Current approaches to adjuvant therapy of melanoma

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The incidence of malignant melanoma is rising faster than any other solid tumour and in young adults melanoma is the most common tumour type. In spite of improved early recognition and early treatment melanoma mortality rates are increasing. The therapeutic management of melanoma is challenging and the tumour remains among the most resistant tumour types to medical treatment. Surgical removal of the primary tumour is virtually the only curative approach presently available.

To prevent disease recurrence in high-risk patients, stage IIB–IIC disease without lymph-node metastases or stage III, who have a 5-year survival of 24–67% [1] different adjuvant treatments have been tested. Up to now interferon alfa-2b has been the most frequently investigated. The Eastern Cooperative Oncology Group (ECOG) E1684 Trial demonstrated prolonged relapse-free survival (RFS) and prolonged overall survival in patients treated with adjuvant high-dose interferon alfa-2b [2]. In the confirmatory Trial E1690, however, this survival benefit could not be reproduced. The E1690 Trial showed improved RFS, but did not show a benefit in overall survival with the high-dose interferon alfa-2b regimen [3].

Since the toxic effects of the high-dose interferon regimen has been of concern the question was raised whether lower doses of interferon alfa-2b would be a less toxic alternative to high doses. The EORTC 18952 Trial explored intermediate-dose interferon alfa-2b and showed significant improvement in RFS, but no effect on overall survival [4]. Similarly, the recent Nordic Melanoma Collaborative Group Trial [5] also demonstrated a significant improvement in RFS compared with untreated controls, but no survival benefit. In the 18991 EORTC Trial with pegylated interferon alfa-2b (PEG-IFN-alfa-2b), a drug preparation allowing more convenient drug administration, i.e. once-weekly injection, demonstrated significant prolongation of RFS, but no significant improvement in overall survival [6].

Meta-analysis

A recent meta-analysis based on 14 published randomised adjuvant IFN-alfa-2b trials published between 1990 and 2008 was able to demonstrate improved disease-free survival and a statistically significant effect on overall survival [7]. The latter finding may partly be explained by the inclusion of the Trials ECOG 1694 and ECOG 2696, which had ganglioside GM2 vaccine as a comparator arm. The validity of inclusion of these trials has been questioned since there are indications that GM2 may have a negative impact on patients' prognosis [8]. Another finding from the analysis was that the beneficial effect of IFN was independent of doses and treatment duration.

HRQoL during adjuvant interferon therapy

Several studies measuring Health Related Quality of life (HRQoL) using EORTC QLQ-30 reporting on data from the PEG-IFN-alfa-2b Trial [9] and from the DeCOG Trial with low-dose IFN-alpha2-b [10] have demonstrated a significant reduction in HRQoL during treatment. In a similar study (Nordic Melanoma Group study), with a higher patient response rate to the questionnaires, there were significant negative effects on HRQoL during treatment, but the effects were reversed when treatment stopped (Y. Brandberg, Karolinska-Institute).

Other adjuvant melanoma therapies

A large number of randomised trials have been performed in stage II/III melanoma to evaluate other adjuvant therapies, such as chemotherapy, non-specific immune stimulants such as bacillus Calmette–Guerin (BCG), levamisole or combinations of these agents with dacarbazine. A number of adjuvant trials with vaccines, based on allogeneic melanoma cells, have also been performed. The Melacine Vaccine Trial in stage II patients demonstrated no benefit [11] while the Canvaxin Trial in stage III patients demonstrated worse outcomes for the treated patients compared

with controls [12]. The EORTC 18961 Trial with adjuvant GM2 in a large group of patients with stage II melanoma was terminated early owing to the possible detrimental outcome in the vaccine-treated patients [13].

Approved drugs for adjuvant melanoma treatment

High-dose IFN-alfa-2b is approved by both the FDA in the United States and the EMA in Europe for patients with high-risk melanoma (stage IIB/III). Based on the EORTC 18991 Trial, PEG-IFN-alfa-2b was recently approved by the FDA for adjuvant treatment for stage III melanoma patients.

Summary

It is well documented that IFN-alfa-2b and PEG-IFN-alfa-2b significantly prolong RFS, but has no significant effect on overall survival. Currently, IFN-alfa-2b is frequently used as adjuvant treatment for high-risk malignant melanoma in the USA and Europe, although the doses and schedules may vary. In the Nordic countries adjuvant IFN has till now hardly been used.

The question is if RFS is the correct endpoint for adjuvant therapies. It should be taken into account that the IFN toxicities reduce quality of life during the treatment and that the RFS gain from five-year IFN therapy is less than a year. Many oncologists regard prolonged survival as the only valid endpoint for adjuvant therapies in cancer patients.

A number of patients, well aware of the toxicities involved, regard possible prolongation of RFS as important and choose to receive adjuvant interferon treatment. The recent approval of two new drugs, anti-CTLA-4 and a BRAF-inhibitor, the first drugs ever to prolong survival in metastatic melanoma patients, may change our current view on RFS as a valid endpoint and it may lead to more patients receiving adjuvant IFN since more effective treatments can be offered for recurrent disease. The newly approved pegylated IFN may make the treatment more practical for the patients.

Conflict of interest statement

The author has no conflict of interest to disclose.

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