Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia


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 study assessed the cost-effectiveness of adding rituximab to fludarabine plus cyclosporine compared with fludarabine plus cyclosporine alone for the management of previously untreated chronic lymphocytic leukaemia in adult patients. The authors concluded that adding rituximab to fludarabine plus cyclosporine was cost-effective from the perspectives of the third-party payer and society. The study used valid and transparent methods that relied on the validity of a clinical trial. The authors’ conclusions appear robust.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The study assessed the cost-effectiveness of adding rituximab to fludarabine plus cyclosporine compared with fludarabine plus cyclosporine alone for the management of previously untreated chronic lymphocytic leukaemia in adults (median age 61 years) with good physical fitness.

Interventions
Rituximab added to fludarabine plus cyclosporine was compared with fludarabine plus cyclosporine alone. Patients received six cycles (28 days long) of treatment. In the fludarabine plus cyclosporine group, patients were given 25mg/m^2/day of intravenous fludarabine and 250mg/m^2/day of cyclophosphamide on the first three days of each cycle. For the regimen of rituximab added to fludarabine plus cyclosporine, 375mg/m^2 rituximab was given intravenously in addition to fludarabine plus cyclosporine before the fludarabine plus cyclosporine infusion on day one of the first cycle; for cycles two to six, 500mg/m^2 of were rituximab were given on day one.

Location/setting
USA/outpatient.

Methods
Analytical approach:
The analysis was based on a Markov model with a 30-year time horizon. The authors stated that the perspective of the third-party payer was adopted, with a societal perspective used in a secondary analysis.

Effectiveness data:
Most clinical inputs for the model were taken directly from a published open-label phase III randomised clinical trial (Hallek, et al. 2010, see ‘Other Publications of Related Interest’ below for bibliographic details). The trial enrolled 817 treatment-naive patients over a five-year follow-up. The main outcome of the trial was progression-free survival after three years of follow-up. Approximately 26% of patients were women. Survival after the trial follow-up was estimated using established methods and with data from a prospective cohort of 403 patients with longest follow-up of over 10 years at a single institution. After 10 years it was assumed that the hazard rates for the two options were equal. Mortality rates were taken from general US population statistics.

Monetary benefit and utility valuations:
Utility valuations for health states of chronic lymphocytic leukaemia treatment were derived from a published cross-sectional study. In a secondary analysis from a societal perspective, the utility values of spouses/partners of patients...
were taken into account using estimates from patients with prostate cancer as a proxy.

Measure of benefit:
Quality-adjusted life-years (QALYs) and life-years were used as the summary benefit measures. A 3% annual discount rate was applied.

Cost data:
The primary analysis included direct medical costs associated with drugs (acquisition and administration), treatment of adverse events, and two lines of salvage therapy. Resource quantities came from the clinical trial (Hallek, 2010). Unit costs for medical items were based on Medicare reimbursement rates and diagnosis-related groups. The estimates for indirect costs were taken from publications on other cancers and official hourly wage rates. Costs were in US $ and were discounted at an annual rate of 3%.

Analysis of uncertainty:
One-way and two-way sensitivity analyses were carried out on the most influential model inputs. A probabilistic sensitivity analysis was conducted to vary all inputs simultaneously using conventional probability distributions for groups of inputs.

Results
In the primary analysis (third-party payer perspective) with fludarabine plus cyclosporine alone, the expected cost was $83,240, the expected life-years (overall survival) were 9.13 and the QALYs gained were 6.60. For rituximab added to fludarabine plus cyclosporine, the expected cost was $110,267, the expected life-years were 10.60 and the QALYs gained were 7.75. The incremental cost per life year gained was $12,558 with rituximab added to fludarabine plus cyclosporine over fludarabine plus cyclosporine alone; the incremental cost per QALY gained was $23,530.

In the secondary analysis (societal perspective and utility decrements for spouses/partners) with fludarabine plus cyclosporine alone, the expected cost was $172,565 and the QALYs gained were 4.51. For rituximab added to fludarabine plus cyclosporine, the expected cost was $205,147 and the QALYs gained were 5.54. The incremental cost per life year gained was $15,140 with rituximab added to fludarabine plus cyclosporine over fludarabine plus cyclosporine alone; the incremental cost per QALY gained was $31,513.

The most influential inputs were the time horizon, discount rate, and drug price of rituximab. A time horizon of 10 years and 25% increase in the price of rituximab led to a three-fold increase in the cost per QALY, while a time horizon of 40 years and a 25% decrease in the price of rituximab resulted in approximately 25% lower incremental cost per QALY. The probability of rituximab being cost-effective at a threshold of $50,000 per QALY was around 94%.

Authors’ conclusions
The authors concluded that adding rituximab to fludarabine plus cyclosporine in previously untreated chronic lymphocytic leukaemia patients was a cost-effective strategy from the perspectives of the third-party payer and society.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear as the proposed treatment was compared with a commonly used first-line regimen for this specific patient population. These treatments were likely to be relevant in other settings.

Effectiveness/benefits:
The authors stated that the clinical analysis was based on the results of the largest randomised trial available for rituximab treatment in this patient population. This represented a head-to-head comparison over a relatively long follow-up. Key details of the trial were reported, but detailed information on the methods and results of the trial were not reported. However, the large sample of patients included in the trial and the use of a randomisation procedure should have ensured the validity of the clinical inputs. Survival estimates after the trial follow-up were based on a prospective cohort study involving a large sample of US patients with characteristics similar to those of the clinical trials. Both benefit measures were appropriate for capturing the impact of the disease on patients’ health and would allow comparisons to be made with the benefits of other health care interventions. In particular, although the specific instrument used to elicit preferences for health conditions was not described, details of the derivation of the utility
valuations were reported. In a secondary analysis, preferences of spouses/partners were taken into account.

**Costs:**
A third-party payer and a societal perspective were adopted; and the cost categories considered were appropriate for these perspectives. The use of two different viewpoints represented a strength of the analysis. Resource quantities were mainly taken from a clinical trial that should have ensured a detailed collection of estimates, although it may not have been completely representative of real clinical practice. Unit costs were obtained from standard US sources. Drug wastage was appropriately considered for rituximab. Costs were treated stochastically in the probabilistic sensitivity analysis. The drug price represented more than 90% of the total costs for rituximab. The price year was not explicitly reported. Costs were discounted at a standard US rate.

**Analysis and results:**
Uncertainty in the model was satisfactorily investigated using deterministic and stochastic techniques; the results of the sensitivity analyses were presented in detail in the appendix. The results were clearly reported. Incremental cost-utility ratios were used to synthesise the costs and benefits of the two strategies using the commonly used threshold of $50,000 per QALY. The authors compared their results with those from other published studies that had generally shown the cost-effectiveness of adding rituximab to fludarabine plus cyclosporine in this group of patients. Transferability of the study results was not explicitly addressed, but it was likely that these findings could be valid for other settings with similar relative prices.

**Concluding remarks:**
The study used valid and transparent methods that relied on the validity of a clinical trial. The authors’ conclusions appear robust.

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