Cost-effectiveness analysis of interferon as adjuvant therapy in high-risk melanoma patients in Spain

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 high-dose interferon (IFN) alpha-2b as adjuvant therapy for high-risk melanoma patients. The dosage rate was 20 MU/m2 per day, 5 days per week for one month followed by 10 MU/m2 subcutaneously, 3 times per week up to one complete year of therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis. The study was conducted from the perspective of the Spanish National Health System.

Study population
The study population comprised hypothetical cohorts of 50-year old patients with 1.7 m² of body surface area, who had been diagnosed as having primary cutaneous melanoma. All patients were categorised as being at high risk of recurrences and had undergone surgery of the primary tumour and elective lymphadenectomy.

Setting
The study was set in secondary care facilities within the Spanish National Health System. The economic analysis was conducted in Madrid, Spain.

Dates to which data relate
The effectiveness data and some resource data were taken from the E1684 trial published in 1996. Additional resource data were derived from the findings of an expert panel, although no dates were given relating to the work of the expert panel. The unit costs of all drugs were taken from the 1998 catalogue of medicinal products. The costs of the procedures and tests were taken from data collected from the institutions of members of the expert panel and from the Basque Country Official Bulletin. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single study and were augmented by additional data provided by an expert panel.

Link between effectiveness and cost data
The costs of the drugs administered and the unit costs for procedures and tests were collected retrospectively from different sources to the E1684 trial. However, the costs considered in this study included those in the E1684 study that were related to normal clinical practice, but excluded those costs of the E1684 study that were associated with the clinical trial.
Study sample
Power calculations were not used to determine sample size as the study involved a hypothetical cohort of 1,000 patients. The sample was defined by the clinical and pathological extent of disease, which was categorised as either stage IIB or III following surgery of the primary tumour and elective lymphadenectomy. This patient sample was consistent with the study population for whom IFN alpha-2b was recognised as an accepted therapy by American and European regulatory bodies. The effectiveness data used in the model were derived using the clinical outcomes of 252 patients (123 observation and 129 IFN alpha-2b) from the E1684 trial. The original patient sample in the clinical trials was 287 patients.

Study design
In terms of time, this was a randomised, clinical trial carried out in a single centre. The median follow-up of the original trial was 6.9 years. The loss to follow-up in the original clinical trial was 12%.

Analysis of effectiveness
The analysis of effectiveness was conducted on an intention to treat basis. The primary health outcome reported in the clinical study was the life-years gained. The comparability of the groups at baseline was not reported in the present study.

Effectiveness results
The original study reported that IFN alpha-2b significantly prolonged the time to post-operative recurrence of the disease when compared with the control group. The time to post-operative recurrence was 1.72 years for the IFN alpha-2b group versus 0.98 years for the control group, (p=0.0023). There were also significant improvements in the overall survival, 3.82 years (IFN alpha-2b) versus 2.78 years (control), (p=0.0237).

Clinical conclusions
Treatment with INF alpha-2b significantly increased the life expectancy of patients with high-risk melanoma in comparison with observation alone.

Modelling
A Markov model was used to estimate the long-term survival of patients in the intervention and control groups after 5 years. Prior to this, survival data following the commencement of treatment were taken directly from the E1684 trial. Longer-term annual state transition probabilities after the 5-year period were determined using information available in the literature, augmented by expert opinion. Patients could remain in their current health state during any one cycle, move to a more advanced stage of the disease, or die, until all hypothetical patients were dead. The time horizon selected for the current study was 35 years.

Methods used to derive estimates of effectiveness
An expert panel was convened. This consisted of 6 medical oncologists and 4 dermatologists treating melanoma across a number of teaching hospitals in Spain. Structured questionnaires and discussion were used to reach consensus on a number of parameters that were to be incorporated into the Markov model. Two health economists also attended the panel meetings.

Estimates of effectiveness and key assumptions
It was assumed that the average time from recurrence to death was constant regardless of the patients’ overall survival, but was dependent on whether the patients were in the intervention or control group.

It was assumed that no negative or false positive screenings were included in the disease-free survival group.
It was assumed that only distant metastases would reoccur. Also, that 80% of the patients would undergo chemotherapy, 10% surgery, 13% radiation therapy and 20% palliative care.

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

The measure of benefit used was the life-years gained.

**Direct costs**

A discount rate of 6% was applied. This was justified on the basis that it was an accepted discount rate for studies in Spain. Alternative discount rates of 0 and 3% were considered in the sensitivity analysis. The use of discounting was appropriate given that the duration of the study was 35 years. The quantities and the costs were reported separately. The costs to the Spanish health service were reported in the study. The direct costs in the analysis included hospital visit (visit 1), hospital visit (rest), hospital stay (per day), day hospital, IFN administration (nurse), routine haematology, routine blood chemistry, chest X-ray (posterior/anterior and lateral), abdominal computed tomography (CT) scan, abdominal ultrasound, chest CT scan, brain CT scan, bone scan, surgery (cutaneous or subcutaneous metastases), surgery (endocranial, hepatic, alimentary tract, lung metastases), whole brain radiation therapy, and bone radiation therapy.

The resource data for the first 5 years of the model were taken from the E1684 study, although those costs deemed to be specifically associated with a trial rather than natural practice were excluded. For subsequent years, projections were made using a Markov model. An expert panel also made a number of assumptions on the resource use. First, there were no differences between the intervention and comparator groups in the costs of routine medical monitoring. Second, there were no differences in the costs of care for recurrence for patients in both groups. Third, administration of intravenous induction therapy would require 7 days' hospitalisation, with subsequent induction therapy provided at day hospital. It was also assumed that maintenance therapy would be provided on an outpatient basis, and that the costs of terminal illness and death were equivalent to a 3-week hospital stay.

The data on the prices and the unit costs or charges were taken from published sources. The unit costs for the procedures and tests were collected at 1998 values from six university hospitals in Spain and from the Basque Country Official Bulletin. The prices of the administered drugs were taken from the Catalogue of Medicinal Products 1998. The incremental costs were reported in the analysis. The price year was 1998.

**Indirect Costs**

The indirect costs were not included in this study.

**Currency**

Spanish pesetas (pta). These were converted to Euros at the official rate of 166.386 pta = 1 Euro.

**Sensitivity analysis**

A one-way sensitivity analysis was carried out using, in the base-case, a 6% discounted cost/life-years gained. Several areas of uncertainty were investigated. The key variables included the generalisability of the results (maximum total dose, different options for administration), variability in the data (cost of recurrence care), extrapolation from the primary data source (modifying the estimated 5-year disease-free survival), the estimation that terminal disease involves no cost, and different discount rates (0, 3 and 6%).

**Estimated benefits used in the economic analysis**

The treatment provided 1.9 life-years gained (undiscounted) over a 35-year period. This was extrapolated beyond the length of the original study that had a median follow-up of 6.9 years. The initial toxicity of the treatment was considered in the analysis.
Cost results
The cost for the intervention (IFN treatment) were Euro 23,280 (discounted at 6%). The costs for the comparator (observation) were Euro 5,997 (discounted at 6%).

The incremental costs were Euro 17,666 undiscounted and Euro 17,283 discounted.

The costs of the intervention and comparator were calculated for a 35-year period. The costs associated with recurrences were considered in the model.

Synthesis of costs and benefits
The incremental cost-effectiveness ratio was Euro 9,215 per life-year gained (undiscounted) and Euro 9,015 per life-year gained (discounted at 6%). The results were robust in the sensitivity analysis with two exceptions. First, only if the discount rate was increased to 6% for both the costs and the life-years gained would the incremental cost per life-year gained approach Euro 20,000 (Euro 19,166). Second, if the disease-free rate for patients in the survival group were increased to 34 from 36%, the incremental cost per life-year gained would be Euro 21,029.

Authors' conclusions
Interferon (IFN) alpha-2b (20MU/m2 per day, 5 days per week for one month, followed by 10 MU/m2, 3 times per week for up to one complete year of therapy) for patients with high-risk melanoma following surgical resection was cost-effective within the "limits established in health economics", compared with an untreated observation group.

CRD COMMENTARY - Selection of comparators
Observation alone was the comparator used in this study. The authors justified their choice on the grounds that this was used in the original E1684 study. However, a number of alternative adjuvant therapies are also available. These include chemotherapy, radiation therapy and immunotherapy, although, as noted by the authors, the response rates to these therapies are low. You should consider whether the comparator chosen is appropriate to your own setting.

Validity of estimate of measure of effectiveness
The study design was appropriate for the question to be examined. Also, it should have a high degree of validity given the randomisation process used in the initial clinical trial of INF alpha-2b. A projection was made for subsequent years beyond the first 5 years included in the original study. The extrapolated long-term survival rates were derived using a mixture of data obtained from expert opinion and published literature. Thus, estimates of the long-term effectiveness may be subject to some degree of uncertainty. The authors did, however, perform a sensitivity analysis to account for some of these issues. The study sample was representative of the study population as a cohort of hypothetical target population patients (based on the average patient in the clinical trial) was used.

Validity of estimate of measure of benefit
The estimation of the benefits was obtained directly from the effectiveness analysis. The choice of estimate was justified.

Validity of estimate of costs
The authors reported that the costs were estimated from the perspective of the Spanish National Health Service. All the relevant direct costs seem to have been included in the analysis. The costs and the quantities were reported separately. The cost data provided were very comprehensive whereas the indirect costs were not included in the analysis. In the case of terminal illness, the wider costs to society due to lost productivity and care-giving responsibilities may be particularly important, and could have been included in analysis. The data on the resource use quantities were taken from published sources and from expert opinion. A sensitivity analysis was conducted on some quantities that were seen as key variables affecting the analysis. The ranges used appear to have been appropriate. The prices (unit costs) were taken from published sources and were collected by an expert panel at six institutions. No sensitivity analysis of the
prices was conducted. Appropriate currency conversions were performed, and discounting was undertaken as the costs were incurred over a 35-year period. The date to which the prices related was reported. These features tend to increase the generalisability of the cost results to other settings.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies. The issue of the generalisability of the results to other settings was also addressed. The authors do not appear to have presented their results selectively. The authors' conclusions are slightly broader than the scope of the analysis. The authors reported several further limitations to their study. First, the design of the study was not intended to evaluate economic parameters. Second, the cost-effectiveness ratios on the four sub-groups of patients were not included, owing to the small sample sizes of the sub-populations in the original clinical trial.

**Implications of the study**
The authors recommend that, following resection for high-risk melanoma (stages IIB, III), high-dose INF alpha-2b should be a standard adjuvant therapy in countries where other adjuvant therapies with similar costs are used to treat other types of cancer.

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None stated.

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**Other publications of related interest**


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