Cost-effectiveness of adjuvant interferon therapy after surgical resection of hepatitis C-related hepatocellular carcinoma

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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.

Health technology
The use of adjuvant interferon (IFN) therapy after surgical resection of primary hepatocellular carcinoma (HCC) caused by hepatitis C virus (HCV) infection. The IFN therapy considered was 6 million units, twice weekly for 36 months.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of identical patients with HCV-related compensated cirrhosis (positive anti-HCV or HCV-RNA) who had undergone resected HCC and who had no co-morbidities that would limit their life expectancy. The reference patient was a 60-year-old man. The analysis focused on patients with resectable carcinomas. These were defined as a solitary tumour (5 cm in diameter) or multiple tumours (up to 3, each being 3 cm in diameter), and no tumour invasion of the blood vessels. HCV eradication was defined as sustained negativity of HCV-RNA after treatment. Patients who achieved sustained HCV eradication were designated as responders, while the remaining patients were classified as nonresponders.

Setting
The setting was tertiary care. The economic study was carried out in Tokyo, Japan.

Dates to which data relate
The effectiveness and resource data were obtained from studies published between 1983 and 2001. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a non-systematic review of completed studies.

Modelling
A Markov-based decision analytic model was used to estimate the costs and benefits. This model described the natural progression of liver disease after surgical resection of HCV-related HCC until death in a cohort of patients. The five disease states in the model were compensated cirrhosis with resected HCC, decompensated cirrhosis with resected HCC, recurrent HCC, orthotopic liver transplantation, and death. The transition cycles were yearly and continued until death. The four cohorts simulated using the Markov model were responders and nonresponders to IFN therapy, patients...
who dropped out from IFN therapy, and patients without IFN therapy after hepatectomy.

**Outcomes assessed in the review**
The outcomes assessed in the review were:

the annual transition probabilities,

the response rate to IFN therapy,

the annual incidence of recurrent HCC after adjuvant IFN therapy, and

the dropout rate owing to IFN-related adverse events.

The rates at which patients moved between the model health states were also obtained from the review. These were used to calculate annual transition probabilities.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
Thirty-four primary studies were included in the review.

**Methods of combining primary studies**
The annual transition probabilities were calculated using the declining exponential approximation of life expectancy (DEALE) method. The weighted averages were then assigned to the model. The other outcomes assessed were combined using weighted averages.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The transition probabilities between different state of health were as follows.

From compensated cirrhosis: to decompensation, 4% (range: 2 - 8); to recurrent HCC, 34% (range: 16 - 63); to death, 5% (range: 3 - 8).

From decompensated cirrhosis: to recurrent HCC, 34% (range: 16 - 63); to liver transplantation, 3% (range: 1 - 6); to death, 10% (range: 7 - 19).
From recurrent HCC to death, 28% (range: 20 - 86).

From liver transplantation; to death in the first year, 21% (range: 6 - 42); to death in the successive year, 6% (range: 2 - 11).

The response rate to IFN therapy was 9.9%.

The annual incidence of recurrent HCC after adjuvant IFN therapy was 8.9%.

The dropout rate owing to IFN-related adverse events was 19.3%.

**Methods used to derive estimates of effectiveness**

A Monte Carlo simulation technique was used to calculate estimates of cumulative survival rates and the proportions of patients, according to each treatment strategy, who experienced recurrence of HCC until they died. The point estimate and 95% confidence intervals (CIs) of the 3- and 5-year survival rates were calculated using the Kaplan-Meier method and Greenwood's formula.

**Estimates of effectiveness and key assumptions**

Recurrence of HCC after partial hepatectomy was observed until death in 87.6% of the patients who underwent no IFN therapy, and in 62.9% of those who underwent adjuvant IFN therapy.

From the model, the 3-year survival rate was 67% (95% CI: 63 - 70) and the 5-year survival rate was 43% (95% CI: 40 - 46).

The key assumptions used in the model were:

- patients receive no IFN therapy before the appearance of HCC;
- the annual incidence of recurrent HCC in patients who dropped out from IFN therapy was estimated to be the same as that in patients without IFN therapy;
- there is no progression from compensated to decompensated cirrhosis during IFN therapy or subsequent follow-up in the responder;
- liver transplantation is only performed for patients with decompensated cirrhosis after a resection of HCC, because liver transplantation for recurrent HCC is not normally performed;
- the re-administration of IFN for nonresponders was not considered;
- there is no spontaneous clearance of HCV; and
- the annual mortality rate in patients after orthotopic liver transplantation assumes both hepatic decompensation and recurrent HCC.

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

The measure of benefit used in the economic analysis was the life-years gained (LYG).

**Direct costs**

The estimated costs of drugs, medical and surgical interventions, and monitoring were summarised according to each health state. The quantities and the costs were not reported separately. The authors used an annual discount rate of 3%. The price year was not reported.
Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were included in the analysis.

Currency
The currency was not reported. However, it is likely that it was US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were performed for all variables. For the response rate to IFN therapy, the analysis was based on the 95% CIs for the estimates of the response rate. The annual incidence of recurrent HCC after adjuvant IFN therapy was evaluated over a range of 0 to 63%. The annual discount rate was varied over a range from 0 to 7%, while the costs were halved and doubled to yield a range for the sensitivity analyses. In addition, the authors performed a threshold analysis of all influential variables identified by the one-way sensitivity analyses, to determine the threshold value that was not cost-effective.

Estimated benefits used in the economic analysis
The discounted benefits were 6.1 LYG for adjuvant IFN therapy and 4.1 LYG for no IFN therapy. The undiscounted benefits were 7.4 LYG for adjuvant IFN therapy and 4.6 LYG for no IFN therapy.

When the annual incidence of recurrent HCC after adjuvant IFN therapy was assumed to be 5%, adjuvant IFN therapy yielded 7.0 LYG. When this rate was assumed to be 16%, IFN therapy yielded 5.1 LYG. Finally, if this rate was set at 35%, IFN therapy resulted in 4.1 LYG.

Cost results
The discounted cost was $77,000 for adjuvant IFN therapy and $46,000 for no IFN therapy. When the costs were not discounted, adjuvant IFN therapy cost $92,000 and no IFN therapy cost $52,000.

Synthesis of costs and benefits
The estimated benefits and costs were combined as the cost per life-year and the incremental cost-effectiveness ratio (ICER). At the discount rate of 3%, adjuvant IFN therapy had an ICER of $15,700/year in comparison with no IFN therapy. When the costs and the effectiveness were not discounted, adjuvant IFN therapy had an ICER of $14,100/year in comparison with no IFN therapy. A threshold analysis showed that adjuvant IFN therapy was not cost-effective (ICER $27,000/year) if the annual incidence of recurrent HCC after IFN was 16% or above.

Authors' conclusions
The authors suggested that adjuvant interferon (IFN) therapy after curative resection of primary hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) improved the patients' life expectancy through the suppression of recurrent cancer, with acceptable medical care costs. Nearly 25% of the patients became free of recurrent HCC after adjuvant IFN therapy. However, the sensitivity analysis showed that, when the annual incidence of recurrent HCC after adjuvant IFN therapy was 16% or greater, no IFN therapy was the optimal choice.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was justified since it represented a valid treatment strategy in the authors' setting. You should decide whether it represents a valid comparator in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness used a non-systematic review of primary studies, and thus it is not possible to rule out bias. The authors clearly reported the methods used to combine the effectiveness estimates from the primary sources. In addition, weighted averages were then applied to the model. This allows the estimate used to reflect the differences in primary study samples. However, it was unclear whether the authors took into account the differences in the primary studies. In addition, a number of assumptions were used to augment the effectiveness data used. The authors conducted various sensitivity analyses and threshold analyses to show the robustness of the results obtained.

Validity of estimate of measure of benefit
The estimation of benefit (LYG) was modelled. The model used to derive the measure of health benefit was clearly described. The use of LYG as a benefit measure enables comparisons to be made with health technologies in other fields.

Validity of estimate of costs
The cost analysis was conducted from the perspective of a health care system, and it would appear that all the relevant costs were included. The source of the cost data was reported, however resource consumption data and unit costs were not. In addition, no price year was reported. These factors limit the reproducibility of the results obtained. The costs were treated deterministically. However, sensitivity analysis was conducted to ensure the robustness of the base-case. The average annual care costs for each health state were reported, but this does little to aid the reproducibility of the study.

Other issues
The authors commented on some of the limitations, problems and uncertainties in the model. In addition, they compared the main study results with results from other studies, thus aiding the external validity of the study. The results were presented in full and the conclusions drawn were within the scope of the analyses. The issue of generalisability was not directly addressed. However, the authors acknowledged that the study results were only valid for a hypothetical cohort that underwent only partial hepatectomy.

Implications of the study
The authors suggested that adjuvant IFN therapy after curative resection of primary HCV-related HCC improved the patients' life expectancy through the suppression of recurrent cancer, with acceptable medical care costs. However, the data should be re-evaluated with results of future trials.

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Bibliographic details

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Other publications of related interest


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