Cost-effectiveness of interferon alfa-2b added to chemotherapy for high-tumor-burden follicular non-Hodgkin's lymphoma

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.

Health technology
The use of interferon alpha-2b (IFN) added to chemotherapy (cyclophosphamide, doxorubicin, teniposide and prednisone; CHVP) for the treatment of high-tumour-burden follicular non-Hodgkin's lymphoma (NHL).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study referred to the hypothetical population of patients suffering from NHL and undergoing CHVP. The typical patient was a 52-year old individual.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence was derived from studies published between 1986 and 1998. No dates for resource use were reported. The price year was not given.

Source of effectiveness data
The effectiveness evidence was derived from published studies and from experts' assumptions.

Modelling
A simple Markov model with embedded Boolean switches was constructed to represent the natural history of NHL, and also to estimate both the costs and benefits of the two study treatments. The model comprised three health states and three periods. The three health states were no progression, progressive disease and death. The three periods were the first 6 months with CHVP, with or without IFN; the next 12 months with reduced CHVP and continued IFN only in those patients who started on that arm; and a tail-off period from therapy unless disease progressed. The cycling process was presented graphically in the article. The simple model was modified to create a two-stage model in which the probability of progressive disease changed before and after the therapy. The two models also differed in the type of survival data used. Both models were found to have slightly underestimated the overall survival in the CHVP plus IFN arm when compared with actual published data entered in the tree, but this was considered to be a conservative approach.
Outcomes assessed in the review
The outcomes estimated from the published studies and used as model inputs in the decision model were:

the probability values of progressive disease with both treatments, IFN toxicity necessitating discontinuation, and excess death rate after treatment failure (disease progression rate); and

the quality of life adjustment values with IFN, progressive disease, with CHVP only, and no progression.

Study designs and other criteria for inclusion in the review
A formal review of the literature was not undertaken and inclusion/exclusion criteria were not relevant. Two of the primary studies used reported the results of the GELF trial (Groupe d'Etude des Lymphomes Folliculaires). This study formed the principal source of the effectiveness data used in the model.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
The effectiveness evidence was obtained from nine primary studies.

Methods of combining primary studies
The primary studies appear to have been combined using narrative methods.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability of progressive disease was 0.0351 per patient-month with CHVP and 0.0246 per patient-month with IFN plus CHVP. The probability of IFN toxicity necessitating discontinuation was 0.0057 per patient-month, and the probability of excess death rate after treatment failure was 0.0397 per patient-month.

The quality of life adjustment value with IFN was -7% per patient-month.

The quality of life values were 70% of those without progression for progressive disease, 100% with CHVP alone and 100% for no progression.

Methods used to derive estimates of effectiveness
Some of the effectiveness estimates used in the decision model were obtained from a panel of four experts in advanced follicular NHL.
**Estimates of effectiveness and key assumptions**

Most of the experts’ assumptions were based on data derived from the literature. The authors assumed that the patients responded variably to the therapy and those with stable disease had similar utilities (conservative assumption). Also, that patients taken off IFN because of toxicity had the same quality of life as those in the CHVP alone arm, and that patients in the CHVP alone arm and those off therapy had a utility of 100. The authors also assumed that the prognosis and quality of life of patients whose disease had progressed did not differ depending on which treatment was received, and that there was no excess risk of death in states before progressive disease.

**Measure of benefits used in the economic analysis**

Quality-adjusted life-months (QALMs) were used as the benefit measure in the economic analysis. These were calculated from data derived from published studies and experts’ assumptions, then modelled into the Markov model. A 3% discount rate was used.

**Direct costs**

A 3% discount rate was used since the costs were incurred over more than 2 years. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic evaluation were IFN, additional follow-up and baseline chemotherapy (CHVP). The cost/resource boundary adopted in the analysis was not stated. The costs and resource consumption were estimated on the basis of the experts’ assumptions, then verified at two academic medical centres. The total costs of the two treatments were obtained by modelling. The price year was not reported.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were not included.

**Currency**

US dollars ($).

**Sensitivity analysis**

One-way sensitivity analyses were conducted to assess the robustness of the estimated cost-utility ratios to variations in most of the model inputs.

**Estimated benefits used in the economic analysis**

The estimated discounted QALMs were 54.98 with CHVP alone and 64.83 with IFN added to CHVP. Thus, IFN added to CHVP led to an extra 9.85 QALMs.

**Cost results**

The total discounted costs were $12,446 with CHVP alone and $26,328 with IFN added to CHVP. Thus, IFN added to CHVP resulted in an incremental cost of $13,882.

**Synthesis of costs and benefits**

An incremental cost-utility ratio was calculated to combine the costs and benefits of the two treatments. The marginal cost per quality-adjusted life-year (QALY) was $16,900 with IFN added to CHVP, compared with CHVP. The sensitivity analyses showed that the model parameters that had the greatest impact on the estimated incremental cost per
QALY were the efficacy and cost of IFN, and the quality of life adjustment for IFN. The incremental cost per QALY remained below the threshold of $50,000 in several cases. These were when the efficacy of IFN in the first 18 months was at least 31%, when the cost of IFN was below $2,580 per month, or when the quality of life adjustment for IFN was above 0.51. The results were fairly insensitive to variations in the remaining model inputs.

Authors' conclusions
Low-dose interferon alpha-2b (IFN) added to chemotherapy (cyclophosphamide, doxorubicin, teniposide and prednisone; CHVP) was cost-effective in the treatment of patients with high-tumour-burden follicular non-Hodgkin's lymphoma (NHL). Although this conclusion was strictly related to the results of a specific trial (the GELF study), conservative assumptions were made and the results were fairly robust to realistic variations in the data used in the decision model.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. CHVP alone was selected as it represented the standard chemotherapy approach for patients with NHL, and the aim of the study was to assess the active value of IFN when added to CHVP. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis mainly used data from published studies. However, a formal review of the literature was not performed and details of the primary studies were not reported. It was unclear whether the authors took differences in the primary studies into consideration when estimating the effectiveness. The primary study estimates were combined using narrative methods. Effectiveness evidence coming from the literature was supported by assumptions made by a group of experts in advanced follicular NHL. Most of the assumptions referred to quality of life adjustments required for the calculation of QALYs. Sensitivity analyses were performed to investigate the impact of variations in the effectiveness estimates on the results of the analysis. The authors made conservative assumptions.

Validity of estimate of measure of benefit
QALYs were used as the benefit measure in the economic analysis. The utility values used to calculate the QALYs were explicitly reported, while the data on survival were derived from published trials. The use of QALYs enhances the comparability of the benefit of the study intervention with those gained with other treatments.

Validity of estimate of costs
The perspective adopted in the study was not reported, thus it was not possible to assess whether all the relevant categories of costs were included in the analysis. The costs and resource consumption were estimated from the experts’ assumptions and then verified in academic medical hospitals. The unit costs were not reported separately from the quantities of resources. In addition, no price year was given, thus making reflation exercises in other settings difficult. The costs were treated deterministically in the base-case, but the impact of variations in key costs was evaluated in the sensitivity analyses.

Other issues
The authors compared their findings extensively with those from published studies concerning IFN therapy and treatments/screening for other diseases. However, the authors acknowledged that comparisons may be difficult due to the differences in assumptions and data. The authors did not address the issue of the generalisability of the study results to other settings. However, some sensitivity analyses were performed, which partly addressed the extent to which the results have applicability to other settings. The study referred to patients with high-tumour-burden follicular NHL and this was reflected in the conclusions of the analysis.

Implications of the study
The study confirms the results of other studies, that the use of IFN added to CHVP for the treatment of patients with NHL increased (quality-adjusted) survival at a cost far lower than the widely used threshold of $50,000.

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