

RESEARCH ARTICLE

A cost analysis of individualized asparaginase treatment in pediatric acute lymphoblastic leukemia

Robin Q.H. Kloos¹ | Carin A. Uyl-de Groot² | Raphaële R.L. van Litsenburg^{3,4} | Gertjan J.L. Kaspers^{3,4} | Rob Pieters⁴ | Inge M. van der Sluis^{1,4}

¹Pediatric Oncology and Hematology, Erasmus MC–Sophia Children's Hospital, Rotterdam, The Netherlands

²Institute of Health Care Policy and Management/Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands

³Department of Pediatric Oncology/Hematology, VU University Medical Center, Amsterdam, The Netherlands

⁴Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Correspondence

Robin Q.H. Kloos, Pediatric Oncology and Hematology, Erasmus MC–Sophia Children's Hospital, Room NA 1723, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands.
 Email: r.kloos@erasmusmc.nl

Grant sponsor: KiKa Foundation.

Abstract

Background: Therapeutic drug monitoring (TDM) of asparaginase is necessary to respond to variability in asparaginase activity levels, detect silent inactivation, and distinguish between real allergies and allergic-like reactions with and without asparaginase neutralization, respectively. In this study, the costs of an individualized and fixed asparaginase dosing schedule were compared.

Procedure: Patients, treated according to the Dutch Childhood Oncology Group ALL-11 protocol (individualized PEGasparaginase treatment, starting dose: 1,500 IU/m²) or ALL-10 protocol (native *Escherichia coli* asparaginase followed by 2,500 IU/m² PEGasparaginase), were included. To focus on TDM of PEGasparaginase, the costs were also calculated excluding patients treated with *Erwinia* asparaginase and compared to a hypothetical protocol with a fixed dose of 1,500 IU/m² PEGasparaginase. Direct asparaginase-related medical costs, including costs for asparaginase use (calculated with the absolute dose), TDM, laboratory tests, daycare treatment, and outpatient clinic visits, were calculated.

Results: Eighty-three ALL-10 patients and 51 ALL-11 patients were included. The asparaginase-related costs were 30.8% lower in ALL-11 than in ALL-10 (\$29,048 vs. \$41,960). The ALL-11 costs of nonallergic patients were 20.4% lower, when using TDM, than the hypothetical protocol with a fixed dose of 1,500 IU/m² (\$13,178 vs. \$16,551). TDM accounted for 12.4% of the costs. Including asparaginase waste, TDM in ALL-11 will be cost saving if three doses can be prepared out of one vial compared to a fixed dose of 1,500 IU/m².

Conclusions: TDM of asparaginase is cost saving if calculated with the absolute asparaginase dose and will be if the waste is minimized by preparing multiple doses out of one vial.

KEYWORDS

acute lymphoblastic leukemia, asparaginase, cost analysis, therapeutic drug monitoring

1 | INTRODUCTION

Asparaginase is one of the key components of the treatment of acute lymphoblastic leukemia (ALL) in children and significantly improves the event-free survival (EFS) if patients are treated intensively.^{1–6} Unfortunately, hypersensitivity reactions may occur, usually resulting in complete neutralization of the drug.^{7,8} In that case, asparaginase formulations should be switched to maintain optimal treatment. Patients can also develop allergic symptoms without asparaginase

neutralization, so-called allergic-like reactions.⁸ A third type of reaction to asparaginase is silent inactivation, which is neutralization of asparaginase without clinical symptoms. Distinction between these three reactions can only truly be made by continual measurement of asparaginase activity levels.

In addition, high inter- and inpatient variability of asparaginase activity levels has been observed,⁹ which requires individualized dosing of the drug. In our previous Dutch Childhood Oncology Group (DCOG) ALL-10 protocol, patients were treated with a fixed dose of 2,500 IU/m² PEGasparaginase.¹⁰ These patients had relatively high asparaginase activity levels (mean 899 IU/L), possibly causing unnecessary toxicity since an asparaginase activity level of >100 IU/L is considered sufficient for complete asparagine depletion.^{11–18} In addition,

Abbreviations: AHA, L-aspartic β-hydroxamate; ALL, acute lymphoblastic leukemia; BSA, body surface area; DCOG, Dutch Childhood Oncology Group; EFS, event-free survival; TDM, therapeutic drug monitoring

8% of the patients turned out to have silent inactivation.⁷ For these reasons, therapeutic drug monitoring (TDM) was implemented in the consecutive DCOG ALL-11 protocol to individualize the asparaginase treatment.

Because asparaginase activity levels are high after the fixed dose of 2,500 IU/m², individualized asparaginase treatment will decrease asparaginase use, consequently reducing the costs. On the other hand, the individualization of asparaginase therapy requires the measurement of asparaginase activity levels and the formulation of dosing advices. This will, in turn, increase the costs. PEGasparaginase treatment accounts for a substantial amount of the total ALL therapy costs.¹⁹ Therefore, a change in asparaginase costs will have a significant impact on the total costs.

The aim of this study was to analyze whether TDM of asparaginase is cost saving when compared to the fixed dosing schedule. For this, we have compared the individualized dosing schedule of the DCOG ALL-11 protocol to the fixed dosing schedule of DCOG ALL-10 (2,500 IU/m² PEGasparaginase) and to a hypothetical dosing schedule with a fixed dose of 1,500 IU/m² PEGasparaginase, the starting dose used in the DCOG ALL-11 protocol.

2 | METHODS

2.1 | Patients

This retrospective study was performed in the Sophia Children's Hospital (Rotterdam, The Netherlands) and the VU University Medical Center (Amsterdam, The Netherlands). Patients with ALL, diagnosed between May 2009 and March 2015, who were treated according to the medium risk group of the DCOG ALL-10 or ALL-11 protocol, were included. These patients were treated with asparaginase most intensively. The study was approved by the Institutional Review Board in accordance with the Declaration of Helsinki.

2.2 | Treatment protocols

ALL-10 contained eight doses of native *Escherichia coli* asparaginase (5,000 IU/m², every 3 days) in induction and 15 doses of PEGasparaginase (2,500 IU/m², biweekly) in intensification. When an allergy occurred, formulations were switched to *Erwinia* asparaginase (20,000 IU/m², three times a week).

In ALL-11, native *E. coli* asparaginase was omitted to prevent hypersensitivity reactions and replaced by three doses of PEGasparaginase (1,500 IU/m², biweekly). The intensification phase contained 14 doses, individualized based on trough asparaginase activity levels. Week levels were measured after the first dose in induction and intensification to detect silent inactivation.

In case of asparaginase inactivation, patients were switched to *Erwinia* asparaginase (20,000 IU/m², three times a week). The dose and dosing schedule were adjusted to ensure adequate levels.

TABLE 1 Cost categories

Cost categories	Costs
PEGasparaginase	\$1,387/vial of 3,750 IU
<i>Erwinia</i> asparaginase	\$850/vial of 10,000 IU
Native <i>E. coli</i> asparaginase	\$77/vial of 5,000 IU
Daycare treatment for asparaginase administration	\$250/day
Outpatient clinic visits preceding an asparaginase dose or week asparaginase activity level	\$152/visit
Laboratory tests ^a	\$7/set of tests
TDM ^b	\$105

TDM, therapeutic drug monitoring.

^aTests routinely measured prior to an asparaginase dose including aspartate transaminase, alanine transaminase, bilirubin, amylase, and glucose.

^bThe TDM costs include the costs for the AHA test and the formulation of the dosing advice.

2.3 | Asparaginase activity analysis

Asparaginase activity levels were measured using the L-aspartic β -hydroxamate (AHA) test as described earlier.^{8,20} Asparaginase inactivation was defined as PEGasparaginase activity <100 IU/l after 1 week or <10 IU/l after 2 weeks (trough level). The targeted trough asparaginase activity level was 100–250 IU/l.

2.4 | Costs

Direct medical costs of the asparaginase treatment were calculated from a hospital perspective and were retrieved from medical files. The different cost categories with corresponding costs are described in Tables 1 and 2. These categories included the costs for asparaginase use (\$1,387 per vial of 3,750 IU PEGasparaginase, \$850 per vial of 20,000 IU *Erwinia* asparaginase, and \$77 per vial of 5,000 IU native *E. coli* asparaginase), daycare treatment for asparaginase administration (\$250 per day), outpatient clinic visits preceding an asparaginase dose or week level (\$152 per visit), specific laboratory tests which were performed prior to an asparaginase dose (\$7 for Aspartate aminotransferase (AST), Alanine transaminase (ALT), bilirubin, amylase, and glucose measurement), and the costs for TDM (\$105 per AHA test and dosing advice). The latter cost category included not only the costs of the test itself but also the costs for the preparation of the blood sample, the dose advice, and the effort of prescribing the adjusted dose (Table 2). Transport costs were not included because this will considerably differ between countries and pediatric oncology centers. The asparaginase-related costs were calculated by counting the amount of cost categories per patient, multiplied with the unit prices. Dutch tariffs were used for unit prices.²¹ All costs were converted to U.S. dollars according to the average currency exchange rate of 2015 (€1 = \$1.067).

2.5 | Analysis

The data were analyzed with the software package SPSS Statistics version 21.0 (IBM Corp., Armonk, NY). To calculate the differences

TABLE 2 Therapeutic drug monitoring costs

	Costs per hour	Duration (min)	Total costs
Preparation of the blood sample	\$30	10	\$5
Test ^a			
Equipment costs	–	–	\$9
Chemicals	–	–	\$24
Technician costs	\$30	41	\$22
Administration costs	\$30	47	\$25
Total costs	–	–	\$80
Advise ^b			
Determine advises dose	\$120	5	\$10
Prescription of medication	\$120	5	\$10
Total	–	–	\$105

^aBased on 1,200 asparaginase activity samples a year.

^bThe formulation of the dosing advices is done by pediatric oncologists.

between the treatment protocols, we used *t*-tests, χ^2 tests, or Mann–Whitney U-tests. Two-sided *P*-values of <0.05 were considered statistically significant.

The following comparisons were made: First, the total asparaginase costs of ALL-11 (individualized dosing, starting with 1,500 IU/m² PEGasparaginase) were compared with ALL-10 (fixed dose of 2,500 IU/m² PEGasparaginase). Second, the two protocols were compared excluding the patients with a hypersensitivity reaction because the occurrence of hypersensitivity reactions and subsequent use of *Erwinia* asparaginase were strongly influenced by the earlier use of native *E. coli* asparaginase in induction, which has a major impact on the costs.¹⁹ Third, the hypothetical costs of ALL-11 with a fixed dose of 1,500 IU/m² and no TDM were calculated using the existing data of ALL-11 and compared with the individualized ALL-11 protocol. Thus, the lower starting dose of ALL-11 compared to ALL-10 was taken into account.

Asparaginase vials must be used directly after opening so waste should be taken into consideration. One vial contains 3,750 IU PEGasparaginase. The number of doses that can be prepared out of a single vial depends on the (mean) absolute dose and the number of patients that are treated with asparaginase on the same day. The total costs per patient were also calculated, taking this into account.

2.6 | Sensitivity analysis

To evaluate the uncertainty of the data, a one-way sensitivity analysis was performed: the cost categories were varied one by one (mean costs $\pm$ 1 SD) to assess their impact on the total costs.

3 | RESULTS

3.1 | Patient characteristics

The patient characteristics are described in Table 3. In total, 134 patients were included: 83 patients were treated according to the ALL-10 protocol with a fixed dose of 2,500 IU/m² and 51 patients were

treated according to the individualized dosing schedule of the ALL-11 protocol. The incidence of hypersensitivity reactions was lower in the ALL-11 protocol than in ALL-10 (10% vs. 22%, *P* = 0.077). The patients who were treated according to the ALL-11 protocol were slightly older and had a higher body surface area (BSA) than the ALL-10 patients (both not significantly different).

3.2 | Asparaginase costs

The total asparaginase-related costs of the ALL-10 protocol and ALL-11 protocol are described in Table 4; the costs of these protocols without patients with a hypersensitivity reaction and the costs of the hypothetical protocol with a fixed dose of 1,500 IU/m² PEGasparaginase and no TDM are described in Table 5.

First, the comparison between the ALL-10 protocol (fixed dose of 2,500 IU/m² PEGasparaginase) and ALL-11 protocol (individualized dosing, starting with 1,500 IU/m² PEGasparaginase) was made: the asparaginase-related costs of ALL-11 were 30.8% lower than ALL-10 (\$29,048 vs. \$41,960, *P* < 0.001). These costs were calculated using the absolute asparaginase dose, disregarding asparaginase waste. If the whole vial has to be used for each asparaginase dose, the asparaginase-related costs for ALL-11 would still be less than for ALL-10, although the difference is smaller: \$47,624 versus \$54,892 for ALL-11 and ALL-10, respectively (*P* < 0.001). One patient of the ALL-11 protocol was initially treated with native *E. coli* asparaginase after silent inactivation of PEGasparaginase but switched to *Erwinia* asparaginase after a few doses. In the ALL-11 protocol, laboratory tests were standardly done before each PEGasparaginase dose, in contrast to the ALL-10 protocol, where they were ordered based on doctor's choice.

Second, the comparison was made between ALL-10 and ALL-11, without patients who had developed a hypersensitivity reaction (Table 5) because the difference in costs for *Erwinia* asparaginase use contributes to a substantial amount of the incremental costs. The risk of switching to this type of asparaginase was higher in ALL-10 due to native *E. coli* asparaginase use in induction. Excluding hypersensitive patients, the total asparaginase-related costs were 42.5% (*P* < 0.001) lower in ALL-11 (\$13,178) when compared to ALL-10 (\$22,916). The

TABLE 3 Patient and treatment characteristics

	ALL-10 (n = 83)	ALL-11 (n = 51)	P-value
Sex (% male) (95% CI)	39% (28–49%)	41% (27–55%)	0.763
Age (years) (median, range)	5.0 (1.5–18.1)	6.4 (1.3–17.1)	0.074
BSA (m ²) (median, range)			
Start intensification	0.8 (0.4–2.0)	0.9 (0.5–2.3)	0.105
Week 19 of intensification	0.8 (0.5–2.1)	0.9 (0.6–2.2)	0.218
Number of PEGasparaginase doses (median, range) (mean)	15 (0–15) (14.5)	17 (1–17) (16.4)	<0.001
Number of <i>Erwinia</i> asparaginase doses (median, range)	0 (0–84)	0 (0–99)	0.170
Number of native <i>E. coli</i> asparaginase doses (median, range)	8 (3–8)	0 (0–4)	<0.001
Number of AHA-tests (median, range)	0	16 (2–53)	<0.001
Number of outpatient clinic visits (median, range)	23 (2–100)	18 (1–41)	<0.001
Number of daycare admissions (median, range)	23 (3–94)	17 (1–105)	<0.001
Number of laboratory tests (median, range)	6 (1–23)	16 (6–40)	<0.001
Hypersensitivity reactions (%) (95% CI)	22% (13–31)	10% (1–18) ^a	0.077
Average absolute PEGasparaginase dose (IU) per patient (median, range)	2,025 (1,225–5,188)	726 (366–2,400)	<0.001
Average PEGasp dose IU/m ² per patient (median, range)	2,500	778 (482–1,500)	<0.001

AHA-test: Method used to measure asparaginase activity levels.

^aFour patients had silent inactivation of PEGasparaginase, and one patient had an allergy to PEGasparaginase.

TABLE 4 Total asparaginase-related costs (\$) per patient

Cost category	Mean $\pm$ SD median (IQR) % of total		ALL-11 (TDM) vs. ALL-10	
	N = 83 ALL-10	N = 51 ALL-11	Mean incremental costs	P (95% CI of the difference)
PEGasparaginase (IU used)	10,604 $\pm$ 6,867 10,064 (5,112) 22.4%	4,363 $\pm$ 2,168 3,733 (3,293) 14.1%	–6,241	<0.001 (4,630–7,852)
<i>Erwinia</i> asparaginase (IU used)	18,624 $\pm$ 40,552 0 (0) 44.4%	13,816 $\pm$ 43,506 0 (0) 47.6%	–4,808	0.159**
Native <i>E. coli</i> asparaginase (IU used)	750 $\pm$ 284 614 (0) 1.6%	8 $\pm$ 54 0 (0) 0.03%	–742	<0.001**
Daycare	8,129 $\pm$ 5,487 5,771 (0) 17.2%	5,874 $\pm$ 5,493 4,265 (0) 19.0%	–2,255	<0.001*
Outpatient clinic visits	3,803 $\pm$ 1,586 3,502 (0) 8.0%	2,953 $\pm$ 1,013 2,741 (152) 9.6%	–850	<0.001**
Laboratory tests	51 $\pm$ 37 43 (50) 0.1%	118 $\pm$ 36 114 (14) 0.4%	67	<0.001*
TDM	0	1,917 $\pm$ 945 1,680 (210) 6.2%	1,917	<0.001**
Total	41,960 $\pm$ 43,205 22,268 (14,529)	29,048 $\pm$ 49,787 13,010 (4,283)	–12,912 (30.8%)	<0.001**

This table shows the mean ($\pm$ SD) and median (IQR) of the different cost categories. Also the percentage of the mean total costs was shown. The costs of asparaginase use were calculated using the amount of asparaginase administered. The right side of the table describes the difference between the ALL-11 and ALL-10 costs for each category and for the total costs.

SD, standard deviation; IQR, interquartile range; TDM, therapeutic drug monitoring.

No CI because of logarithmic transformation* or Mann–Whitney test**.

TABLE 5 Total asparaginase-related costs (\$) per patient in patients without a hypersensitivity reaction to PEGasparaginase

Cost category	Mean $\pm$ SD median (IQR) % of total			(1) ALL-11 (TDM) vs. ALL-10	P (95% CI of the difference)
	ALL-10 (2,500 IU/m ²) N = 66	ALL-11 (TDM) N = 46	ALL-11 (1,500 IU/m ²) N = 46	(2) ALL-11 (TDM) vs. ALL-11 (1,500 IU/m ²) Mean incremental costs	
PEGasparaginase (IU used)	13,015 $\pm$ 5,744	4,672 $\pm$ 2,043	9,675 $\pm$ 4,218	-8,343	<0.001*
	11,063 (5,042)	3,905 (3,204)	8,618 (5,678)	-5,003	<0.001*
	56.8%	35.5%	58.5%		
Native <i>E. coli</i> asparaginase (IU used)	747 $\pm$ 292	0	0	-747	<0.001*
	614 (0)			0	-
	3.3%				
Daycare	5,662 $\pm$ 627	4,107 $\pm$ 640	4,107 $\pm$ 640	-1,555	<0.001*
	5,771 (0)	4,265 (0)	4,265 (0)	0	-
	24.7%	31.2%	24.8%		
Outpatient clinic visits	3,438 $\pm$ 399	2,658 $\pm$ 434	2,658 $\pm$ 434	-780	<0.001*
	3,502 (0)	2,741 (38)	2,741 (38)	0	-
	15.0%	20.2%	16.1%		
Laboratory tests	52 $\pm$ 37	111 $\pm$ 19	111 $\pm$ 19	59	<0.001*
	43 (54)	114 (16)	114 (16)	0	-
	0.2%	0.8%	0.7%		
TDM	0	1,630 $\pm$ 266	0	1,630	<0.001*
		1,680 (131)		1,630	<0.001*
		12.4%			
Total	22,916 $\pm$ 6,373	13,178 $\pm$ 2,660	16,551 $\pm$ 4,626	-9,738 (42.5%)	<0.001*
	20,965 (5,503)	12,548 (3,345)	15,698 (5,911)	-3,373 (20.4%)	<0.001*

In this table, the patients with a hypersensitivity reaction to PEGasparaginase were excluded. The mean ($\pm$ SD) and median (IQR) costs of ALL-10, ALL-11 with TDM, and the hypothetical scenario of ALL-11 without TDM were described. The right side of the table shows (1) the difference between ALL-10 and ALL-11 with TDM, and (2) between ALL-11 with TDM and ALL-11 without TDM. The costs for asparaginase use were calculated with the amount of asparaginase administered.

IQR, interquartile range; TDM, therapeutic drug monitoring.

*No CI because a Mann-Whitney test was performed.

mean costs for the TDM were \$1,630, which was 12.4% of the total costs.

Third, the comparison was made between the ALL-11 protocol and the hypothetical ALL-11 protocol with a fixed dose of 1,500 IU/m² PEGasparaginase and no TDM (Table 5), because the starting dose of PEGasparaginase was 1,000 IU/m² lower in ALL-11 than in ALL-10, which already led to a cost reduction. Furthermore, the fact that three doses of PEGasparaginase were used instead of eight native *E. coli* asparaginase doses in induction resulted in a cost reduction of daycare admissions and outpatient clinic visits. On the other hand, the drug PEGasparaginase is more expensive than native *E. coli* asparaginase (Table 1). The costs of PEGasparaginase use of the ALL-11 protocol (\$4,672) were 48.3% ($P < 0.001$) lower than the PEGasparaginase costs of the hypothetical protocol with the fixed dose of 1,500 IU/m² (\$9,675). Taking into account the costs for the AHA tests as well, in total, still \$3,373 (20.4%) will be saved per patient when using TDM ($P < 0.001$).

In clinical practice, leftover asparaginase after preparation of the dose may have to be discarded if it cannot be used for another patient. However, if patients are treated at the same day, multiple doses can

be prepared out of a single vial. Supplementary Figure S1 shows the total asparaginase-related costs when vials can be shared between patients, taking into account the PEGasparaginase waste. Depending on the number of patients treated at the same day and the amount of PEGasparaginase administered per dose, multiple doses can be prepared out of the same vial, resulting in less waste per dose. Supplementary Figure S1 shows that, in our cohort, TDM is cost saving when compared to a fixed dose of 1,500 IU/m², if three patients are treated with asparaginase on the same day. If only one PEGasparaginase dose can be prepared out of a single vial, TDM would be more expensive than the hypothetical protocol due to the measurement of asparaginase activity levels and the formulation of dosing advices. More information about this analysis is included in the Supplementary Results.

3.3 | Sensitivity analysis

The one-way sensitivity analysis is shown in a tornado diagram (Fig. 1). *Erwinia* asparaginase use has the greatest impact on the total costs. Except for the *Erwinia* asparaginase costs, the maximum costs of

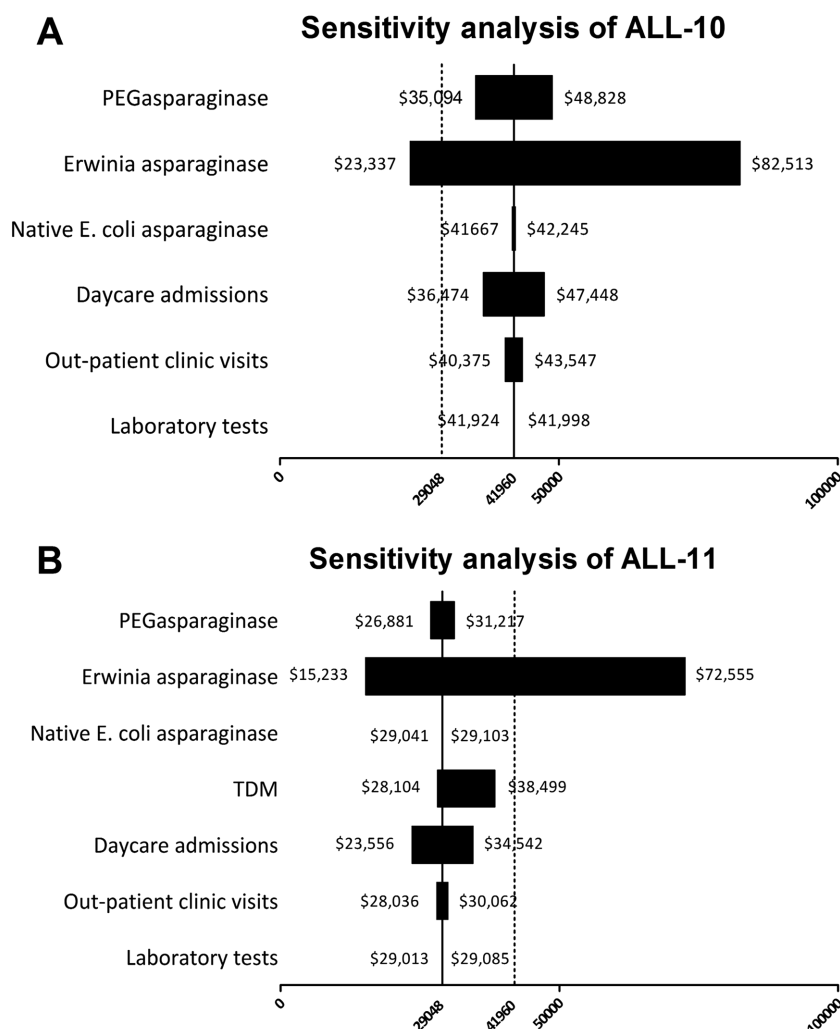


FIGURE 1 One-way sensitivity analysis of the ALL-10 and ALL-11 protocol. (A) The range of mean total asparaginase costs for ALL-10 is shown: for each cost category, the mean $\pm$ 1 SD of each category was varied to calculate the total asparaginase costs. The minimal costs of *Erwinia* asparaginase were $<$ \$0 but were fixed at \$0. The dotted line represents the mean total costs of ALL-11 (\$29,048). (B) The same for the ALL-11 protocol is shown. Again, the minimal costs of *Erwinia* asparaginase were $<$ \$0 and fixed at \$0. The dotted line represents the mean ALL-10 costs (\$41,960)

ALL-11 did not exceed the mean ALL-10 costs when varying the cost categories one by one with 1 SD. The same is true for the minimal costs of ALL-10.

4 | DISCUSSION

In this study, several comparisons were made to study the effect of TDM on the asparaginase-related costs. Although the comparison between real treatment protocols is important, the fairest comparison made was between the ALL-11 protocol and the hypothetical ALL-11 protocol with a fixed dose of 1,500 IU/m² and no TDM. This comparison has shown that TDM is cost saving despite of the extra costs for the asparaginase activity analysis and dosing advices. However, with the current size of PEGasparaginase vials (3,750 IU), the costs will be higher than a fixed dosing schedule if leftover asparaginase from vials cannot be used for other patients: much asparaginase has to be discarded if only one or two doses can be prepared at the same time, which is the case in many pediatric oncology centers. Hence,

centralization of pediatric oncology care would reduce the asparaginase waste and subsequent costs. The size of PEGasparaginase vials is based on the adult asparaginase dose of 2,000 IU/m², for whom the average absolute dose is approximately 3,600 IU as the mean adult BSA is 1.79 m².²² Therefore, for pediatric asparaginase doses and lower doses in adults, smaller vials should become available to reduce the waste.

Among the current treatment protocols used to treat children with ALL, asparaginase treatment differs considerably regarding the number of asparaginase doses and asparaginase dosage. Thus, the expenses that could be saved when using TDM will vary between countries. However, as PEGasparaginase is an expensive drug, a dose reduction of approximately 50% will significantly decrease the total treatment costs in most cases. Moreover, the starting dose of ALL-11 (1,500 IU/m²) is relatively low compared to other treatment protocols, so theoretically the dose could be reduced even more, which will relatively save even more costs.

Several pharmacoeconomic analyses of pediatric ALL treatment and asparaginase treatment have been performed.^{19,23–26} However,

none of these include TDM. Furthermore, analyses about TDM mainly focused on clinical outcomes such as hospitalization or complication rates while our study focused on cost savings due to dose reduction of asparaginase.^{27–30}

In this study, we have only performed a cost analysis, without including the effects of individualized asparaginase doses. In the short term, lower asparaginase activity levels may reduce toxicity such as hepatotoxicity and dyslipidemia. This, however, will have little impact on the total costs but will, of course, be important for the patient. In addition, also the risk of pancreatitis, thromboembolic events, and central neurotoxicity might be reduced, although the incidence of these side effects is relatively low, and patient numbers may be too small to observe an effect.

But more importantly, TDM of asparaginase will improve the long-term outcome of children with ALL: first, silent inactivation of asparaginase will be detected, which will result in a better EFS if formulations are switched.^{31,32} This will probably increase the total costs as relatively more patients will be treated with *Erwinia* asparaginase. However, because of a lower relapse rate, the costs may be lower though, as expensive relapse therapy will be given less frequently. In our ALL-11 cohort, only four cases of silent inactivation occurred, which makes it difficult to draw conclusions regarding these costs. Second, allergic-like reactions can only be distinguished from real allergies by TDM.⁸ The influence on the costs, however, should be studied more closely because not switching to *Erwinia* asparaginase after an allergic-like reaction to PEGasparaginase will reduce the costs, while continuation of asparaginase after an allergic-like reaction to *Erwinia* asparaginase will increase the direct medical asparaginase-related costs. Regardless of these direct costs, TDM allows patients with an allergic-like reaction to *Erwinia* asparaginase to finish their asparaginase treatment, which will improve their outcome and consequently prevent relapse-associated costs.

In our study, the TDM costs accounted for 12% of the total asparaginase-related costs. These costs may be an overestimation because of two reasons: first, the number of asparaginase activity levels measured is relatively high because enough insight into the population pharmacokinetics of PEGasparaginase is lacking. If we would be able to better predict asparaginase activity levels in individual patients, less AHA tests would be needed, which would reduce the costs. Second, our TDM administration costs are relatively high as we now need 47 min per sample for administration. This includes processing the samples before activity measurement and entering all information in the database, which is used for the formulation of dosing advices. Especially the latter is time consuming and is partly caused by entering information, which is irrelevant for the dosing advices, but necessary for research purposes. Without the administration costs, the actual AHA test costs \$55.

In conclusion, TDM of asparaginase will save expenses when calculated with the amount of IU asparaginase administered. TDM will also be cost saving if the asparaginase waste is minimized by preparing multiple doses out of a single vial or if smaller vials become available. Although the effects of TDM were not included in the analysis, TDM has several advantages including the possible prevention of toxicity, the detection of silent inactivation, the distinction between real

allergies and allergic-like reactions, and consequently the improvement of the EFS. Therefore, we recommend TDM of asparaginase from a clinical and cost perspective.

CONFLICT OF INTEREST

R. Pieters and I.M. van der Sluis received research support and consultancy fees from Jazz Pharmaceuticals and Medac.

REFERENCES

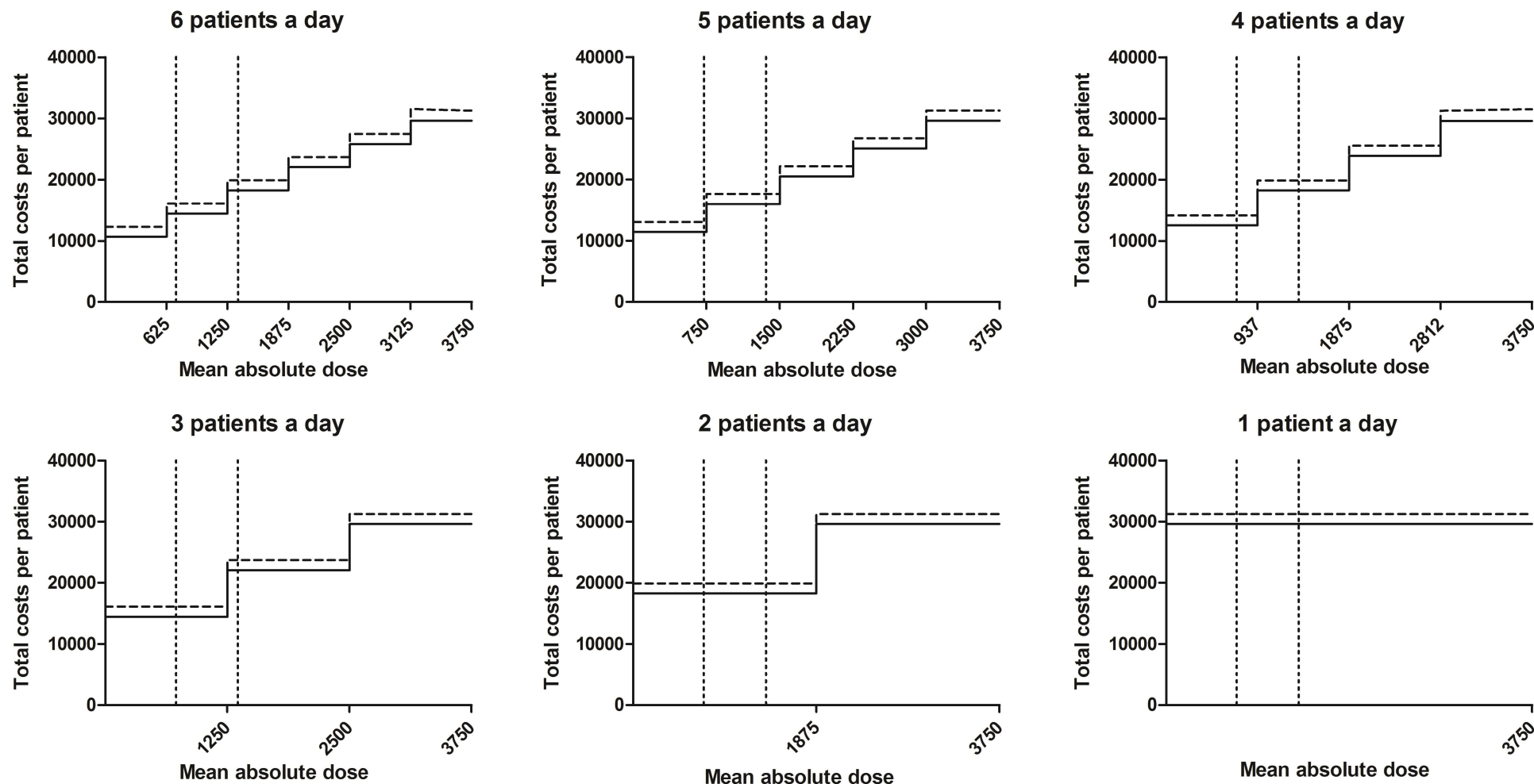
1. Amylon MD, Shuster J, Pullen J, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. *Leukemia*. 1999;13(3):335–342.
2. Duval M, Suci S, Ferster A, et al. Comparison of *Escherichia coli*-asparaginase with *Erwinia*-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. *Blood*. 2002;99(8):2734–2739.
3. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007;109(3):896–904.
4. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2005;23(28):7161–7167.
5. Rizzari C, Valsecchi MG, Arico M, et al. Effect of protracted high-dose L-asparaginase given as a second exposure in a Berlin-Frankfurt-Munster-based treatment: results of the randomized 9102 intermediate-risk childhood acute lymphoblastic leukemia study—a report from the Associazione Italiana Ematologia Oncologia Pediatrica. *J Clin Oncol*. 2001;19(5):1297–1303.
6. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood*. 2001;97(5):1211–1218.
7. Tong WH, Pieters R, Kaspers GJ, et al. A prospective study on drug monitoring of PEGasparaginase and *Erwinia* asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood*. 2014;123(13):2026–2033.
8. Kloos RQ, Pieters R, Escherich G, van der Sluis IM. Allergic-like reactions to asparaginase: atypical allergies without asparaginase inactivation. *Pediatr Blood Cancer*. 2016;63:1928–1934.
9. Hempel G, Muller HJ, Lanvers-Kaminsky C, Wurthwein G, Hoppe A, Boos J. A population pharmacokinetic model for pegylated-asparaginase in children. *Br J Haematol*. 2010;148(1):119–125.
10. Pieters R, de Groot-Kruseman H, Van der Velden V, et al. Successful therapy reduction and intensification for childhood acute lymphoblastic leukemia based on minimal residual disease monitoring: study ALL10 from the Dutch Childhood Oncology Group. *J Clin Oncol*. 2016;34(22):2591–2601.
11. Ahlke E, Nowak-Gottl U, Schulze-Westhoff P, et al. Dose reduction of asparaginase under pharmacokinetic and pharmacodynamic control during induction therapy in children with acute lymphoblastic leukaemia. *Br J Haematol*. 1997;96(4):675–681.
12. Grigoryan RS, Panosyan EH, Seibel NL, Gaynon PS, Avramis IA, Avramis VI. Changes of amino acid serum levels in pediatric patients with higher-risk acute lymphoblastic leukemia (CCG-1961). *In Vivo*. 2004;18(2):107–112.
13. Pieters R, Appel I, Kuehnelt HJ, et al. Pharmacokinetics, pharmacodynamics, efficacy, and safety of a new recombinant asparaginase

- preparation in children with previously untreated acute lymphoblastic leukemia: a randomized phase 2 clinical trial. *Blood*. 2008;112(13):4832–4838.
14. Albertsen BK, Schroder H, Jakobsen P, Muller HJ, Carlsen NT, Schmiegelow K. Monitoring of Erwinia asparaginase therapy in childhood ALL in the Nordic countries. *Br J Clin Pharmacol*. 2001;52(4):433–437.
 15. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*. 2002;99(6):1986–1994.
 16. Riccardi R, Holcenberg JS, Glaubiger DL, Wood JH, Poplack DG. L-Asparaginase pharmacokinetics and asparagine levels in cerebrospinal fluid of rhesus monkeys and humans. *Cancer Res*. 1981;41(11 Pt 1):4554–4558.
 17. Rizzari C, Zucchetti M, Conter V, et al. L-asparagine depletion and L-asparaginase activity in children with acute lymphoblastic leukemia receiving i.m. or i.v. Erwinia C. or E. coli L-asparaginase as first exposure. *Ann Oncol*. 2000;11(2):189–193.
 18. Tsurusawa M, Chin M, Iwai A, et al. L-Asparagine depletion levels and L-asparaginase activity in plasma of children with acute lymphoblastic leukemia under asparaginase treatment. *Cancer Chemother Pharmacol*. 2004;53(3):204–208.
 19. Tong WH, van der Sluis IM, Alleman CJ, et al. Cost-analysis of treatment of childhood acute lymphoblastic leukemia with asparaginase preparations: the impact of expensive chemotherapy. *Haematologica*. 2013;98(5):753–759.
 20. Lanvers C, Vieira Pinheiro JP, Hempel G, Wuerthwein G, Boos J. Analytical validation of a microplate reader-based method for the therapeutic drug monitoring of L-asparaginase in human serum. *Anal Biochem*. 2002;309(1):117–126.
 21. Hakkaart L, Tan SS, M. BCA. Manual for costing research. Methods and guideline prices for economic evaluations in health care. Rotterdam: Health Care Insurance Board; 2010.
 22. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One*. 2010;5(1):e8933.
 23. Kurre HA, Ettinger AG, Veenstra DL, et al. A pharmacoeconomic analysis of pegaspargase versus native *Escherichia coli* L-asparaginase for the treatment of children with standard-risk, acute lymphoblastic leukemia: the Children's Cancer Group study (CCG-1962). *J Pediatr Hematol Oncol*. 2002;24(3):175–181.
 24. Kaul S, Korgenski EK, Ying J, et al. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. *Cancer Med*. 2016;5(2):221–229.
 25. Rahiala J, Riikonen P, Kekalainen L, Perkkio M. Cost analysis of the treatment of acute childhood lymphocytic leukaemia according to Nordic protocols. *Acta Paediatr*. 2000;89(4):482–487.
 26. van Litsenburg RR, Uyl-de Groot CA, Raat H, Kaspers GJ, Gemke RJ. Cost-effectiveness of treatment of childhood acute lymphoblastic leukemia with chemotherapy only: the influence of new medication and diagnostic technology. *Pediatr Blood Cancer*. 2011;57(6):1005–1010.
 27. Deitelzweig S, Evans M, Hillson E, et al. Warfarin time in therapeutic range and its impact on healthcare resource utilization and costs among patients with nonvalvular atrial fibrillation. *Curr Med Res Opin*. 2016;32(1):87–94.
 28. Ostad Haji E, Mann K, Dragicevic A, et al. Potential cost-effectiveness of therapeutic drug monitoring for depressed patients treated with citalopram. *Ther Drug Monit*. 2013;35(3):396–401.
 29. van Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. *Ther Drug Monit*. 1999;21(1):63–73.
 30. Velasco A, Chung O, Raza F, et al. Cost-effectiveness of therapeutic drug monitoring in diagnosing primary aldosteronism in patients with resistant hypertension. *J Clin Hypertens (Greenwich)*. 2015;17(9):713–719.
 31. Panosyan EH, Seibel NL, Martin-Aragon S, et al. Asparaginase antibody and asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group Study CCG-1961. *J Pediatr Hematol Oncol*. 2004;26(4):217–226.
 32. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of *Escherichia coli* L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study—Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *J Clin Oncol*. 2013;31(9):1202–1210.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Kloos RQH, Uyl-de Groot CA, van Litsenburg RR, Kaspers GJL, Pieters R, van der Sluis IM. A cost analysis of individualized asparaginase treatment in pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2017;00:e26651. <https://doi.org/10.1002/pbc.26651>



Supplemental Figure S1: Mean total costs per patient, taking into account the PEGasparaginase waste.

This figure illustrates when TDM is cost saving when compared to a fixed dosing schedule, assuming that vials (3,750 IU) should be used completely after opening. The mean total costs of asparaginase treatment are plotted against the mean absolute asparaginase dose for the situations of six (A), five (B), four (C), three (D), two (E) and one (F) asparaginase administration(s) on the same day: the horizontal dashed lines show the mean total costs of ALL-11 with TDM; the horizontal solid lines the mean total costs per patient of ALL-11 with a fixed dose of 1500 IU/m². The vertical dotted lines represent the mean absolute asparaginase dose of ALL-11 with TDM (726 IU) and with a fixed dose of 1500 IU/m² (1,350 IU, calculated with an overall mean BSA of 0.9 m²). The total asparaginase related costs increase when the absolute amount of asparaginase needed exceeds the content of a vial and an extra vial has to be opened for each new dose.