Adjuvant interferon alfa for melanoma

KEY WORDS

Melanoma, adjuvant, interferon

The Editor,
Current Oncology
July 7, 2009

Re: Hauschild A. Adjuvant interferon alfa for melanoma: new evidence-based treatment recommendations? *Curr Oncol* 2009;16:3–6.

The author poses the question "Why did these study results not lead to a global consensus about interferon treatment as standard of care?"

The answer is quite simple: The E1684 adjuvant high-dose interferon (HDIFN) trial, while initially positive, was later shown to be negative. Remarkably, in spite of a *p* value of 0.09, the principal investigator still interpreted the trial as positive [1]. Cancer Care Ontario's Melanoma Disease Site Group concluded, "The precise reasons for the attenuation in overall survival are not clear." Most clinicians and statisticians agree that mature analysis of E1684 showed no overall survival benefit.

The highly anticipated "confirmatory" trial (E1690) was completely negative for overall survival benefit as a whole and in any subgroup of patients [2].

Although not powered to detect differences in patient subgroups, the E1684, 1690 and 1694 trials found no consistency—or even trend to consistency—in disease-free survival benefit. For example, the largest treatment effects were in clinical stage 2, pathologic stage 2 patients in E1684; in patients with 2–3 involved lymph nodes in E1690; and in patients with T4 primary melanoma without nodal involvement in E1694. Also, the European Organization for Research and Treatment of Cancer (EORTC) 18952 and 18991 trials found a correlation between interferon benefit and *lower* tumour burden, but the E1684 and 1690 trials observed better outcomes in palpable node-positive patients. These conflicting findings fuelled uncertainty among clinicians.

Regarding the Hellenic Cooperative Group trial, which compared 12 months with 4 weeks of modified HDIFN and showed no difference in efficacy [3], the author expressed doubt about the conclusion. Nevertheless, the conclusion accords with the meta-analysis findings that neither the dose nor the duration of adjuvant interferon influence outcome [4]. The range of overall survival benefit in the meta-analysis was, in fact, 1%–5% [4], not 2%–5% as quoted in the editorial. The onus should now be on investigators to prove that more is better.

The selection of observation as the control arm of the E1697 and EORTC 18071 adjuvant trials attests to the lack of confidence that adjuvant HDIFN is standard of care in both North America and Europe. Although HDIFN remains approved in the United States and Canada, physician enthusiasm and HDIFN utilization are tempered by its substantial, albeit manageable, toxicity and quality of life changes; its cost; and its effectiveness, especially when the latter is marginal.

Kenneth S. Wilson MD
Andrew Attwell MD
British Columbia Cancer Agency
Vancouver Island Centre
2410 Lee Avenue
Victoria V8R 6V5

P.S. Since submission of our letter, investigators from the MD Anderson Cancer Center have concluded that, although adjuvant interferon may delay disease recurrence in a small subset of patients, usually for less than a year, the overall risk of recurrence and death is not reduced. Furthermore, interferon is associated with substantial dose-dependent toxicity and reduced quality of life. Use of interferon—regardless of type, dose, and schedule—is unlikely to bring any further progress, and its clinical trial use in unselected patients is no longer justified [5]. However, patients with ulcerated melanoma and lower stage (IIB and IIIA) may still be appropriate subjects for interferon research [6].

REFERENCES

1. Wilson K. High-dose interferon versus GM2 vaccine in high-risk malignant melanoma. *J Clin Oncol* 2001;19:4350.
2. Kirkwood JM, Ibrahim JG, Sondak VK, *et al*. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of Intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000;18:2444–58.
3. Pectasides D, Dafni U, Bafaloukos D, *et al*. Randomized phase III study of 1 month versus 1 year of adjuvant high-dose interferon alfa-2b in patients with resected high-risk melanoma. *J Clin Oncol* 2009;27;939–44.
4. Wheatley K, Ives N, Eggermont A, *et al*. Interferon-α as adjuvant therapy for melanoma: an individual patient data meta-analysis of randomized trials [abstract 8526]. *Proc Am Soc Clin Oncol* 2007;25:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=33295; cited March 14, 2010]
5. Janku F, Kurzrock R. Adjuvant interferon in high-risk melanoma: end of the era? *J Clin Oncol* 2010;28:e15–16.
6. Eggermont AMM, Bottomley A, Suciu S, *et al.* Reply to F Janku *et al. J Clin Oncol* 2010;28:e17–18.