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

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The objective was to assess the cost-effectiveness of chemotherapy alone for childhood acute lymphoblastic leukaemia. The authors concluded that chemotherapy alone was well within accepted ranges of cost-effectiveness, and the new protocol had an acceptable incremental cost-effectiveness ratio. There were some limitations to the study design and outcome measures, which mean that the authors' conclusions should be used with caution.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The objective was to assess the cost-effectiveness of chemotherapy alone for childhood acute lymphoblastic leukaemia.

Interventions
The intervention protocol (ALL10) was chemotherapy, including Escherichia Coli peg-asparaginase, and diagnosis, using minimal residual disease monitoring. The comparator protocol (ALL9) was diagnosis, without minimal residual disease monitoring, and chemotherapy, including Escherichia Coli L-asparaginase. These protocols were those used in two Dutch Childhood Oncology Group studies; the intervention protocol was from 2004 to 2011, and the comparator was from 1997 to 2004.

Location/setting
Netherlands/secondary care.

Methods
Analytical approach:
A retrospective analysis of data from 50 children (aged 18 or younger), from one centre, was conducted. There were 26 patients who received the comparator protocol (30% high risk), and 24 who received the intervention (21% standard risk). The authors stated that a hospital perspective was adopted.

Effectiveness data:
The key effectiveness outcome was the comparative five-year event-free survival. These data were from national sources. For the comparator the rate was 72% for high-risk patients and 84% for medium- and standard-risk patients. For the intervention, a four-year analysis was projected to the five-year rate, using data from a personal communication. The projected event-free survival was 96% for standard-risk patients and 85% for medium-risk patients. Patients who had survived for five years, event free, were assumed to have normal (mean Dutch) life expectancy of 80 years. It was assumed that patients who relapsed died.

Monetary benefit and utility valuations:
Not applicable.

Measure of benefit:
The health benefit was measured by the number of life-years saved. Since the risk groups were not distributed equally, compared with the national cohort, the cost per life-year saved with the intervention, was based on the national risk distribution. Future benefits were discounted at an annual rate of 1.5%.
Cost data:
All the direct costs of treatment were included in the analysis. These were medications, diagnostic tests, in-hospital days, out-patient visits, emergency visits, medical consultations, laboratory tests, imaging studies, transfusions, and surgery. The resource use was from electronic databases at the hospital, medical records and chart reviews. For the most important costs, specific unit prices were calculated; for all other items, Dutch tariffs were used. The effects of admission days on the costs were assessed using linear regression. Prices were reported in 2008 US $, using a conversion rate of one Euro equalled $1.35. Future costs were discounted at an annual rate of 4%.

Analysis of uncertainty:
Sensitivity analysis was conducted to assess how robust the results were to changing the imputation technique, the discount rate, and the life expectancy. The results of these analyses were presented in line graphs, a tornado diagram, and a table.

Results
The mean total direct medical costs were $163,350 for the intervention, compared with $115,858 for the comparator (p<0.001). The discounted costs were $161,779 for the intervention, and $114,777 for the comparator. The total incremental costs, with the intervention, over the comparator, were $47,492 or discounted $47,002.

The mean life-years saved were 60.2 for the comparator, and 66.0 for the intervention.

Total discounted cost per life-year saved was $3,224 for the comparator, and $4,363 for the intervention. The incremental cost per additional life-year saved with the intervention, compared with the comparator, was $8,215, and the discounted incremental cost per additional life-year saved was $13,489.

With a life expectancy of 42.5 years, the incremental cost-effectiveness ratio was $16,428 per life-year saved. Discounting life-years saved at 4% per annum, the ratio was $25,618 per life-year saved. The method used to impute missing data had some impact on the out-patient clinic, emergency room, and medical consultation costs.

Authors' conclusions
The authors concluded that chemotherapy alone was well within accepted ranges of cost-effectiveness, and the new protocol had an acceptable incremental cost-effectiveness ratio.

CRD commentary
Interventions:
The intervention and comparator were partly described, with more details available in online supplements. The authors focused on peg-asparaginase, compared with L-asparaginase, but L-asparaginase was used in both protocols. The most appropriate comparator, previous standard care, was included. The authors did not discuss any other relevant treatment and monitoring options.

Effectiveness/benefits:
The effectiveness estimates and benefit outcomes were clearly reported. The specific events for event-free survival were not stated, but they appear to have been relapse or no relapse. The method used to identify the sources for event-free survival data was not reported; it was unclear whether the best available evidence was used. A measure of health-related quality of life could have provided a more comprehensive assessment of the benefits accrued by patients. Future benefits were appropriately discounted, in line with Dutch guidelines. Two simplistic assumptions were made; patients who survived five years without relapse were assumed to have a normal life expectancy, and patients who relapsed were assumed to have died. The authors acknowledged that late effects and recurrences were common for survivors, and those who relapsed could have survived, but in the sensitivity analysis a reduced life expectancy for survivors did not produce an unacceptable cost-effectiveness ratio.

Costs:
The cost results were clearly reported. The cost categories were appropriate for the perspective, but only for the short term. The future costs of recurrences and treatment-related morbidity were excluded. As with the effectiveness data, the costs are likely to have been inaccurate, due to not accounting for future differences. These results did not represent the costs for treatment in general, but those for chemotherapy only, due to the exclusion of high-risk patients in the
intervention group. The costs appear to have been appropriately discounted, according to Dutch guidelines, and adjusted for inflation.

Analysis and results:
The results of the analysis were clearly reported. Both options were reported to be below an accepted threshold for the willingness to pay for one additional life-year saved, but this threshold was not stated. Deterministic sensitivity analysis was appropriately conducted to assess the impact of key structural and parameter uncertainties on the results. Only a few parameters were assessed, and the impact of uncertainty in the event-free survival estimates was not explored. This was important as they were from single sources. A key limitation was the small, observational study design. The patients were not randomised to each protocol increasing the risk of selection bias. No attempt was made to account for potential confounding factors. The before-and-after design means that changes in outcomes may have been due to other changes over time, rather than a treatment effect.

Concluding remarks:
There were some limitations to the study design and outcome measures, which mean that the authors' conclusions should be used with caution.

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