Economic analysis of adjuvant therapy with interferon alpha-2a in stage II malignant melanoma


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 therapy with low-dose interferon alpha-2a (IFNa-2a) after tumour resection for newly diagnosed stage II malignant melanoma (MM). IFNa-2a was given at a dose of 3x10^6 IU, three times per week for 18 months.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness and cost-utility analyses.

Study population
The study population comprised patients with a resected newly diagnosed stage II MM (according to the AJCC).

Setting
The setting was a hospital and community care. The economic study was carried out in France.

Dates to which data relate
The effectiveness data were obtained from studies published between 1996 and 1998. The cost data were obtained from studies published between 1995 and 1996. The price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, the authors’ assumptions and expert opinion.

Modelling
The costs and benefits over the total lifetime of the study cohorts were estimated through a model. The model considered the prospective lifetime of the patients from diagnosis to death using three sub-periods. Period 1 was from diagnosis to year 5, period 2 from year 6 to year 10, and period 3 from year 10 until death. The type of model used to estimate the costs and benefits together was not stated, although the method of Hakulinen et al. (see Other Publications of Related Interest) was reported to have been used to model the lifetime projections.

Outcomes assessed in the review
The outcomes assessed in the review for both strategies (surgery plus IFNa-2a versus surgery alone) were:

the percentage of patients still alive (without relapse or censored);
the percentage of patients with a relapse, dead after relapse, and dead without relapse 5 years after the diagnosis;
the mean overall survival per patient at 5 and 10 years;
the survival lifetime;
the differences in the overall survivals at 5 and 10 years; and
the difference in the survival lifetime between patients in the IFNa-2a group and the group receiving surgery alone.

The percentage of patients in the IFNa-2a group that reported grade III or IV adverse events during the treatment period, the percentage of IFNa-2a patients stopping therapy because of the side effects, and the mean duration (and range) of the adverse events were also assessed.

Study designs and other criteria for inclusion in the review
At least one randomised controlled trial (RCT) and one statistical data study were included in the review.

Sources searched to identify primary studies
Not applicable (since the authors extracted the data mainly from one randomised controlled study).

Criteria used to ensure the validity of primary studies
The authors mainly obtained the effectiveness data from one published RCT (Grob et al., see Other Publications of Related Interest). Where the data were lacking, the authors included several other studies so that they could run the model.

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

Number of primary studies included
At least three studies were included in the review. One was a RCT, while another seems to have been a statistical data study on the French population.

Methods of combining primary studies
The primary studies were combined using a narrative method.

Investigation of differences between primary studies
The authors did not investigate differences between the primary studies, as the main effectiveness data were extracted from one RCT and the rest of the required data were obtained from another study and from the authors’ assumptions and expert opinion.

Results of the review
For the IFNa-2a group:

59% of the patients were still alive (without relapse or censored);
17% of the patients had a relapse;
24% died after relapse;
0% were dead without relapse 5 years after the diagnosis;
the mean overall survival per patient at 5 years was 4.45 years;
the mean overall survival per patient at 10 years was 7.87 years; and
the survival lifetime was 16.87 years.

For the group receiving surgery alone:
50% of the patients were still alive (without relapse or censored);
18% of the patients had a relapse;
30% died after relapse;
1% died without relapse 5 years after the diagnosis;
the mean overall survival per patient at 5 years was 4.19 years;
the mean overall survival per patient at 10 years was 7.20 years; and
the survival lifetime was 14.28 years.

The difference in the mean overall survival was 0.26 years at 5 years, (p=0.046), and 0.67 years at 10 years. The
difference in survival lifetime was 2.59 years, (p=0.035).

In total, 10% of the patients in the treatment group would report grade III or IV adverse events, and 14% would stop
therapy because of the side effects. The mean duration of the adverse events was 1 month (range: 0 - 6).

**Methods used to derive estimates of effectiveness**
The estimates of effectiveness were derived from the authors’ assumptions and expert opinion.

**Estimates of effectiveness and key assumptions**
The authors assumed that patients entering period 3 free of relapse were already cured of MM, and when they died it
was not due to MM. They also assumed that the annual rate for relapse for period 2 (year 6 to 10) was 5% for both
arms. From the experts’ opinions, it was assumed that 75% of those patients with loco-regional metastasis had tumour
resection and lymph-node resection. The remaining 25% of the patients were assumed to receive systemic treatments
similar to those administered for distant metastases (i.e. dacarbazine, then fotemustine, and finally high-dose interferon
or interleukin). The authors also assumed that, for each type of adverse event, the patients would receive the respective
standard care (as defined by the experts’ opinions).

**Measure of benefits used in the economic analysis**
Two measures of benefits were used in the economic analyses. The measure of benefit in the cost-effectiveness analysis
was the differences in mean survival at 5 and 10 years. The measure of benefit in the cost-utility analysis was the
quality-adjusted time without symptoms and toxicity (Q-TWIST). The utility coefficients used to calculate the Q-
TWIST were 1.00 (time without symptoms and toxicity), 0.8 (time with adverse event from IFNa-2a) and 0.5 (time
with relapse).

**Direct costs**
The resource quantities were not reported separately from the costs, but the authors presented a detailed description of
the resource use associated with different clinical situations. The direct costs considered were those of the third-party
payer. These included therapy administration, ambulatory care, staff, inpatient surgery, systemic treatments, oncology ward and hospitalisation at home. The direct costs included in the economic analysis were obtained from published studies, French data and expert opinion. Some tariffs and prices were considered, instead of costs. Discounting was not performed in the base-case analysis (only in the sensitivity analysis), although it should have been carried out since the study period was longer than two years. The study reported both the average and incremental costs. The price year was not stated.

Statistical analysis of costs
No statistical analyses on the costs were performed.

Indirect Costs
No indirect costs were considered in the economic analysis.

Currency
Euros (Euro).

Sensitivity analysis
Sensitivity analyses were performed to evaluate the robustness of the results to variations in the model assumptions. In particular:

- a higher number of patients receiving chemotherapy for distant metastases was considered;
- the costs for the treatment of relapse were varied by +/- 50%);
- discount rates of 3 and 5% were applied for survival and costs for the 10-year period;
- it was assumed that no survival benefit was observed for IFNa-2a patients after 5 years; and
- the utility coefficients used to calculate the Q-TWISTs were varied.

Estimated benefits used in the economic analysis
The mean overall survival at 5 and 10 years and the incremental mean overall survival have been reported (see the ‘Results of the Review’ section). The authors only reported the incremental Q-TWISTs obtained with surgery plus IFNa-2a at 5 years, compared with surgery alone. This incremental number of Q-TWISTs was 0.286 years. The estimate of the Q-TWISTs gained took side effects into consideration.

Cost results
The average costs per patient during the first 5 years were Euro 11,478 for surgery plus IFNa-2a versus Euro 7,735 for surgery alone. The corresponding costs during the first 10 years were Euro 18,936 (surgery plus IFNa-2a) and Euro 14,490 (surgery alone), respectively. Compared with surgery alone, the incremental cost for surgery plus IFNa-2a was Euro 3,743 during the first 5 years and Euro 4,446 during the first 10 years.

Synthesis of costs and benefits
The estimated costs and benefits were combined using incremental cost-effectiveness ratios (ICERs). Compared with surgery alone, the ICERs of surgery plus IFNa-2a during the first 5 years were Euro 14,394 per life-year gained (LYG) and Euro 13,086 per Q-TWIST gained. During the first 10 years, the ICERs were Euro 6,635 per LYG and Euro 6,656 per Q-TWIST. Over a lifetime, the value was Euro 1,716 per LYG. The authors stated that the results of the study were robust in relation to the variations of the parameters considered in the sensitivity analyses. The most influential
parameter was discounting, although the results did not change dramatically.

**Authors' conclusions**
The cost-effectiveness ratios of low-dose interferon alpha-2a (IFNa-2a) in stage II malignant melanoma (MM) compared favourably with many routinely used therapeutic interventions, both inside and outside of the oncological field.

**CRD COMMENTARY - Selection of comparators**
The comparator chosen (surgery without adjuvant therapy) was justified on the grounds that, currently, there is no effective and well-tolerated adjuvant therapy for MM that is an alternative to IFNa-2a. You should decide whether this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not undertake a systematic review of the literature. The effectiveness estimators were mainly obtained from one RCT. The additional data required were obtained from several other studies, although the authors did not justify their selection. The effectiveness estimators were combined using narrative methods. The effectiveness estimators based on expert opinion were obtained through an interview process. A comparison of the effectiveness estimators used with those from other studies would have been useful, in order to strengthen their reliability. A sensitivity analysis was performed, but only on one of the effectiveness estimators. Not all of the assumptions based on expert opinion were evaluated in the sensitivity analyses.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. Hakulinen's method was used to model lifetime projections, which should have been appropriate. The use of Q-TWIST as one of the summary measures of benefits allowed the benefits of aggressive treatment to be weighted against the likely impact of its toxicity on quality and length of life, as reported by the patients. This is a methodology developed in cancer research, thus, the summary measure of benefit used for the cost-utility analysis appears to have been appropriate. Moreover, LYG were also reported, and sensitivity analyses on the utilities used to obtain Q-TWISTs were performed.

**Validity of estimate of costs**
The perspective of a third-party payer was adopted since there may have been some non-medical direct costs (probably related to the home hospitalisation) that appear to be covered by the French Health Service. Some tariffs and prices were considered, instead of the costs, which may not reflect the true opportunity costs of the interventions. All of the costs relevant to the perspective adopted appear to have been included in the economic analysis. Discounting was not performed in the base-case analysis even though the costs were incurred in a period of more than two years. However, discounting was investigated in the sensitivity analysis. Sensitivity analyses of some costs were also performed. The resource quantities and the costs were not reported separately, although there was a description of the health care services considered in the cost analysis. In addition, the price year was not stated. These issues hinder reflation exercises in other settings. The authors did not report the model used to estimate the benefits and costs together.

**Other issues**
The authors compared some of their findings with those from other studies. However, the issue of the generalisability of the results to other settings was not addressed. The authors' conclusions reflected the scope of the analysis.

**Implications of the study**
The results of this study appear to show that, compared with surgery alone, IFNa-2a therapy after tumour resection for newly diagnosed stage II MM is a cost-effective strategy. However, the caveats identified in this study must be considered when interpreting the results.
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Other publications of related interest


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