal transport through reaction with microtubules within axons,[47,48] eventually leading to axonal degeneration.[49] Although highly toxic to the CNS when administered intrathecally,[50,51] central neurotoxicity from intravenous vincristine is rare, most likely due to poor penetration through the intact blood-brain barrier.[52] Peripheral neuropathy due to vincristine therapy, however, occurs frequently in children with cancer. This is a primarily axonal, symmetric mixed sensory-motor, and autonomic polyneuropathy which is more marked distally.[53,54] Usually, signs of vincristine-related neuropathy regress quickly after discontinuation,[55] but neurological signs in combination with peripheral nerve tract injury have been reported

for up to five years after end of treatment with vincristine in children with ALL.[56-58]

As postnatal development of the brain is not complete until nearly the end of the second decade of life[59] and less mature structures in the CNS are thought to be more vulnerable to neurotoxic damage than more mature ones,[60] children with cancer may be especially vulnerable to possible neurotoxic side-effects of treatment. During childhood and adolescence, white matter increases its overall volume[61] and fiber tracts become more myelinated in a region-specific fashion.[62] There is evidence of a relationship between myelination and functional maturity of the brain.[63-65] The myelination of the prefrontal cortex and of cerebellar-prefrontal networks has a protracted course during childhood and adolescence,[66,67] and consequently these structures may have a large window of vulnerability during development.[68] Evidence for cerebellar-frontal subsystem changes, as detectable by magnetic resonance imaging, has been reported in children with ALL treated with chemotherapy only.[69]

Direct effects of chemotherapy and cranial irradiation on intra-cranial endothelial cells, brain white matter, as well as immunological mechanisms could be involved in the pathogenesis of CNS damage.[24,60,70-72] Also changes in cerebral blood flow and glucose metabolism have been reported.[73] Damage to white matter as well as failure to develop white matter at a rate appropriate to the developmental stage, could partly account for neurocognitive decline in cancer survivors.[74]

NEUROCOGNITIVE EFFECTS OF CANCER TREATMENT

Impairment of attention and information processing are among the most frequently reported neuropsychological side-effects of childhood cancer treatment,[75] and have been suggested to underlie the cognitive deficits and academic difficulties observed following treatment for childhood cancer.[75-79] These functions depend on integrity of neural networks in the brain and efficient exchange of information between distributed brain areas.[80-82]

The basic neuropsychological mechanisms of attention and information processing are critical for normal cognitive development. Deficits in these functions can hamper intellectual, emotional and social development and are associated with learning problems and behavioral disturbances. An increase in the rate of behavioral problems, measured using standardized checklists, has been reported in childhood cancer survivors,[83-85] but these reports are contrasted by studies that suggest that survivors do not differ importantly from controls and/or are within normal limits.[77,86,87] Educational attainment in survivors of has been reported to

be compromised.[88] The reports often concern heterogeneous samples and do not always specify outcome by diagnosis- or treatment group. Regarding neurocognitive outcome, it appears that chemotherapy may not be a benign form of treatment, although its effects may be more subtle than those produced by cranial irradiation.[89-92] Even though mean psychological adjustment in pediatric cancer survivors may be near normal levels, more subtle or specific areas can be adversely affected in long-term survivors.[93]

ASSESSMENT OF NEUROCOGNITIVE FUNCTION

Contemporary neuropsychological models describe the various mechanisms of attentional functioning and information processing consistently as acting together as an integrated functional system, underpinned by a neuroanatomical system.[94-96] This network includes the brain stem, aspects of the subcortex and posterior cortical regions and the prefrontal cortex. These models commonly identify a number of components of attention: processing speed (the rate at which tasks are performed), selective attention (the capacity to attend to relevant stimuli), shifting attention (the ability to move flexibly from one concept to another) and sustained attention (the ability to maintain attention to a task for prolonged periods).[97]

To assess attention and information processing in the participants in our studies, the Amsterdam Neuropsychological Tasks program (ANT)[98,99] was used. Previously, this program has been used to examine a wide range of disorders associated with attention and information processing deficits.[100-102] The paradigms used are designed to tap skills ranging from basic reaction speed and simple perceptual-motor processes to neuropsychological functions underlying the more complex cognitive processes. Attentional components of the tasks are manipulated, while all other parameters are maintained unchanged, in order to assess that certain component of attention. The reaction time paradigms on which the tasks are based, are modeled according to the attention theory of Shiffrin and Schneider.[103,104] Shiffrin and Schneider developed a dual process model where a distinction was made between automatic and controlled processing. Over-learned tasks are assumed to be executed completely automatically, while new tasks require full attention and a conscious controlled effort. Both processes can occur parallel. While automatic processing is almost unlimited in capacity, controlled processing is thought to proceed in a serial manner and is limited in capacity. Because the capacity of the information processing system is limited, attentional mechanisms are necessary to select information. The Additive Factor Method of Sternberg[105] is applied to derive information about each stage of information processing. The increase of the reaction time resulting

from manipulation of separate stages of information processing using specific tasks, provides information on the efficiency of processing at that certain stage. Sanders[106] extended Sternberg's concept to a hierarchical cognitive-energetic model: the efficiency of information processing is assumed to be determined by the interplay of computational processes (processing stages), situational factors (energetical mechanisms: arousal-effort-activation) and executive control/evaluation. Although the model may be criticized, e.g. for the assumption of a strict serial order of computational processes, the model is an important and valuable method in the empirical and clinical research domain.[107,108]

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