Interferon alfa therapy for malignant melanoma: a systematic review of randomized controlled trials

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Authors' objectives
To assess the benefit of interferon (IFN)-alpha therapy in malignant melanoma.

Searching
MEDLINE (from 1966 to March 2001), EMBASE (from 1974 to March 2001) and the Cochrane Controlled Trials Register (Issue 4, 2000) were searched using the MeSH terms 'melanoma' and 'interferon alpha', including all subheadings. In addition, the authors searched the reference lists of identified studies, review articles, textbooks and selected conference proceedings for additional studies. Experts in the field were contacted for other published and unpublished studies. Where possible, the authors of the primary studies were contacted to verify data and provide unpublished data. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible. The median follow-up ranged from 489 days to 6.9 years.

Specific interventions included in the review
To be included in the review, the studies had to assess IFN-alpha monotherapy. The review included studies comparing regimens with or without IFN-alpha adjuvant therapy in melanoma patients. Studies were excluded if they used combination therapy or compared IFN-alpha with some other form of systemic therapy.

The scheduled dose and duration of treatment varied between the studies. Doses of IFN-alpha ranged from 3 MU three times per week to 20 MU/m2 per day. The duration of treatment ranged from 12 weeks to 3 years. Three of the 9 studies used high-dose IFN-alpha, and 3 of the 9 studies had an induction phase. The control group did not receive any adjuvant therapy, and were just observed.

Participants included in the review
Studies of adjuvant therapy in high-risk melanoma patients were eligible. The patients had to have clinically diagnosed cutaneous melanoma with no evidence of metastases in regional lymph nodes or at distant sites (stages I and II) or with regional metastases (stage III). The authors state that the participant demographics and disease characteristics were incompletely reported in the primary studies. The median age reported in three trials ranged from 49 to 55 years in the IFN-alpha group, compared with 50 to 52 years in the control groups.

Outcomes assessed in the review
No inclusion criteria were specified relating to the outcomes in the primary studies. The outcomes included in the review were overall survival, disease-free survival, melanoma recurrence (number of patients who relapsed) and toxicity. The authors did not state how the outcomes were measured.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
A quality evaluation questionnaire was used to score the studies out of a maximum of 81 points. The methodological factors assessed when rating quality included patient selection, randomisation process, trial size, patient characteristics, follow-up and drop-out levels, description of treatment, outcome measures, duration of follow-up, analysis and presentation. It appears that two reviewers applied the quality evaluation questionnaire.
Data extraction
Two reviewers independently extracted the data from each study, and any disagreements were resolved by consensus. Data were extracted on the study characteristics, research design, patient characteristics, disease characteristics, treatment dose and schedule, and outcomes. The authors constructed 2x2 contingency tables for each study. For each outcome of interest, the authors calculated the relative risk reduction, absolute risk reduction, number-needed-to-treat (NNT), odds ratios and associated 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The authors provided a narrative synthesis and calculated summary statistics. No methods to assess publication bias were reported. The authors state that there was wide heterogeneity between the included trials, which made a meta-analysis inappropriate. They did not report the outcomes of any analysis of statistical heterogeneity.

How were differences between studies investigated?
The authors did not state a method for assessing any differences between the studies.

Results of the review
Nine randomised trials were identified, of which one was unpublished. One trial was excluded from the analysis. None of the eight included trials were placebo-controlled. The number of participants in each study ranged from 96 to 654 (total = 3,178).

The quality assessment scores for the studies ranged from 22 to 71 out of a maximum of 81. The mean score was 55.4 (95% CI: 53.8, 57).

Overall survival (6 trials, n=2,771): only one of the primary studies reported a significant impact of IFN-alpha on overall survival, but the reviewers' analysis did not confirm this. The authors calculated the NNT for this data; it did not reach statistical significance.

Disease-free survival (4 trials, n=2,020): one trial found that IFN-alpha was associated with improved disease-free survival, and the reviewers' analysis confirmed this. Another trial found improved disease-free survival only with high-dose IFN-alpha, but this was not confirmed by the reviewers' analysis. Two other trials had inconclusive findings.

Relapse (4 trials, n=1,704): fewer patients treated with IFN-alpha developed metastases compared with the controls (46.9% versus 54.9%, respectively; CIs not provided). The relapse rates ranged from 24 to 58.8% in the groups receiving IFN-alpha, compared with 36.3 to 64.9% in the controls. The ranges overlapped, but the authors did not pool the data because of heterogeneity; therefore, the groups were not compared statistically. Only one trial found a statistically-significant difference in the relapse rates. This favoured low-dose adjuvant IFN-alpha over standard treatment (odds ratio 0.55, 95% CI: 0.34, 0.91; NNT 9, 95% CI: 5, 46).

Toxicity: discontinuation of the treatment due to adverse effects ranged from 3.2 to 35% (reported in 3 trials). Dose reductions ranged from 5.2 to 59% (reported in 4 studies). Two drug-related deaths were reported overall.

Authors’ conclusions
There is no clear benefit of IFN-alpha therapy on overall survival in melanoma patients. A large randomised trial is needed to assess whether a full regimen of IFN-alpha is effective, and to identify subgroups who may benefit from treatment.

CRD commentary
The research question was clearly defined in this review, although some of the inclusion and exclusion criteria could have been specified in more detail. For instance, the authors did not fully rationalise why only IFN-alpha monotherapy
was eligible. This may limit the clinical applicability of the findings.

The search strategy was reasonable, although the authors did not search Cancerlit. The authors attempted to identify unpublished material and there were no language restrictions. This suggests that most of the relevant studies are likely to have been identified. However, publication bias was not assessed. In general, the inclusion and exclusion criteria and methods for assessing validity were described adequately, although the authors did not provide details about how the studies were selected or how many of the reviewers performed the study selection and quality assessment processes. This makes it difficult to assess the quality of the review.

The studies included may have been of limited quality. One of the nine studies identified was excluded without clear reason. None of the studies included were placebo-controlled. The authors state that details of the participants, disease characteristics, study designs and outcomes were not always clearly reported in the primary studies.

The authors did not describe potential biases that could affect the findings of the review. A narrative synthesis was provided, supplemented by summary statistics in a table. This is likely to be appropriate given the (stated) heterogeneity of the data. The authors calculated summary statistics for individual studies, which could have been better presented in the narrative summary.

There are also some difficulties with the outcomes used. The authors did not report the statistical significance of median survival for the individual studies, or state how disease-free survival was analysed. Using outcomes that count the number of participants is problematic in cancer studies, as this does not account for confounding and differences in the time period over which the participants were recruited. A better outcome measure may have been to compare time to events using the Kaplan-Meier method (life tables). It is also possible that non significant findings are due to the sample size of the included studies. Care should be taken when interpreting the findings of small and heterogeneous studies.

Overall, the data appear to support the authors' general conclusions, although the lack of detail about the included studies makes it difficult to assess the generalisability of the findings.

**Implications of the review for practice and research**

**Practice**: The authors suggest there is no evidence that IFN-alpha has a clear survival benefit for people with high-risk melanoma.

**Research**: The authors suggest that a large randomised trial is needed to assess whether a full regimen of IFN-alpha is effective, and to identify subgroups of patients who may benefit from treatment.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.