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Chapter 9

Cost-effectiveness of treatment of childhood acute lymphoblastic leukemia with chemotherapy only: The influence of new medication and diagnostic technology

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Abstract

Background: Survival for childhood acute lymphoblastic leukemia (ALL) has reached 80-90%. Future improvement in treatment success will involve new technologies and medication, adding to the pressure on limited financial resources. Therefore a retrospective cost-effectiveness analysis of ALL treatment with chemotherapy only according to the two most recent Dutch Childhood Oncology Group treatment protocols was performed. The most recent protocol ALL10 included more expensive medication (pegasparaginase) and implemented a new diagnostic technique (minimal residual disease levels) compared to the previous ALL9 protocol.

Methods: Fifty children from a single center cohort were included. All direct medical costs made during treatment, including those in satellite hospitals, were determined. Costs per life year saved (LYS) were calculated. The cost-effectiveness ratio of the most recent treatment protocol was determined. LYS were calculated based on national 5-year event free survival.

Results: Mean total costs were between $115,858 (ALL9) and $163,350 (ALL10) per patient. Hospital admissions (57%) and medication (11-17%) were important drivers of overall costs, and were higher in the most recent protocol ALL10. Costs per LYS were $1,962 (ALL9) and $2,655 (ALL10) and the cost-effectiveness ratio was $8,215.

Conclusion: Treatment of childhood ALL with chemotherapy only is well within accepted ranges of cost-effectiveness. The use of new technology and more expensive medication in the most recent protocol ALL10 lead to higher costs but more LYS. In future (ALL) treatment protocols, costs in relation to effects should be taken into account in order to establish more cost-effective disease management without jeopardizing survival and quality of life.

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 is now 80-85% [2]. Survival is expected to reach 90% in the future, although it is inevitable that further increase in survival will slow down. In addition to survival, late effects and health related quality of life (HRQL) have been recognized as important outcome measures. The economic aspect of childhood ALL has not received much attention until now. Previous work includes a few studies on total costs of childhood ALL treatment and some concerning cost-effectiveness of specific therapeutic regimens such as antibiotics [64, 154, 179, 180]. It is, however, likely that future success in the treatment of childhood ALL will increasingly involve new technologies and medication, which will add to the pressure on limited financial resources. To keep healthcare affordable, resource allocation and costs should be critically examined in order to achieve maximum cost-effectiveness without jeopardizing survival, (long term) morbidity and HRQL. Since costs of treatment of childhood diseases are usually spread over a much longer lifespan, adult data cannot be generalized and additional pediatric information is necessary.

The present study is a cost-effectiveness analysis based on a retrospective single center cohort of children treated for ALL with chemotherapy only. We sought to specify the resource usage of ALL patients treated according to the two most recent Dutch Childhood Oncology Group protocols. The direct medical costs per life year saved (LYS) were estimated and the cost-effectiveness ratio of the most recent protocol, which included the introduction of a new diagnostic tool (minimal residual disease (MRD) monitoring) and the use of more expensive and potentially more effective medication, was assessed.

Methods

ALL treatment protocols

The two most recent ALL treatment protocols were analyzed. ALL9 (1997-2004) and ALL10 (2004-now) were consecutive national front-line ALL treatment protocols. In ALL10 a risk-adjusted treatment mainly based on MRD levels was introduced, leading to treatment reduction for those with a good response to therapy (low MRD levels, low risk of relapse) and a higher treatment intensity for those with less response to therapy (higher MRD levels, higher risk of relapse, Table 9.1). Three risk groups are identified; standard risk (SR), medium risk (MR) and high risk (HR). Treatment for HR patients in ALL10 constitutes of stem cell transplantation and ALL10 HR patients (about 10% of all

Table 9.1 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 >50x109/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 OR	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.

patients) were therefore not included in this study. Treatment intensity 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%. Of the non-HR patients, 30% are SR and 70% MR. Besides MRD-based risk-adjusted therapy a more expensive, and potentially more effective, therapeutic regimen (E. Coli peg asparaginase instead of E. Coli L-asparaginase) was introduced in ALL10. Total dose of pegaspargase was 15 times higher for MR (Figure 9.1) compared to SR.

MRD levels were not used in ALL9, risk group classification was based on different criteria (Table 9.1). Two risk groups were identified, including non-high risk (NHR, 70% of patients) and high risk (HR, 30% of patients) [2]. The more expensive form of asparaginase, pegaspargase, was not routinely used but occasionally substituted E. coli L-asparaginase, e.g. in case of allergic reactions. Compared to NHR, HR treatment included daunorubicin during induction, higher doses of MTX and two consecutive intensification phases (Figure 9.2) [1]. ALL9 did not include stem cell transplantation. This therapy was reserved for patients with refractory disease or relapse, and would have led to treatment according to a different protocol. Therefore, all ALL9 patients

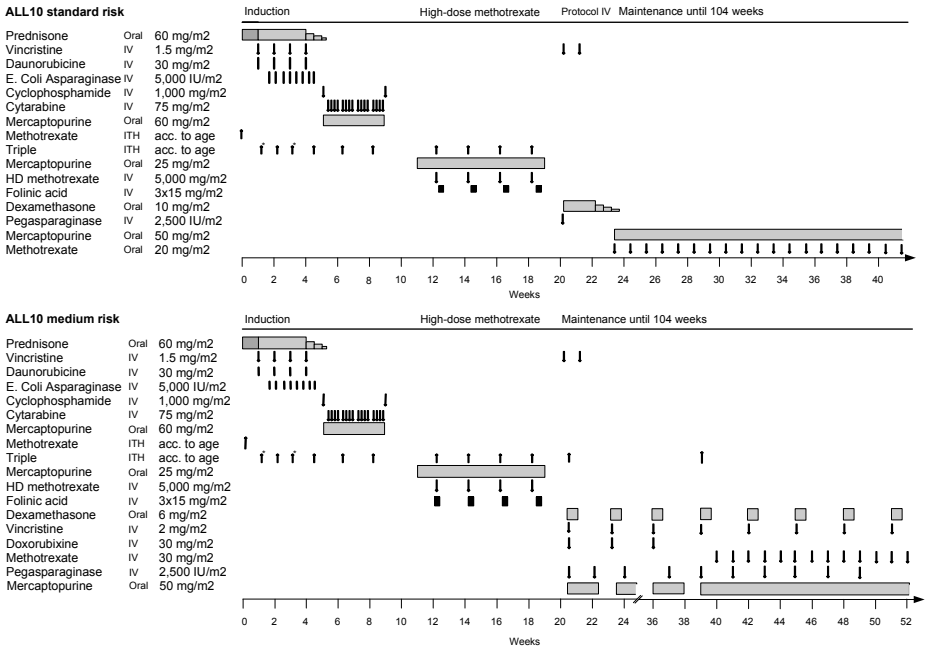

Figure 9.1 Outline of the Dutch Childhood Oncology Group ALL10 protocol.
Introduction and MTX therapy were similar for the standard risk and the medium risk group. In order to achieve therapy reduction in standard risk patients the intensity of maintenance therapy was lowered. Maintenance for standard risk patients consisted of oral medication only. Total dose of pegasparaginase also differed between standard and medium risk patients: 2500 U/m2 and 37500 U/m2, respectively. Blocks indicate daily medication. Intrathecal triple consisted of methotrexate, cytarabine and driadeson F.
* Indicated extra triple therapy for patients with involvement of the central nervous system. Vincristine was maximal 2 mg per dose. Total duration of therapy was 104 weeks.

were eligible for this study. Both treatment protocols have a similar structure including an induction phase, methotrexate phase (MTX), intensification and maintenance phase [2], see figures 9.1 and 9.2. Total duration is about two years for both protocols.

Supportive care

Hospitalization usually occurred during the first phase of induction, for more demanding therapeutic regimens and in case of complications. Daycare treatment and visits to the out-patient clinic were frequent, usually once a week.

Intravenous medication was given through a venous catheter, mostly a portacath. All children received pneumocystis carnii prophylaxis (trimethoprim-sulfamethoxazole, in case of prolonged neutropenia pentamidine was given). Selective bowel decontamination was used during the first part of treatment during ALL10 and in selected patients in ALL9. Patients with neutropenic fever (absolute neutrophil count $<0.5x10^9$/l) were hospitalized and started on empirical intravenous broad-spectrum antibiotics (meropenem). Intravenous antifungal therapy was considered if fever persisted after three days of antibiotic treatment. Antibiotic treatment was stopped when patients were afebrile

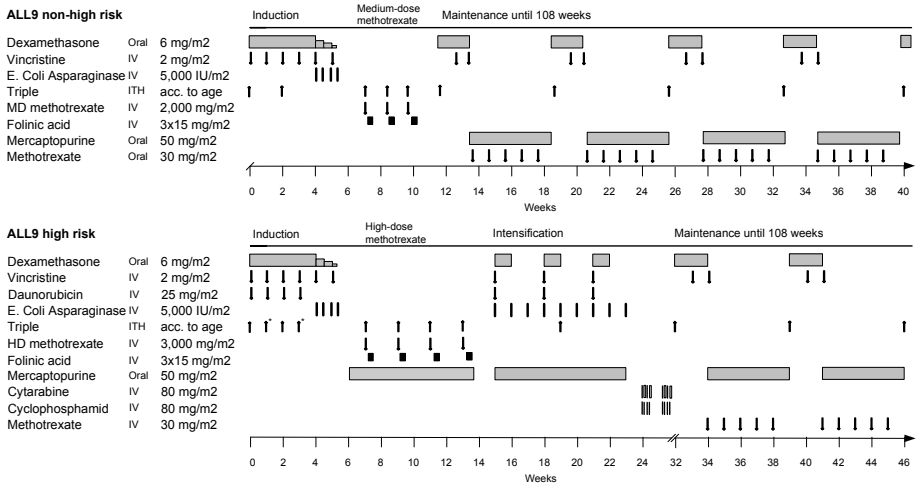

Figure 9.2 Outline of the Dutch Childhood Oncology ALL9 protocol [2]
Blocks indicate daily medication. Intrathecal triple consisted of methotrexate, cytarabine and driadeson F. * Indicates extra triple therapy for those with involvement of the central nervous system. During maintenance treatment triple therapy was given eight times in the non-high risk group and seven times in the high risk group. The high risk intensification phase consisted of a total of six blocks of cytarabine and cyclophosphamid. Vincristine was maximal 2.5 mg per dose. Total duration of therapy was 108 weeks.

for three days and blood cultures were negative after 48 hours. Red blood cell transfusions were given when hemoglobin levels were <5 mmol/l (8 mg/dl). Indications for platelet transfusions were dependent on the child's clinical condition but were given prophylacticly in case of a platelet count <10X10^9/l. Hematopoietic growth factors were not used routinely.

Patients

The study sample size was based on previous research on costs of childhood ALL treatment in Western countries by Luo et al.[179] and Rahiala et al.[154], in which 36 Canadian and 11 Norwegian patients had been evaluated respectively. With 10 to 15 newly diagnosed ALL patients annually at our center, we inferred that a two year inclusion period per treatment protocol would provide reliable information on healthcare usage. The study was approved of by our Institutional Ethical Review Board.

All patients (up to 18 years of age) diagnosed with ALL between 2002 and 2006 at our institution and treated according to ALL9 or ALL10 with chemotherapy only were included. A total of 51 children with ALL were identified in the studied period. One child (2%) was ALL10 HR and was not eligible, so a total of fifty children were included. Twenty-six children were treated according to ALL9, eight (30%) were HR. Twenty-four children were treated according to ALL10; five were SR (21%). Gender, age and body surface area did not differ between ALL9 and ALL10 or between the risk groups (Table 9.2).

Table 9.2 Demographic variables

	ALL 9			ALL 10			ALL9 versus ALL10
	Total	NHR	HR	Total	SR	MR	
N	26	18	8	24	5	19	NA
Boys (N,%)	15 (58%)	12 (67%)	3 (38%)	17 (71%)	2 (40%)	15 (79%)	NS
Age in years at diagnosis (mean±SD)	5.6 ± 3.2	5.8 ± 3.0	5.2 ± 3.9	5.4 ± 3.4	5.5 ± 2.6	5.4 ± 3.7	NS
BSA in m^2 (mean±SD)	0.85 ± 0.26	0.88 ± 0.25	0.77 ± 0.29	0.85 ± 0.31	0.82 ± 0.18	0.85 ± 0.33	NS

NA=not applicable; NS=not significant; NHR=Non-High risk; HR=High risk; SR=Standard risk; MR=Medium risk; BSA=body surface area

Costs

Direct medical costs made during treatment for ALL were calculated from a hospital perspective. Data on the volumes was retrieved from electronic hospital databases at our institution and from medical records where necessary. Resource utilization in satellite hospitals was retrieved through chart review. Indirect medical costs (i.e. treatment for recurrences, follow-up visits, long term morbidity) were not included. For the most important units, specific unit prices were calculated (2008 prices). For all other cost items Dutch tariffs were used. All costs were converted to US dollars (€1=$1.35).

Several cost categories were defined: 1) In-hospital days including room and board, nursing, and physician fees. In-house estimates were used (pediatric-oncology $864/day, satellite hospital $612/day, Pediatric Intensive Care Unit, PICU, $2,082/day); 2) Daycare treatment (in-house estimate $351/day); 3) Medication (chemotherapy and other medication). Chart review was performed to assess dose-adjustments of chemotherapy; 4) Out-patient clinic visits, emergency room visits and medical consultations; 5) Laboratory and microbiology tests; 6) Imaging studies; 7) Diagnostic tests: bone marrow aspirates, lumbar punctures, pathology exams and genetic tests; 8) Blood transfusions; 9) Surgical procedures.

Effects

National five year EFS rates were used as outcome measure. For ALL9 five year EFS was 72% for HR and 84% for NHR [2]. For ALL10 projected five year EFS rates were used, which were confirmed by a four year interim analysis of the ongoing protocol (personal communication R. Pieters). Projected EFS for SR was 96% and 85% for MR. A normal life expectancy based on Dutch mean life expectancy for children born in the first decade of this century (80 years) was assumed for event free survivors [181]. Median age at diagnosis was 5 years for both protocols, leading to the assumption of 75 life years saved for event free survivors. Patients in whom a relapse occurred were treated as if deceased.

Cost-effectiveness

The cost-effectiveness for each risk group was calculated by dividing the mean total costs with the mean LYS. Since ALL10 risk groups were not distributed equally in the studied cohort compared to the national cohort, the costs per LYS for ALL10 were calculated based on the national distribution. The cost-effectiveness ratio for treatment according to the most recent protocol ALL10 was calculated by dividing the incremental costs for ALL10 compared to ALL9 with the incremental LYS for ALL10 compared to ALL9.

Analysis

The Statistical Package for Social Sciences (SPSS) for Windows version 15.0 and Excel 2002 for Windows were used for all data analyses. For the description of data, median and interquartile range (IQR) were calculated for non-normal distributed cost data. For normally distributed data means and standard deviations (SD) were calculated. For the calculation of differences between the ALL9 and ALL10, and the differences between the risk groups, t-tests for independent samples and Mann-Whitney U tests were used. 95% Confidence intervals (CI) were calculated for t-tests. The effect of admission days on costs was assessed using linear regression analysis. Significance level was set at $p < .05$ for all analyses.

Missing data. Information on resource utilization in satellite hospitals was not available for eight children (16%). For these children the information on costs made at our university hospital, where the majority of treatment and admissions occur, was complete. Four children (8%) were treated solely at the university hospital until they were lost to follow-up after the start of maintenance therapy because of emigration. The missing data were imputed per cost category using the mean risk group costs of the complete dataset for resource use in satellite hospitals and the university hospital, respectively.

Discounting. Both costs and effects were discounted to convert future expenses and earnings into their present values. According to Dutch guidelines, costs were discounted at 4% and effects at 1.5% [60].

Sensitivity analysis. To test the robustness of our data, a sensitivity analysis was performed. Missing data was imputed using the minimum and the maximum of the complete dataset. Equal discount levels for costs and effects (both 4%) were used. We varied the life expectancy from 80 years to 67.5, 55 and 42.5 years in order to reflect potential late recurrences and late effects of treatment.

Results

ALL9 and ALL10 costs

Mean total direct medical costs for ALL10 were $163,350 (discounted $161,779), which was significantly higher than $115,858 for ALL9 (discounted $114,777; p<0.001). Total incremental costs for treatment according to ALL10 were $47,492 (discounted $47,002) (Table 9.3). Mean LYS for ALL9 were 60.2, total costs per LYS were $1,962 (discounted

Table 9.3 Total costs and costs per category for treatment according to ALL9 and ALL10 in US dollars

Cost category	Mean ± SD Median [IQR] % of total		Mean incremental costs	p (95% CI of the difference)
	ALL 9 (n=26)	ALL 10 (n=24)		
In-hospital days	50,097 ± 25,308 42,732 [24,509] 43.2%	66,276 ± 25,862 58,019 [32,501] 40.6%	16,178	0.03**
Day treatment	16,162 ± 7,785 13,689 [5,126] 13.9%	27,105 ± 6,772 29,452 [9,990] 16.6%	10,943	<0.001 (6,803-15,086)
Medication*	12,533 ± 6,225 11,128 [9,897] 10.8%	27,440 ± 10,633 24,633 [15,567] 16.8%	14,907	<0.001***
Out-patient clinic, Emergency Room, medical consultations	15,455 ± 6,113 14,850 [4,192] 13.3%	16,288 ± 4,888 17,092 [7,324] 10.0%	833	0.60
Laboratory and microbiology*	6,854 ± 3,298 5,825 [2,948] 5.9%	11,538 ± 3,285 10,112 [4,413] 7.1%	4,685	<0.001***
Imaging studies*	1,378 ± 1,403 840 [743] 1.2%	1,740 ± 764 1,661 [1,115] 1.1%	362	0.002***
Diagnostic tests	6,537 ± 2,493 6,379 [4,132] 5.6%	4,964 ± 1,292 5,068 [1,864] 3.0%	-1,573	0.07 (448-2,697)
Transfusions*	4,385 ± 4,793 3,123 [3,630] 3.8%	5,928 ± 3,946 4,666 [6,985] 3,6%	1,543	0.074***
Surgical procedures	2,458 ± 926 2,036 [359] 2.1%	2,084 ± 165 2,036 [20] 1,3%	-374	0.015***
Total*	115,858 ± 37,781 104,304 [55,060]	163,350 ± 32,630 162,070 [55,836]	47,492	<0.001***
Total discounted*	114,777 ± 37,487 103,302 [54,350]	161,779 ± 32,033 160,565 [56,002]	47,002	<0.001***

* related to total in-hospital days (for the medication category this only applied to medication other than chemotherapy); P-values are based on independent student's t-tests (**no CI because of logarithmic transformation or *** Mann-Whitney tests)

Table 9.4 Sensitivity analysis

		Life-expectancy* (years)				Discounting of LYS** (%)	
		80	67.5	55	42.5	1.5	4
Costs per LYS	ALL9	$1,962	$2,353	$2,942***	$3,922***	$3,224	$6,122****
	ALL10	$2,655	$3,187	$3,984***	$5,311***	$4,363	$8,286****
Cost-effectiveness ratio		$8,215	$9,856	$12,321	$16,428	$13,489	$25,618

* represents non-discounted costs per LYS; ** represents discounted costs (4%) per discounted LYS with a life-expectancy of 80 years; *** p≤0.01 compared to the costs per LYS with a life-expectancy of 80 years (ANOVA); **** p<0.001 compared to 1.5% discounting (Mann-Whitney test)

$3,224). For ALL10 mean LYS were 66.0, costs per LYS were $2,655 (discounted $4,363, Table 9.4) for ALL10. Costs per LYS were significantly higher for ALL10 (p=0.007). The cost-effectiveness ratio for treatment according to ALL10, with ALL9 treatment serving as the reference, was $8,215 (discounted $13,489).

Most categories were more expensive for ALL10 (Table 9.3). In-hospital days accounted for the largest part of total costs (40.6-43.2%), followed by daycare treatment (13.9-16.6%), and medication (10.8-16.8%). Seven children (three ALL9 and four ALL10) had been admitted to the PICU ranging from 1 to 39 days. Mean PICU admission costs for ALL9 (n=3) were $51,073±32,721 and for ALL 10 $14,120±17,970 (n=4). Medication costs were two times higher for ALL10 because of higher chemotherapy costs. Costs for other medication were similar. Asparaginase costs were significantly higher in ALL10 (p<.001), and accounted for 61% of ALL10 chemotherapy costs, as opposed to 15% for ALL9. Pegasparaginase constituted 96% of total asparaginase costs for ALL10 and 49% for ALL9.

In-hospital days were significantly related to total costs, medication other than chemotherapy, laboratory and microbiology tests, imaging studies, and transfusions. Mean in-hospital days were significantly higher for ALL10 compared to ALL9 (85±36 and 57±23, respectively; p<0.005, 95% CI 10-45). Admissions occurred mostly during induction and the MTX phase. No children in the SR group were admitted after the MTX phase.

Induction, MTX, and maintenance were more expensive for ALL10 (p<.001). For both protocols, induction accounted for 33% of total costs and the MTX phase for 15%. Most costs for in-hospital days (42-45%), laboratory (46-51%), imaging studies (51-64%), and transfusions (62-75%) were during induction, while daycare costs occurred mostly during maintenance (70-80%). Total costs were fifty percent higher for the three children who died compared to those who survived ($210,942±48,823 versus $138,352±49,167; p<0.05).

Costs per risk group

For the ALL9 protocol, total costs for HR were $149,885±27,371 (discounted $148,435±27,142) which was significantly higher than total costs for NHR ($100,726±31,682, discounted $99,818±31,514; p<0.005). Costs per LYS were $1,598 (discounted $2,628) for NHR and $2,776 (discounted $4,562) for HR. For ALL10, costs for the MR risk group ($189,548±37,741, discounted $187,577±37,062) were significantly higher than costs for SR ($104,3301±20,677, discounted $103,667±20,447; p<0.001). Costs per LYS were $1,449 (discounted $2,390) for SR and $2,973 (discounted $4,883) for MR.

Most categories were significantly more expensive in the higher risk groups. Due to pegasparaginase, chemotherapy accounted for 12% of the MR total costs, as compared to 3% for NHR and HR, and 7% for SR. The difference in total costs between NHR and HR was mostly due to the HR intensification phase. Higher total costs for MR were mostly due to significantly higher maintenance costs compared to SR (p<0.001).

Sensitivity analysis

The sensitivity analysis is shown in Figure 9.3, Figure 9.4, Figure 9.5 and Table 9.4. Imputing missing data with either the minimum or the maximum of the complete dataset did not lead to a significant change in cost categories, except for the out-patient clinic, emergency room and medical consultations category. In this category imputing the maximum lead to significantly higher costs for ALL9 compared to imputing the mean (p=0.034) and made ALL9 costs higher than ALL10 costs. The stepwise reduction of life-expectancy increased the costs

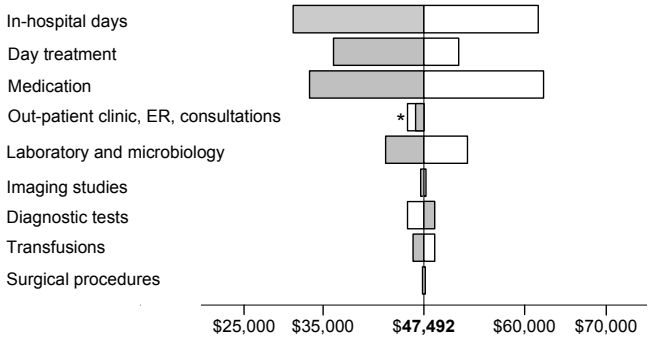

Figure 9.3 Change in incremental costs

Tornado diagram showing the results of the sensitivity analysis with imputation of minimum and maximum for missing data. Change in incremental cost for treatment according to ALL10 is depicted per cost category. Grey columns represent imputation with the minimum of the known dataset. White columns represent imputation with the maximum of the known dataset. * Statistically significant difference for imputation of maximum compared to imputation of the mean, p=0.034.

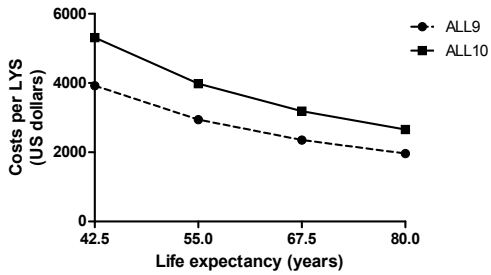

Figure 9.4 Costs per life year saved for ALL9 and ALL10 at different life expectancies

Figure 9.5 Cost-effectiveness ratio for treatment according to ALL10, with ALL9 treatment serving as the reference, using different life expectancies

per LYS for ALL9 from $1,962 (life-expectancy of 80 years) to $2,353, $2,951 and $3,922 per LYS at life-expectancies of 67.5, 50 and 42.5 years, respectively. For ALL10 costs per LYS increased from $2,655 (life-expectancy 80 years) to $3,187, $3,984 and $5,311 per LYS at life-expectancies of 67.5, 50 and 42.5 years, respectively. For both ALL9 and ALL10 costs per LYS were significantly higher at a life-expectancy of 50 and 42.5 years compared to 80 years ($p \leq 0.01$). Decrease in life expectancy increased the cost-effectiveness ratio from $8,188 (life-expectancy of 80 years) to $9,856, $12,321 and $16,428 at life-expectancies of 67.5, 50 and 42.5 years, respectively. Discounting the effects at 4% instead of 1.5% increased the cost-effectiveness ratio from $13,488 to $25,618. The discounted costs per LYS increased as a result of 4% discounting of effects from $3,224 to $6,122 for ALL9 ($p<0.001$) and from $4,363 to $8,286 for ALL10 ($p<0.001$).

Discussion

Treatment for childhood ALL has greatly evolved over the past decades and has lead to increased survival, but further improvement is inevitably slowing down. Increasing strain on healthcare resources calls for a careful evaluation of costs in relation to effects for new treatment protocols. Our study is one of the few reports including a broad spectrum of different aspects of direct medical costs for the treatment of childhood ALL with chemotherapy only and is the first to include costs per LYS.

The present study demonstrates that the total direct medical costs for treatment of childhood ALL with chemotherapy only in the Netherlands varied between $115,858 and $163,350, depending on treatment protocol. This is only slightly higher compared to the most recent studies on costs of pediatric leukemia treatment, performed during the last decade of the previous century when the more expensive form of asparaginase, PEG asparaginase, was generally not yet used [154, 179]. Compared to costs for bone

marrow transplant in patients with standard risk ALL as reported by Lin et al.[182] (2008 $352,885), costs were much lower in this chemotherapy-only cohort. Similar to other studies in childhood cancer [154, 179, 180] was the large percentage of costs (about 50%) spent on in-hospital days and day treatment, and one-third of total costs being spent during the induction phase [154].

Costs per LYS were between $1,962 and $2,655, depending on treatment protocol. Even when reducing the life expectancy to 42.5 years, the costs per LYS are still acceptable ($3,922 to $5,311). Yu et al.[183] reported on the cost-effectiveness of postremission treatment of adult patients with acute leukemia, which was (2003) $11.224 per LYS for the chemotherapy-based regimen. Compared to data on adult leukemia, costs in this pediatric cohort are substantially lower. In comparison to costs per LYS for treatment of other fatal conditions, such as heart transplantation in children with end-stage heart failure as found by Dayton et al.[184] (2004) $43,221, costs for treatment of ALL are lower.

The cost-effectiveness ratio for treatment according to ALL10 compared to ALL9 was $8,215 with a life expectancy of 80 years and $16,428 when assuming a life expectancy of 42.5 years. Benchmarks for acceptable cost-effectiveness differ between various investigators. Greenberg et al.[185] performed a review on cost-utility studies in cancer, and the median incremental cost-effectiveness ratio for hematologic malignancies was $48,000 per quality adjusted life year. Even though our data was not adjusted for the quality of the life years saved, it can be concluded that ALL10 was cost-effective even with a relatively short life expectancy of 42.5 years. Chemotherapy was an important determinant of the difference in costs. Pegasparaginase is an important part of ALL10, and although it is a more expensive type of asparaginase it has a longer half-life and less immunogenicity and associated allergic reactions, and may thus have many clinical benefits [186]. Duration of hospitalization is a known measure of costs [187] and also attributed to the difference between ALL9 and ALL10. In ALL10 MRD levels were used for risk-group directed therapy, leading to treatment intensification for the MR risk group. The use of this new diagnostic technology lead to more frequent admissions in ALL10, and specifically for the MR group, probably due to both chemotherapy treatment and infections as a result of bone marrow suppression.

An important strength of the present study includes the cost-effectiveness analysis. The advantage of such an approach is that is allows for comparisons with other health care interventions. The life expectancy of children diagnosed with ALL during the first decade of this century can, however, not easily be defined. We have assumed a normal life-expectancy for event-free survivors at five years after ALL diagnosis. Yet late recurrences and late effects are common, as has been reported by Oeffinger et al.[8], and may reduce life expectancy [6]. Even though the increased attention to late effects, improvement of supportive care and the absence of radiotherapy in this cohort may

lead to less chronic conditions and a better life-expectancy, a sensitivity analysis with a reduced life expectancy was performed. This did not lead to an unacceptable cost-effectiveness. The sensitivity analysis also showed that using different imputation methods for missing values did not significantly change the incremental costs with the exception of one cost category, which was only a small part of overall costs. Furthermore, since all healthcare usage was assessed for each patient with the use of hospital databases and medical records, no assumptions on the utilization had to be made and no lump sums for procedures or hospital stays had to be used. Finally, the Dutch treatment for ALL is based on international standards and supportive care levels are comparable to other high-income countries, making this study suitable for international comparison and for future reference when evaluating new treatment options.

A limitation of this study is our relatively small cohort, in which individual variations in healthcare usage can influence results at group level. We have excluded patients treated with stem cell transplantation because the associated costs are very different. Since this was the treatment of choice in ALL10 for HR patients, 2% of the studied cohort and up to 10% in the total population, this might have lead to selection bias. Hence, the results do not represent costs for ALL treatment in general, but for treatment with chemotherapy only. Treated with chemotherapy only however, includes the majority of all patients. Additional similar studies are required for patients with ALL that are being treated with stem cell transplantation. Another limitation might be the restriction to direct medical costs, which does not take into account costs of recurrences or treatment-related morbidity. Also, all relapses were treated as deceased, although children suffering from a relapse may still survive and thus add life years saved. A more comprehensive evaluation of costs and effects associated with pediatric ALL will be possible through long-term follow-up of these patients.

In conclusion, treatment of childhood ALL with chemotherapy only is well within the accepted range of cost-effectiveness ($1,962-$2,655 per LYS). The implementation of a new diagnostic technology (MRD) and more expensive medication in the most recent protocol ALL10 lead to an acceptable cost-effectiveness ratio. In future (ALL) treatment protocols, costs in relation to effects should be taken into account in order to establish more cost-effective disease management without jeopardizing survival and HRQL.