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# A cost-effectiveness analysis of *Erwinia* asparaginase therapy in children with acute lymphoblastic leukemia

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## Abstract

**Objectives:** *Erwinia* asparaginase is used as a second-line formulation after a neutralizing hypersensitivity reaction to the first-line formulation of asparaginase. Here, we have performed a cost-effectiveness analysis of *Erwinia* asparaginase treatment.

**Methods:** Children with acute lymphoblastic leukemia treated according to the Dutch Childhood Oncology ALL-10 or ALL-11 protocol were included and initially treated with PEGasparaginase in the intensification phase. The total treatment costs of this treatment phase, quality of life (QoL), and life years saved (LYS) were studied for two scenarios: (a) patients were switched to *Erwinia* asparaginase treatment after a hypersensitivity reaction, or (b) asparaginase would have been permanently stopped.

**Results:** Sixty-eight patients were included. There was no difference in QoL between patients with and without a hypersensitivity reaction. The mean costs of the intensification phase per patient were $40,925 if PEGasparaginase could be continued, $175,632 if patients had to switch to *Erwinia* asparaginase, and $21,190 if asparaginase would have been permanently stopped. An extrapolation of the literature suggests that the 5-year event-free survival would be 10.3% lower without intensive asparaginase treatment if asparaginase is stopped after a reaction. Thus, the costs per LYS were $1892 for scenario 1 and $872 for scenario 2.

**Conclusions:** Switching to *Erwinia* asparaginase increases the costs per LYS by $1020, which is modest in view of the total costs. Moreover, when asparaginase treatment can be completed by switching to *Erwinia* asparaginase, relapses—and consequential costs—will be avoided. Therefore, from a cost perspective, we recommend a switch to *Erwinia* asparaginase to complete asparaginase treatment.

**KEYWORDS**
asparaginase, cost-effectiveness analysis, pediatric ALL

## 1 | INTRODUCTION

Asparaginase is a cornerstone of the treatment of acute lymphoblastic leukemia (ALL) in children as adequate, intensive treatment improves the event-free survival (EFS) significantly.[1–7] However, asparaginase treatment may be hampered by the development of hypersensitivity reactions, generally resulting in complete neutralization of the drug. This requires a switch in formulations to maintain adequate asparaginase activity levels.[8–10] In most developed countries, PEGasparaginase is now used as a first-line formulation and *Erwinia* asparaginase as a second-line formulation. The latter formulation is administered more frequently than PEGasparaginase (three times a week instead of every other week) due to different half-lives of the two drugs, resulting in a substantial increase in therapy costs.[11,12] Due to increasing

Abbreviations: ALL, acute lymphoblastic leukemia; DCOG, Dutch Childhood Oncology Group; EFS, event-free survival; HRQoL, health-related quality of life; HUI, Health Utilities Index; LYS, life years saved; MAU, multiattribute utility; QALY, quality-adjusted life year; QoL, quality of life; SD, standard deviation; TDM, therapeutic drug monitoring

restrictions on health care resources, evaluations of costs in relation to benefits become more important, especially for expensive drugs, such as *Erwinia* asparaginase. Therefore, we have performed a cost-effectiveness analysis in which we have compared the costs, quality of life (QoL), and life years saved (LYS) between two scenarios: according to scenario 1, patients were switched to *Erwinia* asparaginase after a hypersensitivity reaction to PEGasparaginase. Scenario 2, which was unethical and therefore hypothetical, described the situation in which the asparaginase treatment was permanently stopped after a hypersensitivity reaction to PEGasparaginase.

## 2 | METHODS

### 2.1 | Patients

The study was performed in the Sophia Children's Hospital, Rotterdam, The Netherlands and the VU University Medical Center, Amsterdam, The Netherlands. Patients were enrolled prospectively between May 2012 and October 2016 and were treated according to the medium-risk group of the Dutch Childhood Oncology Group (DCOG) ALL-10 (until April 2012) or the consecutive ALL-11 protocol. The study was approved by the Institutional Review Board. Informed consent was obtained from children >12 years old, parents or children's guardians in accordance with the Declaration of Helsinki.

### 2.2 | Treatment protocols

In this study, the treatment costs of the intensification phase, which contained the majority of the asparaginase doses and hypersensitivity reactions to PEGasparaginase, were calculated. According to ALL-10, patients were treated with native *Escherichia coli* asparaginase (eight intravenous doses of 5000 IU/m$^2$) in the induction phase, and 15 doses of PEGasparaginase (2500 IU/m$^2$, biweekly, intravenous) in the intensification phase. According to ALL-11, patients were treated with PEGasparaginase in both induction (three intravenous doses, 1500 IU/m$^2$) and the intensification phase (14 intravenous doses, biweekly). In this protocol, therapeutic drug monitoring (TDM) was used to individualize the doses in the intensification phase based on asparaginase activity levels. In case of a hypersensitivity reaction, defined as an allergy to or silent inactivation of PEGasparaginase, patients were switched to *Erwinia* asparaginase (20,000 IU/m$^2$, three times a week). According to ALL-11, the *Erwinia* asparaginase dose and/or dosing schedule was individualized to ensure adequate asparaginase activity levels. Table 1 describes an overview of the first 30 weeks of the ALL intensification therapy for ALL-10 and ALL-11.

**TABLE 1** Intensification of the DCOG ALL-10 and ALL-11 treatment protocols

| Intensification (30 weeks) | DCOG ALL-10 | DCOG ALL-11 |
|---|---|---|
| Dexamethasone | 6 mg/m$^2$/day orally<br>Days 0–4, every 3 weeks, starting in week 1 | 6 mg/m$^2$/day orally<br>Days 0–4, every 3 weeks, starting at week 1 |
| Vincristine | 2 mg/m$^2$/dose intravenously<br>Every 3 weeks, starting in week 1 | 2 mg/m$^2$/dose intravenously<br>Every 3 weeks, starting in week 1 |
| Doxorubicin | 30 mg/m$^2$/dose intravenously<br>Weeks 1, 4, 7, 10, 13, 16 | 30 mg/m$^2$/dose intravenously<br>Weeks 1, 4, 7, 10<br>Not in case of a TEL/AML1 translocation or Down syndrome patients without a IKZF1 deletion |
| Methotrexate | 30 mg/m$^2$/ dose intravenously<br>1x/week, weeks 20–30 | 30 mg/m$^2$/ dose intravenously<br>1x/week, weeks 13–30 |
| PEGasparaginase | 2500 IU/m$^2$ intravenously<br>Biweekly, weeks 1–29 | Dose adjusted based on asparaginase activity levels<br>Biweekly, weeks 1–27 |
| 6-Mercaptopurine | 50 mg/m$^2$/day orally<br>Courses of 2 weeks starting in weeks 1, 4, 7, 10, 13, 16<br>Daily from weeks 19–30 | 50 mg/m$^2$/day orally<br>Courses of 2 weeks starting in weeks 1, 4, 7, 10<br>Daily from weeks 13–30 |
| Intrathecal methotrexate, cytarabine, and prednisolone | Methotrexate 8–12 mg<br>Cytarabine 20–30 mg<br>Prednisolone 8–12 mg<br>Weeks 1 and 19 | Methotrexate 8–12 mg<br>Cytarabine 20–30 mg<br>Prednisolone 8–12 mg<br>Weeks 1 and 19 |

### 2.3 | Costs data

The direct medical costs of the intensification phase were retrospectively obtained and calculated from a Dutch hospital perspective.[13] All costs were converted to US dollars according to the average currency exchange rate of 2015 (€1 = $1.067). The costs included were costs for (a) PEGasparaginase ($1387 for one vial of 3750 IU) and *Erwinia* asparaginase ($850 for one vial of 10,000 IU), rounded to whole vials to take into account the waste; (b) chemotherapy other than asparaginase; (c) supportive care medication; (d) outpatient clinic visits ($175 per visit in an academic hospital, $85 in a satellite hospital); (e) day care admissions; (f) inpatient days ($689 per day in an academic hospital, $476 in a satellite hospital); (g) intensive care unit days ($2163 per day); (h) blood products, (i) laboratory tests; (j) surgical procedure costs (mainly for bone marrow punctures performed under complete anesthesia); and (k) TDM costs ($105, including asparaginase activity level measurements and the formulation of dosing advices[12]). The costs described included costs for staff, materials used, nutrition, and overhead. Data were adapted from the medical files of the Erasmus MC Rotterdam and the VU University Medical Center. Dutch tariffs (index year 2015) retrieved from the Dutch Healthcare Authority or the hospitals were used for the unit prices.[14] Costs were discounted by 4% per year to account for the time value of money in accordance with Dutch guidelines.[14]

To calculate the costs of scenario 2 for the patients with a hypersensitivity reaction, the number of outpatient clinic visits was assumed to be equal to the median number of visits of patients without a reaction. In addition, in these patients, the day care admissions for

*Erwinia* asparaginase administration only were excluded. And finally, for ALL-11 patients with a hypersensitivity reaction, only the TDM costs that were part of the PEGasparaginase treatment were included.

### 2.4 | Effects data

To assess the health-related quality of life (HRQoL), the Health Utilities Index (HUI) survey version 3.0[15] was completed by the patient and/or parents in weeks 1, 3, 4 (in case of a hypersensitivity reaction), and 19 of the intensification phase. The questionnaire included 10 general attributes (vision, hearing, speech, emotion, pain, ambulation, dexterity, cognition, caretaking, and health) each with five or six levels, describing a patient's health state. The single-attribute utility and multiattribute utility (MAU) scores were calculated, representing the HRQoL for each attribute and overall, respectively. In order to calculate the quality-adjusted life years (QALYs), the MAU scores were multiplied by the total duration of the treatment phase (30 weeks).

Beside the validated HUI questions, several extra questions about the impact of an allergic reaction and change in dosing schedule were added to the questionnaire. These questions were not validated and, therefore, could not be quantified as part of the HUI analysis.

The number of LYS was calculated using the EFS described in literature to indicate the difference in EFS between intensified and less intensified asparaginase treatment: a systematic search was performed to find trials studying the effect of intensified asparaginase treatment. Next, a weighted mean difference of the EFS of patients with and without intensified asparaginase treatment was calculated by multiplying the difference in EFS reported with the number of patients included in the study, and dividing this by the total number of patients.

In our study, patients who were switched to *Erwinia* asparaginase after a hypersensitivity reaction to PEGasparaginase were considered to have the same prognosis as patients without an allergy as they were still intensively treated with asparaginase.[16] Because the inclusion of the ALL-10 protocol has been completed, the EFS of this protocol was used for these patients.[5]

All hypersensitivity reactions occurred during the first or second PEGasparaginase dose in intensification. Therefore, not switching would have resulted in a worse prognosis, similar to ALL treatment without asparaginase treatment during intensification. Hence, for the patients with a hypersensitivity reaction in whom, according to scenario 2, the asparaginase therapy would have been permanently stopped, we have subtracted the weighted mean difference in EFS reported in the literature, from the EFS of ALL-10.[5]

Both the QALYs and the number of LYS were discounted by 1.5% per year to account for the value of time, according to Dutch guidelines.[14] Thus, it is taken into account that LYS in the future are considered as less valuable than LYS today.

### 2.5 | Statistical analysis

Data were analyzed with SPSS Statistics version 21.0 (IBM Corporation, Armonk, New York, USA) and MS Excel 2013 (Microsoft Corporation, Redmond, WA, USA). Multiple imputation was used to impute missing data. *t*-Tests, $\chi^2$-tests or Mann-Whitney *U*-tests were used to calculate the differences between the patients with and without a hypersensitivity reaction, and the two scenarios. The QoL was longitudinally analyzed using generalized estimating equations. A two-sided *p*-value of $<0.05$ was considered statistically different. Data are presented as frequency, median, mean, and standard deviation (SD) when appropriate.

### 2.6 | Decision tree analysis

A decision tree model was developed in order to compare the costs and effects of scenario 1, which included a switch to *Erwinia* asparaginase after a hypersensitivity reaction to PEGasparaginase, to scenario 2, in which the asparaginase therapy was permanently stopped after a hypersensitivity reaction to PEGasparaginase (Figure 1). The mean costs per patient of the intensification phase and the LYS for patients with and without a hypersensitivity reaction were calculated for both scenarios and multiplied by the probability of developing a hypersensitivity reaction. Next, the costs per LYS were calculated by dividing the total costs by the number of LYS.

### 2.7 | Sensitivity analysis

To account for uncertainty in the calculated costs per LYS, a one-way sensitivity analysis was performed. For this, the costs per LYS were calculated by varying the probability of developing a hypersensitivity reaction with the 95% confidence interval, and the mean total costs of the intensification phase with 1 SD for all cost categories. The EFS for patients who would stop asparaginase therapy was varied using the minimal and maximal differences in EFS for intensive and no intensive asparaginase treatment reported.

## 3 | RESULTS

### 3.1 | Patient characteristics

Table 2 describes the patient characteristics. In total, 68 patients were included in the study. Of these patients, 19 (27.9%) have developed a hypersensitivity reaction to PEGasparaginase. Most patients who developed a hypersensitivity reaction were treated according to the ALL-10 protocol. ALL-11 has a lower risk of hypersensitivity reactions because in the induction phase of this protocol, PEGasparaginase was used instead of native *E. coli* asparaginase. All allergies occurred during the first or second PEGasparaginase dose of the intensification phase. The age, gender, and body surface area did not statistically differ between the patients with and without a hypersensitivity reaction.

### 3.2 | Cost analysis

Table 3 describes the mean costs of the intensification phase for the patients with and without a hypersensitivity reaction, for the different scenarios. The mean total costs per patient were $40,925 without a hypersensitivity reaction to PEGasparaginase, $175,632 when patients were switched to *Erwinia* asparaginase, and $21,190 if the asparaginase therapy was permanently stopped after a reaction. The

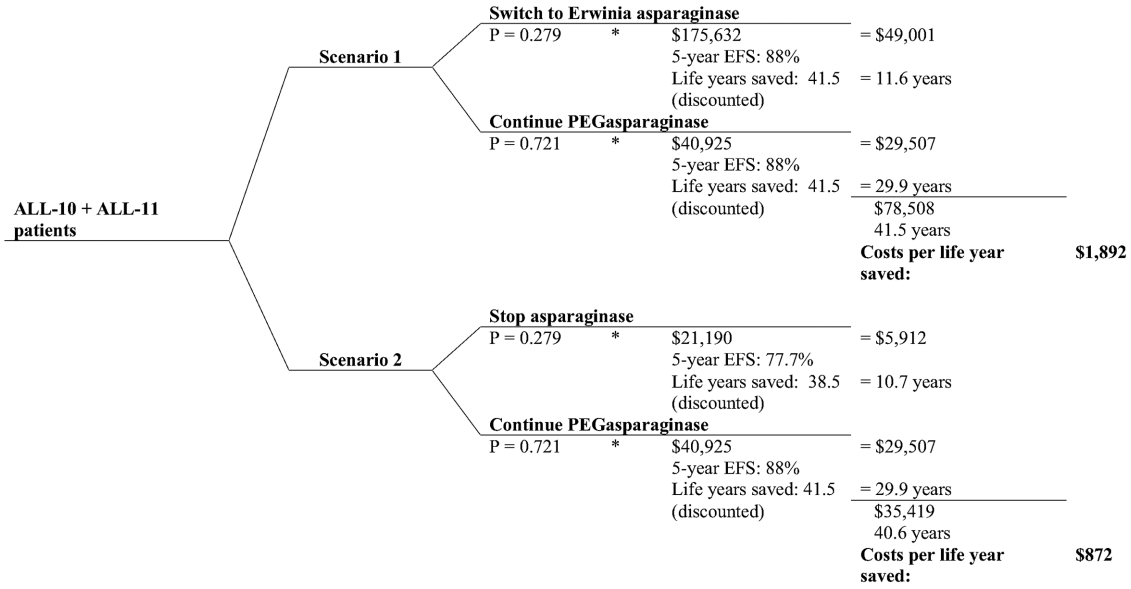


**FIGURE 1** In this figure, the costs and life years saved are calculated for each scenario. The HRQoL did not differ between patients with and without a hypersensitivity reaction and was, therefore, not included in this analysis. Patients were switched to *Erwinia* asparaginase after a hypersensitivity reaction according to scenario 1; asparaginase treatment was permanently stopped after a hypersensitivity reaction according to scenario 2. The Dutch life expectancy in 2015 was 81.9 years, mean age at start intensification was 8.4 years. The life years saved were discounted with 1.5% per year. The mean costs and life year saved were multiplied by the probabilities of each branch and summed up to calculate the totals for each scenario. By dividing the mean total costs by the total number of life years saved, the costs per life year saved were calculated

**TABLE 2** Patient characteristics

| | Total study group<br>*N* = 68 | No hypersensitivity reaction to PEGasp<br>*N* = 49 | Hypersensitivity reaction to PEGasp<br>*N* = 19 | *p*-Value |
|---|---|---|---|---|
| Hypersensitivity reaction (%; 95% CI) | 28% (17–39%) | – | – | – |
| Treatment protocol (%) ALL-10 (95% CI) | 57% (46–69%) | 47% (33–61%) | 84% (67–100%) | 0.006 |
| Sex, % male (95% CI) | 52% (40–64%) | 49% (35–63%) | 58% (35–81%) | 0.594 |
| Age at start intensification (years), median (IQR) | 7.6 (4.8–11.6) | 6.9 (4.3–11.4) | 8.8 (5.4–12.9) | 0.232 |
| BSA start intensification ($m^2$), median (IQR) | 0.92 (0.73–1.35) | 0.87 (0.69–1.30) | 1.03 (0.81–1.44) | 0.194 |

95% CI, 95% confidential interval; BSA, body surface area; IQR, interquartile range; PEGasp, PEGasparaginase; SD, standard deviation.

mean total drug costs for *Erwinia* asparaginase were $126,831, which corresponds with 149 vials of *Erwinia* asparaginase. The costs of the drug asparaginase itself accounted for 44.1%, 74.5%, and 19.2% of the total treatment costs of the intensification phase for the three groups, respectively. The percentage of costs for asparaginase use for the total study cohort was 63.0% of the total intensification phase costs. Because TDM was only implemented in the DCOG ALL-11 protocol, the total TDM costs per patient are relatively low in this cohort.

## 3.3 | Effects analysis

Cross-sectional analyses showed that the QALYs of the patients with and without hypersensitivity did not differ significantly for the questionnaires completed in intensification weeks 1, 3, and 19. The longitudinal analysis showed that the MAU score overall decreased with 0.12 points per time point of the questionnaire ($p < 0.001$), but the occurrence of a hypersensitivity analysis was not a significant covariate. Thus, the development of a hypersensitivity reaction did not result in a significant change in the HRQoL. Therefore, this analysis was not further included in the decision tree analysis.

Analysis of the extra questions about the burden of the allergic reaction and of switching to *Erwinia* asparaginase is described in Tables 4 and 5. The question about the burden of (potentially) switching to *Erwinia* asparaginase was answered by both patients who were switched to *Erwinia* asparaginase and patients without a hypersensitivity reaction (Table 4). There was no statistically significant difference between the scores of both groups at all time points, including week 19, when all patients with a hypersensitivity reaction had been switched. At these time points, patients considered switching to *Erwinia* asparaginase as "no to partially a problem." In patients who did experience an allergic reaction, the reaction was described as severe, resulting in severe illness and major discomfort during the reaction.

The 5-year EFS of the medium-risk group of the DCOG ALL-10 protocol was 88.0% (standard error 2.0%).[5] The EFS of the ALL-11 protocol is not available yet since the protocol is still ongoing. The studies that have reported the effect of asparaginase therapy are

**TABLE 3** Total costs per patient of the intensification phase for the different scenarios

| Costs ($) | 1. No hypersensitivity reaction to PEGasparaginase<br>Mean ± SD (median) | 2. Switch after a hypersensitivity reaction to PEGasparaginase<br>Mean ± SD (median) | 3. Stop asparaginase after a hypersensitivity reaction to PEGasparaginase<br>Mean ± SD (median) | *p*-Value 1 vs 2 | *p*-Value 1 vs 3 |
|---|---|---|---|---|---|
| Outpatient treatment | 4201 ± 723 (4363) | 6567 ± 1912 (6282) | 4373 ± 0 (4372) | <0.001 | - |
| Day care treatment | 8058 ± 1714 (7884) | 27,541 ± 8611 (27,389) | 2686 ± 376 (2905) | <0.001 | <0.001 |
| Inpatient care (aca) | 2942 ± 5033 (0) | 2858 ± 5094 (687) | 2858 ± 5094 (687) | 0.988 | 0.988 |
| Intensive care unit admission (aca) | 992 ± 5908 (0) | 0 | 0 | 0.274 | 0.274 |
| Outpatient treatment (sat) | 20 ± 40 (0) | 14 ± 41 (0) | 14 ± 41 (0) | 0.507 | 0.507 |
| Inpatient care (sat) | 97 ± 307 (0) | 75 ± 180 (0) | 75 ± 181 (0) | 0.923 | 0.923 |
| PEGasparaginase | 18,032 ± 2382 (19,360) | 4076 ± 4527 (2766) | 4076 ± 4527 (2766) | <0.001 | <0.001 |
| *Erwinia* asparaginase | 0 ± 0 (0) | 126,831 ± 51,067 (117,054) | 0 | <0.001 | - |
| TDM | 865 ± 845 (1466) | 600 ± 1469 (0) | 50 ± 123 (0) | 0.041 | 0.001 |
| Blood products | 363 ± 547 (215) | 283 ± 517 (0) | 283 ± 517 (0) | 0.288 | 0.288 |
| Laboratory activities | 1299 ± 1028 (1011) | 2077 ± 1361 (1512) | 2077 ± 1361 (1512) | 0.004 | 0.004 |
| Surgical procedure costs | 567 ± 41 (572) | 557 ± 66 (572) | 557 ± 66 (572) | 0.118 | 0.118 |
| Chemotherapy other than asparaginase | 2077 ± 910 (1944) | 2203 ± 714 (2308) | 2203 ± 714 (2308) | 0.448 | 0.448 |
| Supportive care medication | 1411 ± 1581 (990) | 1948 ± 2325 (1922) | 1948 ± 2325 (1922) | 0.197 | 0.197 |
| **Total costs** | **40,925 ± 10,334 (39,671)** | **175,632 ± 58,765 (174,446)** | **21,190 ± 7221 (19,687)** | **<0.001** | **<0.001** |

aca, academic hospital; sat, satellite hospital; SD, standard deviation; TDM, therapeutic drug monitoring.

**TABLE 4** The burden of switching to *Erwinia* asparaginase

| | Week 1[a]<br>Mean ± SD, median (IQR) | Week 3[a]<br>Mean ± SD, median (IQR) | Week 4[a]<br>Mean ± SD, median (IQR) | Week 19[a]<br>Mean ± SD, median (IQR) |
|---|---|---|---|---|
| Allergy | 1.43 ± 0.65, 1.00 (1.00–2.00) | 1.35 ± 0.61, 1.00 (1.00–2.00) | 1.36 ± 0.63, 1.00 (1.00–2.00) | 2.00 ± 1.18, 2.00 (1.00–3.00) |
| No allergy | 2.11 ± 1.24, 2.00 (1.00–3.50) | 2.05 ± 1.24, 1.00 (1.00–3.00) | - | 2.09 ± 1.16, 2.00 (1.00–3.00) |

IQR, interquartile range; SD, standard deviation.

Scoring system: 1. switching to *Erwinia* asparaginase would not be a problem; 2. switching to *Erwinia* asparaginase would partially a problem; 3. switching to *Erwinia* asparaginase would be a growing problem; 4. switching to *Erwinia* asparaginase would be a major problem.

[a]There was no statistically significant difference between the median scores of patients with and without an allergic reaction.

**TABLE 5** Experience of the allergy

| | Week 1<br>Mean ± SD, median (IQR) | Week 3<br>Mean ± SD, median (IQR) | Week 4<br>Mean ± SD, median (IQR) | Week 19<br>Mean ± SD, median (IQR) |
|---|---|---|---|---|
| Severity of the allergic reaction[a] | 1.50 ± 0.67, 1.00 (1.00–2.00) | 2.75 ± 1.76, 2.00 (1.00–5.00) | 4.55 ± 1.21, 5.00 (5.00–5.00) | 4.31 ± 1.49, 5.00 (4.50–5.00) |
| Extent of physical illness during the allergic reaction[a] | 1.08 ± 0.29, 1.00 (1.00–1.00) | 2.33 ± 1.83, 1.00 (1.00–4.75) | 4.36 ± 1.21, 5.00 (4.00–5.00) | 4.38 ± 1.50, 5.00 (5.00–5.00) |
| Extent of discomfort during the allergic reaction[a] | 1.17 ± 0.58, 1.00 (1.00–1.00) | 2.25 ± 1.66, 1.00 (1.00–3.75) | 4.18 ± 1.40, 5.00 (4.00–5.00) | 4.15 ± 1.52, 5.00 (3.50–5.00) |

IQR, interquartile range; SD, standard deviation.

Scoring system:

Severity of the allergic-reaction: 1. not applicable; 2. no allergic reaction; 3. minor allergic reaction; 4. moderate allergic reaction; 5. severe allergic reaction.

Extent of physical illness during the allergic reaction: 1. not applicable; 2. not ill; 3. minimally ill; 4. moderately ill; 5. severely ill.

Extent of discomfort during the allergic reaction: 1. not applicable; 2. no discomfort; 3. minimal discomfort, hampering of activities; 4. moderate discomfort, hampering some activities; 5. major discomfort, hampering most activities.

[a]Patients who had inactivation of PEGasparaginase without clinical symptoms of an allergy (silent inactivation) were excluded from this analysis ($n = 14$).

described in Supplemental Results S1. The weighted mean of the differences in 5-year EFS reported is 10.3% (range 3.3-17.0%).[1–4,6,7] Of note, this percentage is an indication of the actual difference in EFS. Thus, the 5-year EFS was assumed to be 88.0% for patients without a hypersensitivity reaction to PEGasparaginase and patients who were switched to *Erwinia* asparaginase, and assumed to be 77.7% (88.0% minus 10.3%) when asparaginase would have been permanently stopped. The life expectancy of patients without an event, probably will not differ between the groups. Therefore, if patients had no event within 5 years, their life expectancy was assumed to be equal to the normal population for both groups. However, possible late effects of the ALL treatment could not be taken into account. The mean overall Dutch life expectancy in 2015 was 81.9 years[17]; the mean age of this study population at start of intensification was 8.4 years. Therefore, on average, 73.5 years (81.9 minus 8.4 years) would be saved if the EFS would have been 100%. The EFS was 77.7% if asparaginase would have been permanently stopped after a hypersensitivity reaction so, in this case, the mean number of LYS would have been 57.1 years (77.7% of 73.5 years; discounted by 1.5% per year to account for the value of time, 38.5 years). If patients were treated intensively with asparaginase, the EFS was 88.0%, so the mean number of LYS was 64.7 years (88.0% of 73.5 years; discounted, 41.5 years).

### 3.4 | Decision tree analysis

Figure 1 shows the decision tree of the two scenarios including the costs and LYS. Taking into account the probability of developing a hypersensitivity reaction to PEGasparaginase, the total costs of scenario 1 were $78,508 versus $35,419 of scenario 2. The discounted numbers of LYS were 41.5 for scenario 1 and 40.6 for scenario 2. Thus, the costs per LYS were $1892 if patients were switched to *Erwinia* asparaginase after a hypersensitivity reaction and $872 if asparaginase would have been stopped permanently.

### 3.5 | Sensitivity analysis

In Supplemental Figure S1, the costs per LYS are shown, varying the probability of developing a hypersensitivity reaction (95% confidence interval), the total treatment costs (±1 SD for all cost categories), and EFS for patients who would have stopped with their asparaginase treatment (variation in EFS differences, reported in the literature). This one-way sensitivity analysis shows that mainly the treatment costs and probability of a hypersensitivity reaction influence the costs per LYS for each scenario.

## 4 | DISCUSSION

In this cost-effectiveness analysis of *Erwinia* asparaginase, we have studied the costs of ALL intensification therapy, the HRQoL during asparaginase treatment, and the amount of LYS for two scenarios. According to these scenarios, patients were either switched to *Erwinia* asparaginase after a hypersensitivity reaction to PEGasparaginase or asparaginase therapy would have been permanently stopped when the reaction occurred. The HRQoL was studied using validated HUI-questionnaires and did not significantly differ between patients with and without a hypersensitivity reaction, although this could possibly be addressed by the relatively small number of patients. Also the extra questions, added to specifically study the burden of switching to *Erwinia* asparaginase, did not show a significant impact. Therefore, the decision tree analysis only included the costs and LYS.

Switching to *Erwinia* asparaginase would cost $1020 more per LYS than permanently stopping asparaginase treatment after a hypersensitivity reaction to PEGasparaginase. Eichler et al have reviewed cost-effectiveness thresholds reporting different maximal costs per LYS, for example $93,500 as "rule of thumb" in the United States.[18] Although our study has been performed in the Netherlands and the threshold apply to adult patients, with an increase of $1020 per LYS for switching to *Erwinia* asparaginase, the costs per LYS remain far below these costs, and would be acceptable. Still, it has to be taken into account that health care costs vary considerably between countries hampering the generalizability of this study.

However, the actual costs per LYS may vary for different reasons: first, the actual costs per LYS for patients who would stop asparaginase may be higher. Less asparaginase exposure will not only result in a higher mortality, but also in a higher relapse rate. Ideally, these costs would have been considered in the sensitivity analysis, but cost data from relapse patients were not available. Kaul et al report a threefold increase in costs when patients experience a relapse compared to no relapse, although actual costs of pediatric relapse therapy have not been described.[19] Hence, switching to *Erwinia* asparaginase would save more future costs.

Second, our treatment protocol contains relatively many asparaginase doses and, consequently, many *Erwinia* asparaginase doses in case of a hypersensitivity reaction, which increases the total intensification costs tremendously. For treatment protocols with less asparaginase doses, switching to *Erwinia* asparaginase will have less impact on the costs, and the difference in total costs between permanently stopping asparaginase and switching to *Erwinia* asparaginase will be smaller.

Third, the incidence of hypersensitivity reactions influences the costs per LYS for both scenarios: a lower incidence will result in lower costs per LYS in scenario 1, due to less *Erwinia* asparaginase use, but also in higher costs per LYS in scenario 2 as more patients will complete their asparaginase treatment. Most patients in our cohort were treated with native *E. coli* asparaginase in induction (ALL-10), which increases the risk of developing a hypersensitivity reaction. Nowadays, most treatment protocols, including the DCOG ALL-11 protocol, use only the less immunogenic PEGasparaginase, decreasing the number of reactions significantly. Thus, the difference in costs per LYS between the two scenarios will be even smaller.

Finally, to evaluate the number of LYS, we have used the EFS of the ALL-10 protocol for the patients who completed their asparaginase treatment. For the patients in scenario 2, in which asparaginase would have been permanently stopped after a hypersensitivity reaction, the EFS was calculated by subtracting the difference in EFS between intensive and no intensive asparaginase reported in the literature, from the EFS of ALL-10. One might question the accuracy of this difference as it is based on former treatment protocols. Ideally, the impact of less asparaginase exposure in our patients should be studied within the treatment protocol used. However, this would be unethical to study so

the difference in EFS used is the best available evidence. Besides, the sensitivity analysis showed that varying the EFS only has a minor effect on the costs per LYS as the costs barely changed when the difference in EFS between intensive and less intensive asparaginase treatment was varied between 3.3% and 17.0%.

In conclusion, according to this analysis, the costs per LYS will be higher when patients switch to *Erwinia* asparaginase after a hypersensitivity reaction to PEGasparaginase. However, these costs are only 1% of the costs per LYS that are considered acceptable.[18] Therefore, we recommend switching to *Erwinia* asparaginase after a hypersensitivity reaction to PEGasparaginase, apart from a clinical perspective, also from a cost perspective.

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## CONFLICTS OF INTEREST

Authors Robin Q.H. Kloos, Raphaële R.L. van Litsenburg, Sarah Wolf, Leonoor Wismans, Gertjan J.L. Kaspers, and Carin A. Uyl-de Groot declare that they have no conflict of interest. Authors Rob Pieters and I.M. van der Sluis received research support and consultancy fees from Jazz Pharmaceuticals and Medac.

## LINKED CONTENT

This article is linked to a highlight by Russell (https://doi.org/10.1002/pbc.27497).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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