CURRENT OPINION

Drugs 2003; 63 (11): 1053-1058
0012-6667/03/0011-1053/$33.00/0

Is There a Role for Adjuvant High-Dose Interferon-α-2b in the Management of Melanoma?

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Abstract

The knowledge that melanoma is susceptible to attack by the host's immune system has resulted in the testing of a variety of immunotherapies. Interferon-α-2b, which has several anti-tumour mechanisms including an antiproliferative effect, an anti-angiogenesis effect, the enhancement of natural-killer cell activity and the upregulation of tumour antigen presentation, has shown tremendous potential. Early trials using low-dose and intermediate-dose regimens demonstrated no benefit to survival. However, the Eastern Cooperative Oncology Group trial EST 1684, showed that a high-dose regimen involving an induction phase of intravenous interferon-α-2b 20 MU/m^2 5 days a week for 4 weeks, followed by a maintenance phase of subcutaneous 10 MU/m^2 3 days a week for the remainder of a year, led to significant improvements in both disease-free and overall survival compared with observation. On the basis of these results, the US FDA approved high-dose interferon-α-2b for the post-surgical adjuvant therapy of high-risk melanoma. Unfortunately, the results of subsequent trials involving high-dose interferon-α-2b have not been as clear, and its role in the adjuvant treatment of melanoma remains controversial. Concerns remain regarding the design and interpretation of the clinical trials, the cost and toxicity of treatment, and the appropriate selection of patients who should be treated. This article reviews the existing data and attempt to address the arguments for and against a role for adjuvant high-dose interferon-α-2b in the management of melanoma.

Cytotoxic chemotherapy has limited efficacy against invasive malignant melanoma and currently plays no role in the adjuvant setting. Thus, physicians have traditionally been left with few options to attempt to reduce the risk of recurrence after surgical resection. This is significant, as the risk of recurrence for patients with thick primary lesions (T4N0M0, American Joint Committee on Cancer [AJCC] stage IIB) is approximately 60% and for those with regional nodal metastases (T1-4N1M0, AJCC stage III) is approximately 75%.[1]

It has been known for some time that melanoma is susceptible to attack by the host's immune system. This has resulted in the testing of a variety of immunotherapies, including non-specific immunostimulants, vaccines and systemic cytokines. While the majority of these have not demonstrated any clinical successes, the use of adjuvant interferon-α-2b has shown tremendous potential. While the precise mechanism of action remains poorly understood, there are multiple anti-tumour effects of interferon-α-2b. These include a direct antiproliferative ef-

fect, anti-angiogenesis, the enhancement of natural killer cell activity and the upregulation of tumour antigens and/or human leucocyte antigen class I and class II antigens.[2,3] Initial phase II clinical studies with interferon-α-2b in metastatic melanoma showed response rates in the 10–20% range.[4,5] These response rates were not significant enough to lead to its use in the treatment of metastatic melanoma; however, they prompted multiple clinical trials exploring the use of interferon-α-2b as an adjuvant therapy for melanoma in patients at high risk of recurrence.

In 1995, the Eastern Cooperative Oncology Group (ECOG) trial EST 1684 (E1684) demonstrated a significant prolongation of relapse-free and overall survival with the use of adjuvant high-dose interferon-α-2b.[6] On the basis of this study, the US FDA approved the use of interferon-α-2b for the post surgical adjuvant therapy of high-risk melanoma. The results of subsequent trials have unfortunately not been as clear, and the role of interferon-α-2b in the adjuvant treatment of melanoma remains controversial.

1. Making Sense of the Clinical Trials

Trials involving adjuvant interferon-α-2b for the treatment of melanoma have involved a wide range of dosage regimens.[7] Early trials utilised a low-dose regimen, and while there was a suggestion of some effectiveness,[8,9] re-analysis and additional trials have demonstrated no benefit to survival.[10,11] Creagan et al. and the North Central Cancer Treatment Group (NCCTG),[12] therefore, attempted to increase the interferon-α-2b dose in a randomised trial of patients with melanoma at intermediate and high risk of recurrence. This resulted in a significant increase in disease-free survival for node-positive patients. In this same subset there was a trend towards improved overall survival (47% in the treatment group vs 39% in the observation group) at 5 years, although this did not attain statistical significance.

Kirkwood et al.[6] then dramatically increased the dose of interferon to the maximally tolerated dose in a randomised trial for ECOG, E1684. This regimen involved an induction phase of intravenous interferon-α-2b 20 MU/m^2 5 days a week for 4 weeks, followed by a maintenance phase of subcutaneous interferon-α-2b 10 MU/m^2 3 days a week for the remainder of a year. Although this regimen was more toxic, the results were positive. Patients who were randomised to the treatment group had a significant improvement in disease-free and overall survival compared with the control group. Interferon-α-2b therapy increased the median relapse-free survival by 9 months (1.72 years for patients receiving interferon-α-2b vs 0.98 years for observation patients) and produced a 42% improvement in the 5-year relapse-free survival rate (37% [95% CI 30–46%] for patients receiving interferon-α-2b vs 26% [95% CI 19–34%] for observation patients). In addition, interferon-α-2b therapy significantly increased median survival by 1 year and produced a 24% improvement in the 5-year survival rate (46% for patients receiving interferon-α-2b [95% CI 39–55%] vs 37% for observation patients [95% CI 30–46%]). On the basis of these results, interferon-α-2b was approved by the FDA for the adjuvant treatment of high-risk melanoma.

In order to verify these results and clarify the benefit of adjuvant therapy with melanoma, an ECOG-coordinated intergroup trial, E1690,[13] was initiated as a follow-up to E1684. E1690 compared three groups: a 1-year, high-dose interferon-α-2b regimen; a 2-year, low-dose interferon-α-2b regimen; and observation after patients had undergone a complete resection of all known disease.[13] While the results of this trial confirmed that the disease-free survival advantage for high-dose interferon-α-2b seen in E1684, there was no overall survival advantage.

A third ECOG-coordinated intergroup trial, E1694,[14] compared the efficacy of 1-year, high-dose interferon-α-2b with that of 2 years' treatment with a ganglioside GM2 vaccine, GMK, for the treatment of patients with melanoma. Gangliosides are carbohydrate antigens found on the surface of melanoma cells, as well as normal cells of neural crest origin and tumour cells of other types. A randomised trial that suggested a disease-free survi-

val benefit in patients who were treated with GM2 vaccine plus Bacille Calmette-Guérin (BCG) compared with those treated with BCG alone following resection of stage III disease.[15] In May 2000, the E1694 trial's independent Data Safety Monitoring Committee concluded that high-dose interferon-α-2b was associated with significantly improved relapse-free and overall survival, and mandated that the study be terminated early and the results disclosed.[14]

Advocates of interferon therapy point out that all three high-dose interferon-α-2b trials, described above, demonstrated an improvement in relapse-free survival, and two of the three demonstrated an improvement in overall survival. In addition, advocates of adjuvant interferon therapy point out that the reason that E1690 failed to demonstrate a survival advantage is probably because of differences in eligibility criteria and, more importantly, the subsequent availability of post-relapse interferon-α-2b crossover therapy in the E1690 trial compared with the E1684 trial.[13]

On the other hand, several questions still remain as to whether these trials support a role of interferon-α-2b in the adjuvant setting. Despite the enthusiasm and multiple, large, controlled studies, there has been no demonstrable rationale of the mechanisms of action of this biological response modifier.[16] E1684, the trial that established the adjuvant use of interferon-α-2b is not without its limitations. Patients were not stratified by the number of positive lymph nodes; a recognised prognostic factor. Therefore, it is possible that there may have been an unrecognised imbalance between the treatment and control groups that influenced the outcome. In addition, longer follow-up data on E1684 showed that at a median follow-up of 12.6 years there was a continued disease-free survival advantage for high-dose interferon-α-2b, but the benefit in overall survival loses statistical significance, with the new p-value reported at 0.09.[17,18] Therefore, while high-dose interferon-α-2b clearly improves disease-free survival, the question of overall survival remains controversial.[7]

The concerns about E1684, specifically the possible imbalance between the treatment and control groups, were supposed to be addressed in E1690. As mentioned, however, although there was an improvement in disease-free survival for high-dose interferon-α-2b, the study failed to demonstrate an improvement in overall survival for either high- or low-dose interferon-α-2b. The crossover data from E1690, which advocates of interferon therapy argue as the reason E1690 failed to validate E1684, is retrospective and must be considered an unproven hypothesis. Finally, E1694 appears to confirm the disease-free and overall survival benefit of high-dose interferon-α-2b demonstrated in E1684. However, this study did not have an observation arm. Therefore, a deleterious effect of the GMK vaccine cannot be ruled out. While this appears unlikely, such an effect would lead to the appearance of a benefit for interferon-α-2b in that trial when none existed. With so many differences between the two trials, it is difficult to directly compare the results.

2. Which Patients to Treat?

Even if one was to assume the assertions that the crossover in E1690 led to the failure to demonstrate a survival benefit, and that the GMK vaccine has no detrimental effect on survival in E1694, other questions remain. Specifically, if there is a role of adjuvant therapy with interferon-α-2b, which patients should be receiving it? When discussing a high-risk melanoma patient, we typically refer to either a patient with a thick (>4.0mm) primary melanoma or a patient with metastases to the regional node.

In the NCCTG trial,[12] there was no effect demonstrated in node-negative patients. Patients in the E1684 trial were not stratified for the number of positive nodes, but retrospectively the greatest relapse-free survival appeared to be for patients with one positive lymph node. Patients with thick primary melanoma who were node-negative accounted for only a small subset of total patients (about 11% of the 280 total patients) in the trial, and within this subset, the treatment group actually fared worse. The small size of this subset makes it impossible to determine whether there is truly a difference in the

response of node-positive and node-negative patients to interferon-α-2b treatment. Patients in both the E1690 and E1694 trials were stratified for 0, 1, 2–3 or 4+ nodes. E1690 showed that when patients were stratified by the number of nodes, the relapse-free survival benefit was only significant in patients who had 2–3 positive lymph nodes. Finally, E1694 demonstrated the greatest benefit in the node-negative subset. This leaves open questions as to which population of high-risk patients would benefit from high-dose interferon-α-2b.

3. Cost and Toxicity

In addition to the concerns surrounding the clinical trials, adjuvant therapy with interferon-α-2b is not without substantial cost and toxicity. The cost of a year of interferon-α-2b was estimated to be just under $US29 000 (1984–1990 values) in the original E1684 trial.[19-21] The cost effectiveness was found to be comparable with other recognised medical therapies, between $US32 600 and $US43 200 (1984–1990 values) per year of life saved.[19-21] However, these studies demonstrating the cost-effectiveness of interferon-α-2b as adjuvant therapy are based solely on the E1684 data. These analyses used projections of long-term survival, since data was only available to 5 years. Given the improved survival of the control arms in both subsequent high-dose interferon-α-2b trials, and the lack of demonstrated benefit in the E1690 trial, those analyses may not accurately reflect the economic cost-benefit ratios of using adjuvant high-dose interferon-α-2b.

More importantly, the toxicity surrounding the use of interferon-α-2b is not inconsequential. In E1684,[6] both treatment delays and dosage reductions were required during therapy, including 50% of patients during the induction period and 48% of patients during the maintenance phase. Grade 3 toxicity was seen in 67% of all treated patients at some time in their therapy, while 9% had grade 4 toxicity. Serious adverse effects include fatigue, flu-like symptoms (malaise, fevers, chills, arthralgias), liver function abnormalities (fatal hepatotoxicity have been observed in patients who were not carefully monitored and did not receive appropriate dose reductions in the event of liver function test elevations), neutropenia, nausea and vomiting, and psychiatric symptoms including depression and suicide.

The adjuvant use of interferon-α-2b is supported by the results of a quality-of-life-adjusted survival analysis (Quality-Adjusted Time Without Symptoms and Toxicity [Q-TWiST]). Using the Q-TWiST methodology, patients with stage III melanoma who were randomised to high-dose interferon-α-2b in the E1684 trial were found to have more time without symptoms or toxicity than the observation group.[22] Patients in the treatment group had gained a mean of 8.9 months without disease relapse and 7 months of overall survival compared with the observation group, and they experienced an average of 5.8 months of severe, treatment-related toxicity. This supports the use of interferon-α-2b as adjuvant therapy. If quality of life during the time with toxicity were valued more highly than the quality of life during the time with relapse, the patients receiving interferon-α-2b had significantly greater quality-of-life adjusted time than the observation patients.

However, this is the only study assessing quality of life with adjuvant interferon-α-2b in patients with melanoma, and the issues that follow must be considered.[23] This quality-of-life analysis was done retrospectively using the collected data from E1684. The analysis assigned arbitrary relative values to time with toxicity and time with relapse, rather than assessing the actual quality-of-life valuations of the individual patients in the trial. Also, the improvement in overall survival used in this analysis was not reproduced in E1690, but the Q-TWiST analysis was never updated. More importantly, the Q-TWiST conclusion is based on the assumption that quality of life of a patient who has symptoms but is disease-free is valued more highly than that of a patient with relapse but no symptoms. If one assumes that the relative value is equal, then the gain in quality-adjusted time was not statistically significant for the patients receiving interferon-α-2b compared with the observation group. Patients are certainly averse to the adverse effects of interferon-α-2b; they regularly refuse the recommendation for treatment and

seek alternatives in clinical trials or chose to forgo adjuvant therapy altogether.

4. Conclusion

Regardless of how one interprets the available data, it is clear that many questions regarding the role of interferon-α-2b in the adjuvant treatment of melanoma still remain. We need to better select not only which melanoma patients are at highest risk of relapse, but also which patients are destined to derive the greatest benefit from adjuvant interferon-α-2b. It is imperative to find ways to decrease the toxicity of the current high-dose regimen without losing efficacy, thereby eliminating some of the roadblocks to its use. There may be other effective therapies that can add to or replace interferon-α-2b in the adjuvant setting. Informed high-risk patients who feel that the toxicity of therapy is too high should be encouraged to participate in well-designed controlled trials, and clinical trials in intermediate-risk patients should also continue, including trials of less intense interferon-α-2b regimens and also phase II and III vaccine trials. However, until that information is published, how does one make a decision based on the available data?

The routine use of adjuvant high-dose interferon-α-2b is certainly not without its controversy and opponents. Attempts to clarify the issue through reviews and meta-analyses of the available data have yielded conflicting recommendations and been hampered by methodological limitations.[7,17,18,24,25] Given the lack of effective adjuvant therapies and the devastating problem of recurrence in high-risk melanoma patients, high-dose interferon-α-2b represents an option that should be discussed with these patients. Too many clinical trials demonstrate an improvement in relapse-free survival to deny the fact that high-dose interferon-α-2b alters the natural history of high-risk melanoma. Even if one does not accept the explanation that crossover resulted in the failure of E1690, E1694 should be considered as a clinical trial that documents a significant impact of high-dose interferon-α-2b. The likelihood that vaccination with a ganglioside antigen can result in a markedly increased risk of early dissemination of and death from metastatic melanoma is not reasonable and there is credible evidence that anti-GM2 antibodies, either spontaneous or vaccine-induced, are protective against melanoma relapse.[15,26]

Given the questions surrounding the data, however, it is not unreasonable that informed patients could opt to forego treatment or seek alternate therapies. The crossover effect observed in E1690 suggests that the possibility that untreated high-risk patients who subsequently present with a resectable recurrence might still derive benefit from adjuvant interferon-α-2b, and this should be explained and offered to patients who choose to forego initial interferon-α-2b adjuvant therapy. It must be noted, however, that in most patients with pathological stage II and III disease who develop disease recurrence it will be unresectable, and not have an option for surgical salvage and subsequent adjuvant interferon-α-2b therapy.

What about the question regarding which subset of high-risk melanoma patients should be offered adjuvant interferon-α-2b? One possible explanation of the available data is that the efficacy of interferon-α-2b is consistent across all subsets of high-risk patients, that is, patients with thick node-negative and patients with one or more positive lymph nodes. It must be noted, however, that the subset of high-risk patients with the least clinical trial data is the group of patients that is now most commonly treated with adjuvant interferon-α-2b – namely, those patients with a single, microscopically positive lymph node found on sentinel node biopsy. More data on the results of untreated and interferon-α-2b-treated patients in this subgroup are needed, and would enhance the acceptability of this adjuvant treatment by physicians and patients alike.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. Both Dr Sabel and Dr Sondak serve on the Schering-Oncology speakers bureau.

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