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Original Paper

Systemic Adjuvant Treatment of High-risk Melanoma: the Role of Interferon Alfa-2b and Other Immunotherapies

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Until recently, the prognosis of patients with deep primary melanomas or regionally metastatic nodal disease has been poor, with 5-year survival rates of 25–50%. The results of the Eastern Cooperative Oncology Group (ECOG) trial 1684 represent the first evidence of effective adjuvant therapy for these patients. Interferon alfa-2b (IFN-α2b) administered at maximally tolerated doses for 1 year significantly improved both relapse-free and overall survival. The impact of interferon therapy was observed early during treatment and the effect was durable. The results of this trial represent a breakthrough in the treatment of high-risk resected cutaneous melanoma and identify the new reference standard for new cytokines, vaccines and combinations. The favourable results provide a strong impetus for redoubled research into immunotherapy for treatment of melanoma. Specifically, ganglioside vaccines have been identified that induce antibody responses and may affect patient outcome and peptide/protein vaccines that are recognised by the T-cell have been identified in large numbers. ECOG and the U.S. Intergroup are conducting a phase III trial (E1694) that compares GM2 vaccine to IFN-α2b and a phase II trial evaluating concurrent or sequential use of interferon and vaccines for patients with resectable melanoma. They are also planning phase II trials of peptides for patients with metastatic unresectable melanoma. Laboratory analyses of the immune responses induced by IFN and the several vaccines are anticipated to reveal the fundamental immune mechanisms that are important for relapse-free survival and immunological control of melanoma. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PATIENTS WITH deep primary melanoma (i.e. > 4 mm Breslow depth) or regional lymph node metastasis exhibit a high rate of relapse and mortality ranging from 50 to 90% [1–4]. Adjuvant therapy has not previously demonstrated a meaningful impact upon relapse-free or overall survival in patients with high-risk cutaneous resected melanoma. The Eastern Cooperative Oncology Group (ECOG) trial 1684 has recently demonstrated that treatment with recombinant interferon alfa-2b (IFN-α2b, Schering-Plough) for 1 year significantly improves relapse-free and overall survival in patients at high risk of recurrence following surgical resection of the primary tumour [5]. Node-positive patients comprised nearly 90% of the population in the pivotal E1684 trial and those patients with palpable nodal disease, microscopic non-palpable nodal disease, or nodal recurrence consistently benefited to the greatest degree from IFN-α2b. The results of this study represent the first evidence that treatment of high-risk melanoma patients may be of benefit and establishes the high-dose regimen of IFN-α2b as the new standard of care.

The use of immunotherapy for the treatment of melanoma stems from clinical and pathological evidence suggesting that tumour regression at the site of primary melanoma occurs frequently and is dependent upon the immune system. In addition, antibody responses directed against the melanoma cell surface ganglioside GM2 have been measured in patients with melanoma [6]. Recent studies also have identified multiple specific melanoma antigens that are recognised by T-cells in patients with melanoma [7, 8]. The role of immunomodulation associated with IFN-α2b therapy in

patients with melanoma has yet to be established in relation to antitumour efficacy. As the effector mechanism is identified, the optimal use of IFN and other immunotherapies, particularly cancer vaccines, can be developed in patient groups who are most likely to derive benefit from these therapies.

This paper reviews low-dose and high-dose IFN trials in metastatic disease, which provided the rationale for ECOG 1684 and discusses ECOG 1684 together with its implications for the treatment of high-risk melanoma patients. Finally, an overview of ongoing ECOG studies using IFN and other immunotherapies for the treatment of melanoma is provided.

RATIONALE FOR ECOG TRIAL 1684

The antitumour activities of IFN-α include antiproliferative and immunomodulatory effects, such as modulation of oncogene expression and growth factor production, as well as inducing tumour cell surface major histocompatibility antigen modulation and augmenting the presentation of antigens by dendritic cells [9, 10]. These effects are likely to play a role in the antitumour responses observed with IFN-α in the treatment of metastatic melanoma [11]. Based on the promising experience in advanced disease, IFN-α was investigated at varying dosages as adjuvant therapy in earlier stages of disease where the opportunity to reduce the occurrence of relapse and death might be better than in established advanced metastatic disease.

Low-dose trials

The World Health Organization (WHO) sponsored a multicentre randomised trial that included 444 patients with node-positive malignant melanoma. Patients were randomised after surgical resection of the primary tumour to receive either low-dose IFN-α2a (3 MU) subcutaneously (s.c.) three times a week for 3 years or observation [12]. Of 426 evaluable patients, 208 received surgery alone and 218 received surgery plus adjuvant IFN-α2a. After a median follow up of only 19 months, a statistically significant ($P = 0.01$) reduction in 2 year disease-free survival (DFS) was reported in patients receiving IFN-α2a compared to patients receiving surgery alone (46 versus 27%, respectively). However, with further follow-up, these results were not sustained. An overall survival benefit in the treated, as compared to the observed, population was not provided by low-dose IFN-α2a in the adjuvant setting for patients with node-positive malignant melanoma.

The effect of low-dose IFN-α2a on disease-free interval (DFI) in patients with resected primary melanoma has also been investigated in a French multicentre trial [13]. Patients with intermediate-risk resected melanoma of Breslow depth > 1.5 mm and without clinically apparent regional lymph node disease (AJCC stage IIA) were randomised to receive either IFN-α2a 3 MU s.c. three times a week for 18 months or no treatment. Sequential analyses of the trial data have been performed, with the primary endpoint being a 15% benefit in the DFI for treated patients. After a median follow-up of 2.3 years, IFN-α2a was found to prolong overall survival, but not the DFI, to a significant degree. Treatment with IFN-α2a was well tolerated by most patients, but approximately 21% of patients discontinued treatment before completing the 18-month regimen. No significant difference in overall survival was observed between the two treatment groups after follow up of nearly 5 years, which was recently reported at the 4th World Conference on Melanoma in Sydney, Australia [14]. Adjuvant therapy with low-dose IFN-α2a for 18 months therefore appears to delay recurrence in patients with resected primary melanoma (> 1.5 mm) and no clinical evidence of nodal disease, but does not achieve a durable (curative) response.

High-dose trial

The North Central Cancer Treatment Group (NCCTG) conducted a prospective randomised trial to assess the clinical efficacy of adjuvant IFN-α2a in terms of recurrence rates, time to recurrence and patient survival [15]. Patients eligible for this study had a primary tumour > 1.69 mm in thickness with no positive nodes (clinical stage I) or complete excision of regional nodal disease (clinical stage II). Routine lymph node dissections were not performed unless nodes were clinically involved. A large proportion of patients enrolled in the trial had primary tumours with a Breslow depth of 1.69–4 mm and only approximately 50% of patients had clinically node-positive disease. For patients randomised to the treatment group, IFN-α2a 20 MU/m^2 was administered intramuscularly (i.m.) three times each week for 12 weeks.

IFN therapy did not significantly affect the outcome of patients with stage I disease. After a median follow-up of 6.1 years, median DFS time was 2.4 years for the IFN-α2a group and 2.0 years for the observation group ($P = 0.19$) [15]. Projected median survival times were 6.6 years for the IFN-α2a group and 5.0 years for the observation group ($P = 0.40$). However, for node-positive patients (stage III), median DFS was 17 months in the treatment group and 10.8 months in the control group. This difference achieves nominal statistical significance using a Cox model ($P = 0.04$). In addition, IFN-α2a therapy prolonged median survival of stage III patients in comparison with control (4.1 versus 2.7 years, respectively), although this difference was not statistically significant ($P = 0.44$). These results suggest a possible benefit of high-dose adjuvant IFN therapy in patients with node-positive disease in a trial where the number of subjects with high-risk disease was inadequate to detect a significant benefit.

ECOG TRIAL 1684

Based on the promising dose-dependent antitumour activity of IFN-α2b in metastatic disease and lack of cross resistance with other agents, ECOG initiated a trial (E1684) to determine the efficacy and tolerability of IFN-α2b administered at maximum tolerated doses for 1 year in melanoma patients at high-risk of relapse [5].

Patient selection and study design

Patients were enrolled in E1684 from 1984 to 1990. Unlike prior trials, all patients entering the study had a regional lymphadenectomy to pathologically assess their regional nodal status and consequent risk of relapse [5]. Patients were stratified into 4 groups based on clinical and pathological extent of disease as follows: (1) node-negative deep primary melanomas of Breslow depth > 4 mm; (2) primary melanomas of any tumour stage with pathological evidence of lymph node involvement that was nonpalpable; (3) palpable regional lymph node involvement synchronous with a primary melanoma of T1-4; and (4) regional lymph node recurrence at any

interval after appropriate surgery for primary melanoma of any depth. Table 1 provides the original staging classification and current American Joint Committee on Cancer (AJCC) categories for the four strata.

After stratification by nodal involvement, patients were randomised into either a treatment group or an observation group (standard therapy). Patients assigned to the treatment group received IFN-α2b 20 MU/m^2/day intravenously (i.v.) 5 days per week for 4 weeks (induction therapy), followed by 10 MU/m^2/day SC three times weekly for 48 weeks (maintenance therapy) [5].

Dose modifications were performed using a two-level toxicity scale developed by ECOG. According to this scale, patients with level 1 side-effects (e.g. a granulocyte count < 500 cells/uL and/or liver function parameters > 5–10 times normal limits) had treatment withheld until these side-effects subsided. Thereafter, they received 50% of the initial dose. Patients experiencing level 2 side-effects (e.g. granulocyte count < 250 cells/uL and/or liver function parameters > 10 times normal limits) were withdrawn from therapy.

Outcome measures

The primary endpoints of the study were to determine if IFN-α2b could prevent relapse and death of patients with high-risk resected cutaneous melanoma. Patients were monitored weekly during the first month on study, at intervals of 1–3 months in year 1, every 4 months in year 2 and every 6 months over subsequent years [5]. Site and interval of first and subsequent relapses were recorded in addition to cause and date of death. Planned sequential treatment comparisons for relapse-free and overall survival were conducted in each year in March 1990–1993 using a stratified log-rank test. The Kaplan–Meier method was used to calculate plots of estimated relapse-free and overall survival. Cox's proportional hazards regression was used to assess the impact of treatment after adjustment for other patient characteristics.

Results

The intent-to-treat population included 280 randomised patients, excluding 7 patients for whom follow-up data were incomplete [5]. Of the intent-to-treat population, 143 patients received IFN-α2b and 137 received no treatment. The treatment and observation groups were well balanced for known prognostic factors, with no significant differences in any factor (Table 2). Patients were monitored for a range of 0.6–9.6 years, with a median follow-up among 109 surviving participants of more than 6.9 years at the time of publication in 1996.

Relapse-free survival. The analysis of treatment impact on relapse-free survival is presented in Figure 1. The median

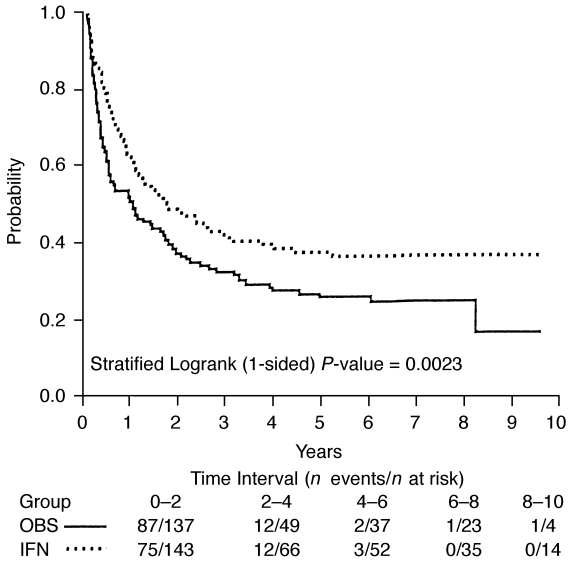

Figure 1. Relapse-free survival of eligible patients, $P_1 = 0.0023$, stratified logrank. Reprinted with permission from *J Clin Oncol* 1996 [5].

relapse-free survival for IFN-α2b-treated patients was 1.72 years (95% confidence interval [CI], 1.07–2.88 years) compared with 0.98 years (95% CI, 0.50–1.65 years) for the observation group [5]. The difference between the two groups was highly statistically significant ($P_1 = 0.0023$), adjusting for disease stage at randomisation. Estimated 5-year relapse-free survival rates were 37% (95% CI, 30–46%) with adjuvant IFN-α2b therapy and 26% (95% CI, 19–34%) with observation. This benefit represents a 42% improvement in the fraction of patients who remain free of relapse 5 years after treatment. Hazard function analyses, which reflect the instantaneous likelihood of relapse, show a sustained difference between treatment and observation groups, with the greatest reduction of relapse risk early during treatment (Figure 2). In contrast to all available data from low-dose trials, at completion of the 1-year treatment, no burst of relapses that would suggest a cytostatic effect was observed. Rather, the data suggest a cytotoxic or durable immunologic effect of IFN therapy.

Overall survival. The impact of IFN-α2b treatment on overall survival is illustrated in Figure 3. The overall median survival was 3.82 years (95% CI, 2.34–7.08 years) for patients receiving IFN-α2b compared with 2.78 years (95% CI, 1.83–4.03 years) for those in the observation group ($P_1 = 0.0237$) [5]. This represents an improvement in median survival of approximately 1 year. The estimated overall 5-year

Table 1. *Original and current disease staging for ECOG* 1684

Tumour characteristics	TNM	Original staging	Current (AJCC) staging
Localised > 4 mm; no palpable nodes; negative node pathology	$pT_4pN_0M_0$	CS1, PS1	IIB
Limited nodal mets; no palpable nodes; positive node pathology	Any TpN_1M_0	CS1, PS2	IIIA
Limited nodal mets; palpable nodes; positive node pathology	Any TcN_1M_0	CS2, PS2	IIIA
Limited nodal mets; regional nodal recurrence; positive node pathology	Any $TxrN_1M_0$ recurrent at regional node	CS2R	Regional nodal recurrence

Reprinted with permission from *J Clin Oncol* 1996 [5].

survival rates were 46% (95% CI, 39–55%) for patients treated with IFN-α2b and 37% (95% CI, 30–46%) for those who received no adjuvant therapy. The impact of IFN-α2b on overall survival was sustained over the median follow-up of nearly 7 years.

Subset analyses of the effects of IFN treatment according to the four risk groups showed differences in the impact of therapy on relapse-free survival between node-negative and node-positive patients [5]. Among the small number of node-negative patients ($n = 31$), no significant impact of therapy was observed. Because an imbalance in the presence of primary tumour ulceration was observed in this group, these subset results are qualified. The small number of patients in this group did not allow further analysis. The combined group of patients with pathologically proven nodal disease, whether palpable or nonpalpable, exhibited the greatest difference with IFN-α2b treatment compared with those who received observation only. This suggests that IFN therapy may affect microscopic metastatic disease and early palpable nodal disease. Similarly, the largest subset of patients, those with disease recurrence ($n = 174$), showed a statistically significant benefit with IFN-α2b treatment. The impact of IFN therapy on all node-positive patients, 90% of patients enrolled in E1684, was highly statistically significant for relapse-free survival and overall survival ($P_2 = 0.0006$ and $P_2 = 0.006$, respectively).

Multivariate Cox regression analysis was used to adjust the estimate of treatment effect based on other factors that may affect outcome. In addition to treatment, these factors included disease stage, age, time to randomisation and presence of tumour ulceration. The results of these analyses showed that

Table 2. Distribution of patient characteristics across treatments for eligible patients

	Observation ($n = 137$)		IFN-α2b ($n = 143$)	
Characteristic	No.	%	No.	%
Age at randomisation, years				
< 50	75	54.7	80	55.9
≥ 50	62	45.3	63	44.1
Performance status				
Fully active	123	89.8	126	88.1
Ambulatory	14	10.2	17	11.9
Strata				
CS1/PS1	15	11.0	16	11.2
CS1/PS2	14	10.2	20	14.0
CS2/PS2	21	5.3	20	14.0
Recurrent	87	63.5	87	60.8
Sex				
Male	79	57.7	90	62.9
Female	58	42.3	53	37.1
Site of primary tumour				
Head/neck	12	8.8	17	11.9
Upper limb	22	16.1	18	12.6
Lower limb	30	21.9	25	17.5
Subungual	2	1.5	0	0.0
Trunk	58	42.3	68	47.6
Anogenital	2	1.5	1	0.7
Other	10	7.3	11	7.7
NA	1	0.7	3	2.1
Type of primary tumour				
Lentigo maligna	4	2.9	6.6	4.2
Superficial spreading	45	32.9	51	35.7
Nodular	67	48.9	60	42.0
Acral lentiginous	1	0.7	0	0.0
Other	4	2.9	8	5.6
NA	16	11.7	18	12.6
Breslow depth (mm)				
< 2	44	32.1	55	38.5
2–3	17	12.4	17	11.9
3–4	14	10.2	18	12.6
> 4	49	35.8	38	26.6
NA	13	11.4	15	10.5
Clark level				
1	3	2.2	3	2.1
2	14	10.2	16	11.2
3	34	24.8	28	19.6
4	58	42.3	69	48.3
5	21	15.3	14	9.8
NA	7	5.1	13	9.1
Ulceration of primary tumour				
No	105	76.6	112	78.3
Yes	23	16.8	23	16.1
NA	9	6.6	8	5.6

NA, not available. Reprinted with permission from *J Clin Oncol* 1996 [5].

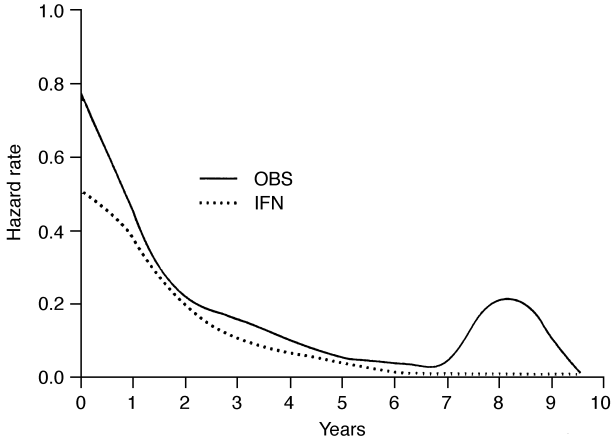

Figure 2. Estimated hazard of relapse over time for eligible patients. Reprinted with permission from *J Clin Oncol* 1996 [5].

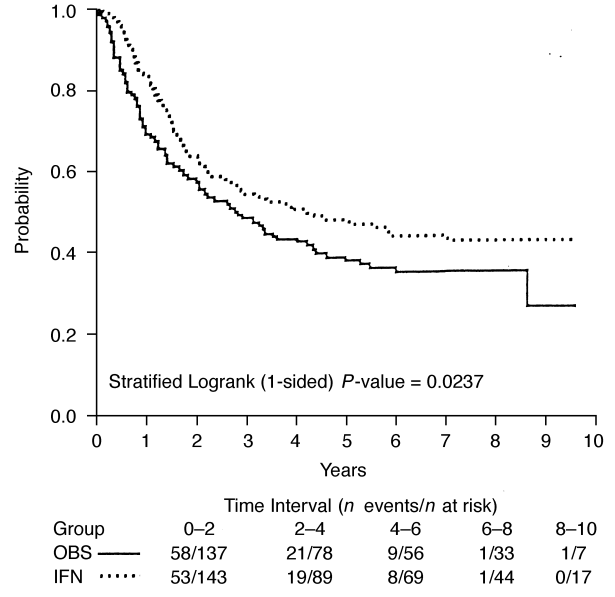

Figure 3. Overall survival of eligible patients, $P_1 = 0.0237$, stratified logrank. Reprinted with permission from *J Clin Oncol* 1996 [5].

IFN-α2b treatment was the most significant factor affecting relapse-free and overall survival ($P = 0.0011$) after stage of disease (CS1/PS2, $P = 0.002$) and interval from diagnosis or first recurrence to randomisation ($P = 0.002$) [5].

Adverse events

The most common toxicities associated with IFN-α2b therapy were constitutional, haematological and neurological [5]. The frequency and severity of side-effects associated with this regimen are shown in Table 3. The majority of patients were able to tolerate therapy and manage toxicity following recommendations for appropriate interventions, dose reductions, dose delays, or dose interruptions. Overall, 37% of patients during induction and 36% during maintenance required dose delays and/or reductions due to toxicity. Only 26% of patients withdrew from the study because of toxicity; therefore, approximately three fourths of patients remained on treatment for the entire duration of the study. The majority of withdrawals occurred during the first 4 months of treatment, after which discontinuation of therapy due to toxicity was a rare event. Approximately 60% of patients were able to maintain at least 80% of the target dose intensity throughout the trial.

FUTURE DIRECTIONS

Active immunotherapy: cancer vaccines

The molecular identification of tumour antigens and the genes encoding these antigens present new opportunities for the development of immunotherapies against cancer. Immunisation strategies include use of proteins and peptides that are the target of the host T-cell response, as well as peptides that have been modified to increase binding to major histocompatibility complex (MHC) molecules, naked DNA encoding cancer antigens, or antigen-presenting cells and the use of each of these antigens with various chemical or biological adjuvants, including recombinant viruses or bacteria containing the genes encoding cancer antigens [7, 8]. The first defined antigen vaccines were the gangliosides, which induce or augment serologic responses including immunoglobulin M (IgM) or IgG. Ganglioside vaccine GM2 combined with bacille Calmette-Guérin (BCG) resulted in the induction of IgM antibodies in a high percentage of melanoma patients (17/24, 71%) [6]. As a follow-up, 122 patients with AJCC stage III melanoma were randomised to receive treatment with the GM2/BCG vaccine or treatment with BCG alone in a double-blind trial [16]. All patients were pretreated with low-dose cyclophosphamide. GM2 antibody was produced in 86% (50/58) of patients treated with GM2/BCG vaccine. Analysis of this trial as randomised showed a trend toward benefit that was not of statistical significance and was confounded by the greater presence of pretreatment anti-GM2 in controls than in vaccine recipients. After a minimum follow-up period of 51 months, GM2/BCG treatment resulted in a 23% increase in DFI and a 14% increase in overall survival, when all patients with pre-existing GM2 antibodies were excluded. In contrast to the vaccinated patients who produced GM2 antibody, the patients who did not produce GM2 antibody after vaccination with GM2/BCG had rapid disease progression. The lack of antibody production in 8 vaccinated patients coupled with the unbalanced occurrence of pre-existing GM2 antibody production in 5 patients in the control group and the small size of this single-institution trial must be considered in interpreting the results of this study.

Table 3. Toxic events by type and degree

	Grade ($n = 143$)				
Type	1	2	3	4	5
Constitutional*	18	53	64	5	0
Myelosuppression	37	57	34	0	0
Hepatotoxicity	30	39	20	0	2
Neurologic	31	47	33	7	0
Worst grade/patient	2	30	96	13	2

*Worst grade of any constitutional toxicity, including fever, chill and flu-like symptoms: fatigue, malaise, diaphoresis. Reprinted with permission from *J Clin Oncol* 1996 [5].

A dose-ranging phase II study of a vaccine consisting of GM2 conjugated to the carrier protein keyhole limpet haemocyanin (KLH) and adjuvanted with 100 μg QS-21 was conducted in 52 patients with AJCC stage III and IV melanoma [17]. Patients were immunised four times at weekly intervals and then at weeks 12, 24 and 36. Greater than 95% of patients produced anti-GM2 IgM antibodies with 10, 30, or 70 μg GM2. Increased responses were observed as the dose was increased to 30 μg, but higher doses did not provide additional benefit. The vaccine was well tolerated and the duration of antibody titres was sustained in comparison to GM2/BCG.

In addition to vaccines, the administration of IFN-α2b may potentiate the cellular immune response in patients with advanced melanoma. In one study, 14 patients with melanoma were treated with IFN-α2b SC according to the following dosage regimen: 5 MU/day three times weekly during the first week, 10 MU/day three times weekly during the second week and 15 MU/day three times weekly thereafter [18]. Five of the melanoma patients achieved a partial response. In all patients, increases in T-lymphocyte proliferation, interleukin 2 (IL-2) production, the expression of IL-2 receptors, and IL-1 production were reported 2 months after treatment with IFN-α2b. In contrast to normal controls, patients with melanoma were reported to exhibit a reduction in these immunological parameters at presentation. IFN-α2b responders were noted to demonstrate improvement in these parameters ($P = 0.0001$). These results bear further evaluation.

Ongoing and future ECOG immunotherapy studies for malignant melanoma with GM2. ECOG has completed a sequel trial to E1684 (E1690) that compares the E1684 dosage regimen of IFN-α2b with a low-dose regimen of IFN-α2b (3 MU s.c. three times weekly for 2 years). A subset of these patients are being evaluated for additional information on the mechanism of IFN action in terms of tumour growth inhibition, antigen modulation and host immune regulation in ECOG trial 2690. ECOG also has initiated a study (E1694) comparing IFN-α2b at the E1684 dose with the GMK vaccine (GM2 linked to carrier molecule KLH with saponin adjuvant QS21). GMK is administered weekly for 4 weeks then at weeks 12, 24, 36, 48 and 60. Additional studies are planned to compare the combination of IFN and GMK vaccine to the vaccine alone and evaluate the administration sequence of IFN and the vaccine.

T-cell antigen vaccines. As techniques to quantitate T-cell response are developed, additional tumour antigens with the potential for use as therapies will be discovered. More than 30 peptides have been cloned, representing the epitopes

recognised by human T cells in melanoma [8]. Six genes encoding antigens recognised by tumour-infiltrating lymphocytes have been identified and include melanoma antigen recognised by T-cells (MART-1), gp100, tyrosinase, tyrosinase-related protein 1 (TRP1), p15 and beta-catenin [7]. MART-1, gp100, tyrosinase, and TRP1 are expressed in the majority of melanomas, normal melanocytes and in the retina, but not in normal tissues. Over the last several years, defined T-cell antigen vaccines have entered clinical trials.

MART-1, gp100 and tyrosinase peptide vaccines promote the induction of tumour reactive cytotoxic T-lymphocytes (CTL) from the peripheral blood of patients with the melanoma antigen HLA-A2+ [19]. In recent clinical trials, vaccines are being used in patients with metastatic melanoma in an attempt to immunise the patients against MART-1 and gp100 [7]. In these trials, patients were immunised with either the MART-1 immunodominant peptide or one of three gp100 immunodominant peptides. Immunisation with the MART-1 peptide increased the frequency of anti-MART-1 precursors in approximately 50% of patients. More potent immunisation resulted from the administration of the gp100 immunodominant peptide, with most patients showing evidence of increased antitumour reactivity *in vitro*.

Additionally, these peptide vaccines were evaluated in a randomised prospective phase I study designed to evaluate safety, *in vivo* CTL induction, delayed-type hypersensitivity (DTH) response to peptide and the induction of antitumour and/or antipigmentary responses [19]. As of May 1996, none of the 8 patients receiving four weekly i.m. injections of peptide plus the MF-59 adjuvant developed significant adverse effects. Although no objective responses were observed, 2 patients displayed transient antipigmentary responses and 2 patients had positive (> 5 mm) DTH responses to peptide antigen in saline. Specific immunotherapy directed at T-cell response to tumour antigens is comprehensively reported in this supplement by Parmiani [20].

CONCLUSIONS

Immunotherapy has improved the prognosis of patients with high-risk resected cutaneous melanoma. In a multicentre, randomised, controlled trial of high-dose IFN-α2b administered over 1 year, relapse-free and overall survival were significantly prolonged. A 42% increase in the fraction of patients who remained free of relapse 5 years after surgery was observed with IFN-α2b therapy and median survival was prolonged by 1 year. These effects were manifest early during treatment and were sustained after completion of treatment through a median follow-up period of nearly 7 years. In contrast, trials using low-dose IFN or high-doses for 3 months did not significantly impact survival. Advances in other immunotherapies for malignant melanoma include GM2 vaccine and identification of melanoma antigens that are recognised by T-cells. Use of GM2/BCG vaccine in melanoma patients induces antibody production and prolongs disease-free and overall survival. It is expected that future trials of IFN in comparison to and in combination with vaccines will increase the understanding of immunomodulation in this disease and potentially improve outcome.

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