Child and parental adaptation to pediatric oncology

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Introduction

Introduction

Parental reactions to childhood cancer [32,33,87] and health-related quality of life of pediatric cancer patients [75] have been the focus of extensive research in the past two decades. In the Introduction of this thesis, first a general overview will be given of the incidence, survival and treatment of pediatric cancer, followed by a paragraph on stem cell transplantation (SCT), a specific treatment for a subgroup of patients. Late effects of cancer treatment and SCT are also presented. Next, the area of pediatric psychology and specific relevant themes will be presented, followed by a discussion of parental reactions to childhood cancer, as well as issues on health related quality of life (HRQoL) in children with cancer, children undergoing SCT and children suffering from a rare and complicated disease called Langerhans Cell Histiocytosis (LCH). Determinants, risk and protective factors of parental reactions to childhood cancer will be described and research areas that are understudied until now will be identified.

Medical aspects

Pediatric Oncology

In the Netherlands, approximately 500 children are diagnosed with cancer annually [21,85]. Most common childhood cancer diagnoses are leukemia (30%), followed by brain tumors (25%), lymphoma, solid tumors (e.g. renal cancers, osteosarcoma, Ewing sarcoma etc.). Treatment of childhood cancer takes place in one of the seven pediatric oncology centres in the Netherlands. Patients are treated according to (inter)national treatment protocols, which consist of regimens of chemotherapy and in some cases radiation therapy or surgery. Treatment duration can range from a few months (e.g. in the case of Non-Hodgkin Lymphoma) to two years (in the case of acute lymphatic leukaemia (ALL).

Cancer treatment has many side effects, such as hair loss, nausea, loss of appetite, diarrhea and oral mucositis (mouth sores), which is painful and can inhibit eating, drinking and taking oral medication. Due to low blood counts, children are very susceptible to infections and thus are forced to live with restrictions for a long period of time (i.e. not going to school or to crowded places like shops or public transportation). Part of the treatment of solid tumors in children consists of surgery, in some cases this involves amputation or rotation plasty, which causes lasting and visible limitations and the need to revalidate for a long period. Brain tumors require neurosurgery, which often results in neurological, endocrine and psychological side effects.

Treatment protocols have become more effective in the past decades and the

duration of clinical treatment has shortened considerably in favour of treatment through outpatient clinics. Five-year survival rates have grown to 70-75%, whereas in the 1960s, only 30% of children with cancer had a 10 year event-free survival [21,76]. Children with ALL, Wilm's tumor and lymphoma generally have the best chances of survival (above 85%) [84], whereas children with Acute Myeloid Leukemia (AML) [31], bone tumor [52], brain tumor [49] or neuroblastoma [88] have a worse prognosis.

Stem cell transplantation

For children with high risk ALL or relapsed malignancies and inborn errors of metabolism, stem cell transplantation (SCT) is a treatment of last resort. In the Netherlands, approximately 60 children are transplanted per year, most of them in the Leiden University Medical Center (30-40), followed by the Wilhelmina Children's Hospital Utrecht (20-30). About ten pediatric transplantations take place in the University Medical Center Nijmegen. The treatment involves high doses of chemotherapy and/or total body irradiation before the stem cells of a donor are infused [55]. If possible, one of the siblings of the ill child will act as a matched donor; if not, an unrelated matched donor will be searched through an international donor base. Stem cell transplantations are usually performed with bone marrow from a donor (allogeneic) but in some instances take place with cells from the patient itself (autologous). In Europe, one in four allogeneic transplants is now performed with marrow from an unrelated donor [80]. If that possibility fails too, parents can act as a haploidentical donor for their child. In recent years and only in a limited number of countries, the possibility exists for parents to perform embryo selection in order to conceive another child with the right haploidentical match to act as a sibling donor for the patient. The debate is whether it is ethical to conceive a 'designer baby' to act as a donor for an ill sibling.

Stem cell transplantation is a hazardous treatment, associated with high morbidity and mortality [17], because children become extremely susceptible to infections, due to high doses of chemotherapy to eradicate any present malignant cells and to suppress the body's natural inclination to reject the donor cells. It involves a lengthy hospital admission in an isolated, germ-free environment during a period of 8-12 weeks. Complications can arise when children suffer from potentially fatal infectious diseases such as adenovirus infections, aspergillus or veno-occlusive disease (VOD): swelling of blood vessels in the liver which causes blocks in the blood flow.

In the first four to six months post-SCT, children are still prone to develop infections and are forced to live with restrictions. They cannot return to school yet and need to avoid crowded places and certain types of food. Re-admissions due to complications (e.g. graft-versus-host disease (GVHD), which is a common complication

of allogeneic SCT in which functional immune cells in the transplanted marrow recognize the recipient as "foreign" and mount an immunologic attack, infections or graft rejection), loss of appetite and chronic fatigue are seen in many children in the first months post-SCT, which places a burden on parents and families.

Langerhans Cell Hystiocytosis

Langerhans Cell Hystiocytosis (LCH) is a rare and serious non-malignant disease that can manifest itself in diverse ways. LCH is the result of an abnormal proliferation of pathologic Langerhans cells, accompanied by other inflammatory cells in various tissues. The lesions are destructive, and healing results in scarring and fibrosis [6,57]. Symptoms can range from a single bone lesion to a life threatening multi-system disorder. The peak onset of LCH is between 1 and 4 years, although it can occur at any age [18]. The incidence is low: 4.1 cases per million per year, which means 15-18 newly diagnosed pediatric cases in the Netherlands every year [73].

LCH-treatment depends on the extent of the disease. Localised disease might be treated with local therapy, including the application of corticosteroids or surgical curettage. In case of disseminated LCH, chemotherapy is often the backbone of treatment [2]. Leiden University Medical Center is one of the expert institutes in the Netherlands on LCH. Whether LCH should be considered a malignant disease is a matter of debate [78]

Late effects

As increasing numbers of children with cancer survive, more attention has been devoted to describing and monitoring the late effects of the disease and treatment [74]. Late effects or sequelae of cancer treatment have been described in terms of physical effects [62], cognitive effects [54], social – and emotional problems [44], effects on health-related quality of life (HRQoL) and the attainment of developmental milestones [74]. The World Health Organisation (WHO) defines HRQoL as 'the individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns'. Long-term survivors of pediatric cancer are more likely to have diminished health status and to die prematurely than are adults who never had childhood cancer [38]. The risk of chronic health conditions is high, particularly for second malignancies, cardiovascular disease, renal dysfunction, severe musculoskeletal problems and endocrinopathies [22,62]. Cranial radiation in pediatric patients with a brain tumor has been shown to have serious consequences for attention/concentration and working memory and, as a result, a decline in intelligence [13]. Whether treatment with chemotherapy alone, now the standard treatment for children with ALL, has a detrimental effect on cognitive functioning is still a matter of debate [30,53], but recent findings show evidence of subtle long-term neurocognitive

effects on attention and executive functioning, while global intellectual functioning is generally preserved [12].

Following SCT, parents and children are faced with the risk of recurrence, chances of chronic graft-versus-host disease (GVHD) and numerous possible late effects such as pulmonary complications, growth problems and infertility [16,42,43,51]. In a recent Dutch study, the cumulative incidence of late effects in SCT-survivors was 93% after a median follow-up time of 7 years [10]. Neurocognitive problems following SCT have not been found in a large recent study among SCT survivors with miscellaneous underlying diseases [66], but children with severe congenital immunodeficiencies do appear to have an increased risk of long-term cognitive difficulties [81]. Fatigue can be a long-lasting problem, but the most worrying sequel to SCT is the high risk of secondary malignancies [43].

Children who have been treated for a complicated non-malignant disease like Langerhans Cell Hystiocytosis (LHC) can suffer from sequelae like Diabetes Insipidus (with a cumulative risk of 26%, 14 years after diagnosis [24]), growth retardation, hearing loss, physical problems, neurological problems (such as ataxia, learning difficulties and intellectual impairment [24,57]).

Pediatric psychology

Pediatric psychology, a fairly new area of expertise, addresses the range of physical and psychological development, health and illness affecting children, adolescents and their families [69]. Pediatric psychologists strive for a combination of research and patient care: science has informed practice in the field and practice has led to important questions that subsequently were put to the test of scientific inquiry [1]. Screening and assessment are hot topics among pediatric psychologists, who are keen on finding the most appropriate assessment instrument to determine which parents and children are most at risk to develop severe stress symptoms. The problem is that many instruments focus on different psychological domains, which also have common characteristics. Reliability and validity of several instruments have not been studied well [50]. Furthermore, there appears to be a split between the measures used in research and those used in clinical practice [14]. There does seem to be consensus about the need to combine generic questionnaires (with the possibility to compare to healthy norm data) with disease-related and disease-specific questionnaires, but the choice for a particular measure is not easily made. The availability of disease-related or disease-specific assessment measures is low in non-English speaking countries and this implies that (back) translation and cross-cultural validation of questionnaires is necessary. The translation in another language

and culture is a lengthy and laborious process and is not always carried out adequately and/or documented properly in research articles [83].

Once the parents most in need have been identified, interventions are needed to reduce distress and to teach parents adaptive coping or problem-solving skills. Pediatric psychologists have proved their worth in designing and applying cognitive-behavioral techniques, problem-solving skills and relaxation skills to help parents cope with their child's illness and its treatment. However, the effects of psychological interventions have scarcely been studied; hence the number of evidence based treatment programs is low. There is a need to evaluate treatments, combinations of modalities, moderators that affect outcome and the processes responsible for change [89]. In the last years, a number of promising intervention programs have been piloted to support parents of children newly diagnosed with cancer [26,34,71,72]. However, results of these studies vary, due to many methodological challenges, such as a low participation rate and early drop out because of unforeseen illness complications.

Psychological aspects

Alongside with fast and promising medical developments in the past decades, more attention has been devoted to counseling patients and families in dealing with the stress of diagnosis, treatment and survival of serious childhood illness. An increased emphasis has been placed on the recognition of psychological and social factors in the individual's (and one's family's) experience of illness and the inclusion of these factors on the development of interventions that can alleviate illness-related symptoms and adverse health outcomes [11].

Parental reactions to pediatric cancer

When parents are confronted with a cancer diagnosis in their child, they often report to feel as if 'their world has fallen apart'. Parents will enter a process of coping, sometimes referred to as an 'unexpected career' [4], because parents are able to show tremendous commitment and competence in caring for their child [8]. Parental stress reactions, (most often operationalized as anxiety, depressive symptoms, uncertainty or posttraumatic stress symptoms, PTSS) is high in most of the parents around the time of diagnosis [7,34]. These emotional manifestations of strain decrease to near normal levels over time in the majority of the parents, but have been found to persist in a substantial proportion of the parents, even many years post-treatment [87].

The psychosocial consequences of the child's illness on parents are best understood in light of contributions of the nature and severity of the child's illness, other

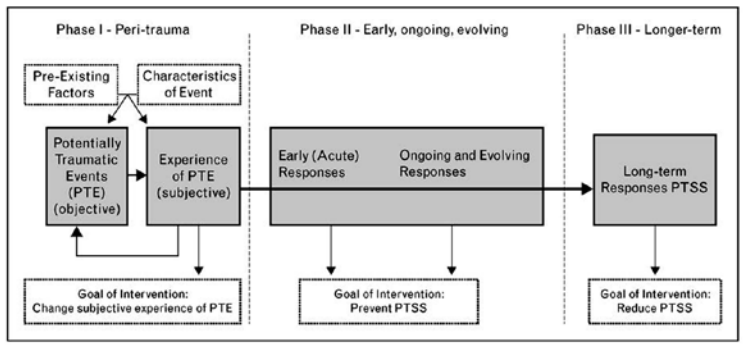
stressors in the family's life, characteristics of the family system, and the parent's coping strategies and capabilities [89]. Risk factors of poor adjustment are found in terms of illness complication factors [28] or demographic factors: parents of children with cancer who are less educated and parents with lower SES [29], single mothers and parents with a 'perceived unsatisfactory financial status' [45] report more depressive symptoms. However, psychological factors seem to have the greatest impact on parental adaptation to childhood cancer. Parents who display the most and highest levels of emotional manifestations of strain at diagnosis continue to experience the highest levels of symptoms, even after treatment ends [87]. Furthermore, pre-existing psychopathology [35,47] and trait anxiety have been identified as predictors of post-treatment PTSS for mothers [9] and fathers [27]. Child behavior problems [7] were found to be predictive of parental depressive symptoms. High levels of care giving demands, past traumatic life events, and less perceived social support [61] have also been identified as risk factors for the development and maintenance of emotional manifestations of parental strain.

One of the most frequently used models to understand the experience of families throughout the course of their child's illness, supported by a growing database of empirical research, is the Medical Traumatic Stress Model [35,36], see Figure 1 (published with permission of the original author, A.E. Kazak). The model contains three stages, i.e. peri-trauma (I), during treatment (II) and long-term sequelae (III). Medical events that may be traumatic (i.e. diagnosis itself, sudden admissions to the intensive care, medical complications) are referred to as Potentially Traumatic Events (PTEs). The term 'potentially traumatic' is used to underscore that events in itself are not necessarily traumatic, but the subjective interpretation of an event can make a particular event traumatic, or not. Phase I, the time around diagnosis, confronts parents with learning that their child has a serious and life-threatening illness. It involves treatment initiation, waiting for test results and taking practical decisions regarding the other children at home. Phase II is the period of time during treatment. It is variable in length and course and continues to expose patients and families to ongoing PTEs (e.g. side effects or complications of treatment, pain, death of other children on the ward, concerns about relapse or relapse itself). Phase III refers to the period after the cessation of treatment. It can involve long-term traumatic stress and sequelae and it includes both families of survivors and families of children who have died. Fear of a relapse, also termed as 'the Damocles syndrome' can linger for a long time in both parents and children [3,37].

Although cancer is an uncontrollable stressor, parents deal with the demands of the situation through actions, behaviors and thoughts, also referred to as coping [41]. Therefore, the experience of a trauma reaction due to childhood cancer is not always a pathological response. In fact, avoidance behavior seems to be functional in the early phase of childhood cancer when parents are overwhelmed with stressors and re-

experiencing is a natural way of processing and resolving difficult experiences. However, in face of active treatment and maintenance, avoidant parental behavior has been related to elevated levels of emotional manifestations of strain e.g., anxiety and depression [27,60]. Hence, only when the 'reexperiencing' or 'avoidance' reactions are extreme, distressing and persistent, they will fall into the area of pathology like Posttraumatic Stress Disorder (PTSD) or Acute Stress Disorder (ASD).

Figure 1. An integrative model of pediatric medical traumatic stress



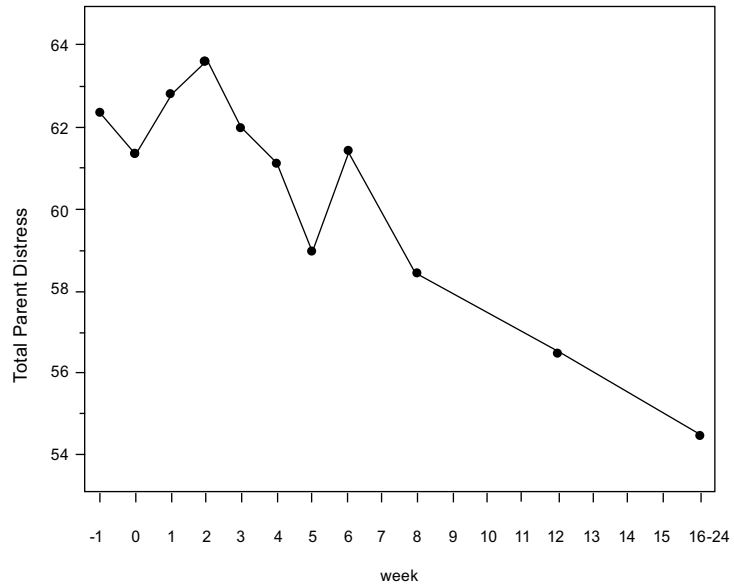
Source: Kazak AE, Kassam-Adams N, Schneider S, Zelikovsky N, Alderfer M, Rourke M. An integrative model of pediatric medical traumatic stress. J Pediatr Psychol 2006; 31: 343–355.

Parental reactions to SCT

Highest levels of parental stress are reported in the period preceding SCT and during the acute phase [86]. Sean Phipps and his study group have assessed parental stress in a longitudinal design from admission for SCT until 24 weeks post-SCT. They found that stress levels decrease steadily in the weeks and months after discharge in most parents [65], see Figure 2 (published with permission of the original author). However, in a subgroup of parents, stress levels still remain elevated for years post-SCT. Risk factors for long-term parental stress are socio-demographic and illness-related factors, such as being a mother [47], having lower socio-economic status (SES) [65] and the number of ICU transfers [48]. Furthermore, parental coping and adjustment at the time of SCT predict psychological functioning later on, e.g. a mother's appraisal of threat to her child's life [17,46] and maternal symptoms of anxiety and depression at admission and during hospitalization [46,47] are identified as predictors of stress post-SCT.

Only one study has been devoted to long-term parental stress reactions post-SCT [20] so far. Results of this qualitative, interview-based study showed that parents still worry about late effects of treatment, the risk of secondary malignancies, their child's

Figure 2. Parent SCT-related distress over time



infertility and their child's psychosocial well-being. Many parents report that their child's illness and treatment is still a source of anxiety, four to eight years post-SCT.

Perceived vulnerability

When parents are confronted with a life-threatening disease or a near-fatal accident of their child, they might react with a long lasting fear of losing their child, even if the immediate threat has disappeared or faded. Green and Solnit [23] introduced the term 'perceived vulnerability' to describe excessive parental anxiety and worrying about a child's health. They suggested that this anxiety often leads to a maladaptive pattern of parent-child interactions and child behavior problems, called the 'vulnerable child syndrome' [79]. Increased perceptions of child vulnerability are related to increased social anxiety and illness uncertainty in children with chronic illness [5,56]. Parents of children on treatment for cancer have shown elevated levels of perceived vulnerability and these perceptions are a significant predictor of child emotional adjustment [15]. In the context of SCT with a long period of uncertainty, perceptions of vulnerability may exist. This has not been studied yet.

Children's reactions to cancer

How children react to diagnosis and treatment for cancer is a widely researched area. The concept that has been studied most during the last years is health-related quality

of life (HRQoL). HRQoL includes different aspects of life, including physical functioning, psychological and social functioning. Children with cancer report a significantly lower HRQoL shortly after diagnosis, consisting of physical complaints, reduced basic motor functioning and autonomy and impaired global positive emotional functioning [39]. One year post diagnosis, most of the children (or their parents who act as proxy-reporters) show a significant improvement of HRQoL [19], but a proportion of the children still report lowered motor functioning and lowered positive emotional functioning [39].

Despite the obvious challenges and trauma cancer treatment can pose on children, the prevalence of psychopathology or social dysfunction is similar to that found in the general population or appropriate comparison groups, suggesting 'hardiness' in children and adolescents with cancer [59]. In numerous studies, children with cancer even report lower levels of affective distress than healthy children [67,68].

Children's reactions to SCT and LCH

Children undergoing SCT report low HRQoL scores during the acute phase, due to low levels of activity, mood disturbance and somatic distress consisting of nausea, mucositis and other physical complaints [64,70]. Within 4–6 weeks post-SCT, distress declines to levels lower than those seen at the time of admission, and a return to a presumed baseline level occurs within 4–6 months post-SCT [64]. As survivors reach 6 months to a year posttransplant and begin to reintegrate into their normal lifestyles, they show some mild disturbances in their self-concept and social functioning [63]. Long-term survivors of pediatric SCT report a 'good' or 'adequate' quality of life [25,58,82], when assessed after 3-5 years. Children report higher HRQoL scores than adult survivors of SCT, possibly due to the lower incidence of chronic graft-versus-host-disease in children [43]. However, a recent study among adult survivors of pediatric SCT showed that they were less satisfied with their physical health, general health, partner relations and sexual function [44].

HRQoL research in pediatric LCH patients is still scarce. In a recent study, more than 50% of the pediatric LCH patients reported a lowered HRQoL [57], especially in the domain 'emotional functioning'. Another study, performed with patients with bone lesions only found no differences in HRQoL with healthy peers [40].

Conclusion

The overview of the literature shows that considerable research has been conducted in the area of child and parental adaptation to cancer, SCT and LCH. However, less attention has been paid to some particular issues:

The availability of psychometrically sound disease-related assessment measures in the Dutch language is low. Most researchers in the Netherlands use non-illness specific questionnaires to assess levels of anxiety, depressive symptoms or PTSS in parents of children with a serious illness. The advantage of these measures is that results can be compared with other international studies more easily, but the disadvantages are that parents are considered to report symptoms of psychopathology. It would be better to consider parental adjustment to childhood illness as a normative process involving additional daily responsibilities, limitations in major life roles and increased strain in close relationships. Hence, there is a clear need of psychometrically sound disease-related and disease-specific measures in Dutch. The Pediatric Inventory for Parents (PIP) seems to be an adequate disease-related measure to use with parents of children with various illnesses. The psychometric qualities of this instrument have been studied by the original author [77], but a factor analysis has not been done yet.

The assessment of parental distress or parenting stress in relation to pediatric SCT is usually performed in itself, without the assessment of HRQoL in children. It would be interesting to find out if the concepts of HRQoL and parenting stress are related and if time since SCT is of influence on parenting stress. If so, this calls for a need of strategies for parents to reduce their own parenting stress and to deal with their child's well-being at the same time.

No quantitative data have been published to this date about long-term parental stress and adaptation post-SCT; all but one (qualitative) study in this area stopped assessing parents after 18 months post-SCT. This finding is surprising, considering the high incidence of late effects in this group. It is to be expected that parents will continue to worry about their child's health and future beyond the period of 18 months post-SCT. Until now, the concept of perceived vulnerability has not been assessed yet in parents of children undergoing SCT, which is unfortunate, because this concept could shed more light on the thoughts and perceptions of parents of long-term survivors and guide psychosocial and psychoeducational interventions.

To examine the psychological effects of a complex illness like LCH in pediatric patients, it is important to study not just HRQoL, but also behavioral aspects and cognitive functioning as well as the interactions between all three aspects. Until now, no study has combined all of these aspects.

Aims of the studies

The aim of the studies included in this thesis was to obtain better insight in psychological reactions of parents and children to the childhood cancer experience, SCT and LCH. We were interested in identifying outcomes and determinants of parental stress and adaptation processes. Specifically, the aims of the studies were:

- to gain more knowledge of the existing literature on parental reactions to childhood cancer and SCT and the way stress is operationalized and assessed.
- to assess disease-related stress in parents of children with cancer by using a newly translated disease-related measure of parental distress. We also aimed to evaluate the psychometric qualities of the instrument.
- to study the relationship between parenting stress and (child and) parent reported HRQoL before and after SCT.
- to assess long-term psychological consequences of pediatric SCT on parents and
- to assess a combination of emotional, behavioral and cognitive effects of the disease and its treatment in LCH survivors.

Outline of the thesis

In *Chapter 2*, results from a review study of 67 articles on stress and adaptation in parents of pediatric cancer patients are reported. *Chapter 3* describes the results of a multicenter study among parents of children on treatment for cancer. The aim of this study was to evaluate the psychometric qualities of the Dutch version of a disease-related instrument measuring parental stress, the Pediatric Inventory for Parents. *Chapter 4* is a review article on parental stress and adaptation among parents of children undergoing stem cell transplantation (SCT). *Chapter 5* contains the results of a longitudinal study on child- and parent reported health related quality of life and parenting stress in parents of children undergoing SCT, before admission and on average 10 months after discharge.

In *Chapter 6*, the results of a cross-sectional study on parental (disease-related and general) stress and perceptions of child vulnerability in parents of children who underwent SCT either 5 or 10 years ago are reported. In *Chapter 7*, cognitive problems, behavior problems and health related quality of life issues of children with Langerhans Cell Hystiocytosis (LCH) are described. *Chapter 8* is formed by the summary and general discussion and *Chapter 9* contains the Dutch summary of this thesis. In *Chapter 10*, the word of thanks, curriculum vitae and the list of abbreviations can be found.

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