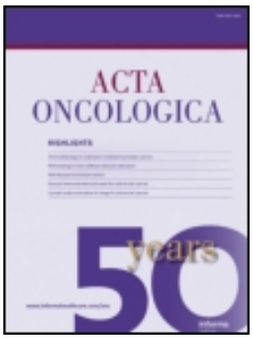

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EDITORIAL

Adjuvant therapy of cutaneous melanoma – current status

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Despite considerable and prolonged efforts, the attempts to develop an efficient adjuvant therapy for patients with malignant melanoma have met with very limited success. During the last decade attention has mainly focused on development of adjuvant interferon (IFN) therapies. Initial optimism was raised by the report of the ECOG E1684 trial in 1996 [1]. This study indicated an improved overall (OS) and recurrence-free survival (RFS) in high risk melanoma patients receiving treatment with high-dose IFN α-2b (20 million units/m^2 I.V. 5 days/week for 4 weeks, followed by 10 million units/m^2 3 times weekly for 48 weeks). The beneficial effects were, however, associated with considerable treatment-induced toxicity. Moreover, a trial, Intergroup E1690, which compared adjuvant treatment with high dose IFN, versus low lose IFN, versus no treatment, showed only an increase in RFS but no improvement in OS in the high-dose IFN arm [2]. The reason for the discrepant results remains unclear, but the lack of OS benefit by high dose IFN in E1690 has been attributed to frequent salvage therapy with high dose IFN in patients in the control arm. In a more recent Intergroup trial, E1694, adjuvant therapy with high-dose IFN showed an improved OS and RFS compared to adjuvant ganglioside GM2 vaccine [3]. This trial has, however, been criticized since it lacks a comparison with an untreated control arm.

Due to the lack of a proven survival benefit and the considerable toxicity associated with adjuvant high-dose IFN therapy, such treatment is not standard of care in Europe, although it is frequently employed in many US centers. In Europe attempts to obtain beneficial effects with less toxic therapies has led to several trials using low or intermediate doses of IFN. In general, while some trials have shown improved RFS, no impact on OS has been demonstrated with these reduced IFN doses.

In an attempt to sort out the differences in results of separate trials and to obtain an estimate of the true benefit, if any, of adjuvant IFN-α therapy delivered at different doses to melanoma patients, a meta analysis of the published trials was reported in 2003 [4]. The analysis summarized the results of 12 different randomized trials and showed a significant improvement in RFS by adjuvant IFN-α therapy, with an estimated HR of 0.83 (95% confidence interval (CI) 0.77–0.90, $p = 0.000003$). In contrast the benefit with respect to OS was not significant with an estimated HR of 0.93 (95% CI 0.85–1.02, $p = 0.01$), a confidence interval compatible with both no benefit and with a moderate but clinically worthwhile benefit. There was some evidence for a dose response relationship with a significant trend for the benefit of IFN-α therapy to increase with increasing dose for RFS (test for trend $p = 0.02$) but not for OS (trend $p = 0.8$). The authors of this meta analysis conclude that additional and more mature data are needed to resolve the issues of any OS benefit from adjuvant IFN-α therapy and that an individual patient data meta analysis should be preformed as has for instance been done with adjuvant therapy for breast cancer by the Early Breast Cancer Trialists' Collaborative Group (EBCTG) [5] and of IFN-α in myeloma by the Myeloma Trialists' Collaborative Group [6].

Following the meta analysis, results of two additional large European studies of adjuvant IFN-α therapy in high-risk melanoma have been reported: the AIM HIGH and the EORTC 18952 trials [7,8]. Thus, the AIM HIGH study from the United Kingdom investigated the effect of low dose IFNα-2a (3 million units 3 times per week for 2 years)

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versus no treatment in 674 patients with high-risk resected melanoma [7]. No significant difference in RFS or OS was seen between the two study arms. The EORTC 18952 trial, which included 1388 patients is the largest randomized controlled trial of adjuvant IFN therapy in melanoma yet reported [8]. Patients with high-risk melanoma were randomized to either 13 months or 25 months if intermediate dose IFNα-2b (4 weeks induction therapy with 10 million units IFNα-2b followed by either 10 million units IFNα-2b 3 times per week for 12 months or 5 million units IFNα-2b 3 times per week for 24 months) or observation. Neither treatment arm showed any significant improvement in distant metastasis free survival or OS.

Several large trials have not yet been reported. Thus, The Nordic Collaborative Melanoma Group has performed a three-armed trial of 855 patients with high-risk melanoma randomized to either intermediate dose IFNα-2b for 1 or 2 years or no therapy (the key difference from the above mentioned EORTC 18952 trial is that in the Nordic trial the same dose of IFN: 10 million units 3 times per week were given for either 1 or 2 years, to directly address whether a prolonged delivery of the same IFN therapy causes an improved effect). The study was closed in 2004 after recruitment of 855 patients and results are due to be analysed shortly.

A tendency towards improved distant metastasis free survival in the 24 month compared to the 12 month IFN arm in the EORTC 18952 trial has prompted the EORTC to explore the concept of very prolonged adjuvant IFN in the recently closed EORTC 18991 trial, in which patients were randomized to either adjuvant therapy for five years with pegylated IFNα-2b or observation only. Finally, the considerable toxicities associated with high-dose IFN therapy has led the US Intergroup to initiate the E1697 trial evaluating the effect of four weeks of IV induction therapy (according to the original high-dose IFN schedule) only without maintenance therapy versus observation in patients with intermediate-risk melanoma. The hypothesis tested is whether significant effects can be obtained with a brief intensive schedule which avoids the toxicities long-term IFN therapy. Due to slow patient inclusion it is planned that this study will open also in Europe and also include patients with high-risk melanoma.

In the present issue of Acta Oncologica, Stadler et al. report remarkable results of a randomized multicentre trial of adjuvant treatment of melanoma patients with dacarbazine (DTIC) and low dose natural IFNα [9]. The trial was conducted on a total of 252 patients with resected stage II-IV melanoma in 19 German centres. Patients were randomized to either adjuvant therapy with two cycles of DTIC 850 mg/m^2 with a 4 week interval, followed by 6 months of human natural human IFNα at a dose of 3 MU S.C. thrice weekly, or no adjuvant treatment. After a median time of 8.5 years the investigators report a significant reduction in melanoma-related deaths (HR = 0.65, p = 0.022) and an almost statistically significant positive effect on OS (HR = 0.71, p = 0.052).

The reported beneficial effect with respect to melanoma related deaths is surprising, since there is no evidence in large controlled trials for a beneficial effect on OS of low-dose adjuvant IFNα therapy in high-risk melanoma [7,10]. The authors suggest that the mixture of various IFNα subtypes present in natural IFN may have beneficial effects not seen with recombinant IFNα preparations, but this remains to be substantiated.

DTIC as adjuvant therapy in melanoma has also failed to show any significant benefit [11]. The rationale for combining DTIC with low-dose IFN is thus not obvious, particularly since there is no evidence for a benefit of this combination in patients with advanced melanoma. Thus, in a large randomized trial addition of IFNα-2b to DTIC in patients with metastatic melanoma did not significantly improve the response rate, time to treatment failure, or survival but significantly increased toxicity [12].

There are several problematic features of the study. Thus, the planned final analysis of the trial performed in 2001 did not show any significant differences between treatment and control arms, with respect to RFS or melanoma related deaths. However an, apparently unplanned, "exploratory" subgroup analysis of 158 patients with stage IIb-III tumors showed a significant difference in RFS between the two arms in this subset of patients. This was the reason for a second, retrospective analysis which was performed by collecting historical information on patient survival. Thus, the results reported derive not from a planned prospective analysis of the trial but from an unplanned retrospective analysis, which was prompted by the results of a prior unplanned subgroup analysis. Surprisingly, although the "exploratory" analysis had shown a difference in RFS, data on this was not collected in the retrospective follow-up, and the authors explain this by the high drop-out rate of patients which would be likely to confound RFS results. The procedures for ascertainment of survival data are unclear, since the paper does not describe how survival information or causes of death were collected in the retrospective analysis.

Some of the features of the reported results are unusual. Remarkably, although the adjuvant therapy was delivered during the first 8 months, the bene-

ficial effect on melanoma-related survival did not appear until after 3–4 years of observation, as shown in Figure 2 in the paper. This is in marked contrast to results of the positive high-dose IFN trial E1684, where the beneficial effect appeared early and survival curves separated already during the first year. This difference is unexplained. Likewise, it is peculiar that the entire benefit in survival was obtained in patients with stage IIb-IV melanoma; whereas the survival curves for stage IIa patients are super imposable. This surprising result would imply some unknown underlying biological difference between these groups.

Since the reported results of the present study were derived from an unplanned retrospective analysis, which was, moreover, prompted by findings of an unplanned subgroup analysis, they must be considered as hypothesis-generating and not conclusive. The results presented would thus need to be confirmed in a second prospective randomized trial in order to have an impact on the management of melanoma patients.

A major reason why adjuvant IFN therapy in melanoma is not widely accepted is the combination of frequent high-grade toxicities, particularly with high-dose IFN, and the fact that only a minority of patients benefit from therapy. The development of predictive tests that may help identify the subset of patients with a high likelihood of therapeutic benefit should therefore have a high priority. The identification of such predictive markers is hampered by the numerous effects of IFN and the uncertainty regarding which mechanism(s) mediate beneficial therapeutic effects. Recently an important report indicated that in patients treated with high-dose IFNα-2b the appearance of autoimmune manifestations is associated with a therapeutic benefit [13]. Autoimmunity was defined by either the appearance of clinical signs of autoimmunity such as vitiligo or thyroid dysfunction, or the appearance of auto antibodies in patient sera. The appearance of autoimmunity was correlated with both an improved RFS ($HR = 0.12$, $p < 0.001$) and OS ($HR = 0.02$, $p < 0.001$). This strongly supports that induction of autoimmunity is an important factor associated with a beneficial effect in melanoma tumors. The observations do not, however, provide a predictive biomarker, since the appearance of autoimmunity was observed only after a median of three months after start of IFN therapy. Thus, the development of autoimmunity cannot be used to select patients for IFN therapy. Further research into factors determining the appearance of autoimmunity may, however, yield useful predictive biomarkers.

The development of improved prognostic markers is essential to select patients for future trials of adjuvant therapies. At present the prognostic tools available are relatively crude and rely mainly on histopathological classification of the primary melanoma coupled with the use of sentinel lymph node biopsy as a staging technique. Little has been known regarding the biological mechanisms responsible for melanoma progression and metastasis. Very recently, however, gene expression profiling performed on primary melanomas was compared with the clinical course of patients [14]. This resulted in the identification of a set of 254 genes whose expression was associated with metastatic dissemination of melanoma. The expression of some of these genes was further studied at the protein level using a panel of antibodies. These interesting and novel findings may lead to an improved understanding of the biology of melanoma progression and metastasis, as well as the development of novel and improved prognostic markers of potential use for selection of patients for investigations of adjuvant therapy.

In conclusion, it must be emphasised that, due to the lack of established efficient adjuvant therapies in melanoma, the appropriate management of high-risk melanoma patients is to provide the opportunity to participate in well-designed prospective clinical trials.

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