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Prospective study of clinical characteristics of melanoma patients with retinopathy caused by a high-dose interferon α-2b

Shijie Lan, Zhihua Cui, Qiliang Yin, Zhigang Liu, Lingling Liang, Hua He, Hesong Liu, Zhen Guo, Yingying Yu and Di Wu

Retinopathy is a rare side effect of interferon α-2b treatment. The goal of this study was to prospectively investigate the clinical characteristics of Chinese patients with melanomas who developed retinopathy following high doses of interferon α-2b (HD-IFN) therapy. The study included 56 melanoma stage I–III patients that were treated with HD-IFN. Fourty-three patients developed HD-IFN-induced retinopathies. Forty-three melanoma patients (76%) developed retinopathy after being treated with HD-IFN. Among these patients, 49% had cotton–wool spots, 19% had retinal hemorrhage, and 30% had retinal hemorrhage. The median time of occurrence of retinopathy was 4 weeks after treatment, and the median time of duration was 4 weeks. No patient showed other symptoms except one who had blurred vision. A comparison of clinical characteristics (age, gender, primary site, stage, and ulceration) and laboratory examinations (white blood cell and platelet counts, hemoglobin, serum lactate dehydrogenase, alanine transaminase, aspartate aminotransferase, triiodothyronine, thyroxine, thyroid-stimulating hormone, and lipid) between the HD-IFN-induced retinopathy patients and nonretinopathy patients did not show any significant differences ($P>0.05$). Although all patients that developed retinopathy had diabetes or hypertension, an equal percentage of patients were without retinopathy had diabetes or hypertension. HD-IFN therapy in patients with melanomas may induce mild retinopathy. Our results; however, do not necessarily suggest to discontinue the HD-IFN treatment because retinopathy is a reversible disorder. *Melanoma Res* 31: 550–554 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Correspondence to Di Wu, PhD, Cancer Center, the 1st Hospital of Jilin University, No.1 Xinmin St, Changchun, Jilin Province, 130021 China
Tel: +86 431 88783170; e-mail:wudi1971@jlu.edu.cn

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Introduction

Retinopathy refers to retinal vascular disorders caused by abnormal blood vessel growth [1]. Retinopathy is broadly categorized into two types, proliferative and nonproliferative. Diabetes retinopathy is the most typical retinopathy, which is an ocular manifestation of systemic disease [2]. The second most common retinopathy is retinopathy of prematurity that occurs in premature babies and is caused by intensive neonatal care with oxygen therapy [3]. Other retinopathies include hypertensive retinopathy, radiation retinopathy, solar retinopathy, and retinopathy associated with sickle cell disease.

High doses of interferon α-2b (HD-IFN) remain the most important adjuvant in Chinese melanoma therapies because of drug accessibility and economic reasons. Although immunotherapy and molecular targeted therapies have been approved as adjuvant treatments for melanoma [4], HD-IFN has been associated with various adverse effects. The most common side effects of HD-IFN include influenza-like syndrome typically presented as chills, fever, myalgias, headache, and arthralgias. Retinopathy; however, is one of the rare side effects of HD-IFN. The typical ocular alteration of HD-IFN-induced retinopathy includes superficial linear and patchy retinal bleeding, as well as white-centered hemorrhages. Retinopathy induced by HD-IFN could occur unilaterally or bilaterally.

Several previous studies suggested that HD-IFN therapy is associated with the occurrence of retinopathy, the incidence of which reached 18–86% [5]. However, most data came from observations of HD-IFN therapy in hepatitis C patients. Indeed, the volume of interferon used in hepatitis C patients is lower than the doses used to treat patients with melanoma. Reported retinopathy cases caused by HD-IFN treatment of melanomas are still limited. In addition, reports of melanoma patients with HD-IFN-induced retinopathy are case reports or retrospective studies. In this study, we prospectively analyzed the clinical characteristics of the HD-IFN-induced retinopathy in Chinese patients with melanomas.

Methods

Ethics authorization

This was a prospective clinical study performed at The Cancer Center and The Department of Ophthalmology

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of The First Hospital of Jilin University. The project was approved by The ethics committee of The First Hospital of Jilin University. All involved patients signed informed consent and agreed to join this study.

Objectives

Fifty-six patients with melanomas who accepted a standard treatment regimen of HD-IFN subcutaneous injections [6] were enrolled in this study from January 2014 to January 2019 in The First Hospital of Jilin University. Among them, 43 melanoma patients with HD-IFN-induced retinopathy were divided into HD-IFN-induced retinopathy groups. Thirteen melanoma patients without retinopathy were included as negative controls (group) during the same time period and at the same institute.

Stage of melanoma

The stage of melanoma was divided based on the 2009 (seventh) Edition of American Joint Committee on Cancer melanoma staging system [7].

High doses of interferon α-2b therapy

The patients with melanoma were treated by induction therapy: 15 million units/m^2 of HD-IFN by intravenous injection, 5 days per week for 4 weeks; and maintenance therapy: 10 million units by subcutaneous injection, for three days per week for 48 weeks.

High doses of interferon α-2b-induced retinopathy

HD-IFN-induced retinopathy was defined by melanoma patients treated with HD-IFN therapy, who developed abnormal fundus vascular alterations, such as cotton–wool spots or hemorrhages, but did not present with any other retinopathies, including diabetes retinopathy, hypertensive retinopathy, radiation retinopathy, solar retinopathy, and retinopathy associated with sickle cell disease.

Gene mutation detection

BRAF and c-Kit gene mutation analyses were performed as previously described [8].

Observations

All patients were evaluated with visual acuity, visual field, and fundus color photography before and 2 weeks after HD-IFN therapy, the day after the whole course of HD-IFN therapy, and each month during the maintenance treatment period. Routine blood, lactate dehydrogenase (LDH), alanine transaminase (ALT)/aspartate aminotransferase (AST), lipid levels, and thyroid function tests were monitored. For patients with hypertension or diabetes, blood pressure and blood glucose levels were controlled in the normal range.

Statistics

All data were analyzed using SPSS (version 22.0) statistical software. The Chi-square test was used for two sets of count data. Comparison between two normal distribution data was performed using *t*-tests. The nonparametric rank sum test was performed for the data that did not conform to the normal distribution. A P value <0.05 was considered statistically significant.

Results

General information

A total of 56 melanoma patients who accepted HD-IFN therapy were enrolled in this study. Among these patients, 43 patients (76%) developed retinopathy. The median age of these patients was 55 (30, 74) years old. Eighteen cases were male (41.86%). The remaining 13 melanoma patients [median age, 52 (21, 74) and four male (30.77%)] without retinopathies were included as negative controls. Both the median age and gender between the groups were not statistically different ($P > 0.05$) (Table 1).

Fundus alterations

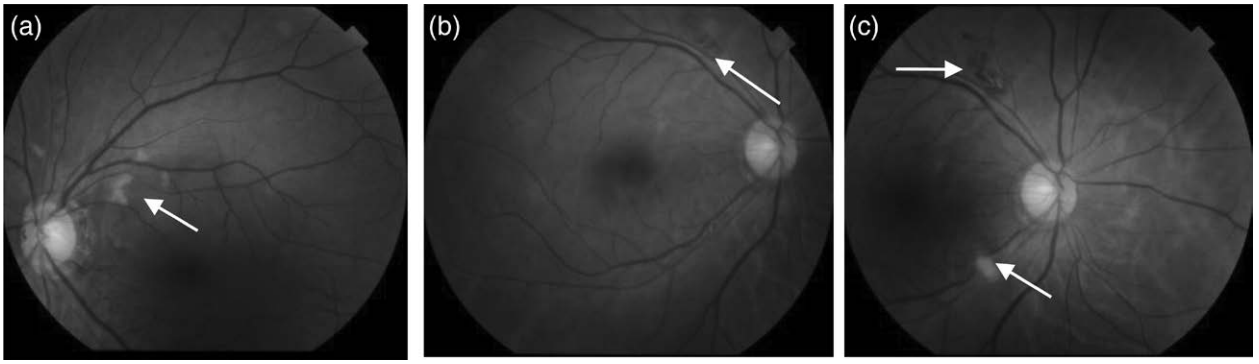
The fundus alterations in melanoma patients with HD-IFN-induced retinopathy included typical cotton–wool spots and hemorrhage (Fig. 1). Among the 43 HD-IFN-induced retinopathies, 22 patients (51%) had only cotton–wool spots, 8 (19%) presented with only retinal hemorrhage and the remaining 13 cases (30%) had both retinal hemorrhage and cotton–wool spots.

Only one HD-IFN-induced retinopathy patient had blurred vision and floating muscae volitantes in the left eye. Color photography of the fundus showed that the retina of the left fundus was scattered in the cotton buds. HD-IFN treatment of the patient was then stopped. Three weeks later, the retinal injury in this patient was relieved. Based on the patient's consent, the original HD-IFN treatment was continued without any similar symptoms. None of the other included patients had any clinical symptoms.

Table 1 Clinical features of 56 patients with melanoma

Items	Retinopathies (n=43)	No retinopathies (n=13)	P value
Age (year, median age)	55(30, 74)	52(21, 74)	0.902
Gender			0.432
Male	18	4	
Female	25	9	
Primary area			0.853
Limb	23	9	
Nonlimb	10	3	
Mucosa	4	0	
Other	6	1	
Staging			0.076
IB	5	2	
IIA	3	0	
IIB	9	2	
IIC	12	3	
IIIA	2	2	
IIIB	3	2	
IIIC	1	0	
Unknown staging	8	2	
Ulceration			0.777
Ulceration	13	5	
No ulceration	16	5	
Gene mutation			0.204
c-Kit	1	2	
BRAF	4	1	
No mutation	13	3	

Fig. 1



Cotton–wool spots and retinal hemorrhages in the fundus of HD-IFN-induced retinopathy. A 51-year-old man with abdominal skin melanoma at stage IIB was examined after 2 weeks of interferon treatment. We found cotton–wool spots (arrowed) in the left eye fundus (a) and retinal hemorrhages in the right eye fundus (b). A 48-year-old man with left foot melanoma at stage IIC was examined after 4 weeks of interferon treatment. We found retinal hemorrhages in the right eye fundus (c). HD-IFN, high doses of interferon α-2b.

Occurrence of HD-IFN-induced retinopathy

The median time of occurrence of retinopathy was 4 weeks (range 1–24 weeks) after treatment. Except for one patient who had clinical symptoms and discontinued the drug, the other patients continued to take the drug, and the fundus lesions were gradually relieved, the median time of duration was 4 weeks (range 2–20 weeks).

Clinical characteristics

When comparing clinical characteristics between the HD-IFN-induced retinopathy patients and the patients without retinopathy, we found no significant differences in primary site, stage, ulceration, or proto-oncogene gene (*c-Kit* and *BRAF*) mutation ($P > 0.05$).

Blood and biochemical examinations

Comparison of laboratory examinations of melanomas before HD-IFN therapy between the HD-IFN-induced retinopathy patients and the patients without retinopathy showed no significant differences in white blood cell and platelet counts, or levels of hemoglobin, serum LDH, AST, blood lipid, ALT, or thyroid function (Table 2) ($P > 0.05$).

Complications

In the HD-IFN-induced retinopathy group, six (10%) patients were complicated with diabetes mellitus, nine cases (16%) had hypertension, and three cases (5%) presented both diabetes and hypertension. However, no significant statistical difference was found in the patients with the above complications compared to patients without retinopathy (the *P* values of the comparison of diabetes was 0.427, hypertension was 0.19, and diabetes combined with hypertension was 0.545) (Table 3).

Table 2 Laboratory examinations of melanoma patients

	Retinal lesions (n=37)	No retinal lesions (n=12)	*P* value
White blood cells	5.42±1.65	4.92±1.15	0.391
Lymphocytes	1.65 (1.32, 2. 13)	1.76 (1.28, 1.85)	0.880
Platelet	228.49±71.85	229.42±87.70	0.961
Hemoglobin	141.32±13.50	131.58±10.63	0.057
LDH	181.00 (151.75, 194.00)	193.00 (160.50, 211.50)	0.254
ALT	24.10 (16.35, 44.70)	25.10 (18.55, 36.30)	0.569
AST	23.90 (19.65, 31.95)	29.55 (22.98, 36.80)	0.189
Triglyceride	1.52 (0.99, 2.12)	1.35 (0.99, 1.62)	0.438
High-density lipoprotein	1.24 (1.03, 1.52)	1.28 (1.19, 1.64)	0.383
Low-density lipoprotein	2.79 (2.30, 3.28)	3.32 (2.56, 3.43)	0.414
T3	4.96 (4.74, 5.33)	4.44 (4.12, 5.22)	0.092
T4	16.11 (14.49, 18.58)	14.98 (13.88, 16.88)	0.218
TSH	1.78 (1.12, 2.95)	1.74 (1.14, 3.61)	0.791

ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

Table 3 Complications of the melanoma patients

Complications	Retinal lesions (n=43)	No retinal lesions (n=13)	*P* value
Hypertension	9	0	0.173
Diabetes	6	0	0.315
Hypertension and diabetes	3	0	0.545

Discussion

Ikebe *et al.* [9] reported the first case of retinal hemorrhage and cotton–velvet spot (retinopathy) in hepatitis C patients treated with interferon in 1990. Since then, there have been some reports and studies concerning interferon-related retinopathy. However, most of these studies focused on the interferon treatment of hepatitis. The dose of interferon for the treatment of hepatitis ranges from low to medium ($3–9 \times 10^6$ U/day), which is markedly lower than the dose used in melanoma adjuvant therapies (20×10^6 U/day). Only a few cases of malignant melanoma were treated with HD-INF [10,11]. This is the first prospective study to investigate the clinical characteristics of 43 cases of HD-IFN-induced retinopathy in patients with malignant melanoma.

A retrospective study of 30 melanoma patients who received HD-IFN reported four patients (13%) with retinopathy [12]. As a comparison, in this study, 76% of the melanoma patients who accepted HD-IFN therapy had retinopathy, which was much higher than the previous incidence, but still in the reported range [5]. This difference seems to indicate that more attention should be given to ocular monitoring during HD-IFN treatment, since clinicians currently only examine the ocular fundus if patients have clinical symptoms. Only fundus examination can reveal retinopathy. Thus, most mild, initial, or nonsymptom retinopathies would be ignored otherwise. Our conclusion is indirectly supported by the findings below. Our data showed that the median time of the occurrence of HD-IFN-induced retinopathy was 4 weeks after treatment, whereas previous literature reported that retinopathy appeared generally within 12 weeks after HD-IFN administration [13]. In our observation, the median time of lesion persistence was 4 weeks. These results were consistent with those reported previously. Cotton–wool spot and retinal hemorrhage are the most common interferon-related fundus diseases. Microaneurysms, neovascular glaucoma, and ischemic optic neuropathy have also been reported [14,15]. All retinopathy cases observed in this study were mild and reversible. Most patients had no conscious symptoms, except one patient whose clinical symptoms were relieved after 3 weeks of withdrawal and symptomatic treatment.

Some risk factors of IFN-related retinopathy have been reported differently. Some studies indicated that age, sex, white blood cells, red blood cells, platelets, hemoglobin, hepatic transaminase, triglyceride, and cholesterol levels were risk factors for IFN-related retinopathy [16,17]; however, other studies did not support these findings [5]. In our observation, none of these factors significantly impacted IFN-related retinopathy. Here, we analyzed other possible risk factors, including the location of primary focus, stage of tumor, ulceration, recurrence, gene mutation status, lymphocyte count, LDG, and thyroid function, and none significantly impacted IFN-related retinopathy.

Hypertension and diabetes can cause fundus microangiopathy, especially in senior patients with a longer history of disease. Meta-analysis showed that [18] patients with hypertension or diabetes were at increased risk of IFN-related retinopathy, however, other studies reported contrary conclusions [19,20]. In this study, nine patients with hypertension, six patients with diabetes mellitus, and three patients with diabetes mellitus and hypertension developed retinopathy during HD-IFN therapy, which is consistent with previous reports. However, compared to patients without diabetes mellitus or hypertension, there was no significant difference. Therefore, hypertension or diabetes mellitus were not sufficiently confirmed to increase the risk of HD-IFN-related retinopathy. Larger clinical trials are thus necessary to clarify this conclusion.

The exact mechanism underlying HD-IFN-induced retinopathy remains unclear. It was previously reported that 52% of patients treated with interferon produce autoantibodies, including thyroid antibodies, anti-nuclear antibodies, and anti-insulin antibodies [21], which can cause or aggravate autoimmune diseases, such as polyarthritis and thyroiditis. Interestingly, most HD-IFN-related retinopathy occur in the early stage of the interferon therapy, rather than in the late stage, indicating that it is not caused by a cumulative effect of long-term drug application. Therefore, many scholars believe that HD-IFN-induced retinopathy is associated with immunity. Guyer *et al.* [22] reported 10 cases of HD-IFN-related retinopathies and first proposed that immune complex deposition in the retinal blood vessels and lymphocytic infiltration cause capillary perfusion, resulting in retinal hemorrhage and lint speckle formation. The majority of scholars agree with this hypothesis. Nishiwaki *et al.* [23,24] verified that interferon could activate white blood cells that adhere to vascular endothelial cells, thus causing micro-infarction of retinal capillaries and necrosis of vascular endothelial cells in a rat retinal microcirculation model. Another group [25,26] found that after interferon treatment, plasma activated complement five increased significantly in patients with hepatitis C, which can promote platelet aggregation and activation, leading to retinal capillary infarction, capillary nonperfusion area, cotton villus, and retinal hemorrhage. Tilg *et al.* [27] found that IFN could promote the production of thrombotic autoantibodies mediated by T cell activation, thus causing retinal capillary infarction. IFN increases the viscosity of circulating effector proteins produced by other cells, leading to decreased perfusion of the capillary layer of the optic disc [28].

Therefore, it is possible that multiple factors work together to cause retinal microcirculation disorder, which eventually leads to retinopathy. However, the exact mechanism requires further study.

Conclusion

This study is the first prospective observational study to investigate the clinical characteristics of HD-IFN-induced retinopathy in patients with malignant melanoma. This study found that up to 76% of melanoma patients treated with HD-IFN had mild retinopathy. Retinopathy symptoms, such as cotton–velvet spot and retinal hemorrhage, gradually reversed without stopping medication. We found no high-risk factors for IFN-related retinopathy. Although some melanoma patients with hypertension or diabetes developed retinopathy, there were no significant differences in the occurrence of retinopathy compared to patients without diabetes or hypertension.

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Clinical trial information: NCT02702973.

Conflicts of interest

There are no conflicts of interest.

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