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Tolerability of Adjuvant High-dose Interferon Alfa-2b: 1 Month *Versus* 1 Year–A Hellenic Cooperative Oncology Group Study

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Abstract. *Background: High-dose interferon alfa-2b (IFN-α2b) as adjuvant therapy for melanoma is associated with substantial dose-limiting toxicity. It has been suggested that the 1-month intravenous (i.v.) induction regimen may be sufficient to reduce the risk of relapse and death. Patients and Methods: The Hellenic Cooperative Oncology Group is conducting a multicenter, randomized trial of 1-month i.v. induction versus 1 year of adjuvant IFN-α2b therapy in patients with stage IIB/III melanoma. Adverse events reported by the first 200 patients to complete therapy are described. Results: Both induction and maintenance regimens were well tolerated. The most common toxicities were flu-like and gastrointestinal symptoms, neutropenia, liver toxicity, and neurologic toxicity. The incidence of grade 3/4 toxicity was low and occurred mainly during the induction phase in both arms. Dose was reduced in 31% of patients during induction. Only 2% of patients discontinued. Dose was reduced in 8% of patients during maintenance and only 5% of patients discontinued. Conclusion: Intravenous induction with 15 MIU/m^2/day IFN-α2b is well tolerated. Efficacy results from this trial are eagerly anticipated.*

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One year of high-dose interferon alfa-2b (IFN-α2b) is currently the standard adjuvant therapy regimen for patients with American Joint Committee on Cancer (AJCC) stage IIB (T4 N0 M0: primary tumor > 4 mm thick; no regional lymph node metastases; no distant metastases) and stage III (any T N+ M0: any tumor thickness; clinically or pathologically positive regional lymph nodes; no distant metastases) cutaneous melanoma (AJCC *Cancer Staging Manual*, 6th edition, Springer-Verlag, New York, NY, 2002). The pivotal Eastern Cooperative Oncology Group (ECOG) trial E1684 demonstrated a significant reduction in the risk of relapse and death among patients treated with high-dose IFN-α2b compared with observation (1). The approved high-dose regimen consists of intravenous (*i.v.*) induction therapy at the maximum tolerated dose of 20 million International Units (MIU)/m^2/day, 5 days per week for 4 weeks, followed by 10 MIU/m^2 subcutaneously 3 times per week (TIW) for 48 weeks as maintenance. Unfortunately, this regimen is

associated with substantial toxicity, which often results in dose reductions or treatment discontinuation, and negatively impacts patient acceptance of this regimen.

The toxicities associated with IFN-α2b include flu-like symptoms (fatigue, fever, myalgia, arthralgia), gastrointestinal toxicity (nausea, vomiting and anorexia), myelosuppression, elevated liver enzymes and neurologic and psychiatric symptoms. The incidence and severity of these adverse events are dose-related, and the majority of patients treated with the high-dose IFN-α2b regimen will experience some degree of toxicity (1-7). Fatigue affects nearly all patients, and up to 25% of patients may experience National Cancer Institute Common Toxicity Criteria (CTC) grade 3 or 4 fatigue. Other constitutional and gastrointestinal symptoms also occur in a high proportion of patients. Myelosuppression and hepatic toxicity have been reported to occur in 60% to 90% of patients, and CTC grade 3 or 4 myelosuppression or hepatic toxicity has been reported in approximately one-third of patients treated in the cooperative group trials (1-3). Some toxicities occur acutely and may demonstrate tachyphylaxis, particularly the flu-like symptoms, whereas others, such as fatigue, are reported more commonly with increased duration of treatment (7).

These adverse events can be dose limiting and may become intolerable. Indeed, dose modification was required in 28% to 37% of patients during induction and in 36% to 52% of patients during maintenance therapy in the cooperative group trials of high-dose IFN-α2b (1-3). Adverse events also resulted in treatment discontinuation for 24% of patients treated with high-dose IFN-α2b in E1684 but for only 10% to 13% of patients treated in trials E1690 and E1694 (J. Ibrahim, personal communication, February 2002). With appropriate dose modifications, 74% of patients treated in E1684 were able to continue treatment for 1 year or until relapse (1).

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The Hellenic Cooperative Oncology Group initiated a randomized trial to evaluate the safety and efficacy of *i.v.* induction with 15 MIU/m^2/day IFN-α2b for 4 weeks compared with the same regimen followed by 48 weeks of subcutaneous maintenance therapy (10 MIU TIW) in patients with stage IIB and III melanoma. This regimen was designed to deliver 75% of the planned E1684 induction dose and approximately 60% of the planned E1684 maintenance dose. This report summarizes the safety data of the first 200 patients to complete study treatment.

Patients and Methods

Patient selection. Inclusion and exclusion criteria were similar to those used in previous ECOG trials. Specifically, patients eligible for this trial had histologically proven, primary or recurrent, AJCC stage IIB or III cutaneous melanoma. Note: Under the revised AJCC staging system, patients with intermediate thickness primary tumors (2 to 4 mm) with ulceration (T3b) are also considered stage IIB but were not included in this study. Patients were required to have received complete surgical excision of the primary tumor with adequate surgical margins. Eligible patients were also required to be ≥ 18 years of age with an ECOG performance status ≤ 1 and normal organ function. Patients were excluded if they had evidence of distant metastatic disease or had received prior adjuvant radiotherapy, chemotherapy, or immunotherapy.

Treatment. Patients were randomized to receive 4 weeks of *i.v.* induction therapy consisting of 15 MIU/m^2 x 5 days per week (Arm A) or the same induction regimen plus 48 weeks of subcutaneous maintenance therapy at a flat dose of 10 MIU TIW (Arm B), which was administered at bedtime. The induction dose of 15 MIU/m^2 was selected because, at trial initiation in 1997, there was concern (based on the toxicity reported in E1684) that the approved 20-MIU/m^2 induction dose was associated with unacceptably high toxicity. The maintenance dose was also modified from the standard US dose of 10 MIU/m^2 for convenience of dosing and administration.

During induction, patients received premedication with acetaminophen (paracetamol) by *i.v.* injection 30 minutes before and 2 to 4 hours after each infusion of IFN-α2b, with additional paracetamol if needed thereafter. Additional nonsteroidal anti-inflammatory drugs were provided if needed to control fever and ameliorate other flu-like symptoms. Patients also received 500 to 1,000 mL of normal or half-normal saline during dosing to ensure adequate hydration. In addition, patients were instructed to drink 2 liters of noncaffeinated, nonalcoholic beverages daily. Intravenous antiemetics (granisetron or ondansetron) and H_2-blocking agents were provided as needed. During maintenance therapy, paracetamol was given orally 1 hour before and 2 hours after injection for the first month. Additional nonsteroidal anti-inflammatory drugs were provided as needed, as were nonsedating antihistamines for headache due to histamine response. Hydration was ensured.

Table I. *Patient demographics and baseline disease characteristics.*

Parameter	Arm A (n = 100)	Arm B (n = 100)	Total (N = 200)
Median age, years (range)	51 (19 - 84)	50 (22 - 72)	
Gender, n			
Male	55	55	110
Female	45	45	90
ECOG performance status, n			
0	92	93	
1	8	7	
Stage of disease, n			
Stage IIB	14	15	29
Stage III	50	47	97
Recurrent node positive	36	37	73
Breslow thickness, n			
≤ 1	2	0	2
1.01 - 2.0	8	9	17
2.01 - 4.0	40	37	77
> 4.0	44	43	87
Unknown	6	11	17
Ulceration, n			
Yes	69	67	136
No	27	25	52
Unknown	4	8	12

Study design. The study design was based on the hypothesis that the 1-month induction regimen (Arm A) would be at least as efficacious as the conventional treatment (Arm B) if the relapse rate at 3 years from study entry was no more than 15% higher in Arm A compared with Arm B. A relapse rate of 60% was assumed for both treatment arms. A sample size of 152 patients per arm was planned to achieve a power of 85% in a one-sided test at a significance level of 0.05. Target accrual was set at 320 (160 patients per arm), anticipating a 5% withdrawal rate (9).

Patients were monitored for adverse events during the induction phase with weekly blood tests, daily evaluation of signs and symptoms using a questionnaire and weekly physical examinations. Baseline assessments of fatigue, depression and body weight were performed. Toxicity during the maintenance phase was assessed monthly with blood tests, evaluation of signs and symptoms *via* a questionnaire, and physical examinations. Patients were monitored for change in body weight, behavior, appearance, and signs of suicidal predisposition. National Cancer Institute CTC were used for assessment and grading of adverse events (10).

Results

Patient characteristics. To date, 300 patients have been accrued to this ongoing study. Of these, 200 patients have completed treatment. Three patients were deemed ineligible because of protocol violations, including receipt of prior adjuvant chemotherapy, a T3a primary tumour, and presence of liver metastases, while 1 patient was lost to follow-up. Therefore, the safety-evaluable population included 196 patients (98 patients in Arm A and 98 patients in Arm B). Patient demographics and baseline disease characteristics, including age, gender, ECOG performance status, disease stage, Breslow thickness and presence or absence of ulceration, were similar between the 2 treatment arms (Table I).

Adverse events. Adverse events reported during intravenous induction therapy for both treatment arms combined (N = 196) are shown in Table II. As expected, flu-like and gastrointestinal

Table II. *Adverse events during intravenous induction therapy (Arms A + B: n=196).*

	Patients, %			
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Flu-like symptoms				
Fatigue	51	36	5	1
Fever	48	46	0	0
Rigors/chills	77	1	0	0
Arthralgia	59	16	1	0
Myalgia	54	35	1	0
Headache	54	35	0	0
Sweating	65	12	0	0
Gastrointestinal				
Anorexia	74	13	0	0
Taste disturbance	77	10	0	0
Nausea	31	9	0	0
Vomiting	20	4	0	0
Constipation	32	3	0	0
Diarrhea	14	1	0	0
Hematologic				
Neutropenia	16	25	15	0
Leukopenia	35	29	5	0
Thrombocytopenia	7	1	0	0
Anemia	10	3	0	0
Hepatic function				
SGOT	36	16	3	1
SGPT	31	18	3	1
Neurologic				
Depressed level of consciousness	58	16	1	0
Cognitive disturbance	59	5	1	1
Depression	25	14	1	0
Insomnia	50	8	0	0
Anxiety	25	2	1	0
Confusion	9	2	1	0
Metabolic				
Hypercholesterolemia	22	1	0	0
Hyperglycemia	24	1	1	0
Hypertriglyceridemia	19	2	0	0
Cutaneous				
Alopecia	8	5	0	0
Miscellaneous				
Urinary frequency	44	1	0	0
Cardiovascular	9	7	3	0

SGOT = Serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT = Serum glutamic-pyruvic transaminase (alanine aminotransferase).

Table III. *Adverse events during subcutaneous maintenance therapy (Arm B: n=95*).*

	Patients, %			
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Flu-like symptoms				
Fatigue	72	13	6	0
Fever	69	15	0	0
Rigors/Chills	32	1	0	0
Arthralgia	39	9	1	1
Myalgia	75	8	3	0
Headache	70	10	3	0
Sweating	49	4	0	0
Gastrointestinal				
Anorexia	69	7	0	0
Taste disturbance	66	4	0	0
Nausea	14	0	0	0
Vomiting	1	0	0	0
Constipation	4	0	0	0
Diarrhea	1	1	0	0
Hematologic				
Neutropenia	3	1	1	0
Leukopenia	13	3	0	0
Thrombocytopenia	1	0	0	0
Anemia	13	1	0	0
Hepatic function				
SGOT	8	3	3	0
SGPT	11	3	3	0
Neurologic				
Depressed level of consciousness	44	4	0	0
Cognitive disturbance	51	3	0	0
Depression	34	11	1	1
Insomnia	42	6	0	0
Anxiety	31	4	0	0
Confusion	7	1	0	0
Metabolic				
Hypercholesterolemia	20	1	0	0
Hyperglycemia	8	6	0	0
Hypertriglyceridemia	17	1	0	0
Cutaneous				
Alopecia	48	8	0	0
Miscellaneous				
Urinary frequency	8	0	0	0
Cardiovascular	8	3	0	0

*Three patients withdrew consent and did not provide data.
SGOT = Serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT = Serum glutamic-pyruvic transaminase (alanine aminotransferase).

Table IV. *Adverse events Arm A (induction only) versus Arm B (induction + maintenance).*

	Patients, %			
	Arm A (n=98)		Arm B (n=98)	
Adverse event	All grades	Grade 3/4	All grades	Grade 3/4
Flu-like symptoms				
Fatigue	90	6	98	11
Fever	92	0	100	0
Rigors/Chills	75	0	83	0
Arthralgia	67	0	88	1
Myalgia	86	0	45	0
Headache	83	0	41	0
Sweating	77	0	84	0
Gastrointestinal				
Anorexia	86	0	94	0
Taste disturbance	84	0	96	0
Nausea	31	1	53	0
Vomiting	20	0	27	0
Constipation	31	0	39	0
Diarrhea	14	0	17	0
Hematologic				
Neutropenia	55	11	60	23
Leukopenia	64	1	74	8
Lymphopenia	9	1	15	0
Anemia	11	0	20	1
Hepatic function				
SGOT	52	5	58	4
SGPT	53	8	58	4
Neurologic				
Depressed level of consciousness	74	1	81	1
Cognitive disturbance	62	2	78	0
Depression	33	0	60	3
Insomnia	55	0	76	0
Anxiety	27	1	46	1
Confusion	14	0	19	1
Metabolic				
Hypercholesterolemia	28	0	29	0
Hyperglycemia	24	0	30	1
Hypertriglyceridemia	27	0	26	0

SGOT = Serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT = Serum glutamic-pyruvic transaminase (alanine aminotransferase).

symptoms were common. However, the majority of reported adverse events were mild to moderate in severity. Only 6% of patients reported grade 3 or 4 fatigue. Hematologic toxicity was also reported in approximately half of patients, and 15% of patients had grade 3 neutropenia. Hepatic toxicity was mostly mild to moderate in severity (< 10% of patients had grade 3 or 4 elevated liver enzymes). The most commonly reported neurologic toxicity was depressed level of consciousness followed by cognitive disturbance, depression and insomnia, but very few patients reported severe symptoms. These neurologic toxicities were largely reversible with treatment interruption or dose modifications, and 95% of patients returned to their pretreatment status within 2 weeks of completing induction therapy. There were no treatment-related deaths.

Adverse events reported in Arm B during the subcutaneous maintenance phase (n=95) are shown in Table III (3 patients withdrew consent and did not provide adverse

Table V. *Number of patients who completed treatment and reasons for discontinuation.*

	Patients, n (%)
Completed induction therapy (N = 196)	190 (97)
Completed maintenance therapy (n = 98)	64 (66)
Reasons for discontinuation	
Induction (N = 196)	
Toxicity	5 (2)
Disease recurrence	1 (0.7)
Maintenance (n = 98)	
Toxicity	6 (6)
Disease recurrence	23 (23)
Death	1 (1)
Withdrew consent	3 (3)
Other	1 (1)

Table VI. *Dose reductions/delays and mean dose delivered.*

Dose reductions/delays	Number of patients (%)
Induction (N = 196)	60 (31)
Maintenance (n = 98)	8 (8)
Median dose delivered	
Induction	15 MIU/m^2
Maintenance	10 MIU
Mean dose delivered	
Induction	14.6 MIU/m^2
Maintenance	9.7 MIU

MIU = Million International Units.

events data during maintenance therapy). The adverse events profile was similar to that occurring during induction therapy, except that there were far fewer grade 3 and 4 adverse events. Notably, only 6% of patients reported grade 3 fatigue, and only 1% of patients had grade 3 neutropenia. Likewise, only 2% of patients developed severe depression or suicidal predisposition during maintenance therapy.

A comparison of adverse events occurring in Arm A (induction only) *versus* Arm B (induction plus maintenance) is shown in Table IV. The full year of therapy was associated with an incremental increase in the incidence of grade 3/4 fatigue (11% *versus* 6%); however, at least half of the total incidence of grade 3/4 fatigue in Arm B occurred during induction therapy. Similarly, Arm B had a higher incidence of grade 3/4 neutropenia and leukopenia; however, as indicated by the separate analysis of induction *versus* maintenance (Tables II and III), nearly all of the severe myelosuppression occurred during induction therapy. Only 1% of patients developed grade 3 neutropenia during maintenance therapy. Patients in Arm B also had a higher incidence of depression, including a slight increase in the incidence of severe depression. The incidence of all other adverse events was fairly well balanced between the 2 treatment arms, suggesting that 1 year of therapy was not associated with a substantial increase in toxicity compared with 1 month of *i.v.* induction therapy.

Treatment discontinuation. The majority of patients in both arms completed the study, and few patients discontinued study treatment due to toxicity (Table V). In Arms A plus B, 190 of 196 (97%) eligible patients completed induction therapy, and 64 of 98 (66%) patients in Arm B completed maintenance therapy. However, disease recurrence was the primary reason for discontinuation during maintenance therapy. Twenty-three (23%) patients discontinued maintenance therapy because of disease recurrence, and only 6 (6%) patients discontinued due to toxicity. One patient in Arm B died of acute respiratory distress syndrome. A postmortem examination was not performed, but staging scans conducted 1 month prior to death showed no sign of disease recurrence.

Dose reductions. Dose reductions or delays were required for 31% of patients during the induction phase (Table VI) due to grade 3 or 4 toxicity (hematologic, hepatic function, depression, fatigue, cardiovascular complications, neurologic, constitutional symptoms, or body aches). In contrast, only 8% of patients required dose reductions or delays during the maintenance phase. This is consistent with the lower incidence of grade 3 or 4 hematologic and hepatic toxicity during maintenance compared with induction therapy. Although a substantial number of patients required dose reduction, the mean delivered dose was only slightly lower than the planned dose. The mean dose delivered was 14.6 MIU/m^2/day (*versus* 15 MIU/m^2/day planned) during the induction phase and 9.7 MIU during the maintenance phase (*versus* 10 MIU planned).

Discussion

High-dose IFN-α2b is currently the only adjuvant treatment for stage IIB and stage III melanoma that has been shown to significantly reduce the risk of relapse and death in this high-risk patient population (1). However, the substantial toxicity associated with this regimen is an impediment to its use, and the high incidence of dose-limiting toxicity may reduce the therapeutic benefit. The current trial was conducted to investigate the safety and efficacy of 1 month of *i.v.* induction therapy, based on the hypothesis that this induction therapy may provide the same sustained clinical benefit as 1 year of adjuvant IFN-α2b therapy while minimizing dose-related toxicities. If this were true, a short *i.v.* course of IFN-α2b therapy could also improve patient quality of life and increase cost effectiveness compared with 1 year of adjuvant therapy.

This preliminary safety assessment based on the first 200 patients to complete therapy has demonstrated that both the induction and maintenance regimens tested in this trial are well tolerated and demonstrated similar toxicity profiles. The majority of dose-limiting hematologic and hepatic toxicities occurred during induction therapy; however, the overall incidence of grade 3 or 4 adverse events was low. Although 31% of patients required dose reductions during induction therapy, the mean delivered dose (14.6 MIU/m^2/day) was not substantially reduced from the planned dose of 15 MIU/m^2/day (only a 2% reduction). In comparison, only 67% of patients in E1684 received > 80% of the target dose during induction therapy when the target dose was 20 MIU/m^2/day, resulting in a mean delivered dose of 18 MIU/m^2/day (*ie*, a 10% decrease from the planned dose) (1,2). Moreover, only 2% of patients in the current study discontinued induction therapy due to adverse events. Thus, the majority of patients were able to tolerate the full *i.v.* induction dose of IFN-α2b.

With respect to Arm B, which received induction plus maintenance therapy, there was an incremental increase in the incidence of grade 3 or 4 fatigue and neuropsychiatric toxicity compared with Arm A, but maintenance therapy did not add substantially to the overall toxicity of this regimen. In fact, the absolute incidence of fatigue, particularly grade 3/4 fatigue, was lower than that reported in the ECOG studies (1-3). This could be explained by the lower dose of IFN-α2b administered in this study or by differences in the toxicity criteria used. Moreover, there was very little grade 3 or 4 myelosuppression and no grade 3 or 4 hepatic toxicity during maintenance therapy. Consequently, only 8% of patients required dose reductions during maintenance therapy, compared with 30% to 50% of patients in the ECOG trials, and the mean delivered maintenance dose (9.7 MIU) was only slightly lower than the target dose of 10 MIU. In comparison, the mean delivered maintenance dose was only 8.1 MIU/m^2 in E1684 (2). Hence, the dose intensity during maintenance therapy in this study was not substantially lower than that achieved in E1684.

These results suggest that with premedication and proactive management of adverse events, the majority of melanoma patients can tolerate a full dose of *i.v.* IFN-α2b at a target dose of 15 MIU/m^2/day for 4 weeks. This dose was selected because it was felt that the approved 20-MIU/m^2 induction dose was associated with unacceptably high toxicity. The low rate of discontinuations due to toxicity in this study is particularly encouraging. If this 1-month induction regimen were as effective at reducing the risk of relapse and death as the standard 1-year regimen, this would be a major improvement in adjuvant therapy for melanoma. Although the regimen being tested in this trial has a lower planned dose than that tested in the ECOG adjuvant trials, it was possible to deliver more of the target dose because of the lower incidence of dose-limiting toxicity. Therefore, the delivered dose was only modestly diminished compared with that achieved in the ECOG adjuvant trials. The efficacy results of this trial are eagerly awaited.

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