Cost-analysis of treatment of childhood acute lymphoblastic leukemia with asparaginase preparations: the impact of expensive chemotherapy

Wing H. Tong,[1] Inge M. van der Sluis,[1] Cathelijne J.M. Alleman,[2] Raphaële R.L. van Litsenburg,[3] Gertjan J. L. Kaspers,[3] Rob Pieters,[1] and Carin A. Uyl-de Groot[2]

[1]Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; [2]Department of Health Policy and Management/ Institute Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands; [3]Department of Pediatric Oncology-Hematology, VU University Medical Center, Amsterdam, The Netherlands

ABSTRACT

Asparaginase is an expensive drug, but important in childhood acute lymphoblastic leukemia. In order to compare costs of PEGasparaginase, *Erwinia* asparaginase and native *E. coli* asparaginase, we performed a cost-analysis in the Dutch Childhood Oncology Group ALL-10 medium-risk group intensification protocol. Treatment costs were calculated based on patient level data of 84 subjects, and were related to the occurrence of allergy to PEGasparaginase. Simultaneously, decision tree and sensitivity analyses were conducted. The total costs of the intensification course of 30 weeks were $57,893 in patients without PEGasparaginase allergy (n=64). The costs were significantly higher ($113,558) in case of allergy (n=20) necessitating a switch to *Erwinia* asparaginase. Simulated scenarios (decision tree analysis) using native *E. coli* asparaginase in intensification showed that the costs of PEGasparaginase were equal to those of native *E. coli* asparaginase. Also after sensitivity analyses, the costs for PEGasparaginase were equal to those of native *E. coli* asparaginase. Intensification treatment with native *E. coli* asparaginase, followed by a switch to PEGasparaginase, and subsequently to *Erwinia* asparaginase in case of allergy had similar overall costs compared to the treatment with PEGasparaginase as the first-line drug (followed by *Erwinia* asparaginase in the case of allergy). PEGasparaginase is preferred over native *E. coli* asparaginase, because it is administered less frequently, with less day care visits. PEGasparaginase is less immunogenic than native *E. coli* asparaginase and is not more expensive. Asparaginase costs are mainly determined by the percentage of patients who are allergic and require a switch to *Erwinia* asparaginase.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer.[1] Annually, approximately 120 new cases of childhood ALL are diagnosed in the Netherlands. The treatment of childhood ALL has improved dramatically and survival increased from 0-5% in the 1960s to 80-85% nowadays.[1] Treatment consists of induction, consolidation, intensification and continuation phases. Asparaginase is one of the key drugs in this treatment.[2-4] Asparaginase is a non-human enzyme which hydrolyses asparagine into aspartic acid and ammonia. Given that leukemic blasts depend heavily on asparagine, deprived of this amino acid, they undergo apoptosis.[5]

Currently, several asparaginase preparations are available on the market: these are derived from *Escherichia coli* in its native form (Paronal® or Asparaginase medac®) or as a pegylated enzyme (PEGasparaginase, Oncaspar®) or extracted from *Erwinia chrysanthemi* (*Erwinia* asparaginase, Erwinase®). Many studies have shown that intensification by asparaginase is essential to improve the event-free survival of children with ALL.[2-4,6-8]

Unfortunately, asparaginase can cause an allergic reaction leading to inactivation of the drug or silent inactivation. Silent inactivation is the formation of anti-asparaginase antibodies which neutralize asparaginase without their being clinical symptoms of an allergy.[9] In the case of allergic reactions to PEGasparaginase, *Erwinia* asparaginase is given instead. *Erwinia* asparaginase is given three times per week. The different dose schedules for native *E. coli* asparaginase, PEGasparaginase and *Erwinia* asparaginase are based on differences in the pharmacokinetics of the three products.

Compared to native *E. coli* asparaginase, PEGasparaginase is expensive,[10] and *Erwinia* asparaginase is even more expensive. Little information is available on the exact costs of asparaginase in the treatment of ALL.[11-12] Recently, Litsenburg *et al.*[13] concluded that medication and diagnostics were the major contributors to the increased costs of the ALL-10 protocol compared to the previous ALL-9 protocol. However, in this study the costs of asparaginase were not analyzed separately and the costs were not related to the occurrence of allergies. Since native *E. coli* asparaginase was not administered during intensification in the ALL-10 protocol, we used hypothetical scenarios to study this strategy. The trial data of the ALL-10 protocol were used to compare PEGasparaginase to native *E. coli* asparaginase. Because of hospital budget restrictions and increasing costs of treatment of childhood ALL more insight into costs of asparaginase preparations is desired.

 doi:10.3324/haematol.2012.073510
The online version of this article has a Supplementary Appendix.
Manuscript received on July 2, 2012. Manuscript accepted on January 23, 2013.
Correspondence: i.vandersluis@erasmusmc.nl

In the present study, we studied the costs of asparaginase in childhood ALL patients treated with PEGasparaginase or *Erwinia* asparaginase during the first 30 weeks of the intensification phase of the ALL-10 medium-risk (MR) protocol. The aim was to assess whether there are savings from using PEGasparaginase as the first-line drug rather than the native *E.coli* asparaginase.

Design and Methods

Overall study design

For this cost-analysis, we compared the costs of asparaginase related to allergy in three treatment scenarios. Scenario 1 is based on trial data from the ALL-10 MR protocol. Scenarios 2 and 3 are based on assumptions. A decision tree model was also used to relate costs for each scenario to different allergy rates.

Patients and the acute lymphoblastic leukemia treatment protocol

From November 2004 to April 2012, children with ALL were enrolled on the DCOG ALL-10 protocol[14] approved by the Institutional Review Board. Patients were stratified into three risk groups after induction treatment: standard risk (SR), MR and high risk (HR).[15] The intensification/continuation scheme for the ALL-10 MR patients, including asparaginase (administered intravenously) is shown in *Online Supplementary Figure S1* and described in the *Online Supplementary Design and Methods* section. For this cost-analysis between April 2005 and October 2009, only MR patients from two pediatric oncology centers were included. Allergic reactions were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Description of three scenarios

The ALL-10 MR protocol was used as scenario 1 (Figure 1). Due to the fact that native *E. coli* asparaginase was not administered during intensification in this protocol, we used two hypothetical scenarios. In scenarios 2 and 3, patients were hypothetically treated with native *E. coli* asparaginase (5,000 IU/m^2, twice weekly) for a duration of 30 weeks (Figure 1). In scenario 2, in case of an allergic reaction to native *E. coli* asparaginase, *Erwinia* asparaginase was given. In scenario 3, patients were switched to PEGasparaginase in case of an allergic reaction to native *E. coli* asparaginase. Scenario 3 was based, among others, on the ALL-10 induction and the ALL-BFM 2000[16] protocols which prescribed PEGasparaginase as second-line and *Erwinia* asparaginase as third-line therapy. In this scenario, it was assumed that an allergy to PEGasparaginase after an allergic reaction to native *E. coli* asparaginase will occur at the second dose which is the case in practically all allergic reactions according to the interim results of the ALL-10 protocol.

Costs data

Data on volumes were adapted from hospital electronic databases and medical files. For the unit prices, we applied the microcosting method[17] and Dutch tariffs. More details are given in the *Online Supplementary Design and Methods* section.

Statistical, decision tree, sensitivity analyses

The data were analyzed with the software package SPSS for Windows version 17.0.2 (SPSS, Chicago, IL, USA). The mean total costs were not normally distributed (as shown by the Shapiro-Wilk test). The non-parametric Mann-Whitney *U*-test was used to compare the subgroups with or without an allergy to asparaginase. A two-sided *P*-value <0.05 was considered statistically significant. Data are presented as mean ± standard deviation and median (range) where appropriate.

We developed a decision tree model to compare costs of PEGasparaginase or *Erwinia* asparaginase to those of native *E.coli* asparaginase, while taking into account the incidence of allergy to asparaginase and the different associated costs

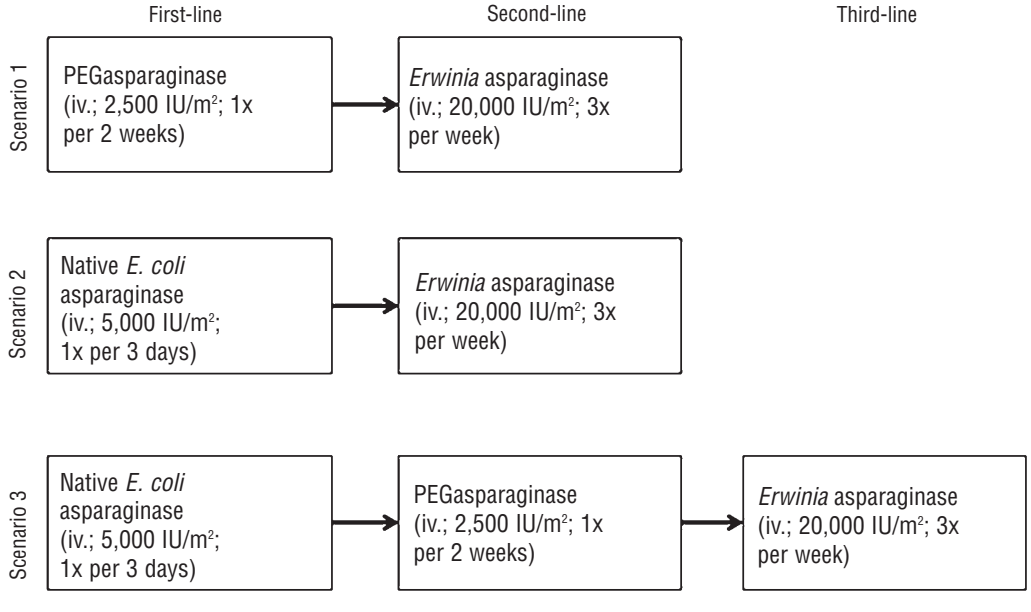

Figure 1. The flowchart of three distinct scenarios of asparaginase treatment in children with acute lymphoblastic leukemia.

(Figure 2). To account for uncertainty in the used prices and calculated costs, sensitivity analyses were performed. More details are given in the *Online Supplementary Design and Methods* section.

Results

Characteristics

In total 84 children with ALL (33 girls) were included in this study. The median age was 5.2 years (range, 1.8-18.6 years) at the start of the intensification. The baseline characteristics of each subgroup are presented in Table 1. In total 20 patients (24%) were switched to *Erwinia* asparaginase because of a proven allergic reaction to PEGasparaginase (grade 2 or higher according to the CTCAE criteria). No grade 1 allergies were seen. Two patients had an allergy to PEGasparaginase in a period (June 2005) that no *Erwinia* asparaginase was commercially available in the Netherlands. Five patients were switched to twice weekly *Erwinia* asparaginase based on sufficient trough asparaginase levels.

Calculated costs (scenario 1)

Table 2 presents the costs per subgroup for all patients. The total mean treatment costs of all patients treated according to the first 30 weeks of the ALL-10 MR protocol were $ 71,147±35,763 per patient. The distribution of these costs was mainly accounted for by asparaginase use (47%) calculated per used vial. Day care treatment and inpatient care accounted for 15% of the total costs. The mean treatment costs for patients with no allergy to PEGasparaginase were $ 57,893±16,247 per patient, which was significantly lower than the costs of the subgroup with an allergy to PEGasparaginase ($ 113,558±47,187 per patient). The total costs were calculated per 2 weeks of asparaginase exposure; for PEGasparaginase ($ 3,860±1,083 per patient), and for *Erwinia* asparaginase ($ 7,571±3,146 per patient).

Simulated costs (scenario 2 and 3)

Table 3 shows the mean costs of the two hypothetical scenarios with native *E. coli* asparaginase administered. The mean costs would be $ 47,610±13,317 for the subgroup with no allergy to native *E. coli* asparaginase. These costs were significantly lower than for patients who developed an allergy to native *E. coli* asparaginase and switched to Erwinia asparaginase with mean costs of $ 133,554±31,252 (P<0.001, scenario 2). A switch from native *E. coli* asparaginase to PEGasparaginase was accompanied by mean costs of $ 53,978±24,538, which are higher but not statistically significantly so, than the costs in the group without an allergy to native *E. coli* asparaginase. A second switch in the intensification to *Erwinia* asparaginase after an allergy to PEGasparaginase had a cost of $ 125,719±30,623 (P<0.001, scenario 3).

Decision tree and sensitivity analyses

The decision tree analysis was used to relate costs for each scenario to different probabilities of allergy. Figure 2 shows that the treatment costs using either native *E. coli* asparaginase as the first-line preparation (scenario 3: $

Table 1. Characteristics of patients with and without an allergic reaction to PEGasparaginase.

Characteristic	No PEG-asp allergy	PEG-asp allergy
Patients (%)	64 (76)	20 (24)
Boys / girls	37 / 27	14 / 6
Age (years), median (range)	5.4 (1.8-18.6)	4.3 (2-14.4)
Body surface area (m^2), median (range)	0.8 (0.5-2)	0.8 (0.5-1.6)
Patients age < 6 years (%)	35 (42)	12 (14)
Patients aged 6-12 years (%)	18 (22)	6 (7)
Patients aged > 12 years (%)	11 (13)	2 (2)
Daycare visits, median (range)	28 (19-42)	61 (6-84)
Inpatient days, median (range)	7 (0-40)	3 (0-77)
PEG-asp infusions, median (range)	15 (14-16)	2 (2)
Time point of PEG-asp allergy in weeks, median (range)	na	2 (2-4)
Erw-asp infusions, median (range)	na	68 (10-84)

ALL-10 MRG: ALL-10 protocol medium risk group; PEG-asp: PEGasparaginase; Erw-asp: Erwinia *asparaginase; na: not applicable.*

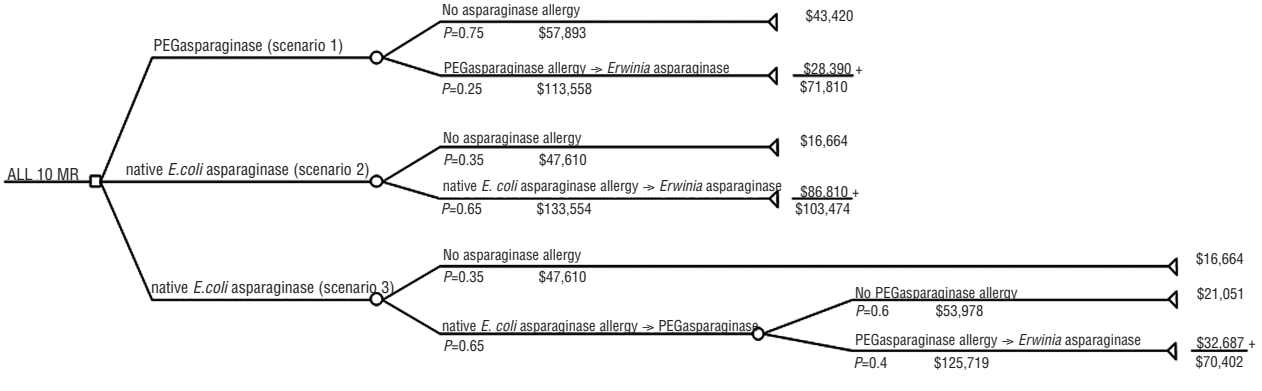

Figure 2. Decision tree of asparaginase treatment in children with acute lymphoblastic leukemia in intensification according to three scenarios. The mean costs after each probability of allergy (P) are the calculated costs per patient in scenario 1. The costs at the end of each branch represent the multiplied costs with each probability of allergy. The costs in scenarios 2 and 3 are simulated costs. The costs after each probability of allergy are the costs per patient. The costs at the end of each branch represent the multiplied costs with each probability of allergy in scenarios 2 and 3. In the last branch of scenario 3, the costs are calculated by multiplying the probability of allergy of 0.65 with the allergy probabilities of 0.6 and 0.4, respectively.

70,402) or PEGasparaginase as the first-line preparation (scenario 1: $ 71,810) were the lowest. The costs of using native *E. coli* asparaginase in the first-line followed by Erwinia asparaginase second line (scenario 2) would be higher ($ 103,474).

One-way sensitivity analysis (Figure 3) showed that the largest range in treatment costs was in the subgroup with allergy to native *E. coli* asparaginase (scenario 2). Furthermore, Figure 3 illustrates that when treatment costs were calculated with the new price of *Erwinia* asparaginase, treatment with PEGasparaginase as the first-line preparation (scenario 1) would be less expensive ($ 100,199) than treatment with the native *E. coli* asparaginase scenario 2 ($ 190,284) and scenario 3 ($ 103,089).

Two-way sensitivity analysis (Figure 4) revealed that treatment with PEGasparaginase (scenario 1) is less expensive than treatment with native *E. coli* asparaginase (scenario 2) for probabilities of allergy to PEGasparaginase ranging from zero to 0.8 with a fixed allergy rate to native *E. coli* asparaginase of 0.65 (Figure 4A). This also holds true if a fixed allergy rate to native *E. coli* asparaginase of 0.4 is used, which is frequently found in studies using less native *E. coli* asparaginase in intensification after native *E. coli* asparaginase in induction.[16,18] The treatment with PEGasparaginase (scenario 1) carries equal costs compared to the treatment with native *E. coli* asparaginase (scenario 3) at a fixed rate of allergy to PEGasparaginase of 0.25 (Figure 4B,C). This holds true if the probabilities for a second allergy to PEGasparaginase allergy are lower than the base case value of 0.4 (Figure 4B) or if the allergy probabilities for native *E. coli* asparaginase are higher than the base case value of 0.65 (Figure 4C).

Discussion

The aim of this study was to assess whether there could be savings from using PEGasparaginase as the first-line drug compared to native *E.coli* asparaginase during the first 30 weeks of the intensification phase of the ALL-10 MR protocol in the Netherlands. We showed that overall costs of treatment with native *E. coli* asparaginase, followed by a switch to PEGasparaginase, and subsequently to *Erwinia* asparaginase in case of allergy were $ 70,402. This sum was equivalent to that of treatment with PEGasparaginase as the first-line drug (followed by *Erwinia* asparaginase in case of allergy) which had overall costs of $ 71,810 (scenario 1), as applied in the ALL-10 MR protocol. Because of the comparable costs of these two scenarios, the latter one is preferable, because PEGasparaginase is administered less frequently (once every 2 weeks *versus* four times every 2 weeks), resulting in a reduced burden for the patient and family. Treatment with native *E. coli* asparaginase, followed

Table 2. Treatment costs with PEGasparaginase (scenario 1) for patients with and without an allergic reaction to PEGasparaginase. Scenario 1: PEGasparaginase used as first-line treatment in intensification; and switch to *Erwinia* asparaginase as second-line after PEGasparaginase allergy.

	No PEG-asp allergy median (mean; SD) ($)	PEG-asp allergy median (mean; SD) ($)	*P*
Cost category			
Chemotherapy without ASP	1,026 (1,163; 450)	949 (1,143; 422)	0.6
PEG-asp per used vials	24,465 (27,324; 7,785)	3,262 (5,384; 4,642)	<0.001
Erw-asp per used vials	na	81,900 (66,424; 34,580)	-
Additional medication	1,467 (2,589; 3,750)	2,110 (4,027; 5,341)	0.03
Daycare treatment	8,627 (8,931; 2,2062)	21,667 (20,202; 8,854)	<0.001
Inpatient care	5,181 (8,879; 9,741)	2,827 (9,138; 16,792)	0.4
Blood products	143 (609; 1,412)	0 (43; 105)	0.05
Laboratory activities	2,498 (3,089; 1,573)	2,055 (2,505; 1,911)	0.04
Other hospital activities	4,812 (5,310; 2,184)	3,981 (4,692; 2,718)	0.2
Total costs	54,587 (57,893; 16,247)	126,613 (113,558; 47,187)	<0.001

PEG: poly-ethylene glycol; ASP: asparaginase; PEG-asp: PEGasparaginase; Erw-asp: Erwinia *asparaginase; na: not applicable.*

Table 3. Treatment costs according to two different hypothetical treatments (scenarios 2 and 3). Scenario 2: hypothetical treatment scenario with native *E. coli* asparaginase used as first-line treatment; and switch to *Erwinia* asparaginase as second-line treatment after allergy to native *E.coli* asparaginase. Scenario 3: hypothetical treatment scenario with native *E. coli* asparaginase used as first-line treatment; PEGasparaginase used as second-line after native *E.coli* asparaginase allergy; and switch to *Erwinia* asparaginase as third-line treatment after PEGasparaginase allergy.

	Native *E.coli* asp as first line, *Erwinia* asp as second line		Native *E.coli* asp as first line, PEG-asp as second line and *Erwinia* asp as third line		
	No PEG-asp allergy	PEG-asp allergy	No PEG-asp allergy	Only *E.coli* asp allergy	*E.coli* ASP allergy and PEG-asp allergy
Cost category	median (mean; SD) ($)	median (mean; SD) ($)	median (mean; SD) ($)	median (mean; SD) ($)	median (mean; SD) ($)
Chemotherapy without asp	1,026 (1,163; 450)	949 (1,143; 422)	1,026 (1,163; 450)	949 (1,143; 422)	949 (1,143; 422)
E.coli asp per used vials	5,337 (5,503; 936)	178 (222; 140)	5,337 (5,503; 936)	178 (222; 140)	178 (222; 140)
PEG-asp per used vials	na	na	na	22,834 (23,731; 5,278)	3,262 (3,425; 729)
Erw-asp per used vials	na	76,650 (87,439; 21,900)	na	na	68,250 (77,936; 19,412)
Additional medication	1,846 (2,981; 3,757)	2,148 (4,129; 5,388)	1,846 (2,981; 3,757)	2,046 (3,985; 5,345)	2,100 (4,042; 5,350)
Outpatient care	19,843 (20,076; 449)	24,341 (24,244; 213)	19,843 (20,076; 449)	8,438 (8,519; 363)	22,718 (22,572; 307)
Inpatient care	5,181 (8,879; 9,741)	2,827 (9,138; 16,792)	5,181 (8,879; 9,741)	2,827 (9,138; 16,792)	2,827 (9,138; 16,792)
Blood products	143 (609; 1,412)	0 (43; 105)	143 (609; 1,412)	0 (43; 105)	0 (43; 105)
Laboratory activities	2,498 (3,089; 1,573)	2,055 (2,505; 1,911)	2,498 (3,089; 1,573)	2,055 (2,505; 1,911)	2,055 (2,505; 1,911)
Other hospital activities	4,812 (5,310; 2,184)	3,981 (4,692; 2,718)	4,812 (5,310; 2,184)	3,981 (4,692; 2,718)	3,981 (4,692; 2,718)
Total costs	42,947 (47,610; 13,317)	118,784 (133,554; 31,252)	42,947 (47,610; 13,317)	47,852 (53,978; 24,538)	111,951 (125,719; 30,623)

asp: asparaginase; E.coli-*asp: native* E.coli *asparaginase; PEG-asp: PEGasparaginase; Erw-asp:* Erwinia *asparaginase; na: not applicable.*

by a switch to *Erwinia* asparaginase is the most expensive alternative with overall costs of $ 103,474 (scenario 2).

We have shown that the distribution of the calculated and simulated costs was mainly accounted for by asparaginase use (47%) and that these asparaginase costs were mainly determined by allergy percentages necessitating a switch to *Erwinia* asparaginase. So, reducing the number of allergies by using PEGasparaginase would also reduce costs. Furthermore, PEGasparaginase is administered less frequently than native *E. coli* asparaginase or *Erwinia* asparaginase and is less immunogenic.[19,20] Scenarios 1 and 3 were less expensive than scenario 2; scenario 1 with PEGasparaginase as first-line treatment is the most patient-friendly option. For these reasons, PEGasparaginase is being used as the first-line drug in induction and intensification in the new DCOG ALL-11 protocol (opened in April 2012).

Two earlier studies investigated the costs of PEGasparaginase. Both found that treatment costs with PEGasparaginase were similar or slightly less than those with native *E. coli* asparaginase.[11,12] This is in line with our observations. However these studies did not study costs related to asparaginase allergy and in these studies asparaginase was given less intensively. Litsenburg *et al.* also studied costs in the ALL-10,[13] but they calculated costs for the total period of treatment and did not study the exact role of asparaginase-related costs.

The costs in the different scenarios were based on actual resource utilization in childhood ALL patients. We also accounted for the costs of discarding unused asparaginase vials by calculating the costs per used vial. Despite of the

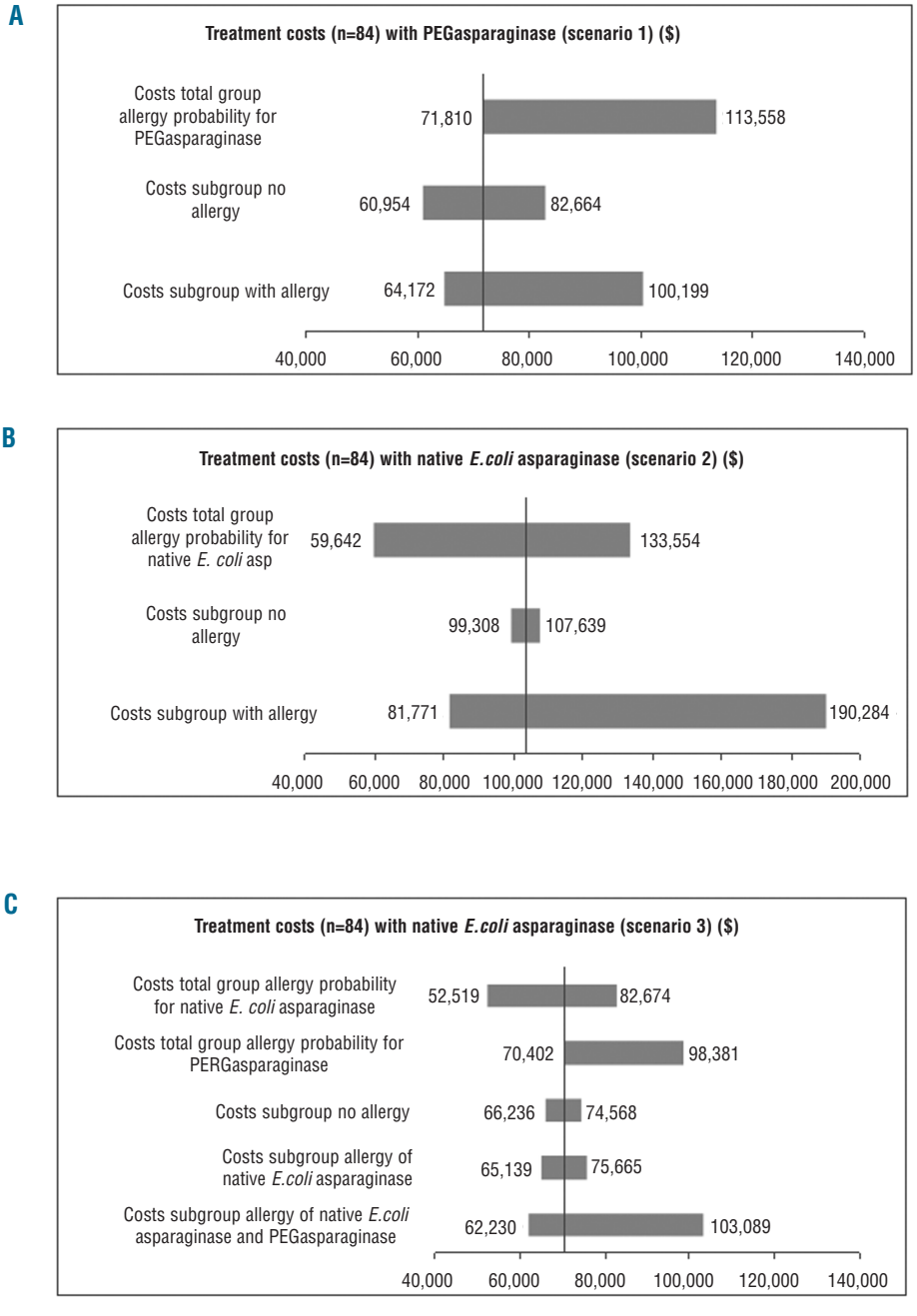

Figure 3. One-way sensitivity analyses of three asparaginase treatment scenarios. Each bar indicates treatment costs per patient when the allergy probability or the costs were varied from the lowest to the highest value. The vertical line indicates the base case value. (A) Treatment costs with PEGasparaginase (scenario 1). The first bar represents the allergy probability ranging from 25% to 100%. In the second and third bars the costs were varied in non-allergic (minus 25% to 25%) and allergic patients (minus 25% to 200%), respectively. (B) Treatment costs with native *E. coli* asparaginase (scenario 2). The first bar represents the allergy probability ranging from 14% to 100%. In the second and third bars the costs were varied in non-allergic (minus 25% until 25%) and allergic patients (minus 25% until 200%), respectively: 200% indicates the new price of *Erwinia* asparaginase (price level as of March 14, 2011). (C) Treatment costs with native *E. coli* asparaginase (scenario 3). The first bar represents the allergy probability ranging from 14% to 100%. The second bar shows the allergy probability ranging from 40% to 100%. In the third bar the costs were varied in non-allergic patients (minus 25% to 25%). The fourth bar represents the costs in patients allergic to native *E.coli* asparaginase (minus 25% to 25%). The last bar shows the costs of patients allergic to native *E.coli* asparaginase and subsequently to PEGasparaginase (minus 25% to 200%).

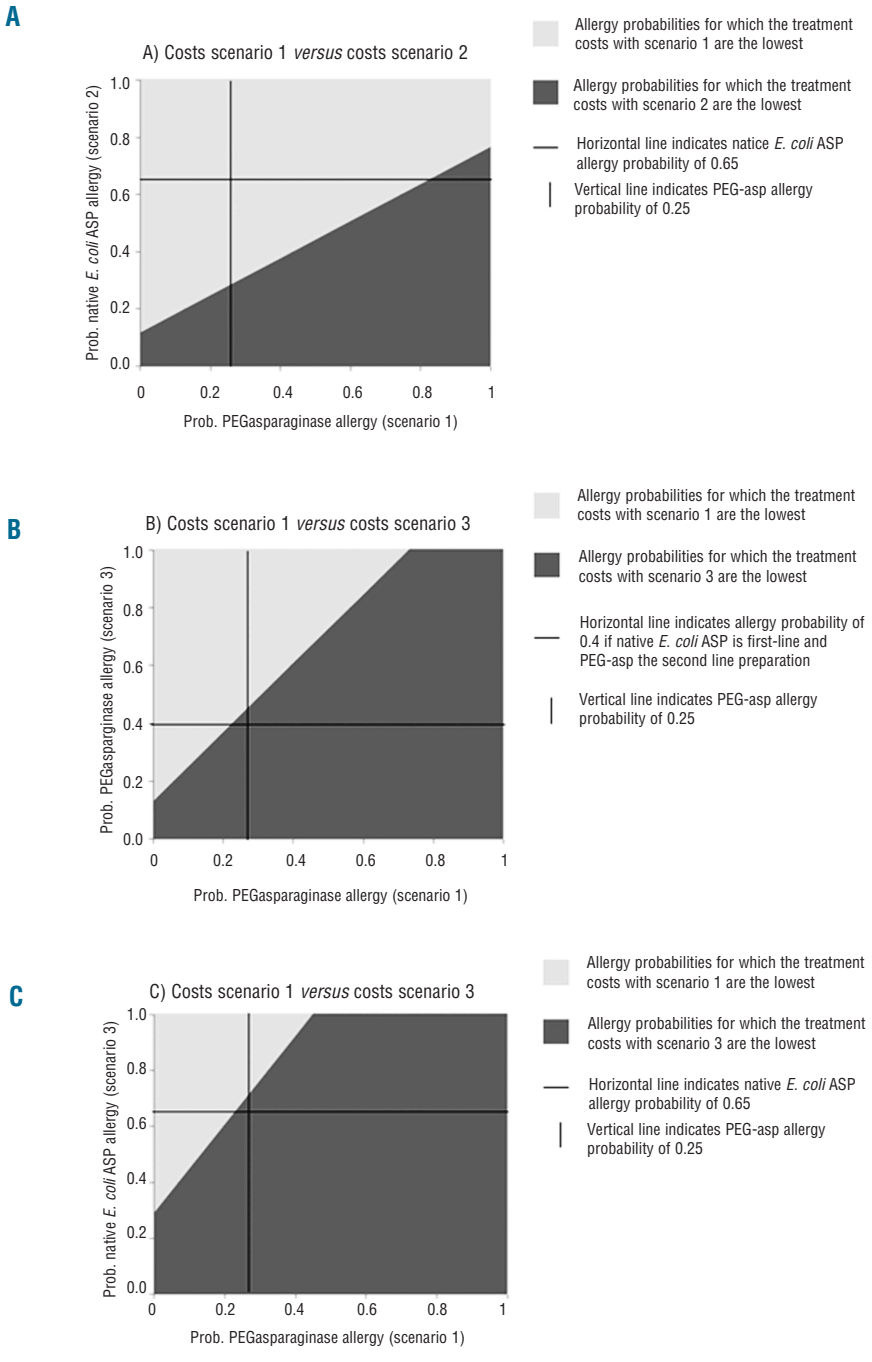

Figure 4. Two-way sensitivity analyses of three asparaginase treatment scenarios. Each graph indicates the comparison between two hypothetical scenarios 2 and 3 with scenario 1 as baseline. For each allergy probability the values are varied, represented as the vertical line or the horizontal line. The intercept between these lines indicates the base case value. In all graphs, the horizontal axis is the same. The light color area indicates for which allergy probability combinations the treatment costs with scenario 1 are the lowest. The dark color area indicates for which allergy probability combinations the treatment costs with scenario 2 in (A) or scenario 3 in (B) and (C) are the lowest. The line between the light and dark colored area represents equal costs in each comparison. (A) For the vertical axis the probability of native *E.coli* asparaginase allergy (scenario 2) is used. (B) For the vertical axis the probability of PEGasparaginase allergy (scenario 3) is used. For the costs of scenario 3, the probability of native *E. coli* asparaginase is assumed to be 0.65. (C) For the vertical axis the probability of native *E. coli* asparaginase allergy (scenario 3) is used. For the costs of scenario 3, the probability of PEGasparaginase is assumed to be 0.4. Prob.: probability, *E. coli*-asp: native *E. coli* asparaginase, PEG-asp: PEGasparaginase.

sensitivity analysis to account for different percentages of asparaginase-related allergy, it is important to note that these percentages depend on several factors such as dose schedule and the type of asparaginase, earlier exposure to asparaginase in induction and the route of asparaginase administration (intravenous or intramuscular).[21] PEGasparaginase has been shown to result in less antibody formation than native *E. coli* asparaginase.[22] The percentage of patients switching to another asparaginase preparation can also depend on silent inactivation of asparaginase.[9] With monitoring of asparaginase activity levels, more cases of inactivation will be detected, necessitating a switch in asparaginase preparations more often.

This study had some limitations. First, we had to simulate part of the treatment in order to calculate costs. To achieve reliable simulations for treatment with native *E. coli* asparaginase, simulations were based on the allergy rates in the ALL-9 HR and ALL-10 MR protocols. Furthermore, some satellite hospitals were not visited to collect data, which were retrieved from academic hospital files. A mean cost based on data collected from satellite hospitals was imputed for the missing data. We did not evaluate silent inactivation of asparaginase; this is now being done in a prospective setting. The generalizability of this study might be limited, because there is tremendous heterogeneity across the world in dose, frequency and type of asparaginase used in the treatment of childhood ALL. Nowadays, the new childhood ALL treatment protocols also include PEGasparaginase, for instance in Germany[23] and the United Kingdom,[24] while native *E. coli* asparaginase and *Erwinia*

asparaginase are used in different countries. We studied the costs of asparaginase preparations which were related to different allergy probabilities. Additionally, the costs were presented for 2 weeks of exposure to asparaginase. Taken together, our results could be generalized for these countries using different asparaginase preparations.

To conclude, we have shown that the costs of PEGasparaginase and native *E.coli* asparaginase in intensification therapy are comparable. However, PEGasparaginase is preferred, because it is administered less frequently, requiring fewer daycare visits and is, therefore, more patient-friendly. PEGasparaginase is less immunogenic than native *E. coli* asparaginase and is not more expensive. Since the price of *Erwinia* asparaginase has been doubled, the saving of costs will be clearly in favor of PEGasparaginase. Finally, asparaginase costs are mainly determined by allergy rates, necessitating a switch to *Erwinia* asparaginase.

Acknowledgments

The authors would like to thank all the cooperating pediatric oncology satellite hospitals and the Dutch Childhood Oncology Group (DCOG) for collecting clinical and laboratory information of the studied children with acute lymphoblastic leukemia. This work was supported by the KiKa® foundation.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med. 2012;366(15):1371-81.
2. Moghrabi A, Levy DE, Asselin B, Barr R, Clavell L, Hurwitz C, 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.
3. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood. 2001;97(5):1211-8.
4. Duval M, Suciu S, Ferster A, Rialland X, Nelken B, Lutz P, 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):2734-9.
5. Bussolati O, Belletti S, Uggeri J, Gatti R, Orlandini G, Dall'Asta V, et al. Characterization of apoptotic phenomena induced by treatment with L-asparaginase in NIH3T3 cells. Exp Cell Res. 1995;220 (2):283-91.
6. Rizzari C, Valsecchi MG, Arico M, Conter V, Testi A, Barisone E, 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):1297-303.
7. Pession A, Valsecchi MG, Masera G, Kamps WA, Magyarosy E, Rizzari C, 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):7161-7.
8. Amylon MD, Shuster J, Pullen J, Berard C, Link MP, Wharam M, 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):335-42.
9. Pieters R, Hunger SP, Boos J, Rizzari C, Silverman L, Baruchel A, et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. Cancer. 2011;117(2):238-49.
10. Fu CH, Sakamoto KM. PEG-asparaginase. Expert Opin Pharmacother. 2007;8(12): 1977-84.
11. Kurre HA, Ettinger AG, Veenstra DL, Gaynon PS, Franklin J, Sencer SF, 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):175-81.
12. Peters BG, Goeckner BJ, Ponzillo JJ, Velasquez WS, Wilson AL. Pegaspargase versus asparaginase in adult ALL: a pharmacoeconomic assessment. Formulary. 1995;30(7):388-93.
13. 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):1005-10.
14. van Tilburg CM, Bierings MB, Berbers GA, Wolfs TF, Pieters R, Bloem AC, et al. Impact of treatment reduction for childhood acute lymphoblastic leukemia on serum immunoglobulins and antibodies against vaccine-preventable diseases. Pediatr Blood. Cancer 2012;58(5):701-7.
15. Pieters R, Appel I, Kuehnel HJ, Tetzlaff-Fohr I, Pichlmeier U, van der Vaart I, 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):4832-8.
16. Willer A, Gerss J, Konig T, Franke D, Kuhnel HJ, Henze G, et al. Anti-Escherichia coli asparaginase antibody levels determine the activity of second-line treatment with pegylated E coli asparaginase: a retrospective analysis within the ALL-BFM trials. Blood. 2011;118(22):5774-82.
17. Drummond MF. Methods for the economic evaluation of health care programmes Oxford medical publications. 2005; 3rd edition (Oxford: Oxford University Press).
18. Nachman J, Sather HN, Gaynon PS, Lukens JN, Wolff L, Trigg ME. Augmented Berlin-Frankfurt-Munster therapy abrogates the adverse prognostic significance of slow early response to induction chemotherapy for children and adolescents with acute lymphoblastic leukemia and unfavorable presenting features: a report from the Children's Cancer Group. J Clin Oncol. 1997;15(6):2222-30.
19. Abuchowski A, van Es T, Palczuk NC, McCoy JR, Davis FF. Treatment of L5178Y tumor-bearing BDF1 mice with a nonimmunogenic L-glutaminase-L-asparaginase. Cancer Treat Rep. 1979;63(6):1127-32.
20. Yoshimoto T, Nishimura H, Saito Y, Sakurai K, Kamisaki Y, Wada H, et al. Characterization of polyethylene glycol-modified L-asparaginase from Escherichia coli and its application to therapy of leukemia. Jpn J Cancer Res. 1986;77(12): 1264-70.
21. Silverman LB, Supko JG, Stevenson KE, Woodward C, Vrooman LM, Neuberg DS, et al. Intravenous PEG-asparaginase during remission induction in children and adolescents with newly diagnosed acute lymphoblastic leukemia. Blood. 2010;115(7): 1351-3.
22. Avramis VI, Sencer S, Periclou AP, Sather H, Bostrom BC, Cohen LJ, 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): 1986-94.
23. Schrey D, Speitel K, Lanvers-Kaminsky C, Gerss J, Moricke A, Boos J. Five-year single-center study of asparaginase therapy within the ALL-BFM 2000 trial. Pediatr Blood Cancer. 2011;57(3):378-84.
24. Qureshi A, Mitchell C, Richards S, Vora A, Goulden N. Asparaginase-related venous thrombosis in UKALL 2003- re-exposure to asparaginase is feasible and safe. Br J Haematol. 2010;149(3):410-3.