Counterpoint: The Case *Against* Adjuvant High-Dose Interferon-α for Melanoma Patients

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Key Words

Melanoma, interferon-α, adjuvant immunotherapy, randomized trials, survival rates

Abstract

High dose interferon-α (HD IFN) is approved by the United States Food and Drug Administration for adjuvant treatment of patients with stage III melanoma after complete surgical resection. Despite this, clinicians and patients around the world and in many parts of the US have failed to embrace this treatment option because of the lack of overall survival benefit and minimal other clinical benefits seen in randomized trials, combined with the therapy's substantial toxicity. This article reviews the data from the randomized trials that lead to this conclusion and discuss why arguments often advanced in favor of using HD IFN are not persuasive. New treatment options are needed for adjuvant therapy of melanoma. In the meantime, the data from the randomized trials make it difficult for many clinicians and patients to have enthusiasm for adjuvant HD IFN. (*JNCCN* 2004;2:69–72)

Patients with stage III melanoma who are free of disease after complete surgical resection present a difficult clinical problem. The five-year survival rates range between 22% and 65%, depending on the number of positive nodes and whether or not the primary tumor was ulcerated,[1] survival rates that patients understandably consider unacceptably low. As a result, both patients and physicians are eager to try adjuvant treatments in the hope of improving the chance of survival. Often few data are available to guide decisions in these difficult situations, but in the case of adjuvant interferon-α, multiple clinical trials using various doses and schedules have resulted in a dizzying jumble of analyses, post-hoc reanalyses, and apologia in general. This situation is unfortunate because, with regard to adjuvant high-dose interferon-α (HD IFN), we can look to two well-conducted, randomized trials that provide a consistent answer. That answer is that HD IFN does not improve overall survival of melanoma patients after complete surgical resection. In this article, I review the data from these two trials that lead to this conclusion and discuss why the arguments often advanced in favor of HD IFN are not persuasive.

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Adjuvant HD IFN Does Not Improve Overall Survival

Two randomized clinical trials were performed in which melanoma patients who had undergone complete surgical resection of involved lymph nodes (American Joint Committee on Cancer [AJCC] stage III) or deep primary melanomas without involved lymph nodes (AJCC stage II) were then randomized to either close observation alone or HD IFN for one year. The HD IFN regimen consisted of 20×10^6 U/m^2 of IFNα 2b administered intravenously once daily Monday through Friday for four weeks. Afterwards, patients received 10×10^6 U/m^2 of IFNα 2b administered subcutaneously three times weekly for the remainder of the year (48 weeks).

E1684: The First Randomized Trial Testing HD IFN

In this trial, 280 patients were randomized to receive either adjuvant HD IFN or observation. HD IFN treatment began no later than 56 days from surgery (42 days from lymphadenectomy in patients who experienced a lymph node recurrence after a past history of primary melanoma). The results of this trial were first published in 1996 at a time when surviving patients had been followed up for a median of 6.9 years.[2] The estimated overall survival rate at five years was 46% for the HD IFN group compared with

37% for the observation group. Using a two-sided log rank analysis, the *P* value was 0.047,[3] indicating that this small difference was statistically significant. Based on these results, the FDA approved the use of HD IFN as adjuvant treatment in melanoma patients at high risk for recurrence.

Given the relatively small number of patients in the trial and the borderline statistical significance of the survival effect, longer follow up information for these patients was of critical interest. Indeed, with longer follow-up times, the overall survival benefit is no longer statistically significant (1-sided $P = 0.09$; 2-sided $P = 0.18$).[4,5] This lack of survival benefit was confirmed when the data were analyzed independently by Lens and Dawes[6] at the University of Oxford. These data led to the conclusion that the small improvement in overall survival in patients treated with HD IFN in this study was not statistically significant and could have occurred by chance.

Proponents of the benefits of HD IFN sometimes argue that all survival curves must eventually come together as patients die of causes other than melanoma and, therefore, that it is not surprising that these two curves are no longer significantly different. If this were true, it is surprising that advocates of HD IFN have not presented melanoma-specific survival data since all causes of death were recorded for patients on this study. Improvement in melanoma-specific survival should not have lost significance. Also, if the longer follow-up did indeed reflect patients dying of non-melanoma causes, the survival curves would come together as they both approached zero. In fact, the shape of the curves has not changed, and they still plateau at approximately 35%. However, with more events, the differences in the curves are no longer significant. That non-melanoma causes of death contributed to the lack of statistical significance does not seem to be indicated.

E1690: The Confirmatory Trial

Using the same eligibility criteria and HD IFN treatment plan, a second randomized trial was conducted in which a total of 642 patients were randomized to receive HD IFN, a low-dose IFN regimen, or observation only. The results, reported after a median follow up of 4.3 years, showed no difference in survival among the three groups.[7] Thus, the results from E1690 confirm the final impression from the first trial (E1684), that adjuvant treatment with HD IFN is not associated with any measurable increase in survival.

As part of a post hoc analysis trying to explain these negative data, some investigators point to the fact that patients in the observation group were more likely to receive IFN-based therapy on relapse than patients who relapsed in the HD IFN group, and that this therapy could have prolonged survival sufficiently to eliminate any difference in survival between the two arms. Indeed, 38 of 121 (31%) patients in the observation arm who relapsed received IFNα-containing treatment at first relapse compared with 17 of 114 (15%) patients who relapsed in the HD IFN arm ($P = 0.003$), a difference of only 21 patients (10% of the total observation group). This argument relies on the belief that IFNa-based therapy after relapse was so effective in improving overall survival that a disparity of 21 patients in the observation group was sufficient to improve the survival for the entire observation group. This suggestion is difficult to reconcile with the fact that IFNα is associated with only a 16% response rate (virtually all partial responses) in patients with metastatic melanoma[3] and does not improve survival when administered alone or in combination with chemotherapy. If, despite this observation, the effects of IFNα-based therapy were somehow so remarkably beneficial in the relapse setting, it would make more sense to treat only relapsed patients rather than treat all patients in the adjuvant setting.

Meta-analyses

One concern is that the benefit of HD IFN might be too small to be detected by clinical trials with only 200 patients per arm. To increase the power of detecting small benefits of HD IFN, several meta-analyses, each with over 3,000 patients, have been performed of pooled data from randomized adjuvant IFN trials.[6,8,9] Admittedly, these analyses included both high- and low-dose IFN trials. None of these meta-analyses showed an overall survival advantage for adjuvant IFN that was statistically significant (relative risk estimates all overlapped 1.0).

Adjuvant HD IFN Can Delay Recurrences

Although adjuvant HD IFN does not appear to affect overall survival, data show that adjuvant HD IFN can delay the time of recurrence. In both randomized HD IFN trials, patients treated with HD IFN showed a small but statistically significant improvement in relapse-free survival (RFS) compared with the observation group. At five years, the improvement in RFS of

HD IFN compared with observation was 11% and 9% in each of the two trials (37% vs. 26% in E1684; 44% vs. 35% in E1690). Interestingly, several trials in which lower doses of IFN were used also showed improvements in RFS,[10,11] although this has not been seen in all low-dose IFN trials.[12,13] The E1690 trial, a three-arm trial, was the only trial to compare HD IFN, low-dose IFN, and observation directly. The RFS curve for the low dose IFN arm was superimposable with the RFS curve for the HD IFN arm over the first 4.5 years, both of which appeared to be superior to the observation arm. Surprisingly, the authors reported an improvement in RFS over observation only for HD IFN (P = 0.054) but not for the low dose IFN arm (P = 0.17).[7] It will be important to see if this remains true with longer follow-up.

The data from these randomized trials comparing adjuvant IFN with observation lead to several conclusions:

- Adjuvant high dose IFN does not prolong overall survival.
- Adjuvant high dose IFN can result in a small but reproducible improvement in time to recurrence (RFS).
- Some evidence that lower doses of IFN can improve RFS exists, but this has not been observed consistently.

E1694: HD IFN as Control Group

Before the data from the two randomized trials had matured, HD IFN was assumed to be better than observation alone in the adjuvant setting. Therefore, HD IFN was used as the control arm for a third randomized trial designed to evaluate an experimental vaccine, designated GMK. This third randomized trial with HD IFN tested the hypothesis that immunization with GMK would result in improved RFS or overall survival compared with the control group receiving HD IFN. The results were published at a median follow-up time of only 16 months showing that GMK was not better than HD IFN.[14] In fact, the trial was stopped early because the RFS and overall survival in the GMK arm was significantly worse than in the HD IFN arm. Although it remains to be seen whether these differences will remain after longer follow-up times, it is critical to recognize that this trial did not test whether HD IFN was beneficial. That had been tested previously in E1684 and E1690, and in the context of the mature results from these trials (discussed previously), it is clear that neither adjuvant HD IFN nor adjuvant GMK improves overall survival.

Toxicities of HD IFN

Virtually all patients treated with HD IFN experience a significant decrease in performance status and quality of life during the year of treatment. HD IFN treatment is commonly associated with grade III fatigue, myelosuppression, hepatotoxicity, and neurologic toxicity.[2,7,14] Fatigue, which occurs in almost all patients and is of grade III severity in over 20% of patients, is the side effect most troubling to patients. Depression is another common side effect of HD IFN. When assessed by oncologists, approximately 10% of patients on HD IFN were found to be depressed.[7,14] However, this number probably significantly underestimates the problem. In one study in which patients being treated with HD IFN were assessed by psychiatrists, 45% of patients developed symptoms consistent with DSM-IV criteria for major depression.[15]

Conclusions

The results from both randomized trials and the meta-analyses comparing HD IFN with observation fail to show an improvement in overall survival with HD IFN. This, together with the significant toxicities and the universal decline in quality of life during the year of treatment, make it difficult for many physicians and patients to justify adjuvant HD IFN treatment. Some advocates of HD IFN point out that no other options for adjuvant therapy are currently available for these patients, but this does not justify administering a toxic treatment that we know does not prolong survival. It is time to put adjuvant HD IFN behind us and focus our attention and resources on exploring new and promising strategies for adjuvant therapy.

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