Pediatric acute lymphoblastic leukemia: Quality of life and cost-effectiveness of treatment

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Chapter 3

Determinants of quality of life during induction therapy in pediatric acute lymphoblastic leukemia

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Abstract

Improvement in survival of pediatric Acute Lymphoblastic Leukemia (ALL) has increased the attention to quality of life (QoL). QoL is impaired during maintenance treatment, but little is known about QoL during induction therapy. Identification of patients with poor QoL during induction will provide opportunities for early interventions, and may subsequently improve future QoL. The aim of this national multi-centre study was to assess QoL and its determinants during ALL induction treatment. Proxy-reports of the Child Health Questionnaire (CHQ) and the PedsQL cancer version were collected. Child, treatment and parental characteristics were analyzed as potential determinants in a multiple regression model. 130 parents of children participated (response rate 82%), median child age was 5.7 years and 48% were female. QoL as measured with the CHQ was significantly lower than the norm, the effect sizes were large and the differences were clinically relevant. Physical QoL was more often affected than psychosocial QoL. On the PedsQL pain was most affected. Regression models could be constructed for 7/14 CHQ scales and 7/9 PedsQL cancer scales, accounting for 7 to 36% of the variance in scores. Impaired QoL was most often associated with older children and girls. Also, father-respondents seem to have a lower QoL perception compared to mother-respondents although this needs to be confirmed in future research. Specific counseling for these subsets of patients during the early phases of therapy is warranted.

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common type of childhood cancer. Over the past decades survival following treatment for childhood ALL has improved substantially and has now reached 80-85% [2, 63]. Besides survival and morbidity, quality of life (QoL) has been recognized as an important outcome measure, which has led to an increase of studies incorporating QoL over the last two decades. In ALL survivors QoL is usually similar to healthy controls on physical domains, but diminished on psychosocial domains [25]. During treatment QoL is impaired compared to the norm on the majority of domains [90, 92]. Recently, Sung et al. performed a study to identify predictors of QoL in a large group of children during ALL treatment [103]. This study included children at least two months after diagnosis and found that gender and age predicted QoL in high-risk (HR) patients, and socioeconomic factors predicted QoL in standard-risk ALL. Other studies have also identified risk factors for impaired QoL during maintenance treatment. Higher treatment intensity [90, 92], the use of corticosteroids [77, 92, 106] and female gender [82, 103] are associated with poorer QoL. Age influences each QoL domain differently, with lower overall QoL in older children but lower QoL in younger children for anxiety and communication domains [82, 90].

Little is known on QoL and its determinants during the initial part of therapy, the induction/consolidation phase. Identification of patients most at risk for an impaired QoL during this period can help to optimize care and counseling in an early phase. This may subsequently improve future psychosocial functioning and QoL. This study is part of a national longitudinal study of QoL during ALL treatment, designed to assess QoL throughout therapy, describe the evolvement of QoL and identify potential determinants. The results of the first assessment of QoL and its determinants during induction therapy are reported here.

Methods

Patients

A longitudinal prospective multi-centre cohort study was designed. Parents of children from six of seven Dutch pediatric oncology centers were enrolled: Emma Children's Hospital Academic Medical Center Amsterdam, University Medical Center Groningen, Leiden University Medical Center Leiden, Radboud University Medical Center Nijmegen, Wilhelmina Children's Hospital University Medical Center Utrecht, and VU University Medical Center Amsterdam. Parents of children between the ages of 2 and 18 years diagnosed with ALL and treated according to the Dutch Childhood Oncology Group (DCOG) ALL10 protocol were eligible. Parents were required to be fluent in Dutch.

Children with an important pre-existing condition (e.g. Down syndrome), potentially affecting baseline QoL, were excluded. The eligibility of patients was further determined by medical and psychosocial circumstances and was decided by the treating physician. All patients received the same 64 day induction/consolidation treatment, including prednisone, vincristine, daunorubicine, asparaginase, cyclophosphamide, cytarabine, mercaptopurine and intrathecal therapy. Risk groups were assigned after the induction/consolidation phase or during induction for a subset of HR patients with a poor response to prednisone treatment at day 8.

Procedure

From October 2006 till October 2009 parents of newly diagnosed patients were invited to participate in the study. Parents willing to participate were approached within the first weeks after diagnosis by one of the principal researchers and received additional verbal and written information on the study. A booklet containing the QoL measures and additional questions concerning child (age, gender) and family characteristics (respondent's age, gender, ethnicity, highest education and family situation) were distributed together with a stamped return envelope to the participating families. Parents were contacted by one of the researchers if the booklet was not returned within two to three weeks. The contact was repeated if necessary. Families that continued to indicate willingness to participate but did not return the booklets after two reminders were considered withdrawn from the study due to medical or psychosocial circumstances. The number of hospital admission days preceding completion of the QoL measures was recorded for children treated at two of the six research sites (Radboud University Medical Center Nijmegen and VU University Medical Center Amsterdam, 56% of patients in this study) using hospital records. Information on risk group and treatment toxicity was available through DCOG databases. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria. All serious toxicity (grade 3-4) during induction/consolidation treatment was included in the analysis. The study was approved of by each of the medical ethical review boards of the participating institutions.

Measures

Parent-proxy reports were collected using a generic and a disease specific instrument. The Dutch version of the Child Health Questionnaire (CHQ) 50 items parent-form is a generic QoL assessment tool that has shown good reliability and validity [107, 108]. This instrument covers the physical, emotional and social well-being of children and allows for two summary scores (physical and psychosocial). Items are scored using a four to six point Likert scale and converted to a 0 to 100 point continuum, with higher scores indicating better QoL. Dutch norms are available and allow for a comparison with the Dutch healthy population [108]. The Pediatric Cancer Quality of Life Inventory 3.0^{tm} Acute

Cancer Version (PedsQL) is a 27-item multidimensional cancer specific questionnaire. It is a reliable and valid QoL assessment tool with subscales for determining problems in relevant areas during cancer treatment such as pain, nausea, treatment and procedural anxiety, worry, cognitive problems, perceived physical appearance and communication. Items are scored using a four point Likert scale and reflect on the past week. Higher scores indicate better QoL. Reference scores consisting of 183 patients with different types of cancer on treatment with a mean age of 8.2 years are available [99].

Statistics

The Statistical Package for Social Sciences (SPSS) for Windows version 15.0 was used for all the analyses. Differences in demographic variables between the study group and the non-participants were calculated using Mann-Whitney U tests and chi-square tests. The difference in QoL scores between the ALL group and norms was assessed using one sided t-tests. Effect sizes were calculated as follows: [mean (a) – mean (b)/largest standard deviation score (SD)], which means that differences between groups are expressed in units of the largest within-group standard deviation. Effect sizes between 0.2 and 0.5 were considered to indicate a small effect, effect sizes between 0.5 and 0.8 a moderate effect, and effect sizes ≥0.8 were considered to represent a large effect [109, 110].

The difference in QoL between the ALL group and the norm was further explored by calculating the number of ALL patients with a clinically meaningful impaired QoL. Varni et al. [111] previously established that in healthy children scores one SD below the population mean indicate a clinically meaningfully impaired QoL, since this is similar to scores in a population with severe chronic conditions. Following previous research in this field, for the comparison of our cancer population with healthy CHQ norms a cut-off point of -2SD was employed [102, 103]. For the PedsQL, a cut-off of -1SD was used since the comparison was made with cancer norms as opposed to healthy norms.

The potential determinants of QoL were classified into child characteristics (age, gender), treatment characteristics (days since diagnosis, risk group, admission days and treatment toxicity) and parent characteristics (age, gender and highest education of the respondent, family situation). To determine which factors determine the correlates of QoL, first a univariate linear regression analysis was performed. Factors associated with QoL with a p-value <0.1 were entered in a forward selection multiple regression model. Significance level was set at two-sided $p<0.05$ for all analyses.

Results

Demographics

In the studied period, 255 children were newly diagnosed with ALL at one of the participating centers. Thirty-two patients were not eligible and 59 patients were not invited to participate due to a variety of reasons (medical and psychosocial complications, advice of the treating medical team, organizational problems), see Figure 3.1 for details. A total of 164 families were invited to take part in this study and 159 agreed. Completed questionnaires were returned by 131 parents (response rate 82%). One questionnaire was returned long after the induction phase, this patient was excluded from the analysis. The demographic variables of the 130 participants are demonstrated in Table 3.1. The median age of the patients was 5.7 years (interquartile range, IQR, 6.1), 62 (48%) were

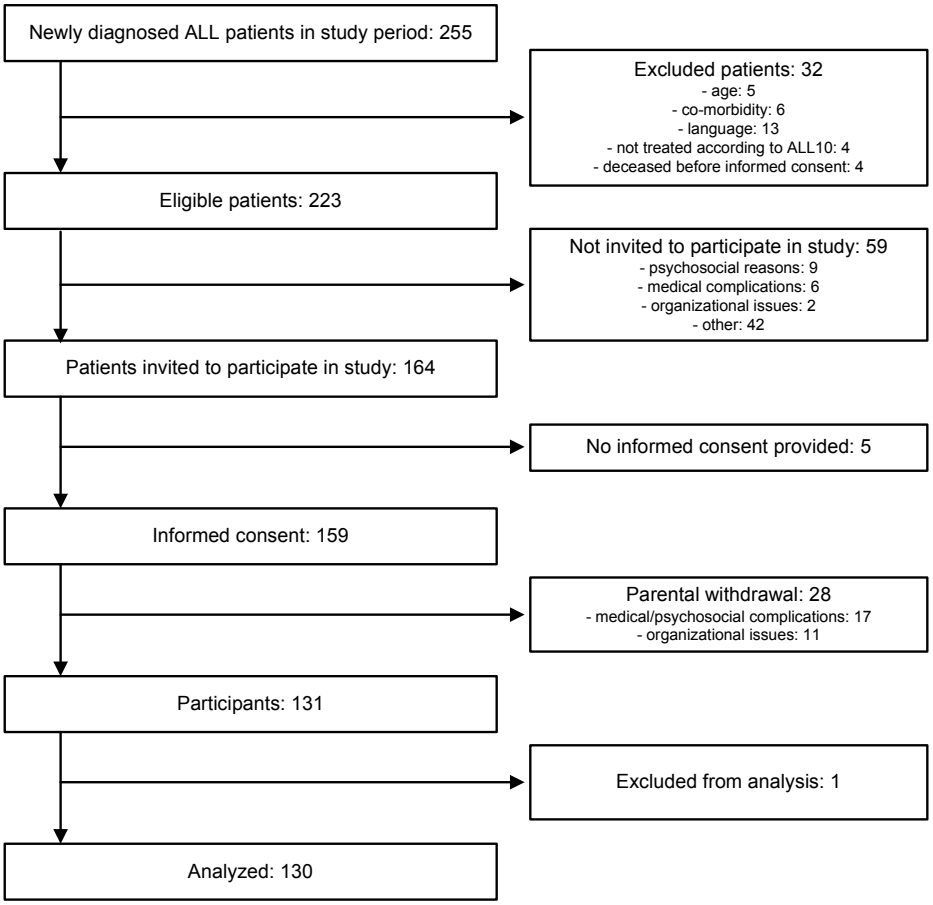

Figure 3.1 Study participants and non-participants

Table 3.1 Demographic variables of the participating ALL patients

Variable	N	Value
Child factors:		
Age: N (%)	130	
2-4 years		52 (40)
5-7 years		36 (28)
8-12 years		28 (21)
≥13 years		14 (11)
Female: N (%)	130	62 (48)
Time since diagnosis in days: median (IQR)	129	38 (28.5)
Risk group: N (%)	130	
Standard		30 (23)
Medium		82 (63)
High		18 (14)
Admission days: median (IQR)	71	15 (14)
Parent factors:[1]		
Age in years: mean (SD)	130	38 (6)
Female: N (%)	130	112 (86)
Highest education	130	
High school		15 (12)
Vocational training		63 (48)
College		36 (28)
University		16 (12)
Single parent[2]: N (%)	128	15 (12)

[1] respondent characteristics, [2] child living with one parent or alternately with either parent

female. Questionnaires were filled out at a median time since diagnosis of 38 days (IQR 28.5). Eighteen children (14%) had a HR ALL, which was based on a poor prednisone response on day 8 in 13 patients. The median number of admission days prior to the submission of the questionnaires was available for 71 children and was 15 (IQR 14). Respondents were mostly mothers (86%), mean age 38±6 years. Most children (93%) had one or both parents born in the Netherlands. There were no statistically significant differences between the study group and the eligible patients that did not participate in the study. The median age of the non-participants was 5.6 (IQR 6.0) years (p=0.66), 47% was female (p=0.89) and 23% had a HR ALL (p=0.22).

Child Health Questionnaire

QoL as measured with the CHQ was significantly (p<0.001) impaired compared to healthy controls on all scales except for family cohesion (Table 3.2). Scores were higher on the family cohesion subscale in the ALL population compared to the norm (p<0.01)

Table 3.2 Child Health Questionnaire: ALL scores compared to healthy norm scores

	ALL Mean (SD)	Norm[1] Mean (SD)	Effect Size[2]	p-value[3]	95% CI of the difference
Physical Functioning	41.6 (27.6)	99.1 (4.3)	2.1	<0.001	52.7-62.3
Role Limitations: emotional/behavioral	49.7 (41.2)	97.9 (7.2)	1.2	<0.001	41.0-55.4
Role Limitations: physical	27.9 (33.8)	95.8 (15.6)	2.0	<0.001	62.0-73.8
Bodily Pain	38.8 (25.4)	85.7 (17.2)	1.8	<0.001	42.5-51.3
Behavior	72.5 (13.9)	78.5 (13.1)	0.4	<0.001	3.6-8.4
Mental Health	62.6 (14.7)	81.4 (12.1)	1.3	<0.001	16.3-21.4
Self-esteem	59.6 (19.1)	79.2 (11.0)	1.0	<0.001	16.3-23.0
General Health Perception	59.2 (18.4)	82.9 (13.4)	1.3	<0.001	20.5-26.9
Parental Impact: emotional	42.8 (22.8)	86.3 (15.2)	1.9	<0.001	39.5-47.4
Parental Impact: time	43.9 (26.8)	94.0 (13.0)	1.9	<0.001	45.4-54.7
Family Activities	44.1 (19.0)	91.5 (11.9)	2.5	<0.001	44.1-50.7
Family Cohesion	76.9 (19.2)	72.2 (19.4)	-0.2	<0.01	-1.4- -8.0
Physical Summary Score	20.2 (14.2)	56.4 (5.7)	2.5	<0.001	33.7-38.6
Psychosocial Summary Score	40.5 (9.3)	53.2 (6.4)	1.4	<0.001	11.1-14.3

Higher scores indicate better QoL. Physical and Psychosocial summary scores are based on a factor-analytical model on U.S. population samples. A score of 50 (10) represents the mean (SD) in the general U.S. population. [1] Dutch norm scores consist of a sample of healthy school-aged children aged between 5-13 years [108]. [2] Effect size = [mean(a) – mean (b)/largest standard deviation score (SD)]. Small effect: 0.2-0.5, moderate effect: 0.5-0.8, large effect ≥0.8. [3] One-sided t-test.

indicating a better QoL, although the effect size was small (0.2). Most effect sizes were large, ranging between 1.0 to 2.5, but a small effect size was found for general behavior (0.4). The number of children with scores below -2SD of the norm was over 30% on most scales: physical functioning 125/130 (96%), emotional/behavioral role limitations 86/129 (67%), physical role limitations 98/129 (76%), bodily pain 95/130 (73%), mental health 44/130 (34%), self esteem 54/128 (42%), general health perception 61/130 (47%), parental emotional impact 93/130 (72%), parental time impact 110/130 (85%), family activities 115/130 (88%), physical summary score 121/127 (95%) and psychosocial summary score 63/127 (50%). Fewer children had scores lower than -2SD on the subscales behavior (17/130, 13%) and family cohesion (6/130, 5%).

In the univariate analysis (Table 3.2a), child characteristics such as older age and female gender were associated with lower QoL. Among the treatment characteristics, more days since diagnosis was significantly associated with a better QoL on the bodily pain scale (B=0.4, p=<0.001) and the mental health scale (B=0.2, p<0.001). For parental characteristics, respondent gender and highest education were associated with QoL on a number of scales. Mothers tended to rate a better QoL than fathers as did lower educated parents compared to highly educated parents.

Table 3.3 demonstrates the results of the multiple regression analysis. Because child and parent age were highly correlated (correlation coefficient 0.62, p<0.001), only child

Table 3.2a Univariate analysis of determinants for the Child Health Questionnaire scores

	Child characteristics P-value (B ± s.e.)		Treatment characteristics P-value (B ± s.e.)				Parent characteristics P-value (B ± s.e.)			
	Age in years	Female	Days since diagnosis	High risk group	Admission days	Treatment toxicity	Age in years	Female	University education	Single parent
Physical Functioning	0.40 (-0.49±0.58)	0.096 (-8.06±4.81)	0.57 (0.06±0.11)	0.20 (9.06±6.98)	0.097 (-0.25±0.15)	0.30 (-0.36±0.34)	0.73 (-0.13±0.39)	0.02 (16.74±6.87)	0.02 -16.93±7.24	0.46 (-5.48±7.41)
Role Limitations: emotional/ behavioral	0.11 (-1.42±0.87)	0.14 (-10.81±7.28)	0.35 (0.15±0.16)	0.68 (4.49±10.85)	0.29 (-0.24±0.22)	0.40 (-0.44±0.52)	0.20 (-0.75±0.58)	0.08 (18.30±10.47)	0.65 (5.10±11.13)	0.67 (-4.76±11.11)
Role Limitations: physical	0.04 (-1.45±0.70)	0.56 (-3.53±5.97)	0.28 (0.14±0.13)	0.75 (-2.78±8.83)	0.60 (-0.10±0.19)	0.33 (-0.41±0.42)	0.10 (-0.78±0.47)	0.03 (18.44±8.47)	0.07 (-16.40±8.95)	0.82 (2.08±8.94)
Bodily Pain	0.02 (-1.29±0.52)	0.07 (-8.13±4.42)	<0.001 (0.36±0.10)	0.26 (7.23±6.45)	0.09 (-0.23±0.14)	0.06 (-0.59±0.31)	0.20 (-0.46±0.36)	0.17 (8.89±6.43)	0.09 (-11.43±6.74)	0.12 (-10.54±6.76)
Behavior	0.14 (0.43±0.29)	0.90 (-0.32±2.45)	0.17 (0.08±0.05)	0.84 (0.73±3.54)	0.67 (-0.03±0.08)	0.37 (-0.16±0.17)	0.75 (0.06±0.20)	0.40 (2.98±3.53)	0.42 (-2.99±3.71)	0.34 (-3.54±3.71)
Mental Health	0.61 (-0.16±0.31)	0.04 (-5.24±2.56)	<0.001 (0.22±0.06)	0.13 (5.71±3.72)	0.32 (-0.08±0.08)	0.03 (-0.39±0.18)	0.73 (0.07±0.21)	0.14 (5.57±3.72)	0.70 (-1.51±3.95)	0.10 (-6.49±3.93)
Self Esteem	0.52 (-0.26±0.40)	0.79 (-0.89±3.40)	0.96 (0.004±0.08)	0.60 (2.60±4.87)	0.99 (0.003±0.19)	0.89 (0.03±0.24)	0.21 (-0.34±0.27)	0.09 (8.49±4.94)	0.36 (-4.69±5.11)	0.79 (-1.39±5.15)
General Health Perception	0.06 (0.73±0.38)	0.90 (-0.42±3.25)	0.48 (-0.05±0.07)	0.36 (-4.33±4.69)	0.16 (0.13±0.09)	0.19 (0.30±0.23)	0.08 (0.45±0.26)	0.77 (1.37±4.70)	0.16 (-6.91±4.91)	0.093 (-8.24±4.87)
Parental Impact: emotional	0.28 (-0.51±0.48)	0.02 (-9.14±3.93)	0.03 (0.18±0.09)	0.06 (11.02±5.72)	0.34 (-0.12±0.13)	0.81 (-0.07±0.28)	0.47 (-0.23±0.32)	0.004 (16.39±5.62)	0.11 (-9.63±6.04)	0.97 (0.23±6.05)
Parental Impact: time	0.91 (-0.07±0.56)	0.07 (-8.61±4.65)	0.03 (0.23±0.10)	0.21 (8.48±6.78)	0.67 (-0.06±0.14)	0.22 (0.41±0.33)	0.93 (-0.04±0.38)	0.01 (16.60±6.66)	0.64 (-3.38±7.16)	0.59 (-3.87±7.15)

Table 3.2a Univariate analysis of determinants for the Child Health Questionnaire scores (continued)

	Child characteristics P-value (B ± s.e.)		Treatment characteristics P-value (B ± s.e.)				Parent characteristics P-value (B ± s.e.)			
	Age in years	Female	Days since diagnosis	High risk group	Admission days	Treatment toxicity	Age in years	Female	University education	Single parent
Family Activities	0.60 (0.21±0.40)	0.23 (-4.01±3.33)	0.18 (0.10±0.07)	0.80 (-1.22±4.85)	0.31 (-0.11±0.10)	0.21 (-0.30±0.23)	0.67 (-0.12±0.27)	0.19 (6.32±4.81)	0.09 (-8.72±5.04)	0.34 (4.89±5.06)
Family Cohesion	0.84 (-0.08±0.40)	0.73 (1.18±3.38)	0.39 (-0.07±0.08)	0.14 (7.16±4.84)	0.39 (-0.09±0.10)	0.26 (-0.27±0.24)	0.40 (-0.23±0.27)	0.14 (-7.16±4.84)	0.83 (-1.08±5.14)	0.05 (-10.29±5.07)
Physical Summary Score	0.12 (-0.46±0.30)	0.18 (-3.37±2.52)	0.22 (0.07±0.06)	0.77 (1.08±3.71)	0.46 (-0.11±0.14)	0.57 (-0.10±0.18)	0.42 (-0.17±0.20)	0.02 (8.70±3.63)	0.01 (-9.38±3.72)	0.43 (-2.99±3.79)
Psychosocial Summary Score	0.49 (-0.14±0.20)	0.07 (-2.99±1.64)	0.02 (0.09±0.04)	0.13 (3.67±2.41)	0.84 (-0.02±0.10)	0.57 (-0.07±0.12)	0.48 (-0.09±0.13)	0.02 (5.65±2.38)	0.95 (-0.17±2.50)	0.37 (-2.24±2.49)

s.e. = standard error. Positive B coefficients indicate that the (increasing value of the) determinants are associated with a better QoL, negative B coefficients indicate that the (increasing value of the) determinants are associated with a poorer QoL..

age was included into the model if both child age and parent age qualified for inclusion. The variance in score (R square) was determined for 7% by the gender of the responding parent and child age for physical role limitations. Days since diagnosis, child gender and age, parental highest education and treatment toxicity together determined 24% of the bodily pain score variance. Mental health was independently associated with days since diagnosis and child gender (R square 17%). General health variance was accounted for 7% by child age and single parent situation. The subscales parental emotional impact and parent time impact and the psychosocial summary score were independently determined by gender of the responding parent and child gender, and days since diagnosis (R square 13%, 11% and 11%, respectively).

Table 3.3 Multiple linear regression analysis of the determinants associated with the Child Health Questionnaire scores

Scale	Determinant	P-value	B ± s.e.	R square
Role Limitations: physical	Parent female	0.03	18.41±8.35	0.07
	Child age	0.04	-1.45±0.69	
Bodily Pain	Days since diagnosis	<0.001	0.37±0.09	0.24
	Child female	0.009	-11.06±4.15	
	Child age	0.004	-1.42±0.48	
	Treatment toxicity	0.04	-0.60±0.29	
	University education	0.04	-12.69±6.10	
Mental Health	Days since diagnosis	<0.001	0.24±0.05	0.17
	Child female	0.004	-7.10±2.43	
General Health	Child age	0.01	0.96±0.39	0.07
	Single parent	0.03	-10.83±4.89	
Parental Impact: emotional	Child female	0.01	-9.59±3.82	0.13
	Parent female	0.01	13.79±5.48	
	Days since diagnosis	0.02	0.20±0.09	
Parental Impact: time	Parent female	0.04	14.02±6.59	0.11
	Days since diagnosis	0.02	0.24±0.10	
	Child female	0.04	-9.75±4.60	
Psychosocial Summary Score	Parent female	0.05	4.73±2.34	0.11
	Days since diagnosis	0.01	0.09±0.04	
	Female child	0.03	-3.54±1.62	

s.e. = standard error. Positive B coefficients indicate that the (increasing value of the) determinants are associated with a better QoL, negative B coefficients indicate that the (increasing value of the) determinants are associated with a poorer QoL.

Pediatric Quality of Life Inventory Cancer version

QoL as measured with the PedsQL (Table 3.4) was significantly impaired compared to the reference population on the subscales pain (p<0.001, effect size 0.9), procedural anxiety (p=0.03, effect size 0.2) and communication (p<0.001, effect size 0.4). For these

domains, a clinically meaningful lower QoL was found in 47%, 22% and 37% of patients, respectively. QoL was better than the reference population on the worry subscale (p<0.001), although the effect size was small (-0.3). ALL patients did better compared to the reference population on the following scales: nausea 15/130 (12%), treatment anxiety 11/130 (8%), cognition 20/129 (15.5%), worry 6/128 (5%) and physical appearance 10/129 (8%).

In the univariate analysis (Table 3.4a) the effect of child age was dependent on the QoL domain. For example, younger age was associated with a poorer QoL for procedural anxiety (B=4.0, p<0.001) and treatment anxiety (B=1.6, p=0.002) and older age was associated with a lower QoL for worry (B=2.1, p<0.001), cognitive functioning (B=1.2,

Table 3.4 Pediatric Quality of Life Inventory Cancer version: ALL scores compared to cancer norm scores

	ALL Mean (SD)	Norm[1] Mean (SD)	Effect Size[2]	p-value[3]	95% CI of the difference
Total	66.2 (13.4)	-	-	-	-
Pain	46.6 (24.2)	70.3 (26.3)	0.9	<0.001	19.5-27.9
Nausea	69.7 (19.2)	70.6 (24.6)	0.04	0.58	-2.4-4.3
Procedural anxiety	48.1 (32.1)	54.5 (31.7)	0.2	0.02	0.8-12.0
Treatment anxiety	71.5 (24.8)	67.4 (29.7)	-0.1	0.06	-8.4-0.2
Worry	81.6 (22.2)	70.7 (31.7)	-0.3	<0.001	-14.8 - -7.0
Cognitive	72.3 (18.2)	75.0 (22.4)	0.1	0.09	-0.5-5.9
Physical appearance	76.7 (22.4)	75.7 (26.0)	-0.04	0.62	-4.9-2.9
Communication	65.2 (29.2)	78.0 (22.3)	0.4	<0.001	7.7-17.8

Higher scores indicate better QoL. [1] reference sample consisting of 177 oncology patients during treatment, mean age 8.2 years [99]. [2] Effect size = [mean(a) – mean(b)/largest standard deviation score(SD)]. Small effect: 0.2-0.5, moderate effect 0.5-0.8, large effect ≥0.8. [3] One sample t-test, 95% confidence interval of the difference.

p=0.001) and perceived physical appearance (B=1.9, p<0.001). Child gender was also associated with QoL: a lower QoL was reported for girls. Among the treatment characteristics, more toxicity, fewer days since diagnosis and more days spent in the hospital were related to a lower QoL. A better QoL was reported for HR patients, mainly on the pain subscale (B=16.8, p=0.006). For parental characteristics, respondent gender was most often associated with QoL: mothers tended to rate a better QoL than fathers.

The multiple regression model demonstrated that the variance in QoL (R square) on the pain subscale was determined for 16% by stratification to the HR group, child age and days since diagnosis (Table 3.5). Nausea was independently determined by admission days and respondent gender (R square 24%). Procedural anxiety scores were determined by child age and treatment toxicity (R square 31%). Worry was influenced by child age, gender of the responding parent and single parent situation (R square 22%). Cognitive functioning and physical appearance were both determined by child

Table 3.4a Univariate determinants for the Pediatric Quality of Life Inventory Cancer version scores

	Child characteristics P value (B±s.e.)		Treatment characteristics P value (B±s.e.)				Parent characteristics P value (B±s.e.)			
	Age in years	Female	Days since diagnosis	High risk group	Admission days	Treatment toxicity	Age in years	Female	University level	Single parent
Pain	0.04 (-1.02±0.50)	0.51 (-2.8±4.3)	0.003 (0.28±0.09)	0.006 (16.80±5.99)	0.29 (-0.15±0.14)	0.09 (-0.51±0.30)	0.16 (-0.48±0.34)	0.88 (0.93±6.17)	0.65 (2.95±6.48)	0.23 (-7.83±6.48)
Nausea	0.69 (-0.16±0.40)	0.89 (-0.45±3.39)	0.49 (-0.05±0.08)	0.23 (5.86±4.87)	<0.001 (-0.38±0.10)	0.24 (-0.27±0.24)	0.74 (-0.09±0.27)	0.04 (9.94±4.82)	0.66 (-2.30±5.15)	0.92 (0.51±5.16)
Procedural Anxiety	<0.001 (3.99±0.58)	0.01 (-14.05±5.53)	0.20 (0.16±0.13)	0.32 (8.14±8.16)	0.17 (-0.26±0.19)	0.005 (-1.10±0.39)	0.002 (1.39±0.44)	0.52 (5.29±8.18)	0.57 (-4.93±8.60)	0.45 (6.53±8.56)
Treatment Anxiety	0.002 (1.56±0.50)	0.12 (-6.88±4.34)	0.12 (0.15±0.10)	0.28 (6.78±6.30)	0.47 (-0.11±0.14)	0.15 (-0.45±0.31)	0.01 (0.89±0.34)	0.29 (6.66±6.30)	0.98 (-0.14±6.66)	0.63 (3.24±6.66)
Worry	<0.001 (-2.13±0.43)	0.91 (-0.43±3.94)	0.70 (-0.03±0.09)	0.72 (2.05±5.66)	0.85 (0.04±0.23)	0.41 (0.23±0.28)	0.03 (-0.69±0.31)	0.02 (13.24±5.68)	0.35 (5.58±5.93)	0.01 (-15.18±5.82)
Cognitive	0.001 (-1.24±0.37)	0.99 (-0.06±3.21)	0.15 (0.10±0.07)	0.49 (3.23±4.62)	0.72 (-0.07±0.19)	0.98 (0.01±0.23)	0.73 (-0.09±0.26)	0.007 (12.24±4.50)	0.45 (3.66±4.86)	0.06 (-8.95±4.78)
Physical Appearance	<0.001 (-1.92±0.44)	0.46 (-2.93±3.96)	0.79 (-0.02±0.09)	0.88 (0.88±5.71)	0.42 (-0.19±0.23)	0.83 (-0.06±0.28)	0.004 (-0.91±0.31)	0.03 (12.18±5.61)	0.90 (-0.73±6.01)	0.44 (-4.69±5.99)
Communication	0.17 (0.86±0.61)	0.11 (-8.19±5.12)	0.23 (0.14±0.12)	0.09 (12.41±7.36)	0.009 (-0.77±0.29)	0.49 (-0.26±0.36)	0.21 (0.52±0.41)	0.35 (6.96±7.42)	0.48 (-5.51±7.81)	0.99 (-0.07±7.86)
Total	0.83 (0.06±0.28)	0.04 (-4.82±2.32)	0.04 (0.11±0.05)	0.04 (7.05±3.36)	<0.001 (-0.26±0.07)	0.04 (-0.34±0.16)	0.62 (0.09±0.19)	0.01 (8.33±3.34)	0.99 (0.07±3.59)	0.40 (-3.05±3.60)

s.e. = standard error. Positive B coefficients indicate that the (increasing value of the) determinants are associated with a better QoL, negative B coefficients indicate that the (increasing value of the) determinants are associated with a poorer QoL.

Table 3.5 Multiple linear regression analysis of the determinants associated with the Pediatric Quality of Life Inventory Cancer version scores

Scale	Determinant	P-Value	B ± s.e.	R square
Pain	Days since diagnosis	0.006	0.25±0.09	0.16
	HR group	0.002	18.38±5.78	
	Child age	0.02	-1.13±0.48	
Nausea	Admission days	<0.001	-0.40±0.10	0.24
	Parent female	0.02	15.41±6.44	
Procedural Anxiety	Child age	<0.001	3.84±0.57	0.31
	Treatment toxicity	0.01	-0.86±0.33	
Worry	Child age	<0.001	-1.87±0.43	0.22
	Parent female	0.01	13.57±5.21	
	Single parent	0.04	-11.37±5.46	
Cognitive	Child age	0.001	-1.23±0.36	0.14
	Parent female	0.005	12.21±4.32	
Physical appearance	Child age	<0.001	-1.92±0.44	0.17
	Parent female	0.02	12.13±5.24	
Total	Admission days	<0.001	-0.24±0.06	0.36
	Days since diagnosis	0.004	0.18±0.06	
	Parent female	0.02	9.88±4.17	
	Child female	0.03	-6.40±2.85	

s.e. = standard error. Positive B coefficients indicate that the (increasing value of the) determinants are associated with a better QoL, negative B coefficients indicate that the (increasing value of the) determinants are associated with a poorer QoL.

age and gender of the responding parent (R square 14% and 17%, respectively). The overall QoL score was associated with admission days, days since diagnosis, parent and child gender. This model accounted for 36% of the variance in score.

Discussion

This study investigated QoL in children during ALL induction/consolidation treatment and determined factors associated with QoL. QoL as measured with the CHQ was statistically impaired compared to the healthy norm. The effect sizes were large and clinically relevant, as demonstrated by the large percentages of children with scores under -2SD of healthy norms [111]. Generally, physically oriented QoL was more often impaired than psychosocially oriented QoL. Similar results have been reported by Sung et al.[103]

QoL measured with the disease specific PedsQL also showed impaired QoL compared to a heterogeneous sample of oncology patients on certain subscales, although most effect sizes were small. Pain was the most impaired subscale, followed by communication and procedural anxiety. The studied cohort, however, scored significantly better

than the reference population on the worry subscale. The main differences between the reference population and the studied cohort are age (the reference population is a little older) and the variety of diagnosis in the reference group. Younger age was associated with a poorer QoL on anxiety in this study, and with anxiety and communication in previous research [82, 90], so the age difference could partly explain the impaired QoL in our cohort. Such an association has to our knowledge not been described for worry and, moreover, worry was associated with a poorer QoL in older children in this cohort. The age difference can therefore not account for a better QoL on this subscale. We hypothesize that ALL patients receive more positive counseling regarding prognosis compared to some other patients groups, leading to less worries.

We have also attempted to identify determinants of QoL. Some studies have identified single determinants of QoL during ALL treatment such as age [82, 90], gender [82] and treatment related variables [77, 90, 92], but to our knowledge only Sung et al.[103] have attempted to include several determinants in one model before, but not during induction/consolidation therapy only. Statistically significant models could be constructed for seven of 14 CHQ scales and seven of nine PedsQL cancer scales, accounting for 7 to 36% of the variance in scores. Gender of the responding parent was most often associated with QoL, this determinant was involved in nine QoL scores. Mothers scored better than fathers or mothers and fathers combined. It is unclear whether this is an actual discrepancy in QoL perception between parents, or whether this is the result of other underlying mechanisms. The number of father respondents was small (n=18) and it is important to note that father-respondents were significantly older than mother-respondents (p=0.003). Also, there was a trend towards more fathers having an university education than mothers (p=0.05). This could contribute to the reported differences. Although the level of agreement between self and proxy reports has been extensively investigated [36, 37], literature on the agreement between mother and father proxies is sparse. Mulligan et al.[112] reported that there is a frequent non-systematic difference in mother and father ratings of QoL in children with juvenile idiopathic arthritis. To our knowledge, no such research has yet been performed in pediatric oncology. Confirmation of these differences between parents in future research could provide us with new tools in the counseling of families caring for a child with cancer. Child age was a significant determinant of QoL on eight scales; older age was associated with a worse QoL on six scales, younger age on two. Child gender was a determinant of QoL on six scales, with girls having a poorer QoL than boys. Increased time since diagnosis was associated with improvement in QoL on seven scales. These associations generally are a confirmation of previous research [78, 82, 85, 90, 102, 103, 113, 114]. For the remaining determinants, single parents and more admission days were each associated with two scales, and non-HR ALL and higher parental education each with one scale. The former two determinants influenced QoL negatively, as may be expected. The latter

two determinants both were associated with poorer QoL on the pain subscale, which was more surprising. All children received the same introduction treatment, so risk group was not expected to have an influence on QoL besides social/emotional scales for those who were stratified to the HR group based on a poor prednisone response at treatment day 8. No relation between higher parental education and impaired QoL was found in two other large cohorts before [102, 103], and this association may prove to not be clinically relevant.

The strengths of this study include the large homogeneous cohort, all treated according to the same protocol and assessed during the same phase of therapy. The response rate was good, although a relatively large number of families was not recruited to the study or withdrew from participation. However, there were no significant differences in age, gender or HR-ALL between the study group and the non-participants. Also, the study group was representative of the national ALL10 cohort (unpublished data). Another limitation was the restriction to parent-proxy reports only. It is well known that children and parents do not always agree on QoL [36] and that several perspectives can provide valuable information. Unfortunately, children with cancer are often either too young or too ill to participate in QoL assessments, and this applies to our cohort as well. Furthermore, the CHQ was designed for children five years and up. Although the Infant and Toddler Quality of Life Questionnaire would have been more appropriate for the younger children in our study sample [99], at the time of the design of this study, no validated Dutch version and norms were available. Finally, complete information on potential determinants of QoL was not available. Household income and health state of siblings have been found to be important determinants of QoL in the previous research performed by Sung et al.[102, 103] Also, some studies have found a relation between parental psychosocial health and child QoL [114, 115]. These determinants should be included in future studies.

In conclusion, QoL of ALL patients during induction treatment is greatly diminished and physical QoL and pain are most affected. Impaired QoL was most often associated with older children and girls. Also, father-respondents seem to have a lower QoL perception compared to mother-respondents although this needs to be confirmed in future research. Follow-up of this cohort will provide more information on the change in QoL during treatment and its determinants, and help to identify more possibilities for counseling. Meanwhile, this study highlights several subsets of pediatric ALL patients for whom specific counseling during induction therapy is warranted.

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