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Original Paper

Strategy of the EORTC-MCG Trial Programme for Adjuvant Treatment of Moderate-risk and High-risk Melanoma

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Trials in high-risk melanoma patients evaluating the role of postoperative adjuvant treatment with interferons or other cytokines, ganglioside-based vaccines, or vaccines based on melanoma cells are ongoing or planned internationally. In Europe, the two largest randomised trials are carried out by the European Organization for Research and Treatment of Cancer—Melanoma Cooperative Group (EORTC-MCG). In stage IIA patients (T3N0M0) with a moderate risk of micrometastatic disease (35–40%), Trial 18961 compares observation with ganglioside GM2 vaccination. This trial will be activated during the spring of 1998 and is expected to enrol 1000 patients. In stage IIB–IIIB (T4N0M0-TxN1-2M0) patients with a high risk of micrometastatic disease (approximately 80%), trial 18952 compares observation with adjuvant therapy using two intermediate dosage regimens of interferon alfa-2b (IFN-α2b). These trials and the philosophy of the EORTC-MCG programme allow more toxic treatment regimens to be investigated in patients with high-risk disease and only treatments with minimal toxicity to be evaluated in patients with moderate- to low-risk disease. Recently completed and other ongoing trials also are discussed. Overall, if clinical efficacy is demonstrated, the toxicity, impact on quality of life and treatment costs determine the acceptance and applicability of a treatment.

Key words: melanoma, adjuvant therapy, trials, interferon, ganglioside, vaccine
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RISK OF MELANOMA RELAPSE IN PATIENTS WITH MODERATE-RISK (STAGE IIA) OR HIGH-RISK (STAGE IIB-IIIB) DISEASE

THE UNPREDICTABLE biological behaviour of malignant melanoma is well known. Patients with thin melanomas (< 0.76 mm) are easily cured by excision of the primary tumour, but a small fraction (up to 5%) may develop late recurrences, even beyond 10 years of follow-up and die. Because of this potential for late recurrence, the concept of 'cure' for melanoma is not particularly meaningful [1]. The risk of recurrence for patients with stage IA–IIB melanoma (i.e. no signs of lymph node or distant metastases) is determined by tumour thickness. Kelly and associates [2] and McCarthy and colleagues [3] have provided data on post-surgical annual recurrence rates for melanomas of different thickness and Rogers and coworkers [4] and Slingluff and associates [1] have provided further insight regarding the annual risk of melanoma progression in melanoma stage IA–IIB patients. Patients with very thick melanomas (> 4.0 mm; stage IIB) usually have early metastases after tumour excision and have a prognosis very similar to that of node-positive (stage IIIB) melanoma patients.

Taken together, the following statements can be made regarding prognosis: (1) for melanomas < 0.76 mm, the recurrence risk is approximately 1% and this risk is distributed evenly over 15 years and does not decrease with time; (2) for tumours between 0.76 and 1.5 mm, a relatively constant recurrence risk of approximately 5% per year exists; (3) for melanomas 1.5 to 4.0 mm thick (stage IIA), the recurrence risk is 12–19% per year in the first 2 years and then gradually declines to an annual risk of 5% by the fifth year; and (4) for tumours > 4 mm in thickness, the recurrence risk is greater than 30% in the first year and is about 12% from the second to fourth years. Our own observations in the recently closed EORTC 18832 trial evaluating the role of prophylactic isolated limb perfusion in stage I patients with high-risk primary melanoma (> 1.5 mm) confirm estimates described in the literature and demonstrate a disease-free

survival (DFS) of 64% and an overall survival of 77% at 5 years [5]. Cascinelli and colleagues [6] and Callery and coworkers [7] showed that greater than 50% of patients with metastases to regional lymph nodes will develop distant metastases or die within 2 years after diagnosis.

ADJUVANT THERAPY FOR MODERATE-RISK TO HIGH-RISK CUTANEOUS MELANOMA

Many adjuvant therapy trials of stage IIA, IIB and IIIB malignant melanoma using various agents have been performed over the last 20 years. With the exception of two trials that evaluated treatment with interferon alfa (IFN-α), virtually all trials have failed to identify a benefit for adjuvant therapy. Eleven negative reports of adjuvant therapy with dacarbazine (DTIC, with or without lomustine or carmustine) and/or bacille Calmette-Guérin (BCG) or levamisole were published [8–18]. The 1991 study report by Quirt and associates [15] showed a benefit of adjuvant levamisole treatment but no impact of BCG alone or BCG plus levamisole. Since two other trials of adjuvant therapy with levamisole have been negative [11, 16], levamisole is not regarded as an active agent. Three randomised trials using adjuvant *Corynebacterium parvum* also have been reported, all with negative results [19–21]. Results of five sizable trials of active specific immunotherapy with either whole tumour cell vaccines [22–24] or viral lysates of melanoma cells [25, 26] have shown no survival impact by any of these adjuvant regimens. Finally, phase III trials by the Southwestern Oncology Group (SWOG), one using vitamin A [27] and another using interferon-γ [28], also reported negative results.

Adjuvant IFN-α trials in moderate-risk melanoma

At present there are no mature data on the efficacy of adjuvant therapy with IFN-α in patients with stage IIA melanoma. In patients with primary melanomas > 1.5 mm who are clinically node negative, three trials in Europe have completed accrual. These three trials were similar in design and all used IFN-α2a at low-doses (3 MU daily). The Austrian Melanoma Cooperative Group two-arm trial [29] compared observation with IFN-α2a 3 MU subcutaneously (s.c.) daily for 3 weeks followed by 3 MU s.c. three times weekly (TIW) for 12 months. This trial reported a benefit in DFS but no results regarding overall survival are available. The French National trial, a two-arm trial comparing observation with IFN-α2a 3 MU s.c. TIW for 18 months, reported a significant ($P < 0.05$) prolongation of DFS as well as overall survival in the IFN-treated arm after the second interim analysis [30]. However, due to a lemon-shaped curve, overall survival was no longer significant at the third interim analysis (median follow up of 4.5 years) [31]. In 1995, results of the first interim analysis of the Scottish Melanoma Cooperative Group trial, a two-arm trial comparing observation to treatment with IFN-α2a 3 MU SC TIW for 6 months, were presented at the First International Conference on the Adjuvant Therapy of Malignant Melanoma in London and showed a trend in favour of IFN-α2a treatment. A more recent analysis with additional follow-up no longer shows an advantage for IFN-α2a (M Cornbleet, data not shown). 5–7 years median follow-up in stage IIA disease may be necessary to achieve maturity and accurately assess the impact of therapy on survival. Therefore, mature results of the Austrian and Scottish trials must be awaited.

Adjuvant interleukin-2 + IFN-α in moderate-risk melanoma

In a Swiss-German study of clinically node-negative patients with primary melanomas thicker than 1.5 mm, the effects of adjuvant therapy with interleukin-2 (IL-2) 9 MU s.c. daily on days 1–4 every 6 weeks in combination with IFN-α2b 3 MU s.c. TIW over 48 weeks were compared to observation alone [32]. At the end of 1995, 227 patients were enrolled. After a median follow up of 37 months, 87% of patients who received treatment and 83% of patients in the observation arm were disease free, respectively. Obviously, these data need to mature before the results of this trial can be declared negative.

EORTC-MCG trial 18961*: ganglioside vaccination in stage IIA patients*

Gangliosides and ganglioside vaccines. Since 1975 Livingston and coworkers at Memorial Sloan-Kettering Cancer Center (New York, U.S.A.) have performed a series of clinical trials vaccinating melanoma patients with intact irradiated autologous and allogeneic melanoma cell vaccines that express a variety of glycoprotein and ganglioside antigens [33–35]. The melanoma antigen recognised most frequently by the induced antibodies in postvaccination sera was a ganglioside termed GM2 [33]. Studies performed on melanoma specimens demonstrate that ganglioside GM2 is present on 95% of melanomas [36, 37]. Naturally occurring IgM antibodies against GM2 have been detected in 5–10% of melanoma patients and the disease-free interval and overall survival rate of these patients are significantly prolonged compared to patients without antibodies against GM2 [34, 38]. These antibodies are exclusively IgM and of moderate titre. Patients with vaccine-induced antibodies also had a more favourable disease-free interval and overall survival rate [35]. Although a whole cell vaccine was able to induce anti-GM2 IgM antibodies in the majority of patients immunised, BCG with GM2 adherent to the surface proved easier to prepare and resulted in comparable or slightly higher antibody titres. Later, it was shown that the introduction of keyhole limpet haemocyanin (KLH) as a carrier molecule and QS-21 (a homogenous triterpene glycoside fraction isolated from bark extracts of a South American tree, *Quillaja saponaria* Molina) as an adjuvant resulted in the highest and most consistent induction of high antibody titres [39].

Results of the first randomised phase III trial in stage III melanoma. A randomised trial of GM2/BCG adjuvant therapy following surgery for stage III melanoma was conducted in 122 patients at Memorial Sloan-Kettering Cancer Center between 1987–1988 [35]. Anti-GM2 IgM antibodies were induced in a majority (86%) of treated patients and natural antibodies against GM2 were identified in a small subset of control (unvaccinated) patients. Serologic response against GM2 was demonstrated again to be a favourable prognostic factor. In addition, the vaccinated group of patients has shown a trend toward prolongation of relapse-free survival; however, this is confounded by the unanticipated presence of pre-existing anti-GM2 antibody among 6 control patients. With exclusion of these patients, the therapeutic impact of GM2/BCG vaccination upon relapse-free survival was significant ($P = 0.02$).

Ongoing trials with the ganglioside GM2-KLH/QS-21 vaccine. Patients with a low risk for micrometastatic disease (stage IIA) are generally undesirable candidates for toxic adjuvant therapy and good candidates for nontoxic adjuvant agents.

The GM2-KLH/QS-21 vaccine is chemically defined and consistent in formulation; it is nontoxic and has been well tolerated over many months of therapy. In addition, the vaccine is associated with the induction of a readily measured immunological endpoint, anti-GM2 antibody. The presence of anti-GM2 (IgM) antibody has been demonstrated as a favourable prognostic factor. Finally, this vaccine subsequently may be coupled with other effective therapeutic modalities for the prevention of melanoma relapse. As part of a policy to accept only a degree of treatment toxicity that correlates with the risk of micrometastatic disease, the EORTC-MCG deemed this vaccine a suitable candidate for evaluation in stage IIA melanoma patients. EORTC trial 18961 is scheduled to begin during the spring of 1998 and to enrol 1000 patients. The Eastern Cooperative Oncology Group (ECOG) Trial 1694 is comparing efficacy of the vaccine to the ECOG 1684 IFN-α2b regimen in stage IIB/IIIB patients and in the U.K., a trial of stage IIIB patients will be activated in 1998 comparing this vaccine to a placebo vaccine.

Adjuvant IFN-α therapy in high-risk melanoma (stage IIB–IIIB)

High-dose IFN-α: ECOG 1684 *trial.* A significant improvement of both DFS and overall survival in melanoma patients treated with an intensive schedule of IFN-α2b for 1 year was demonstrated in ECOG 1684 [40]. IFN-α2b was administered at a dose of 20 MU/m^2/day intravenously (i.v.) 5 days per week for 4 weeks followed by 10 MU/m^2/day s.c. TIW for 48 weeks. Toxicity during the first 4 weeks of daily i.v. therapy required dose delays/reductions in 37% of patients. Toxicity during the subsequent 11 months of treatment was associated with dosing delays/reductions in 36% of patients. Constitutional, haematologic and neurologic toxicity were most frequently observed and reversible on withdrawal of IFN treatment. Hepatotoxicity was less frequently observed and generally mild-to-moderate in severity. However, 2 patients, possibly with underlying antecedent liver disease, succumbed to hepatotoxicity in the first to third months of treatment. In conclusion, the survival benefit of adjuvant IFN-α treatment was established in this trial. A retrospective quality-adjusted survival analysis (Q-TWIST) and an economic analysis of the ECOG 1684 trial were recently published by Cole and associates [41] and Hillner and colleagues [42], respectively to address questions regarding quality of life and cost effectiveness of this treatment.

The North Central Cancer Treatment Group (NCCTG) trial. The NCCTG trial [43] demonstrated that IFN-α2a 20 MU/m^2 administered intramuscularly (i.m.) TIW for only 12 weeks resulted in a trend towards a survival benefit in TxN1M0 melanoma patients but not in node-negative patients with a high-risk primary melanoma thicker than 1.7 mm. Similarly, significant toxicity was observed with this treatment.

Low-dose IFN-α: WHO-16. Considerable excitement was raised by the interim analysis results of the WHO-16 trial [44] in 444 stage IIIB patients regarding the efficacy of a well tolerated, prolonged adjuvant therapy with low-dose IFN-α2a. In patients surgically treated for regional lymph node metastases IFN-α2a 3 MU s.c. TIW for 3 years resulted in a highly significant prolongation of DFS for all patients and in a survival benefit for some subgroups [44]. One year later, however, the survival curves of the IFN-treated patients and the control patients converged to produce the typical 'lemon-shaped curve phenomenon'. Differences between the two treatment arms were no longer significant [45].

ECOG 1690. Results from this three-arm trial comparing observation, high-dose IFN-α (ECOG 1684 schedule) and prolonged low-dose IFN-α (WHO-16 schedule) in stage IIB–IIIB patients are expected to be reported in 1998.

EORTC 18871. This three-arm trial of 850 stage IIB ($T_{>3\,mm}$N0M0)-IIIB patients completed accrual in 1996. The first interim analysis of the very low-dose IFN-α2b treatment (1 MU s.c. on alternative days for 1 year) did not suggest benefit in these melanoma patients (Kleeberg UR, EORTC, EORTC trial 18871 interim analysis reported at the German Oncology Congress, Berlin, 1996).

RATIONALE FOR INTERMEDIATE-DOSE IFN-α TRIALS IN STAGE IIB–IIIB PATIENTS

High-dose IFN-α treatment has been shown effective in the adjuvant setting in one trial. Low-dose IFN-α treatment currently has not been effective in the adjuvant setting. Since IFN-α may have a threshold dose level to exert its activity, it is mandatory to explore the activity of intermediate-dose levels of IFN-α that are better tolerated and may be more widely applicable and accepted. It is the position of the EORTC-MCG that the results of the ECOG 1684 high-dose IFN-α trial need to be confirmed by the ECOG 1690 trial in order to recommend this intensive and expensive treatment as standard therapy. Meanwhile, the efficacy and toxicity of intermediate doses of IFN-α will be investigated to try and find an alternative with equal efficacy, decreased toxicity and decreased costs.

Two trials have been activated in Europe recently. The Scandinavian-MCG three-arm trial activated late in 1996 compares observation to IFN-α 10 MU s.c. daily 5 days per week for 4 weeks followed by 1 or 2 years of 10 MU s.c. TIW. The EORTC-MCG activated trial 18952 in the middle of 1996 comparing observation (200 patients) with IFN-α2b treatment (800 patients) at a dosage of 10 MU s.c. daily 5 days per week for 4 weeks followed by either (arm-A; 400 patients) 1 year of IFN-α2b 10 MU s.c. TIW or (arm-B; 400 patients) 2 years of IFN-α2b 5 MU s.c. TIW. This trial is accruing very rapidly and will complete accrual within 3 years. One year later, a final analysis comparing treatment with observation will be possible due to the unbalanced randomisation. Prospective assessments of quality of life and cost will further determine the realistic value of adjuvant IFN-α treatment. Since not all melanoma patients whose extent of disease at treatment initiation may range from node negative (T4N0M0) to node positive (TxN1-2M0) may benefit to the same degree (if at all) from adjuvant therapy, additional studies are being carried out in this trial to identify the value of new prognostic factors including stratification for sentinel node as the only positive node, detection of circulating tumour cells by polymerase chain reaction (PCR), angiostatin levels, S-100 levels, expression of plasminogen activator inhibitors (PAI-UPAI) on immunohistochemistry, and multivariate analysis of 'new' and 'old' prognostic factors.

Melanoma cell-based vaccination trials

Five sizable active specific immunotherapy trials using either whole tumour cell vaccines [22–24] or viral lysates of melanoma cells [25, 26] have not identified a survival impact for any of these adjuvant regimens. Morton's polyvalent melanoma cell vaccine (PMCV) has been shown to cause

regressions in some stage IV patients [46] and its activity in the adjuvant setting will be tested in a randomised phase III trial to be activated in 1997 or 1998. Mellacine, another allogeneic melanoma cell line-based vaccine given in combination with the adjuvant DETOX, also has been reported to produce an occasional response in stage IV melanoma patients [47]. This vaccine was evaluated in the adjuvant setting in stage IIA–IIB (T3-4NOM0) patients in a phase III SWOG trial. This trial reached full accrual in 1996 and thus mature data is expected around the year 2000.

CONCLUSIONS

The role of postoperative adjuvant therapy for melanoma patients at risk of metastatic disease is under intense evaluation. Interferons, other cytokines, vaccines and combinations of these immunotherapies are being investigated in numerous studies to identify efficacy, tolerability and optimal dosage regimens. The identification of effective adjuvant therapy for high-risk melanoma that is tolerable, widely applicable and cost-effective is the goal of the EORTC-MCG trial programme. Results of ongoing trials analysed over the next few years may provide a reference standard for new phase III trials to evaluate new treatments, such as vaccines using peptides or genetically modified cells.

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