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Interferon-α versus interleukin-2 in Chinese patients with malignant melanoma: a randomized, controlled, trial

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The US Food and Drug Association has approved interferon-α (IFN-α) and interleukin-2 (IL-2) as adjuvant therapy in malignant melanoma. The objective of the study was to compare efficacy and safety of subcutaneous interferon-α with continuous intravenous IL-2 in Chinese patients with malignant melanoma. A total of 250 patients with unresectable malignant melanoma were subjected to randomized in 1 : 1 ratio. Patients received subcutaneous 9×10^6 IU/m^2 IFN-α (IFN-α group, $n = 125$) or continuous intravenous 9×10^6 IU/m^2 IL-2 (IL-2 group, $n = 125$) at every 21 days for 4 months. The response, progression-free survival, overall survival, adverse effects, and cost were evaluated by experts in the field. IL-2 and IFN-α were effective in improvement of malignant melanoma after 4 months of intervention. IL-2 was effective in improving brain metastasis. Patients of the IL-2 group had a higher overall survival ($P < 0.0001$) and a higher progression-free survival ($P = 0.002$) than those of IFN-α group. The IL-2 group reported hypotension, kidney dysfunction, liver dysfunctions, flu-like symptoms, and capillary leak syndrome as adverse effects. IFN-α group reported thrombocytopenia and neutropenia as adverse effects. Healthcare management and expert charges lead to increase in the cost of treatment for IL-2 group patients than IFN-α group ($P < 0.0001$). Continuous intravenous IL-2 should be recommended in relapse-free Chinese patients with malignant melanoma. Level of Evidence: I. *Anti-Cancer Drugs* 30:402–409 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Keywords: brain metastasis, interferon-α, interleukin-2, malignant melanoma, melanocytic tumor, thrombocytopenia

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Introduction

Malignant melanoma is a tumor of melanocytes in the skin [1]. Malignant melanoma rarely occurs (only 4%) in skin cancer [2]. Among all dermatologic cancers, 80% of cases are lethal [3]. Research prospectus and clinical efforts in the prognosis of advancement of the stage of malignant melanoma are poor. Its prognosis in Chinese patients is high (20 000 new cases/year) [4]. Therefore, the therapeutic management of malignant melanoma needs to be addressed soon as there are a large number of patients affected in People's Republic of China.

Interferon-α (IFN-α) is mainly produced endogenously by macrophages and has proved anticancer effects in the experimental studies and the clinical trials [5]. It has improved overall survival and disease-free survival in patients with high-risk cutaneous melanoma [6], but the mechanism of action is unclear yet [7]. Treatment-emergent adverse effects are increased and cause a financial burden on patients when it is used with a chemotherapeutic agent(s) [6].

Interleukin-2 (IL-2) has complex biological effects and exerts an antitumor effect by enhancing cytotoxic T lymphocyte and natural killer cell lysis. Intravenously infused high dose of IL-2 ($100–150 \times 10^6$ IU/m^2/day) is more toxic than low dose (10^6 IU/m^2/day) [4,8]. Subcutaneous administration of IL-2 is less toxic than intravenous infusion [4]. Continuous infusion is more toxic than continuous dripping [4] and has capillary leak syndrome and flu-like symptoms as adverse effects [4]. However, it has higher efficacy for Chinese patients than US patients because Chinese patients get long response duration than White patients because of changes in its pharmacokinetics in different populations [9].

Although the US Food and Drug Association has approved IFN-α and IL-2 as adjuvant therapy in malignant melanoma [4,10]. These forms of treatment have no guidelines associated with them in China, and the rationale for carrying out the study is to shed more light on the requirements of their inclusion.

The primary aim of the study was to treat Chinese patients with malignant melanoma using a high dose of

subcutaneous IFN-α or continuous intravenous IL-2 for 4 months. The secondary end point of the trial was to compare the efficacy and safety of IFN-α therapy with IL-2 therapy and to do the research that Chinese guidelines are inadequate when it comes to using of IFN-α as a cancer treatment.

Patients and methods

Drugs

IFN-α and IL-2 were purchased from Essex Pharma GmbH (Munich, Germany).

Compliance with ethical standards

The study had been registered in the Research registry (*http://www.researchregistry.com*), UID No. researchregistry4361, dated 9 January 2015. The protocol of the study (CMU/CL/03/15 dated 7 January 2015) had been approved by the Cancer Hospital of China Medical University Review Board. The study had adhered to the law of China, consolidated standards of reporting trials (CONSORT) [11], and Declaration of Helsinki (V2008) [12]. An informed consent form with regard to interventions, pathology, and publications of the study including personal data and images in all formats (hard and/or electronic) irrespective to time and language had been signed by patients and their relatives (legally authorized persons).

Inclusion criteria

All patients age 18 years and above with histologically confirmed and unresectable malignant melanoma, admitted to the Cancer Hospital of China Medical University (Shenyang, China), and the referring hospitals from 13 January 2015 to 1 December 2017 were included in the trial. Patients with Eastern Cooperative Oncology Group performance status (0–5 scale, with regard to disease progression, where 0: fully active patient and 5: dead [13]) score of 2 or less were included in the study. Patients who had adequate functioning of vital organs (kidney, heart, brain, lungs, and liver) were included in the trial. The demographic parameters of the enrolled patients are presented in Table 1.

Exclusion criteria

Patients who have received steroids and had forced expiratory volume less than 75% were excluded from the study. Patients who had not signed an informed consent form were also excluded from the trial.

Design of experiment

A total of 250 patients were subjected to simple randomization (1 : 1 ratio). All the patients have been treated identically before the trial. Prefilled envelopes were used for the purpose of randomization. The physicians involved in the randomization were not involved in the treatment. The sample size was calculated using OpenEpi 3.01-English (Open Source Epidemiologic Statistics for Public Health, Los Angeles, USA). The sample size was found to be 125 for both groups. The other factors, two-sided confidence intervals were 80%, the outcome in both groups was 95% ($\alpha = 0.05$), the risk ratio detected was 1, and the normal approximation was 9.917%. The flow diagram of the study is presented in Fig. 1.

Table 1 Demographic characteristics of the enrolled patients

Intervention	Groups: IFN-α ($n = 125$) Subcutaneous interferon-α	Groups: IL-2 ($n = 125$) Continuous intravenous interleukin-2	Comparison between groups (P value)
Age (years)			
Minimum	20	21	0.072
Maximum	62	61	
Average	47.52 ± 3.52	44.15 ± 4.45	
Sex			
Male	86 (69)	81 (65)	0.591
Female	39 (31)	44 (35)	
ECOG status			
0	75 (60)	71 (57)	0.267
1	49 (39)	53 (42)	
2	01 (1)	01 (1)	
Type of melanoma			
Cutaneous	97 (77)	95 (76)	0.366
Mucosal	13 (10)	16 (13)	
Acral lentiginous	15 (13)	14 (11)	
Stage of unresectable melanoma[a]			
IIIA	27 (22)	32 (26)	0.71
IIIB	3 (2)	2 (2)	
IIIC	95 (76)	91 (72)	
Lactate dehydrogenase level[b]			
Normal	102 (82)	99 (79)	0.228
Above normal	23 (18)	26 (21)	
Lymph node status			
≥ 4	19 (15)	14 (11)	0.35
2–3	37 (30)	31 (25)	
1	69 (55)	80 (64)	
Ulceration of primary lesions			
No	71 (57)	76 (61)	0.61
Yes	54 (43)	49 (39)	
Breslow thickness/Clark number[c] (mm)			
< 1	75 (60)	69 (55)	0.22
1–2	25 (20)	31 (25)	
2.01–4	15 (12)	21 (17)	
> 4	10 (8)	04 (3)	
Primary site			
Lower extremity	28 (22)	23 (19)	0.68
Head	19 (16)	21 (17)	
Neck	20 (16)	14 (11)	
Upper extremity	29 (23)	33 (26)	
Trunk	29 (23)	34 (27)	

Continuous parameters reported as mean ± SD and constant parameters reported as *n* (%).

ECOG, Eastern Cooperative Oncology Group performance (0: fully active, 1: carry out work with light nature, 2: capable of all self-care but not able to perform work activities, 3: capable of only limited self-care, 4: completely disabled, 5: dead); IFN, interferonl IL, interleukin; RECIST, Response Evaluation Criteria in Solid Tumors.

Repeated measures analysis of variance was used for continuous data and the χ^2-independence test was used for constant data.

[a]RECIST v1.1.

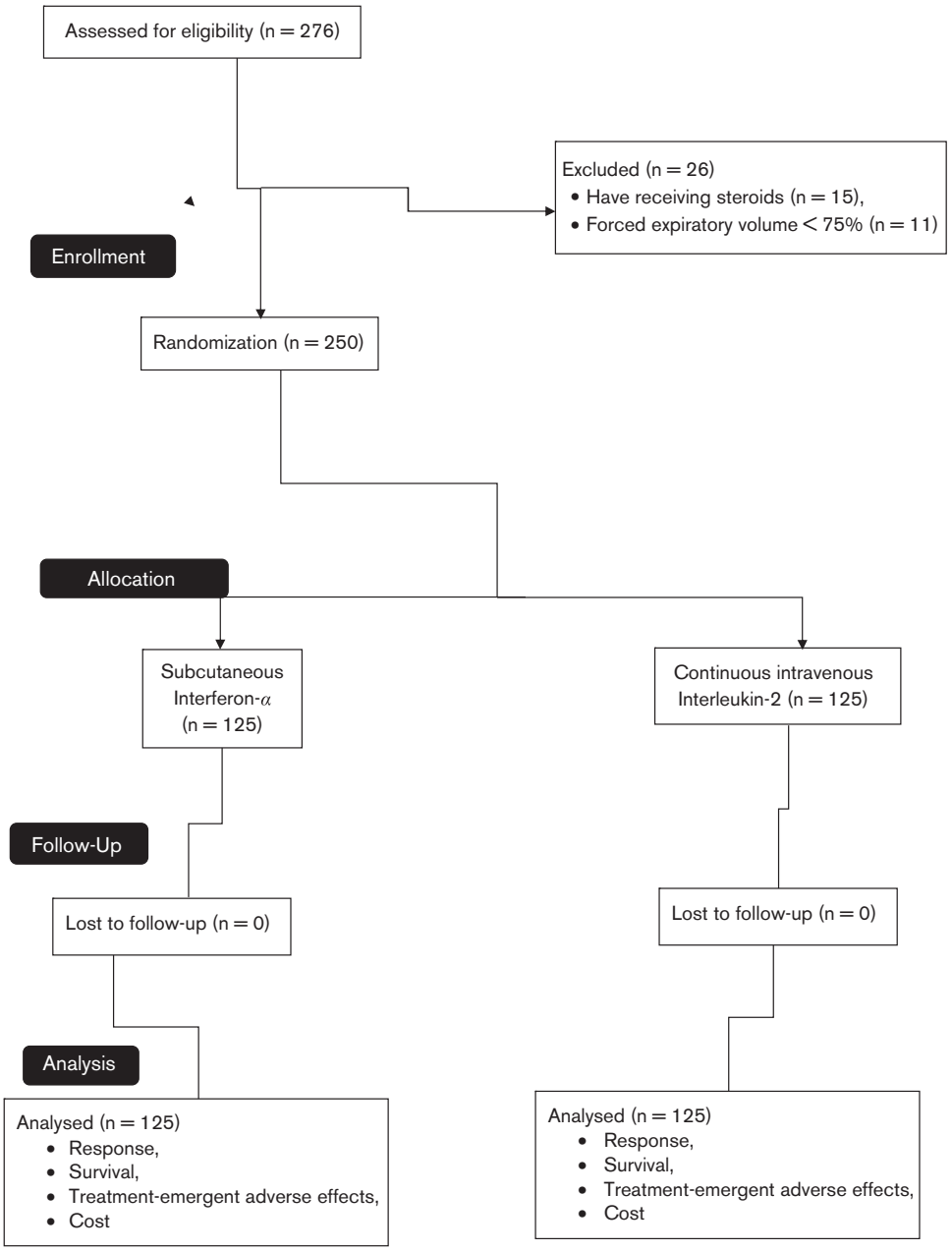
[b]Normal level: 140–333 IU/l.

[c]The total vertical height of the melanoma.

Intervention

As first-line therapy, patients of IFN-α group received subcutaneous 9×10^6 IU/m^2 IFN-α at every 21 days for 4 months [1]. Patients of IL-2 group received continuous (over 96 h) intravenous 9×10^6 IU/m^2 IL-2 at every 21 days for 4 months [14].

Fig. 1



CONSORT flow diagram of the study. Two-sided confidence intervals: 80%, outcome in both groups: 95%, the risk ratio detected: 1, and normal approximation: 9.917%. Intention-to-treat method of analysis was adopted.

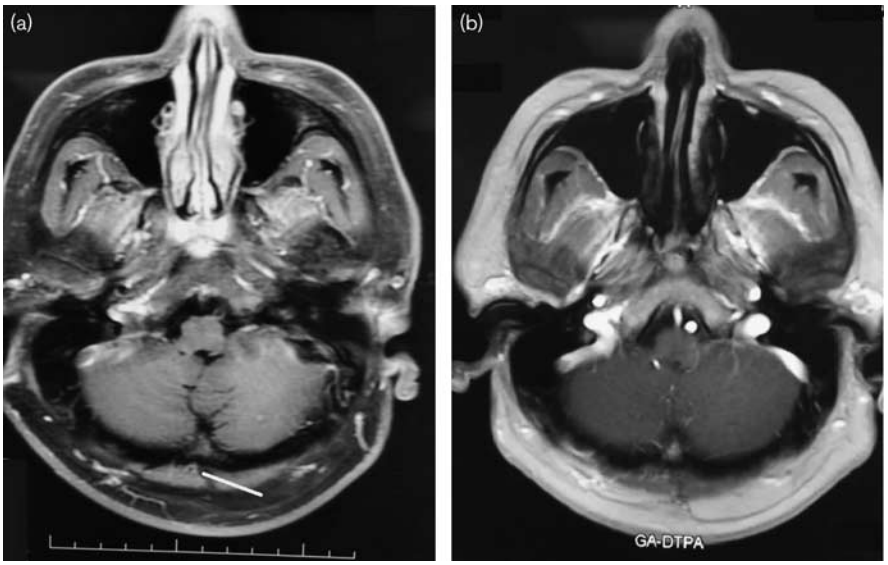
Response evaluation

The Response Evaluation Criteria in Solid Tumors v1.1 guideline was used for evaluation of disease progression and tumor response [15]. The computed tomography of the pelvis, abdomen, and the chest and MRI of the brain were used to assess the treatment response. Times to tumor progression were considered from the time of intervention initiation to proof of tumor progression. Overall survival was considered from the time of detection of malignant melanoma to the death [14].

Treatment-emergent adverse effects

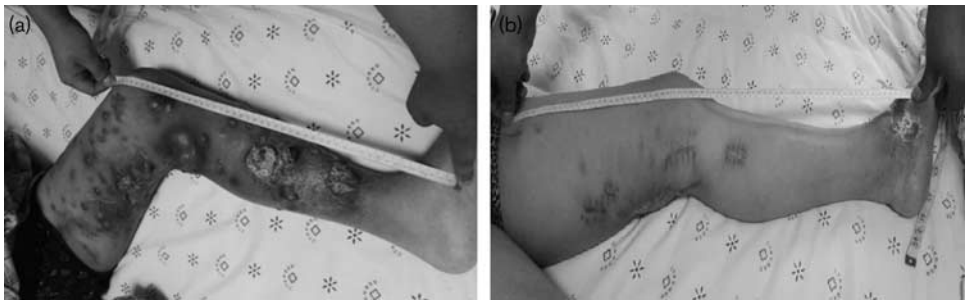
The US National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 were used for evaluation of toxicity [16]. Patients subjected to an anatomical characterization and laboratory tests. Lactate dehydrogenase (lactate dehydrogenase test), complete metabolic panel (blood and urine glucose level, blood sodium, blood potassium, blood carbon dioxide, blood chloride levels, and liver function test), and complete blood count (red blood cell count, hemoglobin, white blood cell count,

Fig. 2



(a) Brain metastasis before treatment. MRI of the brain of a patient with cutaneous melanoma at the time of the enrollment. ECOG status: 2. Breslow thickness: 1.8 mm. Line indicates tumor. (b) The treatment response for interleukin-2. MRI of the brain of a patient with cutaneous melanoma after 4 months of interleukin-2 intervention. ECOG status after intervention: 1. Breslow thickness after intervention: 0.9 mm. Tumor was absent after intervention. Patient age 48 years. Sex: male. The site of melanoma: left lower extremity.

Fig. 3



(a) Patient with ulcerated cutaneous melanoma at the time of the enrollment. ECOG status: 2. Breslow thickness: 2.5 mm. (b) Patient with cutaneous melanoma after 4 months of interleukin-2 intervention. ECOG status after intervention: 2. Breslow thickness after intervention: 2.0 mm. Patient age 32 years. Sex: male. The site of melanoma: left lower extremity. The RECIST v1.1 guideline was used for evaluation of tumor response.

and platelet count) during and before every cycle were evaluated [14].

Cost of treatment

The purpose of calculating the cost in the study was to check the need for financial help for treatment to patients or not. Cost of treatment was included in the cost of diagnosis, interventions, healthcare management, and expert charges. The cost was considered from the time of detection of malignant melanoma to the death.

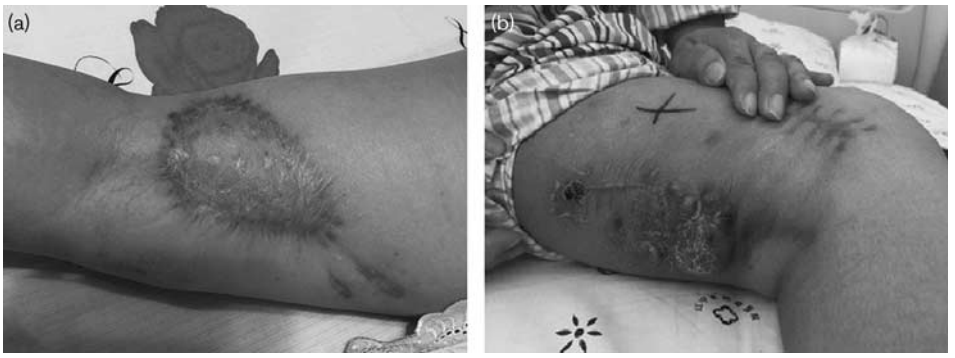
Statistical analysis

InStat (version Window; GraphPad, Indiana, San Diego, California, USA) was used for statistical analysis. Repeated measures analysis of variance was used for continuous data and the χ^2-independence test was used for constant data. Results were considered significant at 95% of confidence level. Intention-to-treat method of analysis was adopted.

Results

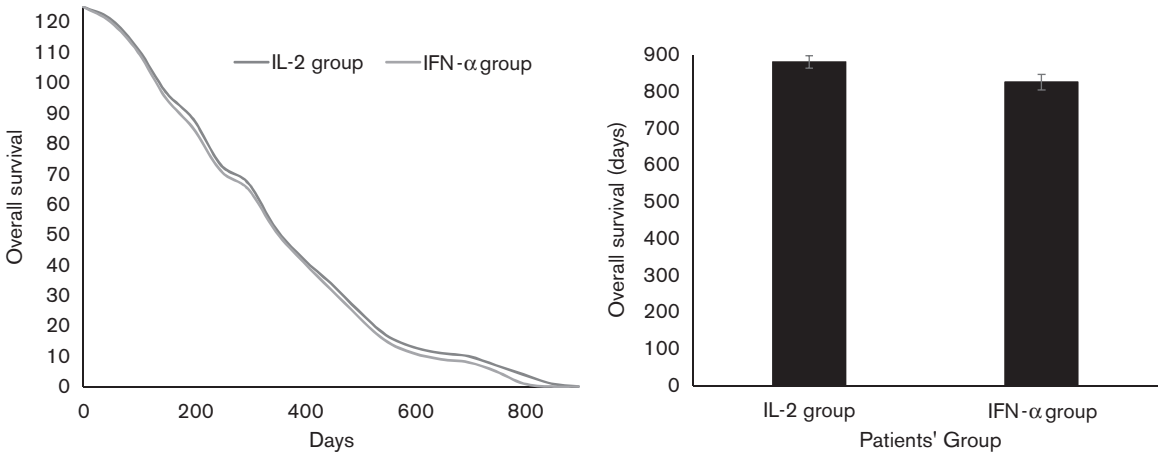
Radiographic images concluded that after 4 months, patients of both groups had an absence of brain, lung, heart, and liver metastases in the patients who had no brain, lung, heart, and liver metastases before treatment. Even if brain metastasis was present at the time of enrollment (Fig. 2a), IL-2 was effective to improve brain metastasis after 4 months of intervention (Fig. 2b). However, IFN-α failed to improved metastasis after 4 months of intervention.

Fig. 4



(a) Patient with cutaneous melanoma at the time of the enrollment. ECOG status: 1. Breslow thickness: 0.8 mm. (b) Patient with cutaneous melanoma after 4 months of Interferon-α intervention. ECOG status after intervention: 1. Breslow thickness after intervention: 0.6 mm. Patient age 55 years. Sex: female. The site of melanoma: Left lower extremity. The RECIST v1.1 guideline was used for evaluation of tumor response.

Fig. 5



Overall survival of the patients. Overall survival was considered from the time of detection of malignant melanoma to the death. 0: At the time of completion of the intervention. The χ^2-independence test was used for statistical analysis. A $P < 0.05$ was considered significant. The sample size: 125 for both groups. Data were represented as mean ± SD of all.

Compared with before treatment (Fig. 3a), IL-2 was effective in improving malignant melanoma after 4 months of intervention (Fig. 3b). In a similar manner, as compared with before treatment (Fig. 4a) IFN-α was also effective in improving malignant melanoma after 4 months of intervention (Fig. 4b).

The overall survival was counted up to 800 days of the follow-up period, and progression-free survival was counted up to 500 days of the follow-up period. Patients of the IL-2 group had a higher overall survival ($P < 0.0001$; Fig. 5) and a higher progression-free survival ($P = 0.002$; Fig. 6) than those of IFN-α group.

Hypotension, kidney dysfunction, and liver dysfunctions were major continuous intravenous IL-2-emergent adverse effects. Thrombocytopenia and neutropenia were major subcutaneous IFN-α-emergent adverse effects (Table 2).

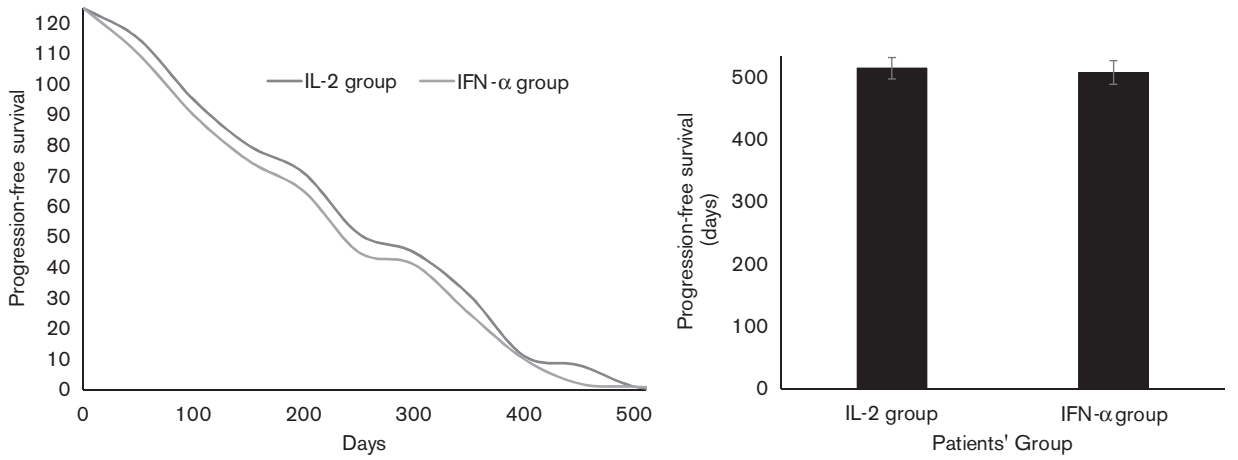
Continuous intravenous IL-2 caused flu-like symptoms (chills, muscle pain, and fever) and capillary leak syndrome (systemic edema, pulmonary edema, weight gain, ascites, and pleural effusion; Table 3).

Healthcare management and expert charges lead to increase in the cost of treatment for IL-2 group than IFN-α group (total cost of therapy: 105 345 ± 9845 ¥/patient vs. 95 656 ± 7586 ¥/patient, $P < 0.0001$; Fig. 7).

Discussion

In the study, subcutaneous IFN-α or continuous (dripping over 96 h) intravenous IL-2 as a first-line therapy in patients with malignant melanoma was preferred instead of using a chemotherapeutic agent(s). The chemotherapeutic agents used in malignant melanoma like cisplatin induce thrombocytopenia, acute renal failure, and peripheral neuropathy [14].

Fig. 6



Progression-free survival of patients. Progression-free survival of patients was considered as time without any progression to new cutaneous/subcutaneous metastases (skin), lymph node metastases, or distant metastases (systemic). 0: At the time of completion of the intervention. The χ^2-independence test was used for statistical analysis. A $P < 0.05$ was considered significant. The sample size: 125 for both groups. Data were represented as mean ± SD of all. IFN-α, interferon-α; IL-2, interleukin-2.

Table 2 Hematological treatment-emergent adverse effects after 4 months from the time of intervention initiation

	Groups		
Intervention	IFN-α ($n = 125$) Subcutaneous interferon-α	IL-2 ($n = 125$) Continuous intravenous interleukin-2	Comparison between groups (P value*)
Hypotension	3 (2)	40 (32)[a]	< 0.0001
Liver dysfunction[b]	2 (2)	35 (28)[a]	< 0.0001
Kidney dysfunction[c]	2 (2)	17 (14)[a]	0.0008
Thrombocytopenia[d]	39 (31)[e]	5 (4)	< 0.0001
Neutropenia[f]	38 (30)[e]	6 (5)	< 0.0001
Anemia	7 (6)	7 (6)	NA
Lymphopenia	2 (2)	3 (2)	0.651

Data are represented as *n* (%).
The χ^2-independence test was used for statistical analysis.
IFN, interferonl IL, interleukin; NA, not applicable.
[a]Significant continuous intravenous interleukin-2-emergent adverse effects.
[e]Significant subcutaneous interferon-α-emergent adverse effects.
[b]Bilirubin > 3 mg/dl.
[c]Serum creatinine > 1.8 mg/dl.
[d] < 50 000 cells/ml.
[f]Absolute neutrophil count 300 cells/ml.
*$P < 0.05$ was considered significant.

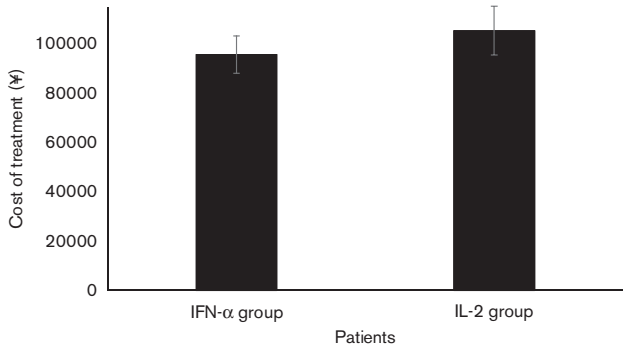
Table 3 Nonhematological treatment-emergent adverse effects after 4 months from the time of intervention initiation

	Groups		
Intervention	IFN-α ($n = 125$) Subcutaneous interferon-α	IL-2 ($n = 125$) Continuous intravenous interleukin-2	Comparison between groups (P value*)
Diarrhea	5 (4)	7 (6)	0.767
Nausea	3 (2)	4 (3)	0.701
Fatigue	10 (3)	3 (2)	0.087
Headache	4 (3)	5 (4)	0.734
Skin rash	1 (1)	1 (1)	NA
Constipation	3 (2)	2 (2)	0.651
Pruritus	1 (1)	0 (0)	0.316
Neuropathy	1 (1)	1 (1)	NA
Taste alteration	1 (1)	1 (1)	NA
Vomiting	4 (3)	3 (2)	0.701
Flu-like symptoms[b]	1 (1)	11 (9)[a]	0.008
Infection	2 (2)	3 (2)	0.651
Capillary leak syndrome[c]	1 (1)	15 (12)[a]	0.0008
Rhabdomyolysis	0 (0)	9 (7)[a]	0.007

Data are represented as *n* (%).
The χ^2-independence test was used for statistical analysis.
IFN, interferon; IL, interleukin; NA, not applicable.
[a]Significant continuous intravenous interleukin-2-emergent adverse effects.
[b]Chills, muscle pain, and fever.
[c]Systemic edema, pulmonary edema, weight gain, ascites, and pleural effusion.
*$P < 0.05$ was considered significant.

Vinca alkaloids and nab-paclitaxel induce neurotoxicity and neutropenia [17]. Docetaxel and carboplatin have adverse effects like neutropenia, anemia, and thrombocytopenia [18]. Fresolimumab may develop hyperkeratosis [19] and squamous cell carcinomas [20]. Moreover, combination therapies of chemotherapeutic agent(s) with IFN-α or IL-2 may have somewhat higher tumor response but have severe toxicities and the less overall survival of the patients [17]. IFN-α has immunoregulatory, antiangiogenic, antiproliferative, differentiation-inducing, and proapoptotic effects [21]. IL-2 is a natural part of the immune system. It is a messenger molecule (cytokine) that is secreted from specific cells to alert other cells about an infection. 10^6 IU/m^2/day (low dose) of IL-2 is not effective and its high dose ($100–150 \times 10^6$ IU/m^2/day) is toxic [8]. 700×10^6 IU/m^2/week subcutaneous administration of IL-2 is less toxic than 100×10^6 IU/m^2/day intravenous infusion but more toxic than 9×10^6 IU/m^2/3-week dripping over 96 h [4]. Overall survival irrespective of disease conditions is higher for patients who received subcutaneous IFN-α than those who

Fig. 7



The total cost of treatment of patients. Repeated measures analysis of variance was used for statistical analysis. A $P < 0.05$ was considered significant. Data were represented as mean ± SD of all. The sample size: 125 for both groups. The cost was considered from the time of detection of malignant melanoma to the death. IFN-α, interferon-α; IL-2, interleukin-2.

received the same dose of continuous IFN-α [22]. With respect to the regimen selected in the study for patients, the researchers justified interventions to improve overall survival and quality of life with or without disease activity of patients.

The trial was performed with IL-2 and IFN-α for six cycles only at the interval of 21 days. Previous studies have reported that administration of IFN-α for short period (4 weeks) and long period (1 year) has the same relapse-free survival in White patients [1,23] and administration of IL-2 for a longer period of time is not tolerated by patients [4,24]. With respect to interventions of the subjects, the trial was designed so that they achieve maximum response with minimum toxicities.

After 4 months, patients of both groups had an absence of brain, lung, heart and liver metastases. However, kidney and liver dysfunctions and hypotension were reported in the patients who had received continuous intravenous IL-2. IL-2 has cardiovascular toxicities [9]. Continuous intravenous IL-2 has urogenital and hepatic adverse effects [4,25]. Even patients of the IL-2 group had flu-like symptoms and capillary leak syndrome as measured by nonhematological adverse effects. Hypovolemia owing to capillary leak syndrome may reduce blood perfusion in the brain, resulting in dysfunction of the body [4]. However, low dose of IFN-α (intravenous 10×10^6 IU/m^2) has only flu-like symptoms, nausea, and nonhematological adverse effects [26]. In considering the adverse effects of the study, subcutaneous IFN-α is the reasonable treatment option for patients with malignant melanoma but Chinese guidelines for treatment of malignant melanoma has not recommended low and medium doses of subcutaneous IFN-α because it does not improve the survival, and there is no experience of using higher subcutaneous dose (10×10^6 IU/m^2/3 weeks) of IFN-α in Chinese patients [4]. Therefore, Chinese guidelines for treatment of malignant melanoma are required to update in terms of adjuvant treatment of malignant melanoma.

The treatment with subcutaneous IFN-α was cheaper than continuous intravenous IL-2 but had less overall survival and less progress-free survival. Subcutaneous IFN-α has no significant effects as compared with placebo [4,27,28] but has better response in ulcerated primary melanoma [29]. Subcutaneous IFN-α could be recommended in relapse-free patients.

There were several limitations of the study, for examples, the results of the study were applicable to Chinese patients only. The effects of demographic characteristics on the response were not evaluated. Measures used to control adverse effects were not discussed. The effects of measures to maintain toxic effects on overall survival and quality of life of patients were not discussed. The blinded procedure has more reliable results, but in the study, blinding was not possible. The change in immune cells and other cell types and their effect/role in disease progression and tumor response were not examined.

Conclusion

Subcutaneous IFN-α is a safer option than continuous intravenous IL-2 in patients with malignant melanoma. However, the good response may be reported in continuous intravenous IL-2 in short treatment period with moderate adverse effects.

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Authors' contributions: All contributing authors listed on the manuscript are aware of and agree to the submission of this manuscript. S.L. and X.W. equally contributed to the conceptualization, the design, and formal analysis of the study. P.C. was the project administrator and contributed to visualization and the design of the study. Y.P. contributed to the conceptualization, data curation, supervision, and validation of the study. K.Z. contributed to the design, resources, and investigation for the study. W.W. contributed to the methodology, resources, and software for the study. E.Q. contributed to the conceptualization, data curation, formal analysis, and supervision of the study. X.Z. contributed to the conceptualization, data curation, and the draft and edited the manuscript for intellectual content. The authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Availability of data and materials: The datasets used and analyzed during the current study were available from the corresponding authors on reasonable request.

Conflicts of interest

There are no conflicts of interest.

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