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

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Online Supplementary Design and Methods

Patients and the acute lymphoblastic leukemia treatment protocol

Medium-risk (MR) group patients from two pediatric oncology centers, Erasmus MC - Sophia Children's Hospital (Rotterdam) and the VU University Medical Center (Amsterdam), were included in this study. The ALL-10 protocol was approved by the Institutional Review Board and informed consent was obtained from parents or children's guardians in accordance with the Declaration of Helsinki. All patients received native *E. coli* asparaginase (5,000 IU/m^2 per dose) eight times every 3 days in the induction phase. A patient stratified to the MR group was given PEGasparaginase (2,500 IU/ m^2 per dose) every 2 weeks during the first 30 weeks of the intensification. In the case of an allergy to PEGasparaginase, the patient was switched to *Erwinia* asparaginase (20,000 IU/ m^2 per dose) three times per week for 30 weeks. In the case of high serum levels of *Erwinia* asparaginase, the frequency was reduced to twice a week. All asparaginase preparations were administered intravenously.

Costs of scenario 1

Treatment costs in the first 30 weeks of intensification were based on patient level data and according to intention-to-treat analysis. Direct medical costs were calculated from a hospital perspective. Each component of resource use was collected for every patient and linked to a unit price. Data on volumes were adapted from hospital electronic databases and medical files. Some patients were partly treated in satellite hospitals: in these cases volume data were retrieved from chart review.

For the unit prices, we applied the microcosting method1 and Dutch tariffs. All costs were converted to US dollars (€1 = $ 1.40) according to the price level in 2010.

Different cost categories were used: (i) inpatient care including room and board, nursing and physician fees. Inpatient care estimates were for a pediatric ICU day in an academic hospital ($ 2,213), inpatient day in an academic hospital ($ 942) and an inpatient day in a satellite hospital ($ 589); (ii) daycare treatment, this estimate was $ 325 for academic hospitals and $ 290 for satellite hospitals; (iii) chemotherapy other than asparaginase; (iv) PEGasparaginase per used vial, one vial contains 3,750 IU ($ 1,729); (v) *Erwinia* asparaginase per used vial, one vial contains 10,000 IU ($ 560); (vi) native *E. coli* asparaginase per used vial, one vial contains 10,000 IU ($ 85); (vii) additional medication such as antibiotics; (viii) laboratory activities; (ix) other hospital activities (e.g. imaging, placement of Port-a-Cath® device, bone marrow puncture), and (x) blood products.

Costs of scenario 2 and 3

In the two hypothetical scenarios, it was assumed that all other treatment besides asparaginase was according to the ALL-10 MRG protocol. Only the costs of asparaginase, number of daycare visits and anti-emetic drugs administered together with asparaginase were changed. For all parameters, each item was multiplied by the number needed by the patient to calculate the costs. The number of daycare visits was adjusted for the type of asparaginase, according to the dose schedule in the protocol. The costs of anti-emetic drugs (always combined with asparaginase) were calculated according to changes in the dose schedule and the body surface area of the patients.

Decision tree analysis

We developed a decision tree model with TreeAge for Health Care (TreeAge Pro 2009, TreeAge Software, Williamstown, MA, USA) 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 2).

For scenario 1, the allergy rate to PEGasparaginase of the interim results of the ALL-10 MRG protocol was 25%, and this served as the base case value. In scenario 2, the historical allergy rate to native *E. coli* asparaginase in the intensification phase of the ALL-9 protocol after exposure to native *E. coli* asparaginase in induction was 65%.[2] This served as the base case value in this scenario. In scenario 3, the base case value for allergy was the same as that in scenario 2: 65%. If patients subsequently also had an allergic reaction to PEGasparaginase, they were switched to *Erwinia* asparagi-

nase. The base case value of PEGasparaginase allergy after native *E. coli* asparaginase allergy in the intensification was estimated at 40%.

In every branch of this tree, either the calculated or the simulated costs and the base case probabilities were included. We used the mean values of costs in this decision tree model.

Sensitivity analysis

To account for uncertainty in the used prices and calculated costs, a sensitivity analysis was performed. With one-way sensitivity analysis, costs and allergy probabilities were changed one by one to assess the impact of each change. The costs of subgroups with or without allergy who did not receive *Erwinia* asparaginase were varied 25% each way.[1] Because the price of *Erwinia* asparaginase was doubled in March 2011 when analyzing all cost data, the costs were varied from minus 25% up to 200%. The allergy probabilities were varied according to the lowest probability found in clinical trials 14%[3] to 100%.

Two-way sensitivity analysis was used to assess the effect of different allergy percentages on treatment costs. These percentages were varied from zero to 100%. For every allergy probability the treatment costs of PEGasparaginase or *Erwinia* asparaginase (scenario 1) were compared to those of native *E. coli* asparaginase (either scenario 2 or 3).

Missing data

Missing information from satellite hospitals was retrieved from medical files of the academic hospitals. To account for missing data, estimations based on duration of treatment in the satellite hospitals and the costs were also imputed for each patient.

References

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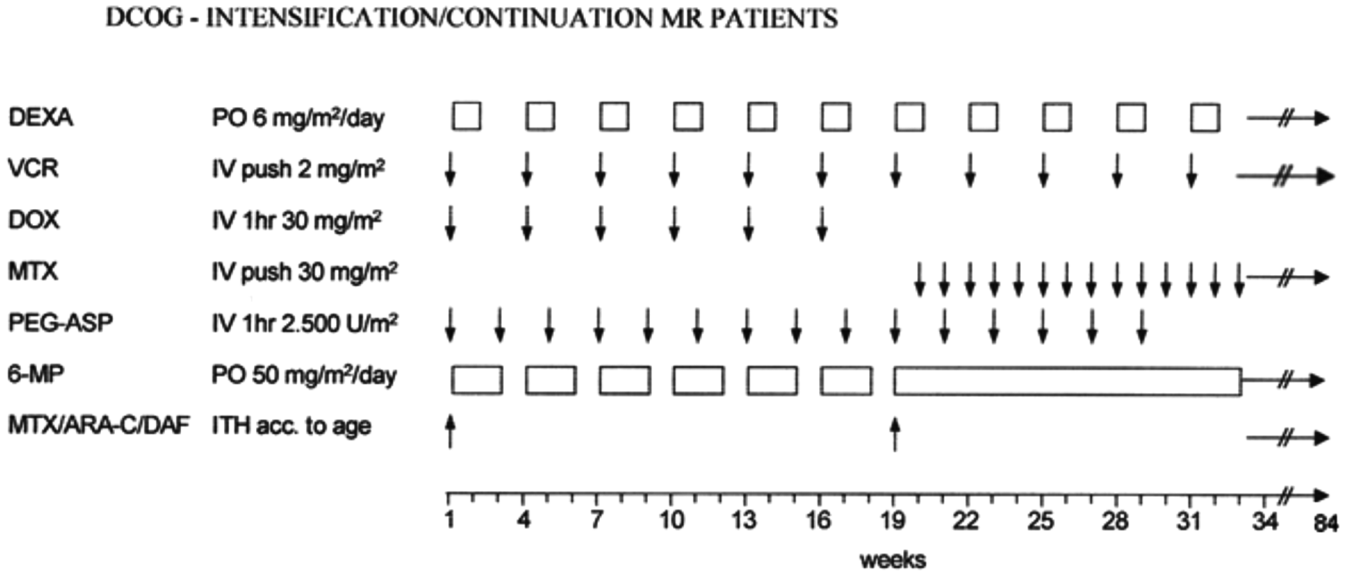

Online Supplementary Figure S1. The intensification/continuation phase of the ALL-10 MR protocol. This material is reproduced with permission of John Wiley & Sons, Inc. Pediatric Blood & Cancer 2012;58(2):317-8. Copyright © 2012 Wiley-Liss, Inc.