Adjuvant interferon for melanoma

In their recent review, Punt and Eggermont [1] state that “combined data from low-dose IFN-α [interferon-α] trials does not suggest a benefit in ... DFS [disease-free survival]”. This conclusion is inconsistent with the results of a meta-analysis of these trials [2]. It is surprising that Punt and Eggermont [1] do not mention this study, especially as the latter was an author on the meta-analysis. The meta-analysis indicates a significant benefit for IFN-α on DFS: odds ratio (OR) = 0.87, 95% confidence interval (CI) 0.79–0.96, \( P = 0.007 \). The corresponding OR for high-dose trials was 0.76 (95% CI 0.65–0.89, \( P = 0.0009 \)). Overall, there is good evidence that IFN-α reduces recurrence (OR = 0.84, 95% CI 0.77–0.92, \( P = 0.0001 \)), but the appropriate test for interaction (\( P = 0.2 \)) provides no clear evidence that high-dose is more effective than low-dose (Figure 1).

It is important not to interpret \( P \) values over simplistically, i.e. \( P < 0.05 \) means that treatment is beneficial/harmful and \( P > 0.05 \) means that it is not. The conventional level of significance is an arbitrary cut-off on a continuum of probability. It is preferable, and should lead to less misinterpretation, to use estimation and confidence intervals [3] and express trial results as ORs with CIs, as in Figure 1. Most IFNα trials were underpowered to detect moderate, but potentially worthwhile, benefits (~800 patients are needed to detect a difference of 10% at \( P = 0.05 \) with 80% power) and may have given ‘false negative’ results. (Perhaps the best oncology example is tamoxifen in breast cancer—most individual trials showed no significant benefit, yet meta-analysis demonstrated an incontrovertible benefit that led to a great increase in usage worldwide [4].) Punt and Eggermont [1] report that “a UKCCCR trial ... shows no differences in DFS” [5]. However, the OR for DFS in this trial (0.88) is entirely consistent with that observed for low-dose trials in the meta-analysis (OR = 0.87), so the absence of a significant difference (\( P = 0.2 \)) cannot be taken as evidence that there is no difference. It is important to distinguish between “evidence of lack of effect” and “lack of evidence of effect”—the latter is more frequent given the small size of many trials. Alternatively, when several trials have addressed a particular question, it is likely that some will, by chance, overestimate the true effect and give false positive

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**Meta-analysis of trials of adjuvant interferon v. control in melanoma: Disease-free survival**

<table>
<thead>
<tr>
<th>Group</th>
<th>Recurrences/Patients</th>
<th>Statistics (O–E)</th>
<th>Odds Redn. (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFN</td>
<td>Control</td>
<td>Var.</td>
</tr>
<tr>
<td>High dose (3 trials)</td>
<td>281/492</td>
<td>315/483</td>
<td>-41.0</td>
</tr>
<tr>
<td>Low dose (8 trials)</td>
<td>754/1461</td>
<td>805/1464</td>
<td>-52.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1035/1953</td>
<td>993/1735</td>
<td>-85.9</td>
</tr>
</tbody>
</table>

Test for heterogeneity between groups: \( \chi^2 = 1.9; P = 0.2 \)

Figure 1. Meta-analysis of trials of IFN-α as adjuvant therapy for melanoma. The endpoint is disease-free survival. Trials are grouped into high- and low-dose categories and the results are presented in standard meta-analysis format with a test for interaction between the two groups. The totals in the control column are less than the sum of the two separate groups since control patients in one three-arm trial are only counted once in the overall total. O–E, observed minus expected; Var., variance; OR, odds ratio; CI, confidence interval; Odds Redn., odds reduction; SD, standard deviation.
results. The E1684 high-dose trial may be an instance of this, since a survival advantage was not seen in the confirmatory E1690 study (see Punt and Eggermont [1] for references).

The use of qualitative scoring systems (i.e. simple ‘+’ or ‘−’ depending on statistical significance or not) to review treatment efficacy is unsatisfactory and potentially misleading. It is preferable to employ the quantitative methods of systematic meta-analysis. Thus, we agree with Punt and Eggermont that the evidence for a survival benefit with IFN-α remains unclear, at all doses, and that a further meta-analysis of all the trials should be undertaken. This should use individual patient data, thereby permitting the inclusion of more mature data, with longer follow-up, than are available in most publications and investigation of whether particular types of melanoma patient benefit from adjuvant IFN-α therapy.

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References

DOI: 10.1093/annonc/mdf224