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Adjuvant pegylated interferon α-2b therapy for melanoma

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Abstract. Although adjuvant high-dose interferon α-2b therapy significantly improves recurrence-free survival vs. observation in high-risk resected melanoma, the overall survival benefit is presently unclear. Pegylation of interferon α-2b (peginterferon α-2b) allows for a reduction in the dosing frequency with increased drug exposure. Adjuvant peginterferon α-2b therapy has also been shown to provide a significant, sustained improvement in recurrence-free survival compared with observation in patients with stage III melanoma. We report on the use of adjuvant peginterferon α-2b (3 μg/kg/week) in clinical practice in a series of 8 patients treated at the Universitätsklinikum Essen in Germany following complete resection of primary melanoma at intermediate- and high-risk of recurrence (stage II-III). Treatment duration ranged from 2 to 29 months, with 4 patients receiving long-term therapy (≥24 months). Following treatment, 5 patients (stage II) remained disease-free at 33, 33, 37, 39 and 43 months from the time of diagnosis. In 2 patients, peginterferon α-2b was terminated 4 and 9 months after treatment initiation due to disease progression. Once-weekly subcutaneous administration of peginterferon α-2b was convenient in all patients. In 3 patients experiencing adverse events, dose reductions led to a resolution of symptoms and enabled treatment to continue long-term. Three further patients discontinued therapy due to adverse events at 2, 8 and 27 months of therapy (persistent elevation of γ-glutamyl transpeptidase, liver transaminase elevation and urosepsis); dose modifications were not applicable in these patients. Thus, long-term adjuvant peginterferon α-2b therapy was feasible in the clinical practice setting and was generally well tolerated in these intermediate- and high-risk melanoma patients.

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Introduction

High-dose interferon α-2b is the only adjuvant therapy currently FDA-approved for high-risk resected melanoma. The high-dose regimen of 20 MU/m^2/day intravenously (i.v.) 5 days a week for 4 weeks, then 10 MU/m^2 subcutaneously (s.c.) three times per week for 48 weeks has been shown to significantly improve recurrence-free survival vs. observation (1-5). The survival benefit is remains unclear, with significant effects noted vs. observation in only one trial of high-dose interferon (3). Clinical trial data suggest that efficacy is associated not only with dose but also with the duration of therapy (1,3,6). However, high-dose interferon α-2b is associated with significant toxicity and an inconvenient three-times-weekly maintenance dosing schedule.

Pegylation of interferon α-2b (peginterferon α-2b) does not affect its biological activity but results in decreased clearance and increased half-life, allowing for a reduced dosing frequency and potentially greater efficacy owing to the altered pharmacokinetic profile and increased drug exposure (7-9). In the EORTC 18991 phase III study, peginterferon α-2b therapy at 6 μg/kg/week for 8 weeks s.c. (induction) followed by 3 μg/kg/week s.c. (maintenance) for an intended duration of 5 years provided a significant, sustained improvement in recurrence-free survival compared with observation in patients with stage III melanoma (6). However, no improvement in survival was observed at 3.8 years of follow-up. There was evidence for a greater benefit of peginterferon α-2b therapy in stage III patients with microscopic nodal disease (N1) vs. clinically palpable lymph nodes (N2). Similar findings were observed with interferon α-2b in this patient subgroup (2). For the primary analysis, the median treatment duration was 12 months (interquartile range 3.8-33.4).

In the 18991 study, the toxicity profile of peginterferon α-2b was acceptable for up to 5 years of therapy. The most commonly reported grade 3/4 adverse events (AEs) observed were fatigue, hepatotoxicity, pyrexia, headache, myalgia and depression (6). The discontinuation rate due to toxicity was 31% in the peginterferon α-2b arm, and AEs most frequently associated with discontinuation were fatigue, depression, anorexia, hepatotoxicity, myalgia, headache, nausea and pyrexia. The incidence of the most common AEs was higher early in treatment and appeared to decrease with prolonged treatment.

The present study describes the use of adjuvant peginterferon α-2b (Pegintron®; Schering-Plough Corporation, Kenilworth, NJ, USA), following complete resection in 8 patients with

primary melanoma at intermediate- and high-risk of recurrence (stage II-III) treated at the Universitätsklinikum Essen in Germany, with a focus on tolerability. As peginterferon α-2b is not currently registered for the treatment of melanoma, it was administered under compassionate use in these patients.

Patients and Results

The characteristics of the primary melanoma at diagnosis for the 8 patients are shown in Table I, along with a summary of peginterferon α-2b dose and treatment duration. Following the complete excision of the primary melanoma, standard follow-up care was a three-monthly clinical and sonographic assessment of lymph nodes for 3 years; assessment was then carried out every 6 months. The American Joint Committee on Cancer (AJCC) 2002 staging was used throughout. Informed consent was obtained from all patients before the administration of peginterferon α-2b. The dose administered to the patients participating in this study was the maintenance dose administered in the EORTC 18991 trial (3 μg/kg/week) and was prepared according to EORTC 18991 study methods, based on the subject's body weight. Peginterferon α-2b powder for injection was provided in vials (3 μg/0.5 ml) and reconstituted in 0.7 ml sterile water for injection. The volume (ml) of reconstituted solution to be withdrawn and injected was calculated according to vial size, and the required dose was based on the subject's body weight.

Patient J.P. (date of birth 04/01/69) was diagnosed in October 2005. A wide excision with 2-cm safety margins was carried out. The left axillary sentinel lymph node biopsy (SLNB) was negative and computed tomography (CT) showed no metastasis. Peginterferon α-2b was administered at a dose of 3 μg/kg/week s.c. from December 2005 to September 2006. In August/September 2006, suspected pulmonary and mediastinal lymph node metastases identified on a thoracic CT scan were confirmed by thoracotomy and pulmonary biopsy. From September 2006 onwards the patient received numerous courses of polychemotherapy (DTIC, cisplatin and vindesine on days 1 and 8) achieving a partial response on the CT scan. In May 2007, there was no evidence of mediastinal lymph node metastasis or residual lung metastasis by CT; PET indicated that lung metastases were inactive. In September 2007, progression of the residual lung metastasis and suspected hepatic metastases (segment 8) was noted and confirmed by excision 2 months later. From November 2007 to December 2008, further polychemotherapy achieved a partial response. In December 2008, CT staging indicated stable disease, and no further antineoplastic therapy was administered. In March 2009, progression of the lung metastasis was observed. Therefore, three courses of paclitaxel plus carboplatin (days 1 and 28) were administered, resulting in symptomatic pancytopenia (CTC grade 3). In June 2009, stable disease was present (stage IV; pT3aN0M1c).

Patient S.S. (date of birth 14/04/1980) was diagnosed in November 2005. She underwent wide excision with 2-cm safety margins; the left axillary SLNB was negative. In December 2005, CT staging indicated no evidence of metastasis. Peginterferon α-2b 3 μg/kg/week s.c. was started in January 2006, with dose reduction to 1.5 μg/kg/week s.c. in July 2006 due to neutropenia; a dose that was continued until June 2008. There was no evidence of metastasis by CT staging in January 2008 and 2009. In June 2009, disease stage was IIA (pT3aN0M0).

Patient M.D. (date of birth 24/06/1966) was diagnosed in March 2006. He underwent wide excision with 2-cm safety margins. SLNB for both axillae was negative, and the CT scan indicated no evidence of metastasis. He began therapy with peginterferon α-2b 3 μg/kg/week s.c. in May 2006. In June 2006, the dose was reduced to 1.5 μg/kg/week s.c. due to neutropenia. In August 2006 the occurrence of neutropenia required further dose reduction to 1 μg/kg/week s.c., which was continued until May 2008. In February 2007, the patient tested positive for thyroid peroxidase antibodies (Hashimoto's thyroiditis and hypothyroidism). CT staging in May and November 2007, and November 2008, indicated no evidence of metastasis. In June 2009, disease stage was IIA (pT3aN0M0).

Patient K.S. (date of birth 28/08/1942) was diagnosed in May 2006. In July 2007 he underwent wide excision with 2-cm safety margins. SLNB of the right axilla was negative, and the CT scan showed no evidence of metastasis. Peginterferon α-2b 3 μg/kg/week s.c. was initiated in July 2006, but discontinued in September 2006 due to persistent elevation of γ-glutamyl transpeptidase. Staging CT in June 2008 showed no evidence of metastasis. In June 2009, disease stage was IIA (pT3aN0M0).

Patient A.F. (date of birth 09/04/1946) was diagnosed with two separate primary melanomas in September 2006. He underwent wide excision with 2-cm safety margins. SLNB of the right axilla was negative, and the CT scan showed no metastasis. From November 2006 he received peginterferon α-2b 3 μg/kg/week s.c., which was discontinued due to persistent massive elevation of liver transaminases in July 2007. Staging CT in October 2007 and 2008 showed no evidence of metastasis. In June 2009, disease stage was IIC (pT4bN0M0) and IA (pT1a).

Patient S.B. (date of birth 08/12/1969) was diagnosed in September 2006. She underwent wide excision with 2-cm safety margins. SLNB of the left lower abdomen was negative, and CT staging indicated no evidence of metastasis. The patient received peginterferon α-2b 3 μg/kg/week s.c. from January 2007. The dose was reduced in April 2007 to 1.5 μg/kg/week s.c. due to Grade III neutropenia (Common Toxicity Criteria v3.0). This latter dose was continued until January 2009 at which point no evidence of metastasis on CT staging was noted. In June 2009, disease stage was IIA (pT3aN0M0).

Patient H.H. (date of birth 31/05/1948) was diagnosed in July 2006. He underwent wide excision with 2-cm safety margins. SLNB of the right axilla was negative, and there was no evidence of metastasis on CT. Peginterferon α-2b 3 μg/kg/week s.c. was administered from August 2006 but discontinued in December due to disease progression. In-transit metastasis in the right dorsal shoulder was identified, but PET-CT/cranial nuclear magnetic resonance staging showed no evidence of distant metastasis. R0-resection (all margins histologically free of tumor) of the metastasis was carried out. However, the patient refused adjuvant high-dose interferon α-2b therapy. He was then lost to follow-up until February 2009, when he returned with a clinical s.c. metastasis on his upper back, a right caudal cervical lymph node metastasis and

Table I. Patient characteristics at diagnosis and summary of pegylated interferon α-2b therapy.

Patient	Gender	Location	At diagnosis				Peginterferon α-2b therapy			June 2009 Stage (AJCC/TNM)
			Ulceration	Breslow index (mm)	Clark level	TNM stage	Dose (μg/kg/wk)	Duration (months)	Reason for discontinuation	
J.P.	F	Back	No	3.50	IV	pT3a	3.0	9	Progression	IV/pT3aN0M1c
S.S.	F	Left scapula	No	3.50	IV	pT3a	3.0 1.5	6 23	None	IIA/pT3aN0M0
M.D.	M	Left abdomen	No	2.29	IV	pT3a	3.0 1.5 1.0	1 2 21	None	IIA/pT3aN0M0
K.S.	M	Lower back	No	2.80	III	pT3a	3.0	2	Persistent ↑ GGT	IIA/pT3aN0M0
A.F.	M	Right back	Yes	5.60	Unknown	pT4b	3.0	8	Persistent ↑↑ liver transaminases	IIC/pT4bN0M0
		Left back	No	0.62	III	pT1a			IA/pT1a	
S.B.	F	Mons pubis	No	2.60	III-IV	pT3a	3.0 1.5	3 21	None	IIA/pT3aN0M0
H.H.	M	Right dorsal shoulder	Yes	5.20	Unknown	pT4b	3.0	4	Progression	IV/pT3aN3M1a
H.J.	M	Lower left arm	No	1.50 0.00	IV	pT2a	HDI LDI 3.0	6 12 27	- - Urosepsis	IIIC/pT2aN3M0

GGT, γ-glutamyl transpeptidase; HDI, high-dose interferon α-2b; LDI, low-dose interferon α-2b; TNM, tumor, node and metastasis staging.

two right pulmonary metastases identified by CT (stage IV). In April 2009, he underwent R0-resection of the s.c. metastasis on his upper back and R1-resection (microscopic residual disease remaining) of the right caudal cervical lymph node metastasis. In May 2009, CT staging indicated progression of the pulmonary metastasis and sonography indicated suspicious right axillary lymph nodes. In June 2009, disease stage was IV (pT3aN3M1a).

Patient H.J. (date of birth 08/09/1930) was diagnosed in September 1998 and underwent wide excision (unknown safety margins). In May 2005, disease recurrence was identified with an in-transit metastasis (stage III). He underwent R0-resection of two in-transit metastases of the left upper arm. The left axillary sentinel lymph node excision was positive. High-dose interferon α-2b (FDA-approved schedule) was administered until January 2006. At this time, CT staging indicated left axillary lymph node metastasis. Thus, complete left axillary lymph node dissection (2+/11) was carried out, and adjuvant radiation (60 Gy) was administered to this region from March to May 2006. R0-resection of one in-transit metastasis of the left upper arm was carried out. The CT scan showed no evidence of distant metastasis. The patient then received low-dose interferon α-2b (3 MIU three times-weekly s.c.) from May 2006 to 2007. At this time, CT staging indicated lymph node metastasis in the left axilla. R0-resection was therefore carried out. Peginterferon α-2b 3 μg/kg/week s.c. was initiated in June 2007 but discontinued due to urosepsis in September 2008. Following staging CT, R0-resection of the s.c. left axillary metastasis was carried out in April 2009. A clinical follow-up in May 2009 showed no evidence of disease. In June 2009, disease stage was IIIC (pT2aN3M0).

Discussion

This study described the disease course of 8 patients who received adjuvant peginterferon α-2b therapy for the treatment of resected, intermediate- and high-risk stage II (n=7) or III melanoma with regional metastases (n=1). Five patients who received peginterferon α-2b after resection of the primary tumor (stage II) remained disease-free in June 2009 (months since diagnosis: 33, 33, 37, 39 and 43). In 2 patients (J.P. and H.H.), peginterferon α-2b was terminated due to disease progression 4 and 9 months after treatment was initiated. Patient H.J. initially received high-dose, then low-dose interferon α-2b following subsequent resections of stage III melanoma, and finally peginterferon α-2b following additional resection. The treatment duration in these 8 patients ranged from 2 to 29 months, with 4 patients receiving long-term therapy (≥24 months).

The EORTC 18991 study implemented a 'dosing to tolerance' schedule, with stepwise reductions specified in the protocol to manage toxicities while maintaining good performance status, as well as aiming to achieve long-term therapy, thereby maximizing the efficacy benefits of therapy (6). Once-weekly s.c. administration of peginterferon α-2b was convenient in our patients. In 3 patients experiencing AEs on peginterferon α-2b, dose reductions led to the resolution of symptoms and enabled treatment to continue long-term. Five further patients discontinued peginterferon α-2b due to AEs at 2, 8 and 27 months of therapy or disease progression; dose modifications were not attempted or applicable in these patients.

High-dose peginterferon α-2b has a similar toxicity profile to high-dose interferon α-2b, with similar common toxicities (hepatotoxicity, fatigue, depression and hematologic) (10). Practical guidelines for managing interferon toxicity have been published by Hauschild *et al*. These guidelines focus on initial patient assessment, ongoing monitoring, aggressive management of AEs, and recognizing when dose adjustment or discontinuation is needed (10). Patient education prior to therapy and throughout the treatment period increases awareness and recognition of possible side effects, thereby aiding in the reduction of the severity of AEs. Consequently, the likelihood that the patient will complete therapy increases (10). Patient M.D. showed signs of autoimmune disease (Hashimoto's thyroiditis) during adjuvant peginterferon α-2b therapy. The development of autoimmune diseases such as thyroid dysfunction has been associated with greater efficacy benefits with high-dose interferon therapy (11,12), although this association is regarded as controversial. More recent data from an EORTC trial (18952) and the Nordic IFN trial now suggest that this correlation is only weak, if it exists at all (13).

For the patients participating in this study, adjuvant therapy with peginterferon α-2b was feasible and generally well tolerated for intermediate- and high-risk melanoma. Our findings therefore indicate that long-term therapy can be maintained in the clinical practice setting.

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