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Treatment patterns of adjuvant interferon-α2b for high-risk melanoma: a retrospective study of the Grupo Español Multidisciplinar de Melanoma – Prima study

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Adjuvant interferon-α2b (IFN-α2b) has been studied extensively in clinical trials, but there have been few studies of real-world use. The aim of this study is to describe the IFN-α2b real-world patterns in patients with high-risk melanoma in Spain. This was a retrospective and multicentre chart review study of an unselected cohort of patients with melanoma at high risk for relapse (stage IIB/IIC/III) treated with IFN-α2b. Patterns were assessed in terms of dose and compliance to planned treatment. A survival analysis was carried out for the full population and according to Kirkwood scheme compliance and the presence of ulceration. Of 327 patients treated with IFN-α2b, 318 received a high-dose regimen following the standard Kirkwood scheme; thus, patterns are described for this regimen. A total of 121 (38%) and 88 (28%) patients had at least one dose reduction during the induction and maintenance phases, respectively. Dose delay was required in fewer than 10% of patients. A total of 78, 40 and 38% of the patients completed the induction phase, maintenance phase and completed treatment, respectively. The median progression-free and overall survival for the full population were 3.2 and 10.5 years, respectively. There were no differences in progression-free survival and overall survival according to Kirkwood scheme compliance and the presence of ulceration. The most frequent adverse events were neutropenia (31%) and fatigue (30%). High-dose IFN-α2b is the most frequently used regimen in Spain as an adjuvant systemic treatment for high-risk melanoma. Despite poor compliance, in this retrospective study, IFN-α2b treatment provided a benefit consistent with that described previously. *Melanoma Res* **26:278–283**

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Introduction

Melanoma causes almost 80% of all skin cancer deaths and its incidence is increasing worldwide [1,2]. In Spain, both melanoma incidence (5.2 cases per 100 000 inhabitants/year) and lethality are increasing [3,4]. Little has changed in the last 20 years in the adjuvant treatment of completely resected melanoma. Patients with and without high-risk features are treated with radical surgery with safety margins, but the former, particularly those with lymph node metastases, are also eligible to receive

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adjuvant systemic treatment with interferon-α2b (IFN-α2b) [3]. The Eastern Cooperative Oncology Group (ECOG) 1684 trial, which compared adjuvant high-dose IFN-α2b with no adjuvant treatment in patients with melanoma and high-risk features, showed improved outcomes in both progression-free survival (PFS) and overall survival (OS) [5] but, in the long term, the effect in OS was no longer statistically significant [6]. The most recent meta-analysis of adjuvant interferon in melanoma confirmed a longer disease-free interval (hazard ratio 0.83) in 17 trials and improved OS (hazard ratio 0.91) in 15 trials [2].

However, adverse IFN-α2b tolerability, mainly flu-like symptoms, mood changes and mental alterations, may lead to patient refusal, discontinuation or poor compliance [1,7]. Impairments in compliance may theoretically impact outcomes. Hence, an accurate assessment of practice patterns is warranted to ascertain whether the trial results can be reproduced in the real-world setting.

Little is known about the prescribing patterns and the compliance to IFN-α2b in Europe. Therefore, the Grupo Español Multidisciplinar de Melanoma (GEM) (Spanish Melanoma Multidisciplinary Group) sought to analyse the pattern of treatment, compliance and outcomes of patients with completely resected melanoma and at high risk for recurrence treated with adjuvant IFN-α2b.

Methods

Twenty centres participated in this retrospective study. Data were collected from May 2013 to January 2014. The Institutional Review Board(s) of all centres approved the study protocol. All nondeceased patients provided written consent. The protocol was carried out in accordance with the Declaration of Helsinki (Seoul 2008 version) and local laws and regulations.

Adult patients who fulfilled the following criteria were included: diagnosed, histologically confirmed, with primary cutaneous melanoma (January 2000–December 2009); completely resected stage IIB/IIC/III disease (American Joint Committee on Cancer 2009) or any resected metastasis; treated with at least one dose of IFN-α2b; no previous history noncutaneous malignancy; and nondeceased patients with more than 2 years of follow-up.

The high-dose regimen followed the Kirkwood scheme [5]: 20 MU/m^2/day intravenous in the induction phase (20 doses: 5 days/week during 4 weeks) and 10 MU/m^2/day subcutaneous in the maintenance phase (3 days/week during 48 weeks). The intermediate dose consisted of 10 MU/m^2/day intravenously in the induction phase (5 days/week over 4 weeks) and 5–10 MU/m^2/day subcutaneously in the maintenance phase (3 days/week for varying durations) [8] and low-dose regimens consisted of 3 MU/m^2/day subcutaneous, 3 days per week for varying lengths of time [9]. The treatment was complete if the patient received at least 18 doses in the induction phase and was treated for at least 45 weeks in the maintenance phase.

The sample size was calculated with a 95% confidence interval (CI) and a 0.05 α error assuming that 67% of patients will complete induction and 41% will complete the entire treatment [1]. Thus, 325 patients should be included.

Quantitative variables were characterized using means (SD) and median (range), whereas qualitative variables were characterized using frequencies and percentages. Quantitative variables were compared using the Student–Fisher *t*-test. Kaplan–Meier analysis was used to estimate survival times for the overall population and stratified according to patient compliance to the Kirkwood scheme (i.e. with no doses reduction nor delays) and the presence of ulceration; comparison was performed using the log-rank test. The Cox regression model was used to calculate multivariate predictive models.

Patients could have received high-dose, intermediate-dose or low-dose IFN-α2b. However, because there were very few patients with low and intermediate doses ($n = 5$), only high-dose regimen patients (322; 99%) who fulfilled the selection criteria were included in the analysis.

Results

A total of 330 and 323 individuals were included in the safety and analysis population, respectively. For the high-dose interferon-based regimen, the evaluable population included 322 patients for the safety analysis and 318 patients for the outcome analysis. All the patients included provided their written informed consent. In all, 98% of the patients were white, 54% were men, and the median age was 51 years (19–81) (Table 1). The most common locations of primary lesion were the extremities (43%) or the trunk (39%).

A total of 249 (78%), 127 (40%) and 121 (38%) patients completed the induction phase, the maintenance phase and the entire treatment, respectively. The median treatment duration was 45.4 (range = 0.6–98.4) weeks. Forty out of 56 patients (71%) who discontinued the induction phase later continued to the maintenance phase. Thus, treatment was discontinued in 16 patients (5%) during the induction phase and in 176 (55%) during the maintenance phase (Fig. 1).

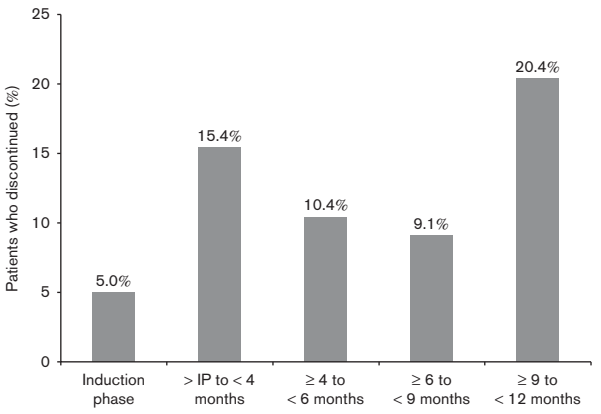
In total, 121 patients (38%) had at least one dose reduction during the induction phase, the most common being a single reduction (66% of these patients); in 46% of patients, the dose after the first reduction ranged between 12.5 and 15 MU/m^2 (Table 2). The mean duration from treatment initiation to the first dose reduction was 15.2 (8.2) days. In the maintenance phase,

Table 1 Demographic characteristics[a] of the patients

	Overall population ($N=318$)
Age at melanoma diagnosis (years)	51 [19–81]
Sex	
Male	172 (54)
Female	146 (46)
ECOG performance status[b]	
0	243 (76)
1	37 (12)
2	2 (1)
Location of primary lesion[b]	
Face	20 (6)
Trunk	123 (39)
Extremity	136 (43)
Other	35 (11)
Pathological stage AJCC 2009[b]	
IIB	37 (12)
IIC	21 (7)
IIIA	91 (28)
IIIB	84 (26)
IIIC	47 (15)
IA	7 (2)
IB	11 (3)
IIA	8 (3)
History of sentinel node biopsy	
Yes	222 (70)
No	96 (30)
History of complete lymphadenectomy	
Yes	235 (74)
No	83 (26)
Breslow thickness[b] (mm)	
<1	22 (7)
≥ 1 to ≤ 2	58 (18)
>2 to ≤ 4	105 (33)
>4	105 (33)
Ulceration[b]	
Yes	138 (43)
No	146 (46)
Clark level[b]	
I	1 (0.3)
II	10 (3)
III	78 (25)
IV	137 (43)
V	37 (12)
Regional lymph nodal status[b]	
N0	70 (22)
N1	131 (41)
N2	77 (24)
N3	23 (7)
Extracapsular extension[b,c]	
Yes	29 (14)
No	157 (75)
Macroscopic or microscopic involvement[b,c]	
Macroscopic	66 (32)
Microscopic	99 (48)
No	21 (10)
In-transit metastases or satellite lesions[b]	
Yes	35 (11)
No	272 (86)

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.
[a]All variables, except for age, which is in median [range], are categorized in *n* (%).
[b]In this variable, the remaining percentage up to 100% corresponds to missing data.
[c]Only reported if regional lymph nodal status was N1 or N2.

Fig. 1



Patients who discontinued the treatment. IP, induction phase.

Table 2 Dose modifications and delays

	Induction phase ($N=318$)	Maintenance phase ($N=318$)
Patients with dose reduction	121 (38)	88 (28)
Number of dose reductions[a,d]		
1	80 (66)	48 (54)
2	32 (26)	28 (32)
3	9 (7)	5 (6)
4		2 (2)
5		2 (2)
6		1 (1)
7		2 (2)
Number of days until the first dose reduction[d]		
≤ 7 days	32 (26)	4 (5)
>7–14 days	43 (35)	5 (6)
>14–21 days	29 (24)	4 (5)
>21–28 days	17 (14)	8 (9)
>28 days to 6 months		59 (67)
>6–12 months		7 (8)
>28 days to 2 months		21 (24)
>2–3 months		15 (17)
>3–4 months		12 (14)
>4–5 months		4 (5)
>5–6 months		7 (8)
>6–12 months		7 (8)
Patients with dose delay[b]	19 (6)	28 (8)
Number of dose delays		
1	18 (95)	24 (86)
2	1 (5)	4 (14)
Patients with dose reduction or delay	128 (40)	103 (32)
Reason for dose reductions or delay[c,e]		
Patient symptoms	68 (53)	57 (55)
Grade 3 AE	61 (48)	46 (45)
Grade 4 AE	5 (4)	2 (2)
Patient decision not symptom related	0 (0)	1 (1)

All variables are categorical in *n* (%).
AE, adverse event.
n (%) reported for patients who had: [a]dose reduction, [b]dose delay, [c]reductions or delay.
[d]In this categorical variable, the remaining percentage up to 100% corresponds to missing data.
[e]The reasons listed are not mutually exclusive.

88 patients (28%) had at least one dose reduction, and nearly half of these patients reported a single reduction; in 44% of patients, the dose after the first reduction ranged between 6 and 7.5 MU/m^2. A dose delay was required in 19 (6%) and 28 (8%) patients during the induction and maintenance phase, respectively. The most common reason to delay or modify the dose in the induction and maintenance phase was patients' symptoms [not fulfilling the criteria of a grade 3 or 4 adverse

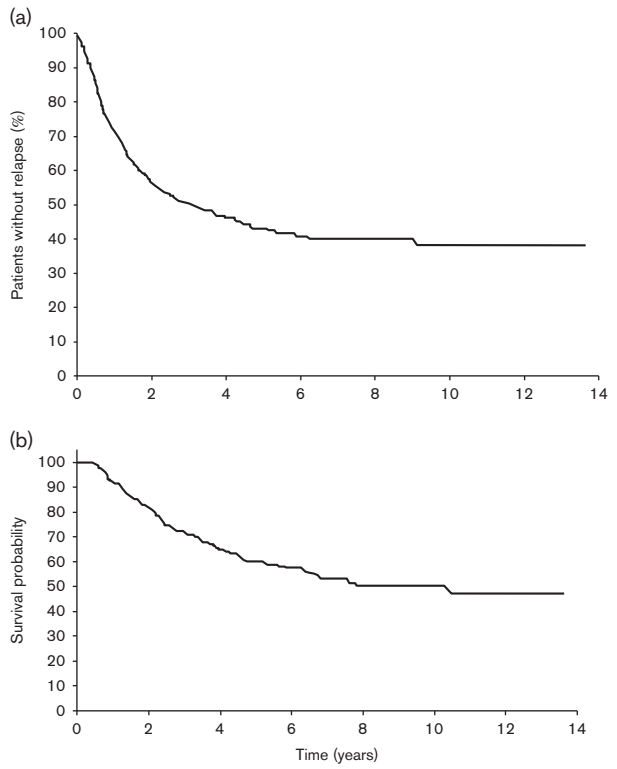
event (AE), 53 and 55%], followed by grade 3 AEs (48 and 45%), respectively.

The Cox regression analysis showed that patients with a diagnosis at 60–69 years of age and older than 69 years of age remained in the treatment 1.8 times more often (95% CI: 1.2–2.6; $P = 0.0052$) and 3.1 times more often (95% CI: 1.9–5.1; $P < 0.00001$), respectively, than patients who were diagnosed at younger than 40 years of age. The analysis also showed that dose reduction during the induction phase did not affect the duration of treatment (data not shown). In contrast, the number of days until the first dose reduction during the induction phase affected the duration of treatment negatively; thus, the longer the time until the first dose reduction, the shorter the duration of treatment [hazard ratio: 0.97 (95% CI: 0.95–0.99); $P = 0.0108$].

In all, 134 patients (42%) died and 177 patients (56%) experienced relapse. The median PFS and OS times (95% CI) for the overall population were 3.2 (2.1–4.5) and 10.5 years [6.4–not reached (NR)], respectively (Fig. 2). Excluding 66 patients (21%) who discontinued because of disease recurrence, 52 patients (16%) followed the Kirkwood scheme, whereas the remaining 200 patients (63%) had at least one dose modification. There were no statistically significant differences in the median times of PFS and OS between patients who received 100% or lower dose intensity: NR vs. 9.1 (4.5–NR) years for the PFS ($P = 0.8668$); the OS medians were NR ($P = 0.6703$). Similarly, the median PFS and OS were similar between patients with and without ulceration: 2.1 (1.5–3.6) vs. 4.2 years (2.3–NR) ($P = 0.1723$) and 6.8 (4.5–NR) vs. NR years ($P = 0.2872$), respectively.

Overall, 71% of the patients ($n = 254$) experienced at least one AE. However, none of the patients developed life-threatening AEs. The most frequently reported AEs of any grade were neutropenia in 100 patients (31%) and fatigue in 97 patients (30%) (Table 3).

Fig. 2



Kaplan–Meier survival curves for disease-free survival (a) and overall survival (b).

Discussion

Few adjuvant IFN-α2b clinical practice studies have been carried out in Europe [10]. This retrospective study, which describes the treatment patterns as well as the outcomes of a large, unselected and multi-institutional series of patients with high-risk melanoma treated with adjuvant IFN-α2b within the routine clinical practice in Spain, is one of the largest studies in the European real-world practice setting.

This study showed that the high-dose adjuvant ECOG scheme is the most frequently used IFN-α2b regimen in Spain for patients with high-risk melanoma. However, this regimen required dose modifications in most patients because of AEs. The entire two-phase treatment was completed by 38% of patients and 16% of the patients completed the two-phase following the planned high-dose scheme. One-third of the patients required dose reduction from the planned treatment, and the fact that more patients had reduced the dose during the induction phase than during the maintenance phase (38 vs. 28%)

Table 3 Main adverse events

Adverse event	Overall population ($N = 322$)
Neutropenia	100 (31)
Fatigue	97 (30)
Influenza-like symptoms	68 (21)
Hepatotoxicity	64 (20)
Fever	40 (12)
Increased transaminases	76 (24)
Anorexia	50 (16)
Depression	29 (9)
Anxiety	15 (5)
Insomnia	6 (2)
Reason for discontinuation/delay (induction phase)	
Recurrent disease	7 (2)
Patient symptoms	12 (4)
Grade 3/4 adverse event	17 (5)
Unknown/not documented	5 (2)
Missing	16 (5)
Reason for discontinuation/delay (maintenance phase)	
Recurrent disease	63 (20)
Patient symptoms	48 (15)
Grade 3/4 adverse event	32 (10)
Patient decision nonsymptom related	6 (2)
Unknown/not documented	13 (4)
Missing	19 (6)

All variables are categorized in *n* (%).

suggests that during the maintenance phase, both doctors and patients were less likely to attempt a dose reduction to complete the 12-month treatment regimen.

Despite the issues of tolerability, the efficacy results are remarkably favourable. Indeed, the median PFS and OS (3.2 and 10.5 years, respectively) compare favourably with the previous clinical trials with high-dose IFN-α2b (1.7 and 3.8 years, respectively) [5] and with pegylated IFN-α2b (2.9 years and NR, respectively) [11], and with a German retrospective study with high-dose IFN-α2b (1.7 and 6.1 years, respectively) [12]. These improved outcomes are unquestionable on PFS, but have been largely debated in terms of OS [13]. The results of the most recent meta-analysis also showed a benefit in OS [14]. Although these better outcomes are statistically significant, the frequency and severity of toxicity and drug acquisition costs have limited broad acceptance of adjuvant high-dose IFN-α2b in practice [7] Some trials have attempted to use an intermediate/low dose to avoid disabling AEs while seeking to improve tolerability [8,9]. In terms of the tolerability, on comparing our data with the ECOG 1684 trial [5], we observed lower numbers of patients with dose reduction in the maintenance phase (28 vs. 35%) and with dose delay in the induction phase (6 vs. 34%) and the maintenance phase (8 vs. 41%), whereas the number of patients with dose reduction in the induction was similar (38 vs. 36%). Similarly, the number of patients who continued was similar after 4 months of treatment in the current study and 3 months in the ECOG 1684 trial (80 vs. 77%, respectively). Thus, in clinical practice, doctors were less likely to delay doses or reduce doses in the maintenance phase and this practice does not seem to affect the continuation rate in the first few months of the maintenance phase.

The feasibility in terms of tolerability and duration in treatment as the ECOG 1684 trial [5] has also been investigated in a small Italian study with 26 patients. In this series, 83% of the patients completed the full 52-week expected treatment [15]; other larger studies reported figures similar to those reported here. A Canadian study with 225 patients showed that 41% completed the full therapy [1]. In the present study, a Cox regression analysis showed that age was a strong predictive factor. Indeed, younger patients discontinued the treatment more frequently than older patients. To our knowledge, this is the first study to report a possible association between age and duration of IFN-α2b treatment in patients with high-risk melanoma. The observation that in our series patients older than 59 years of age remained in the treatment more often than patients younger than 40 years of age raises the question of the relevance of how low-grade but chronic IFN-α2b-related AEs affect the quality of life of the employed and economically productive population. Paradoxically, in this group of patients, a younger age makes them less tolerant to the prevalence of symptoms, which reduces their working productivity or general capabilities to maintain a productive life. Other studies of adjuvant treatments in oncology have also reported that younger patients were more likely to discontinue the treatment than older patients [16,17], reinforcing the idea that occupational status is a plausible factor to consider.

Another feature of our analysis that deserves special consideration is the fact that the time until the first dose reduction in the induction period determines the duration of the therapy. This observation suggests that dose adjustment is particularly relevant for treatment tolerance and should be considered as soon as side effects appear. This has also been observed elsewhere [1].

Treatment compliance and ulceration did not show statistical differences in the PFS and OS in our series. Also, the German–French–UK study did not find differences in the comparison of patients who received at least 90% and less than 90% of the projected interferon dose [12]. Because of the reversible nature of most IFN-α2b AEs, although studies on quality of life show a clear detrimental impact [18], when patient preferences are considered, PFS is more valued than toxicity in patients with melanoma [19,20].

Although the data of the current retrospective study were collected carefully, some bias and confounders cannot be overlooked. A possible bias is an excess death rate as all deceased patients were screened, whereas living patients had to provide written consent to be included. Similarly, relapse was not histologically confirmed, but was assessed according to clinical and radiological standard procedures by the participating investigators. However, the documented follow-up after the end of treatment, in some cases over 10 years, is a clear strength of the current study.

Conclusion

This study shows that an IFN-α2b high-dose regimen is the most frequently used treatment approach in Spain for patients with high-risk melanoma. Despite poor compliance because of AEs and the need to focus future clinical trials on selected patients [21], an IFN-α2b high-dose regimen is a valid reference to consider in our setting until the advent of the newest adjuvant trials currently underway [22], with targeted therapies and immune check point inhibitors.

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New Jersey, USA – provided financial support to carry out the study.

Conflicts of interest

Maria V. Tornamira, Patricia del Barrio and Kendal Stevinson are full-time employees at Merck Sharp & Dohme (MSD). The authors were also study investigators, and their institutions received financial compensation for the enrolment of patients in the study.

Alfonso Berrocal has received honoraria as a consultant and as a speaker, as part of the advisory board and has given expert testimony for BMS, Roche and MSD. Luis de la Cruz-Merino has received honoraria as a consultant for Roche, BMS and MSD and as a speaker for Roche and MSD. Enrique Espinosa has received honoraria as a consultant and a speaker from MSD, BMS, GSK and Roche and for the educational presentations development for MSD, BMS, GSK and Roche. Josep Malvehy has received honoraria as a consultant and a speaker for Roche, BMS, GSK and AMGEN and for the educational presentation development for Roche, BMS, GSK and AMGEN. Iván Márquez-Rodas has received honoraria as a consultant and a speaker for Roche, BMS, AMGEN, GSK and Celgene and honoraria for travel/accommodation from BMS, Roche and GSK. Salvador Martín-Algarra has received honoraria as part of the MSD, GSK and Novartis advisory board. Elia Samaniego has received honoraria for travel/accommodation from Almirall, Ife, BMS, Roche, Leo Pharma, Italfamarco, Wyeth and La Roche Posay and for the educational presentations development for Leo Pharma and Avene. Ainara Soria has received honoraria as a consultant and a speaker for BMS, Roche, Celgene and GSK, for travel/accommodation from GSK and BMS and for the educational presentations development for BMS, Roche, Celgene and GSK. Isabel Palacio has received honoraria for travel/accommodation from BMS and payment for lectures from GSK and BMS.

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