Adjuvant therapy for high-risk melanoma

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Thus far the development of adjuvant therapies in melanoma has suffered greatly from the lack of effective drugs for stage IV melanoma. This has led to adjuvant therapies that are not uniformly used because of rather marginal benefits.

1. Adjuvant therapies other than with interferon

1.1. *Early trials with immune stimulants*

More than 25 randomised trials have been conducted in stage II/III melanoma with non-specific immune stimulants – such as BCG (bacillus Calmette–Guerin), *Corynebacterium parvum*, levamisole or combinations of these agents with dacarbazine – without identifying clear benefits [1].

1.2. *Adjuvant vaccine trials*

Adjuvant vaccine trials in melanoma thus far have failed, results ranging from ineffective (three randomized controlled trial (RCTs) [1]) to harmful (three RCTs [2–4]). Two large trials with Canvaxin ended early because of a detrimental outcome for the vaccine arm. Two large trials with the GMK vaccine (ganglioside GM2/KLH/QS-21) were also stopped early because of inferior outcome in the vaccine arms compared with high-dose interferon (HDI) in the Eastern Cooperative Oncology Group (ECOG) 1694 trial [3] and compared with observation in stage II patients (European Organisation for Research and Treatment of Cancer (EORTC) 18961 trial) [4], evoking fears that prolonged, multiple administrations of vaccines could be harmful [5].

Regarding the adjuvant use of granulocyte–monocyte colony-stimulating factor (GM-CSF), a recent report of the ECOG E4697 trial failed to demonstrate a significant impact on survival [6]. In two randomised trials the GM-CSF-containing arms did worse than the vaccine-alone arms [7,8], again indicating that multiple vaccinations might be harmful.

New vaccine trials are ongoing. The MAGE-A3 protein combined with the immunostimulant AS15 is being evaluated in an RCT in stage III patients after encouraging results were obtained in a randomised phase II EORTC trial [9]. Moreover, a potentially predictive gene profile, characterising mostly immunomodulatory factors, is used to stratify and analyse the results of the RCT [10]. Also a study of an oncolytic herpes simplex virus vector encoding GM-CSF is ongoing in stage III/IV patients after interesting results in phase II patients were obtained [11,12].

1.3. *Adjuvant therapy with interferon*

Twenty-five years of RCTs in melanoma with interferon-alpha (IFNα) are a testimony that efficacy of adjuvant therapy with IFN is modest at best. Meta-analyses of phase III trials demonstrated that IFN has a consistent effect on relapse-free survival (RFS) but no or only a marginal effect on overall survival (OS) [13–15]. No relationship between dose or duration of treatment and outcome has been demonstrated. These findings suggest that only a minority of patients are sensitive to IFN, and demand that we identify these patients. Based on the EORTC 18991 trial in 1256 patients, the US Food and Drug Administration (FDA) approved pegylated interferon α-2b (PEG-IFN; Sylatron™) in 2011 for stage III melanoma patients [16]. The EORTC 18952 trial in 1388 stage IIB/III melanoma patients compared intermediate doses of interferon α-2b (IFN) with observation [17].

These EORTC RCTs stratified patients by SN-staging (microscopic involvement only: stage III-N1) or gross macroscopic relapse (stage III-N2) as well as by presence or absence of ulceration in the primary tumour. Both stage and ulceration are key prognostic factors [32]. Patients with only micrometastases have a much better prognosis than patients with palpable node metastases [18]. Palpable nodal disease may represent more aggressive disease from the onset or by acquisition of additional mutations over time. Regarding ulceration, for the same Breslow thickness, patients with an ulcerated primary have a 10–25% lower survival probability at 10 years, indicating a distinct biological entity [19]. Also, ulcerated primaries have (a) a distinct gene profile [20]; (b) a severely immunosuppressed status of sentinel nodes [21] and (c) a different stromal response [22].

The meta-analysis of the two largest adjuvant IFN/PEG-IFN RCTs involving 2644 patients demonstrated that both tumour load in the lymph nodes and ulceration of the primary are independent predictive factors for adjuvant IFN therapy [23]. Patients with favourable stage (IIb/III-N1) and/or ulcerated primary tumour benefited significantly from IFN/PEG-IFN treatment (hazard ratios (HRs) 0·56–0·69) with regard to RFS,

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distant-metastasis-free survival (DMFS), and OS, whereas patients with stage III-N2 disease or non-ulcerated primary tumour did not. Ulceration of the primary was the overridingly important predictive factor for IFN sensitivity. In a meta-analysis of 1393 patients with ulcerated melanomas – reported in a variety of trials that did not include EORTC 18991 – Wheatley et al reported a hazard ratio (HR) of adjuvant IFN therapy for OS of 0.77 (99% confidence interval (CI) 0.63–0.93), whilst there was no impact of adjuvant IFN therapy in the 2118 patients without ulceration (HR 0.98; 99% CI 0.87–1.17) [23]. Treatment interaction between ulceration and IFN has been investigated retrospectively in the Sunbelt and the Nordic trials [24,25]. In the Sunbelt trial, which enrolled SN-positive patients only, a significant treatment benefit occurred only in patients with ulcerated primaries [24]. In the Nordic trial, almost all patients had palpable nodal involvement and, consistently with the EORTC trials, no significant benefit was conferred by the presence of ulceration [25]. The role of ulceration is currently being evaluated prospectively in the adjuvant PEG-IFN trial EORTC 18081 in 1200 patients with stage II ulcerated primary melanomas.

Research on tissue samples to identify gene profiles and cytokine profiles potentially predictive for IFN sensitivity is ongoing [26]. In contrast to findings by Gogas and Kirkwood [27], the prognostic and potentially predictive value of the presence of autoimmune antibodies in the EORTC and Nordic trials was evaluated and found not to be a strong prognostic factor, neither did it have predictive value [28,29].

In 2012, the results of the adjuvant phase III trial of adjuvant biochemotherapy (CVD + IL2 + IFN) demonstrated a significant improvement in RFS but no improvement in OS. These results are interesting but not practice-changing [30].

2. New adjuvant trials with novel agents

2.1. *Immunomodulators*

For patients with advanced stage III melanoma, a double-blind RCT comparing adjuvant ipilimumab versus placebo recently completed accrual of 950 patients (EORTC 18071; ClinicalTrials.gov, number NCT00636168) [31]. Preliminary data from another small trial suggest adjuvant ipilimumab activity in advanced resected stage III/IV disease [32]. New adjuvant trials evaluating anti-PD-1 are being prepared.

2.2. *BRAF inhibitors and MEK inhibitors*

New adjuvant trials in lymph-node-positive melanoma patients have been launched involving BRAF inhibitors either alone or in combination with MEK inhibitors [33,34]. The basis for these trials is their success in stage IV patients. Trials are ongoing, and design and pros and cons will be discussed.

Conflict of interest statement

None declared.

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