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A randomised phase II trial of 1 month versus 1 year of adjuvant high-dose interferon α-2b in high-risk acral melanoma patients

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ABSTRACT

Background: High-dose Interferon-α-2b (HD-IFN) is an adjuvant treatment for melanoma. However, clinical trials for HD-IFN have not been reported in acral melanoma (AM), the predominant subtype of cutaneous melanoma in Asian population.

Methods: Patients with resected high-risk (stage IIb–IIIc) AM were randomly assigned to a regimen of 4-week (arm A: 15×10^6 U/m^2 d1–5/w × 4w) or 1-year adjuvant HD-IFN (arm B: 15×10^6 U/m^2 d1–5/w × 4w + 9×10^6 U tiw × 48w), respectively. The endpoints were relapse-free survival (RFS), overall survival (OS) and toxicities.

Results: A total of 158 patients were enrolled in this study and 147 patients were eligible for survival analysis. With a median follow-up of 36.1 months, median RFS for arm A and arm B were 17.9 months and 22.5 months, respectively ($P = 0.72$). Stratified analysis showed that RFS curves of patients in stage IIIb–IIIc were statistically different between arm A and arm B ($P = 0.02$). The median RFS of patients with more nodal metastases ($n \geqslant 3$) was shorter ($P = 0.004$) in arm A (3.3 months) than that in arm B (11.9 months). Grade 1/2 adverse effects were observed in both groups. However, patients in arm B showed higher incidence of reversible Grade 3/4 hepatotoxicity ($P = 0.03$).

Conclusions: The induction dose of 15×10^6 U/m^2 and the maintenance dose of 9×10^6 U were tolerable, which may be the optional dose intensity for adjuvant IFN-α-2b therapy in Chinese high risk AM population. No statistical significance was detected in RFS between the 4-week and 1-year regimen while a 1-year regimen may show clinical benefits in patients with stage IIIb–IIIc AM or with ⩾3 nodal metastases.

1. Introduction

Melanoma is a malignant tumour of melanocytes, which are predominantly found in the skin. Approximately 20% of patients with resected primary tumour typically die as a result of distant metastasis,[1] with patients with stages IIb–IIIc melanomas having the highest risk of recurrence.[2] The 3–5 years post-surgical relapse rates in patients with stages IIb and IIIc melanomas are 40–55% and 40–80%, respectively.[3]

The manifestation and prognosis of Asian patients are quite different from those of Caucasians.[4–6] Acral melanoma (AM) is the most frequent subtype of cutaneous melanoma

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in Asian populations, accounting for 47.5–65% of all melanomas; however, it is rare in Caucasians.[7–11] Patients with AM often show worse prognosis than those with melanomas at other sites.[12] More importantly, almost no studies have demonstrated strong evidence of adjuvant therapy for AM in Asian patients.

Interferon-α (IFN-α) has been the only drug observed to improve relapse-free survival (RFS) in postoperative melanoma patients at high risk, and the US Food and Drug Administration (FDA) approved high-dose IFN-α (HD-IFN) for this indication in 1996. A meta-analysis of HD-IFN trials shows a 24% reduction in the odds of recurrence for IFN-α-treated patients ($P = 0.0009$).[13] Other studies also show that HD-IFN, as adjuvant treatment, can improve overall survival (OS) in melanoma patients with high risk of relapse.[14] However, there remains some controversies about the effects of HD-IFN on OS.[15–17] For example, the significant toxicities and financial burden of conventional 1-year regimen would influence the quality of life to some extent. Pectasides et al. have reported that 4-week HD-IFN treatment provides the comparable sustained clinical benefit to 1-year HD-IFN therapy while it decreases toxicity in the Greek population.[16,17] Whether 4-week or 1-year HD-IFN may be preferred for melanoma patients need further evidence and should be tested in other populations.

Therefore, in this randomised phase II trial conducted in Chinese high-risk AM patients, we tried to explore an optional dose intensity and duration of an HD-IFN regimen.

2. Methods

2.1. Patient selection

Eligibility criteria included the following: histologically confirmed primary AM melanoma that has been completely excised with adequate surgical margins before randomisation; primary AM melanoma depth of >4 mm or metastatic to regional draining lymph nodes (stages IIb–IIIc)[18]; no prior systemic adjuvant therapy; no evidence of distant metastatic disease identified by means of lymph nodes ultrasound and whole body spiral computed tomography (CT) or positron emission tomography-CT; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate organ and marrow function; and no significant medical history of cirrhoses of the liver, autoimmune diseases, and severe depression. This single-centred trial was reviewed and approved by the Institutional Review Board of Peking University Cancer Hospital and Institute. All patients were required to provide written, informed consent prior to enrolling in this study.

2.2. Study design

Patients were randomly (simple randomisation method was used) assigned to two groups: arm A, 4 weeks of intravenous (IV) induction therapy of IFN-α-2b (15×10^6 U/m^2/d, 5 days per week); arm B, 4 weeks of intravenous (IV) induction therapy of IFN-α-2b (15×10^6 U/m^2/d, 5 days per week), followed by 48 weeks of subcutaneous (SC) maintenance therapy at a dose of 9×10^6 U three times per week. The dosage was selected according to both the previous trial regimen[16] and our own experience in Chinese patients. The dose was lower than the standard HD-IFN dose used in the ECOG trials,[14,19–21] but more applicable to Chinese patients, for whom the standard dose is too toxic to tolerate.

2.3. Tumour evaluation

Ultrasound of superficial lymph nodes and CT scans of chest, abdomen, and pelvis were performed every 3 months for the first year of the trial; every 6 months during years 2 and 3; and annually for the duration of the trial. Magnetic resonance imaging scans of the head and Single-Photon Emission Computed Tomography of bone were obtained every 6 months during the first 3 years of the trial and then repeated annually. These tests were conducted regularly to monitor for recurrence. Appropriate testing was performed to evaluate the presence of metastasis as clinically indicated.

2.4. Safety evaluation

Toxicity was recorded and evaluated according to the National Cancer Institute Common Toxicity Criteria established by the National Cancer Institute Cancer Therapy Evaluation Program. For both arms, blood tests, liver function tests, and blood urea nitrogen and creatinine tests were performed prior to treatment, weekly during 4-week induction treatment and monthly during subcutaneous maintenance treatment.

Dose adjustment was conducted in accordance with the severity of the toxicity. If Grade 3/4 toxicities occurred, treatment was withheld until the patient recovered, and a 33% dose reduction was performed for subsequent treatment. When the same toxicity occurred for a second time, a 66% dose reduction was instigated. Once Grade 4 hepatotoxicity occurred, treatment was discontinued immediately.

2.5. Statistical analysis

A parallel, two-group, equal sample allocation design of 70 patients in each group was required to provide a power of 0.90 with a two-sided significance level of 0.05 and to detect a median RFS time of 1 year[22] (for 4-week HD-IFN) compared with 2 years[14,16] (for 1-year HD-IFN) according to Lakatos.[23,24] Considering the poor prognosis of AM, we took the lower values of RFS reported in these trials. An accrual of 70 patients in each group was planned to allow a 10% dropout rate, with a planned accrual time of 12 months and a follow-up time of 24 months.

The primary end-point was RFS. Secondary end-points included OS and safety. Efficacy analyses were performed using one-sided log-rank test based on evaluable populations. The probability of RFS and OS were estimated by the Kaplan–Meier method. Significance levels were evaluated by the log rank test. The distribution of potential prognostic factors and toxicity was compared between treatment groups using the Fisher's exact test.

3. Results

3.1. Patient characteristics and treatments

A total of 158 patients (79 patients in each group) were enrolled in the trial from May 2007 to May 2008 (about 64% of patients

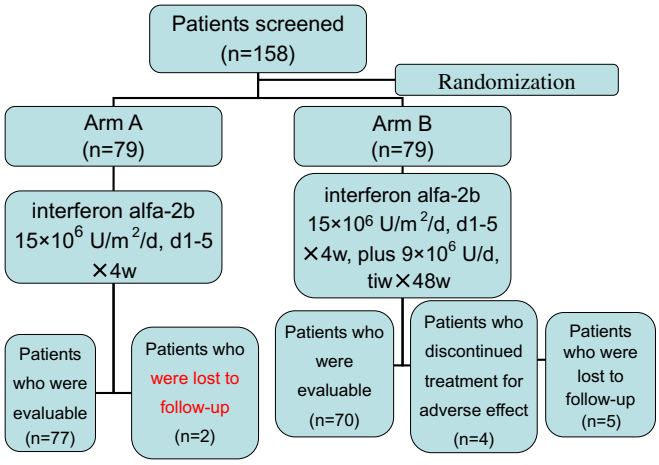

Fig. 1 – Disposition of patients (study flow chart, CONSORT diagram).

were enrolled in the first 6 months), and 147 patients were eligible for survival end-points (77 patients received the 4-week regimen, and 70 patients received the 1-year regimen). Two patients in arm A and 5 patients in arm B were lost to follow-up, and 4 patients in arm B withdrew from the study because of repetitive Grade 4 haematologic toxicity, vomiting or Grade 4 hepatotoxicity (for study flow chart, see Fig. 1). Patient's baseline demographical characteristics were balanced between the two treatment arms (Table 1).

3.2. *Clinical response*

By October 2010, more than 60% of patients developed recurrence or metastasis, with a median follow-up time of 36.1 months (range: 13.2–41.3 months). The median RFS for arm A was 17.9 months (range: 0.9–41.3 months, 95% confidence interval [CI]: 4.8–31.0), while the median RFS for arm B was 22.5 months (range: 1.2–41.5 months, 95% CI: 15.0–30.0). RFS was longer in arm B than that in arm A, although the difference was not statistically significant ($P = 0.72$). The Kaplan–Meier curves of RFS are presented in Fig. 2. The estimated 2- and 3-year RFS rates for arm A were 43.9% (95% CI: 32.1–55.7%) and 37.4% (95% CI: 26.6–48.2%), respectively. The estimated 2- and 3-year RFS rates for arm B were 44.4% (95% CI: 32.7–55.9%) and 35.6% (95% CI: 23.8–47.4%), respectively.

Stratified analyses were performed amongst the clinical factors including age (<65 years versus ⩾65 years), gender (male versus female), primary ulceration (positive versus negative), risk status of recurrence (moderately-high-risk versus very-high-risk) and numbers of positive lymph nodes ($n = 1$ or 2 versus $n \geqslant 3$).

For patients in stage IIIb–IIIc, we found that the overall RFS curves showed significant difference between arm A and arm B ($P = 0.02$) (Fig. 3) by Kaplan–Meier method and log-rank test.

Table 1 – Baseline demographical and clinical characteristics.[a]

Characteristics	Arm A ($n = 77$) N (%)	Arm B ($n = 70$) N (%)	P value[b]
Gender			0.741
Male	40 (52%)	39 (56%)	
Female	37 (48%)	31 (44%)	
Age (years)			0.821
Median (range)	49 (22–73)	48 (23–76)	
<65	64 (83)	60 (86)	
⩾65	13 (17)	10 (14)	
Ulceration			0.727
Positive	53 (69%)	46 (66%)	
Negative	24 (31%)	24 (34%)	
Stage			0.289
II	34 (44%)	28 (40%)	
III	43 (56%)	42 (60%)	
Risk group			0.41
High risk (IIb–IIIa)	40 (52%)	31 (44%)	
Higher risk (IIIb–IIIc)	37 (48%)	39 (56%)	

[a] Patient's baseline demographical characteristics were balanced between the two treatment arms.
[b] Fisher's exact test.

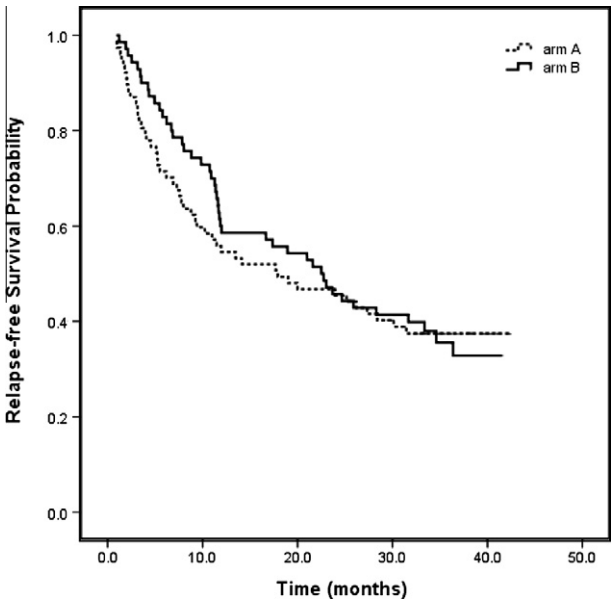

Fig. 2 – Kaplan–Meier curves for relapse-free survival for the two groups. Dotted line: arm A ($n = 77$); solid line: arm B ($n = 70$). Median RFS was 17.9 months and 22.5 months, respectively ($P = 0.72$).

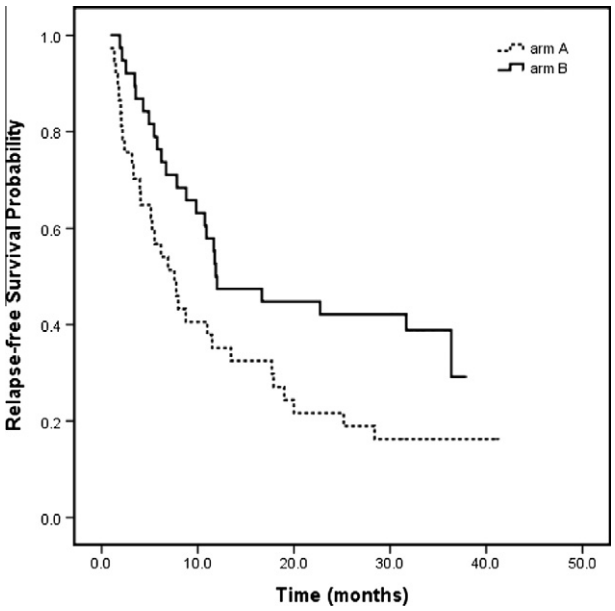

Fig. 3 – Kaplan–Meier curves for relapse-free survival in the very-high-risk subgroups. Dotted line: arm A ($n = 37$); solid line: arm B ($n = 39$). Median RFS was 7.6 months and 12.0 months, respectively ($P = 0.02$).

The median RFS was 7.6 months in arm A and 12.0 months in arm B.

Amongst 35 patients with more than three nodal metastases ($n \geqslant 3$) in this study, the median RFS time was 3.3 months (range: 0.9–31.2 months, 95% CI: 1.2–5.4) for arm A and 11.9 months (range: 2.1–36.4 months, 95% CI: 11.2–12.6) for arm B ($P = 0.004$) (Fig. 4).

There were no statistical differences between groups stratified by other clinical factors such as age, gender and primary ulceration. The study may be not powered to detect such differences, given the sample size of the study (especially for ulceration). Overall, 30 deaths occurred up to the cutoff time of follow-up. Analysis of the impact of treatments on OS was not carried out because the median OS was not reached in both groups.

3.3. *Toxicities*

Seventy-nine patients in arm A and 74 patients in arm B had adequate toxicity data available and thus were available for the safety analyses. The most common toxicities observed were flu-like symptoms, fatigue, hepatotoxicity, haematologic toxicity and anorexia (Table 2), most of which were Grade 1 or 2 toxicities. The incidences of all-grades toxicities were comparable between the two arms. Rates of all-grades hepatotoxicity ($P = 0.003$) and rates of Grade 3/4 hepatotoxicity ($P = 0.03$) were significantly higher in arm B than those in arm A. Treatment delays as well as dosage reductions occurred during treatment. Treatment delay within a week was required by approximately 15% of patients in arm A and by 25% of patients in arm B. The incidence of dosage reductions were 2% and 10% for arm A and arm B, respectively. No treatment-related deaths occurred in either treatment arm.

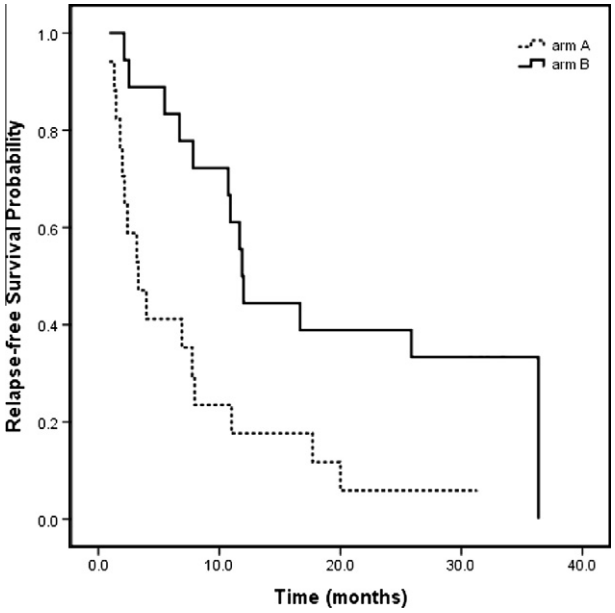

Fig. 4 – Kaplan–Meier curves for relapse-free survival in the N3 subgroups. Solid line: arm B ($n = 18$); dotted line: arm A ($n = 17$); N3, $\geqslant 3$ node metastases. Median RFS was 3.3 months and 11.9 months, respectively ($P = 0.004$).

4. Discussion

Our trial demonstrated that there was a trend towards longer RFS in the 1-year IFN arm than that in the 4-week arm, although the difference was not statistically significant ($P = 0.72$). However, the stratified analysis showed that overall RFS of very-high-risk status patients (IIIb–IIIc) achieved more

Table 2 – Adverse events and selected laboratory abnormalities.

Side-effects	Arm A ($n = 79$) N (%)		Arm B ($n = 74$) N (%)		P value	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Leukopenia	46 (58)	10 (13)	41 (55)	13 (18)	0.746	0.498
Fever	56 (71)	0	41 (55)	0	0.064	–
Fatigue	51 (65)	0	41 (55)	0	0.322	–
Increased aminotransferase[a]	35 (44)	4 (5)	52 (70)	12 (16)	0.003	0.03
Anorexia	19 (24)	0	14 (19)	1 (1)	0.556	–

[a] The incidence of either all-grade hepatotoxicity or Grade 3/4 hepatotoxicity was significantly higher in arm B than that in arm A.

benefits from the 1-year regimen than the 4-week regimen ($P = 0.02$), and that patients with more nodal metastases showed longer RFS duration in the 1-year regimen than the 4-week regimen ($P = 0.004$). As compared with the reports of Pectasides et al.[16] no significant differences were observed in RFS between 1 month versus 1 year of adjuvant HD-IFN-α-2b therapy in patients with resected, high-risk melanoma. Our trial thus suggests that patients with very-high-risk melanoma or node metastases $\geqslant 3$ would more likely benefit from the 1-year IFN treatment and that patients with earlier stage melanoma may benefit as much from a 4-week regimen. This may be the first prospective clinical trial to demonstrate potential optional duration of IFN-α-2b regimen for Asian patients with AM.

Clinical trials of IFNα-2b adjuvant therapy have never previously been reported in the AM subtype. In the ECOG trials, the median RFS ranged from 20.4 to 30 months for high-risk melanomas.[14,19–21] The median RFS in our trial was around the lower limit of this range, which may be conferred by three contributing factors. Firstly, AM is considered to be a subtype with worse prognosis, and is often associated with factors indicating poor prognosis, such as greater tumour thickness and more advanced stage at diagnosis.[25] Secondly, AM was typically associated with a higher degree of ulceration. Several studies have confirmed that ulceration is associated with shorter survival. Finally, sentinel node biopsy is not widely used in China while lymph node metastases were diagnosed by ultrasound or selective lymph node dissection. Thus the stages of AM may be ambiguous and some patients, who may not have been diagnosed accurately, may already have reached later stages than recorded in our trial.

An interesting finding in our trial is that patients in stages IIIb–IIIc or with more nodal metastases, but not those with ulceration, achieved more benefits from the 1-year regimen than the 4-week regimen. In the stratified analysis, the ulceration group showed no more benefits as compared to the non-ulceration group. However, it is reported that melanoma patients with primary ulceration treated with either conventional or PEGylated IFNα-2b showed better response than patients with non-ulcerated primary melanomas.[16,26,27] A meta-analysis has shown that patients with an ulcerated primary melanoma are far more sensitive to IFNα-2b than patients without ulcerated primary melanomas.[28] In our trial, the incidence of primary ulceration was 67% (partially due to the tendency in China to delay visits to the doctor), which is twice as high as that (32%) reported in the meta-analysis.[28] Given the incidence of ulceration and the study sample size, it may be hard to detect IFNα-2b sensitivity in patient populations that had both N1 and N2 disease.

Safety analysis demonstrated that the incidence of most toxicities in Chinese patients were higher than that of the Greek trial,[16] even though dose reduction was performed. Although adverse effects were common, most of these were Grade 1/2 and reversible. Patients in arm B required more treatment delays and dosage reductions than those in arm A, but most patients tolerated treatment reasonably well. It was debated that the dose intensity in the Greek trial,[16] which delivered 75% of the planned E1684 induction dose, was an unconventional and unapproved IFNα-2b scheme. However, our trial demonstrated that 12.7% (10/79) of patients in the 1-year regimen could not tolerate the 1-year modified IFN treatment. As the conventional treatment would make higher incidence of dropout, the dose intensity we designed for the trial was well tolerable for the Chinese AM population, which may require further investigations.

In conclusion, our trial demonstrated that the induction dose of 15×10^6 U/m^2 and the maintenance of 9×10^6 U was tolerable and may be the optional dose intensity for Chinese AM patients. For high-risk AM patients in stages IIb–IIIa, 4-week HD-IFN treatment might be adequate for patients who could not tolerate 1-year regimen. In contrast, for patients in stage IIIb–IIIc or with multiple node metastases, the 1-year regimen may be preferred. The results of the trial may warrant further phase III clinical trials in AM patients of other ethnicity, and phase II clinical trials with more strict enrolment strategy (e.g. patients in stage IIIb–IIIc) and larger sample size may be optimal for clinical selection of IFN-α-2b dosage and duration.

Contributions of authors

Jun Guo, Lu Si and Lili Mao were involved in the conception and design of the study. Lili Mao and Lu Si wrote the manuscript. Zhihong Chi, Chuanliang Cui, Xinan Sheng, Siming Li and Bixia Tang provided study material. Lili Mao and Lu Si collected the data. Lili Mao and Lu Si analysed and interpreted the data. All authors validated the report.

Conflict of interest statement

None declared.

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