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Chapter 1

General introduction

Acute Lymphoblastic Leukemia

Epidemiology and cause

Pediatric cancer is rare. In the Netherlands about 600 children are diagnosed annually with cancer. Leukemia is the most frequent type of cancer and about 120 children are diagnosed each year with acute lymphoblastic leukemia (ALL) [1].

Survival of pediatric cancer in general and of ALL specifically has greatly improved over the last decades. ALL evolved from a fatal disease in the early sixties, to 33% survival at the end of the seventies and 67% survival one decade later. With current therapy the 5 year event-free survival has increased to 85% and is expected to reach 90% in the near future [2].

The precise mechanism of ALL development is unknown, but it is thought that it originates from genetic lesions that are involved in the control of lymphoid cell homeostasis. This leads to a deregulated clonal expansion of immature lymphoid progenitor cells. Prenatal genetic abnormalities have been found in neonatal blood spots (*hielprikaart*) of healthy newborns, but only a fraction of these children develop ALL. It seems that additional, post-natally acquired genetic aberrations are needed for leukemic transformation [3-5].

Clinical presentation at diagnosis

The presenting features of ALL are often non-specific and include pallor, fatigue, infection, fever and increased bleeding tendency. These features are caused by anemia, neutropenia and thrombocytopenia as a result of proliferating leukemic blasts in the bone marrow. Infiltration of other tissues, such as the periost, peripheral lymph nodes and lymph nodes in for example the mediastinum can lead to musculoskeletal pain, lymphadenopathy, respiratory distress, dysphagia and swelling of the neck, face or limbs. Involvement of the central nervous system (CNS) and the testes can lead to headache, focal neurological deficits and to a painless testicular enlargement, although these presenting symptoms are rare. Physical examination often reveals enlarged liver and spleen in addition to the previously mentioned abnormalities.

Risk assessment

Assessment of the risk of relapse is important in order to provide therapy that will maintain high cure rates or improve less favorable cure rates and avoid excessive and unnecessary toxicity. The improved treatment has changed or even abolished the prognostic strength of many clinical and biological variables that were previously related to treatment outcome. T-cell and mature B-cell phenotypes, black or Hispanic ethnicity and male gender were traditionally associated with poorer outcomes but now fare no worse than their counterparts. Three aspects are important in the assessment of

the risk of relapse. First, clinical characteristics, especially age and leukocyte count at diagnosis are still strong prognostic factors of outcome. Children aged 1-9 years have a better outcome compared to infants and adolescents. Leukocyte count under $50 \times 10^9/l$ is associated with a better prognosis. Second, biological factors influence prognosis. Certain genetic abnormalities of the leukemia cells are associated with a better outcome (TEL-AML1 fusion, trisomy 4, 10 and 17) whereas other abnormalities have an unfavorable prognosis (such as t(4;11) with MLL-AF4 fusion, and hypodiploidy -less than 44 chromosomes-). Third, the response to treatment is of importance in the determination of outcome. Morphologic response in blood and bone marrow are traditionally being used, but have a limited sensitivity to measure cytoreduction. Very low levels of leukemic cells (one leukemia cell in 10^4 to 10^6 normal cells) can be detected with PCR; this is called minimal residual disease (MRD). MRD is a very strong prognostic factor.[4, 5]

Treatment

Treatment for pediatric ALL involves an induction phase, a consolidation phase followed by intensification (reinduction), and maintenance therapy to eliminate residual disease. Treatment is also specifically directed to the CNS to prevent relapse due to residual leukemic cells.

The induction phase is aimed at achieving remission and restoring normal hematopoiesis [4, 5]. It typically lasts 4 to 6 weeks. Most regimens include three drugs: glucocorticosteroids (prednisone or dexamethasone), vincristine and asparaginase. A fourth drug, mostly anthracyclines, is usually added in higher risk patients but for all patients in some protocols. Intrathecal therapy is given additionally. In the consolidation phase residual leukemic cells are targeted. There is no consensus on the duration and best regimen for the consolidation phase. The most recent strategy in the Netherlands includes mercaptopurine, cytarabine and cyclophosphamide followed by high dose methotrexate in combination with mercaptopurine and intrathecal therapy to prevent bone marrow and CNS relapse [5]. Prognosis is improved when adding an intensification, or reinduction, phase. It resembles induction therapy and usually consists of corticosteroids, vincristine, asparaginase and anthracyclines. The dose-intensity of asparaginase is an important aspect of improved prognosis. Maintenance therapy is given up to 2-3 years from the initial diagnosis in order to eliminate MRD and thus prevent relapses. Even though two-thirds of patients can be cured with a shorter duration of therapy, these patients can not yet be identified. Maintenance treatment consists of weekly methotrexate and daily mercaptopurine. Dose is adjusted according to the leukocyte and/or platelet counts to ensure adequate dose intensity. The effectiveness of vincristine and dexamethasone or prednisone pulse therapy remains to be proven and is likely to depend on the intensity of the preceding therapy. Allogenic stem cell transplantation (SCT) is associated with

substantial morbidity and mortality. It is reserved for specific subgroups of patients that benefit from this procedure, such as those with a poor response to treatment [4, 5].

Adverse effects of treatment

The improved survival rates have led to an increasing group of childhood cancer survivors. The increased survival does, however, come with costs. Overall cumulative mortality at 30 years for all pediatric cancer diagnoses has remained stable around 18%. Nevertheless the pattern of late mortality is changing over the years, with a decrease in mortality due to recurrences and an increase in death attributable to secondary neoplasms and cardiac or pulmonary problems largely due to treatment-related causes. Among the treatment-related factors that increase mortality risk are radiotherapy, anthracyclines and alkylating agents.[6] However, survivors of ALL that have not received irradiation and attain ten year of more survival, are expected to have a normal life expectancy [7].

Survivors also experience a high rate of physical and psychosocial morbidity. Studies have shown that over half of (long term) ALL survivors experience at least one chronic condition and that 20-47% report a severe or life threatening chronic condition. Chronic conditions are more common in survivors that received irradiation [8-10]. It is important to note that 83-92% of non-irradiated, non-relapsed survivors do not have severe or life threatening conditions [9, 10]. Of special interest in survivors of ALL are anthracycline-induced cardiotoxicity, corticosteroid-exposure associated osteonecrosis, obesity and the metabolic syndrome [11]. Neurocognitive deficits are also reported [11], but seem subtle in long-term survivors that have been treated with chemotherapy only [12]. Secondary malignancies are becoming more apparent now that management of the primary disease has become more successful. Most secondary malignancies occur in irradiated patients and the risk for non-irradiated patients seems to be small [7, 9, 13, 14]. Central nervous system tumors are the most commonly seen secondary neoplasms, other malignancies include lymphomas and acute myeloid leukemias. Survival rates as low as 39% have been reported after secondary neoplasms [14]. Survivors of ALL are at increased risk of elevated levels of psychological distress, including depression and anxiety, attention deficits and social problems [15, 16]. Educational levels are lower than in healthy peers, especially in irradiated patients, although employment rates are normal in non-irradiated, non-relapsed survivors [7, 9, 17, 18]. Psychosexual problems are also frequent in childhood cancer survivors [19].

Treatment for childhood cancer not only influences the child, but also has psychosocial consequences for the family. Parents can experience higher levels of emotional distress, such as anxiety or depression, during and after treatment [20-23]. Siblings of children with cancer are at higher risk of experiencing post-traumatic stress symptoms, negative emotional reactions such as fear, anxiety, worry and sadness, and a poor

QoL and school functioning. These symptoms seem to subside as time since diagnosis increases [24].

ALL in the Netherlands

In the Netherlands all pediatric cancer care is coordinated by the Dutch Childhood Oncology Group (DCOG, or *Stichting Kinder Oncologie Nederland, SKION*), previously known as the Dutch Childhood Leukemia Study Group. The DCOG registers all new diagnoses, relapses, treatment results and issues guidelines for the treatment of pediatric cancers. All patients are managed in pediatric oncology centers that are situated in five academic hospitals. Less complicated care is usually shared with satellite hospitals situated near the patients' domicile. Allogenic SCT is performed in two specialized centers, of which one also treats patients with leukemia or lymphoma.

The two most recent DCOG front-line ALL treatment protocols were called ALL9 and ALL10. ALL9 was open for inclusion from 1997 to 2004 for children with de novo ALL, >1 year of age. Patients with a mature B-ALL phenotype, secondary ALL or who had been pretreated were excluded. Risk assessment was based on clinical and biological factors and two risk groups were predefined: non-high risk (NHR, 70%) and high risk (HR, 30%), Table 1.1. Total duration of therapy was 109 weeks for both risk groups. Compared to NHR, HR patients received daunorubicin during induction, higher doses of MTX, more frequent intrathecal therapy and two consecutive intensification phases. ALL9 did not include allogenic SCT. Five year event free survival (EFS) was 81%: 85% in NHR patients and 72% in HR patients. Overall survival at 5 years was 86% (90% in the NHR group, 78% in the HR group). [2]

The ALL10 protocol (2004-now) includes patients aged between 1-19 years with de novo ALL. Patients with a mature B-ALL phenotype, secondary ALL or who have been pretreated are excluded. Patients with Philadelphia positive ALL (translocation t(9;22) (q34;q11) and/or the BCR/ABL fusion transcript) are treated according to a separate protocol that includes a tyrosine kinase inhibitor.

Risk assessment is not only based on clinical and biological factors, response to therapy plays an important role as well. Based on the criteria outlined in Table 1.1 three risk groups are identified: standard risk (SR, 26%), medium risk (MR, 62%) and high risk (HR, 12%). Treatment intensity after the methotrexate phase is reduced for SR patients in whom five year event free survival (EFS) is expected to be >95%. Treatment for MR patients is intensified in order to increase EFS from 78% (in historical controls) to 85%. PEG-asparaginase substitutes native *E. Coli* asparaginase during maintenance therapy because of its favorable pharmacokinetic and toxicity profile. Treatment duration is 104 weeks for SR and MR patients. HR patients are expected to have a poor prognosis and therefore receive further intensified therapy, which includes allogenic SCT whenever

Table 1.1 Inclusion criteria per DCOG treatment protocol for newly diagnosed ALL

Protocol	Inclusion	Duration of therapy (weeks)
ALL 9 NHR (70%) [2]	- No HR criteria	109
ALL9 HR (30%) [2]	- initial leukocyte count >50x10 ⁹ /l - presence of mediastinal enlargement - initial CNS or testicular involvement - presence of t(9;22) or BCR-ABL, t(4;11) or 11q23 with MLL rearrangement - T-cell immunophenotype	109
ALL10 SR (26%)	- good response to prednisone on day 8 AND - CR at day 33 AND - MRD-negativity at day 33 and 79 AND - no presence of t(9;22) translocation or the BCR-ABL fusion gene AND - no presence of t(4;11)(q11;q23) translocation or the MLL/AF4 fusion gene AND - no initial CNS or testicular involvement	104
ALL10 MR (62%)	- good response to prednisone on day 8 AND - CR at day 33 AND - MRD-positivity at day 33 and/or at day 79, but MRD level at day 79 <10 ⁻³ AND - no presence of t(9;22) translocation or the BCR-ABL fusion gene AND - no presence of t(4;11)(q11;q23) translocation or the MLL/AF4 fusion gene	104
ALL10 HR (12%)	- poor prednisone response on day 8 OR - MRD level ≥ 10 ⁻³ or unknown at day 33 and MRD level of ≥ 10 ⁻³ at day 79 OR - presence of the t(4;11) (q11;q23) translocation or the corresponding fusion gene MLL/AF4 OR - no complete remission at day 33	104*

ALL9 enrolled patients between 1997-2002 and ALL10 from 2004-now. NHR= non-high risk; HR= high risk; SR= standard risk; MR= medium risk; CNS=central nervous system; CR= cytomorphological complete remission based on <5% leukemic cells in the bone marrow, recovery of normal hematopoiesis, absence of peripheral blood leukemic cells and no evidence of disease at any other site; MRD= minimal residual disease; MLL= mixed lineage leukemia. * children with a suitable donor receive a stem cell transplantation about 5-6 months after the start of treatment.

possible. In an interim-analysis 4 year EFS was 87% (97% for SR, 87% for MR and 75% for HR). Overall survival at 4 years was 92% (SR 99%, MR 94%, HR 80%) [1].

Background and focus of this thesis

The success of pediatric ALL treatment over the past decades has made other outcome measures besides survival, such as quality of life (QoL) and cost-effectiveness of treatment, more and more relevant. Treatment for ALL is long and intensive and clinical experience as well as the literature shows us that it is demanding on our patients and their families. Even though QoL improves over the course of time, as survivors of ALL have better QoL compared to patients on treatment, QoL does generally not normalize.

Most studies report impaired QoL in survivors, especially on psychosocial domains [25, 26]. In order to improve QoL in (long term) survivors, it seems imperative to start interventions and counseling at an early stage. Therefore, it is important to identify patients with a low QoL compared to their ALL-peers as well as to identify patients with insufficient recovery of QoL. These patients can then be targeted for specific interventions and counseling.

Besides clinical endpoints that are relevant to the individual or the whole ALL patient population (i.e. survival, morbidity, QoL), other endpoints such as the cost-effectiveness of treatments are more relevant to society. It is likely that further progress in the treatment of pediatric ALL will slow down now that nearly 90% of patients survive. Progress will be possible by rearranging the combinations of chemotherapy available, by introducing new drugs and perhaps new treatment modalities and adjusting the intensity of treatment according to increasingly individual-based risk assessments. It is likely that new drugs and technology, and the increasingly individualized treatment strategies will come with higher (monetary) costs. Without endangering the progress of improvement in survival, and the efforts to improve late outcomes and QoL, it is important to take the cost-effectiveness of new ALL treatments into account. This is especially relevant when new treatments are likely not to make a significant impact on survival progress.

The first focus of this thesis was to evaluate the development of QoL during and shortly after childhood ALL treatment and to identify determinants of QoL. In a large prospective study, which was an add-on study to the national DCOG ALL10 treatment protocol, QoL was longitudinally studied during and shortly after treatment. The potential determinants that were evaluated in this study were medical factors (such as treatment intensity and complications), child characteristics (i.e. age, gender) and parental or family aspects (e.g. respondent gender, family situation, highest education). The effects on QoL of treatment with glucocorticosteroids, which are known to cause emotional and behavioral issues [27-30], were evaluated in a multi-center study performed in a cohort of patients treated according to ALL9. Based on the clinical observation that sleep problems are a frequent but underreported problem in ALL patients that can potentially affect QoL, this relationship was evaluated in a small multi-center cohort of ALL10 patients.

The second focus of this thesis was to evaluate the cost-effectiveness of pediatric ALL treatment. The cost-effectiveness of the DCOG protocol ALL10, in which more expensive medication and a new diagnostic technology were introduced, was compared to cost-effectiveness of the previous protocol ALL9 in a single-center cohort of patients. A lack of complete and robust information on preference-based QoL (utility) scores in pediatric ALL necessitated the restriction to a cost-effectiveness in stead of a cost-utility analysis. To complete the available information in the literature, utility scores were evaluated in a single-center cohort of short-term survivors.

The following sections will elaborate on QoL in pediatrics and sleep in cancer patients. It will also provide some background information on economic evaluations. Finally, the outline of this thesis is described.

Quality of life

Concept

The changing epidemiology of childhood disease has shifted focus from survival only to survival (or disease management in case of chronic conditions) with optimal QoL. The appraisal of QoL depends on the individual's physical, social, cultural, spiritual and historical circumstances, and on the approach that is taken. Several approaches can be identified, such as the philosophical, economical, sociological, psychological and the medical approach [31]. In the economical approach, QoL is measured in terms of acquired wealth (clean water, housing, adequate food, improvement in life-expectancy, the access to education etcetera). Although these advances are a basic part of QoL, they are not equivalent to happiness or a high QoL. The sociological and psychological approaches emphasize that QoL is subjective, dependent on cultural aspects and related to the achievement of life goals, respectively. The medical approach assesses the impact of health and illness on QoL, called health related quality of life (HRQL). It incorporates all previously described approaches.

In the 1980's the first reports on QoL in childhood cancer emerged. Lansky and colleagues published the proxy instrument *Play Performance Scale for Children*, which is a simple instrument assessing the child's activity level [32]. Other, more sophisticated instruments have emerged since. There is a distinction to be made between instruments that assess QoL and those that assess related concepts such as functional status, health status and well-being. Functional status assesses an individual's ability to perform normal daily activities. It focuses on what the individual can actually do rather than what they feel able to do. Health status comprises of an individual's level of wellness or illness in the context of biological or physical dysfunction, symptoms and functional impairment. Well-being adds the individual's coping mechanism or positive well-being to the negative assessment of health states in functional and health status measures. [31] QoL adds the individual's perspective to the assessment of more objective factors as measured by the before mentioned concepts, although these concepts are often referred to as QoL. In medical research, HRQL is often referred to as QoL, as it will be in this thesis. QoL may be converted to preference-based QoL scores that are based on community preferences concerning health states or QoL. The more preferable an outcome, the higher the utility associated with it. Preference-based QoL scores are also referred to as utility scores and are scored on a 0 to 1 scale, in which scores

of 0 represent being dead and 1 living in perfect health. Utility scores can be used to calculate quality-adjusted life-years (QALY). In QALY, the length of time affected by a certain health state is adjusted by the utility value. It thus captures gains from reduced mortality (quantity gains) as well as gains from reduced morbidity (quality gains) [33].

There is general consensus that QoL is a multidimensional concept. The World Health Organization (WHO) defined health in 1948 as “the state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. From the WHO QoL group definition of QoL dating from 1993 (“an individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”), six QoL domains can be identified: physical health, psychological health, level of independence, social relationships, environmental features and spiritual concerns. Contemporary QoL instruments usually comprise of at least physical, psychological and social domains.

Measurement of QoL in pediatric (cancer) patients

Several issues are relevant when measuring QoL in pediatric (cancer) patients, such as the choice of instrument and of respondent, and the concept of response shift in longitudinal studies.

A classification into generic and disease specific QoL instruments can be made. Generic instruments allow for a comparison with healthy population norms and can be used across a wide range of patient populations. Disease specific instruments offer the advantage of assessing disease related aspects of QoL, such as side-effects of chemotherapy. They are more sensitive to detect changes in QoL over time or between disease groups than generic instruments. They can however, not be used for comparison across patient groups with different conditions. [31, 34] Which instrument to use depends on the research aims, although it seems useful to include both instruments to achieve a more comprehensive evaluation of QoL.

Child QoL can be evaluated by several respondents: the child itself, the parents or guardians, or the healthcare providers involved. In pediatric cancer children are often too young or too ill to answer themselves, especially during treatment, and respondents are typically the parent(s). However, perceptions of QoL can differ between assessors. Children often perceive their QoL to be better than their parents perceive it [35], although the opposite has been reported as well [36]. More agreement is generally seen on observable domains like physical health than on non-observable domains like emotional functioning [37]. Therefore the consensus is to include self-reports whenever possible, i.e. when the child is not too ill or too young. This requires pediatric instruments not only to assess developmentally appropriate abilities, but also to have a developmentally appropriate format [34].

The perception of QoL is influenced by normal development. In pediatric cancer for example, it is uncommon for toddlers to be bothered by the loss of hair, but this often represents a great burden to adolescents who are concerned about their appearance. Besides the developmental change in QoL perception, changes can also result from a phenomenon called response shift. Response shift describes the change in the patient's perception of QoL due to the accommodation to the disease process [38]. It means that the perception of QoL can change even though functional abilities or health status does not. Although it can be seen as a source of bias in longitudinal studies, it can also emphasize the importance of the individual's perspective in the assessment of QoL.

Sleep

Sleep disturbances

Sleep disorders in children can lead to significant behavioral and cognitive morbidities. The prevalence of sleep problems in children in the general population is up to 30% [39, 40]. Gender and age influence sleep [40-42], and some sleep problems are more common during certain stages of child development, such as night wakings during infancy [43] and sleep onset delay in older children [40]. Children with sleep difficulties experience higher rates of behavioral problems, depression, anxiety in adulthood, impaired cognitive function, learning disabilities, and emotional development [43-48]. Sleep problems are more common in certain medical conditions, such as chronic pain, attention deficit hyperactivity disorder, and autism [49-51].

Sleep in cancer

In adult cancer, sleep disturbances are reported among 30-75% of patients, which is twice as often compared to healthy adults [52]. Insomnia is the most common sleep disturbance. Contributing factors are the cancer itself (if it for example leads to pain), treatment-related side-effects, medication (corticosteroids, chemotherapy, narcotics), environmental factors (hospital noises and disturbances), psychosocial disturbances (anxiety, depression) and comorbid medical problems (headaches, primary sleep disorders).

Studies are starting to emerge on sleep in pediatric cancer. These studies have reported sleep disturbances, decreased sleep efficiency and longer sleep duration. Treatment with corticosteroids, hospitalization and pain seem to be contributors to impaired sleep [41, 42, 53, 54]. Impaired sleep has been found to negatively influence QoL in children across diagnostic groups [55], including children during cancer treatment [56]. Treatment of sleep disturbances may result in the improvement of QoL.

Cost-effectiveness

Background

In economic evaluations, the costs and effects of two or more treatment alternatives are compared. It assesses whether the effects of treatment warrant the monetary and non-monetary costs it takes to produce them [57]. The essence of economic evaluations is the scarcity of resources: people, time, facilities, equipment and knowledge [33]. Increasing pressure on limited resources calls for a careful evaluation of healthcare costs. This is important since resources spent on healthcare cannot be spent on other sectors such as education and safety. Also, future patients should have an equal claim to healthcare resources.[58]

Types and methods of economic evaluations

Depending on the type of effect studied, three major types of economic evaluations can be identified. First, in cost-effectiveness analysis, effects are measured in life years saved (LYS). Outcomes are reported as costs per LYS. Second, cost-utility analysis takes into account the quality of the life years saved with the use of utilities. Outcomes are reported as costs per QALY. Third, cost-benefit analysis measures effects in monetary terms. The last form is less frequently used because it is difficult to quantify the monetary value of health effects [57]. In each of the three forms the incremental cost-effectiveness ratio (ICER) represents the incremental costs per incremental effect. The ICER helps to determine the effectiveness of treatments in terms of their effects. Treatments that cost less and have better effects are the preferred choice. Treatments that are more expensive and produce fewer effects are easily considered not worthwhile. It is more difficult to draw conclusions from more expensive treatments with better effects or cheaper treatments with fewer effects. Benchmarks of acceptable cost-effectiveness vary between investigators and societies.

Economic evaluations can be performed according to several perspectives. The societal perspective comprises all costs of care regardless of who pays and is recommended by Dutch guidelines [59]. It includes costs to the healthcare system as well as costs to patients and their family. Other perspectives are also possible, such as the perspective of healthcare insurances, hospital, patients, government or employer.

The time horizon determines the length of time in which costs and effects are included. Direct costs (and effects) occur during the studied treatment alternatives, for example during ALL treatment. Indirect costs (and effects) occur in the added life-years. Studies with a short time horizon are at risk of presenting incomplete data, although it can be argued that the contribution of future costs is limited due to discounting (see below). Indirect costs can be related to the studied disease, such as the costs for treatment of recurrences or late effects after ALL, or unrelated to the studied disease,

for example the costs for work-related repetitive strain injury. Dutch guidelines [59] recommend to include related costs only.

Costs within and outside of the healthcare system can be included. Components of costs within the healthcare system, also called medical costs, may be hospitalization costs, outpatient care, physician services, services of other health-care professionals such as nurses and physical therapists, laboratory and other diagnostic tests and medication. Costs outside of the healthcare system, or non-medical costs, include costs borne by patients or parents: out-of-pocket expenses (such as over-the-counter drugs, mileage and parking at the hospital) and loss of income.[57, 58] It also includes costs for specialized education, and costs associated with the loss of productivity because of disability or death [59].

When multiple time periods are studied, costs and effects incurred in the future should be converted into their contemporary equivalent. For this purpose, a discount factor (like an interest rate) is used to convert future costs and effects into their present value. Discounting is based on two principles. The first principle is positive time preference; most individuals prefer to acquire positive effects (such as health) as soon as possible and postpone negative effects (costs). The second principle is the investment-argument: because of interest, costs and effects that can be invested now are more valuable than investments that occur in the future. The choice of the discount rate is somewhat arbitrary and varies between guidelines.[57, 60]

Sensitivity analyses allow for the assessment of the effect of uncertainties about estimates in a study. Uncertain factors are varied from a best estimate to a plausible range from a more conservative to a more optimistic estimate. Costs as well as effects can, or should, be varied. The effects of the variations on the economic model are subsequently presented in the study results.[57]

Economic evaluations in pediatric ALL

It is likely that the progress of success in pediatric ALL will slow down in future years and that it will increasingly involve (expensive) new technologies and medication. The economic aspects of childhood ALL have, however, not yet received much attention. Some data on adult ALL is available, but this is not comparable to pediatric ALL both in terms of treatment and in terms of effects [61]. Treatment of adult ALL more often involves SCT, which has much higher associated costs. The effects are less favorable, survival is lower and the life years gained are shorter than in (young) children. Separate pediatric information is therefore necessary. It needs to be borne in mind however, that healthcare consumption is much lower in children compared to (elderly) adults, illustrated by the fact that the overall costs of pediatric healthcare (curative and preventive) constituted 15.6% of overall healthcare costs in 2005 [62]. Costs of pediatric curative healthcare represented 5.9% of overall curative healthcare costs in the Netherlands

[62]. Only 1.8% of curative healthcare costs in children up to 19 years of age was spent on cancer in 2005 [62]. Even though pediatric cancer is rare and costs are relatively low, economic evaluations of cancer treatments are still useful and necessary to make informed decisions.

Outline of this thesis

The first part of this thesis focuses on QoL, its development during and after pediatric ALL treatment and its determinants. In chapter 2 we present the findings of a systematic review of non-preference based QoL in pediatric ALL. Chapters 3 and 4 report on the longitudinal assessment of QoL during ALL10 treatment. In chapter 3 QoL and its determinants during induction/consolidation treatment is described. In chapter 4 the follow-up of this cohort until shortly after the end of treatment is analyzed. The development of QoL and change in its determinants is evaluated. Chapter 5 discusses the development of QoL during maintenance treatment in a cohort of ALL9 patients and analyses the effect of treatment with dexamethasone on QoL. In chapter 6 the effect of sleep on QoL in children during ALL10 maintenance treatment is studied.

The second part of this thesis focuses on utility scores associated with pediatric ALL and the cost-effectiveness of treatment. In chapter 7 we report on a systematic review of health status utilities in pediatric ALL. Chapter 8 reports on utility scores in a short-term ALL survivors. Chapter 9 deals with the results of a cost-effectiveness study, in which the effect of the introduction of expensive medication and a new diagnostic technology in ALL10 is compared to ALL9. Finally, the results reported in this thesis are discussed and put into perspective in chapter 10.