Am J Transl Res 2021;13(5):5380-5385
www.ajtr.org /ISSN:1943-8141/AJTR0129928

Original Article

Clinical application effect of Pembrolizumab in the treatment of advanced cutaneous malignant melanoma

Lei Fu[1*], Hui Zhang[2*], Jingwen Jiang[2], Xuewu Chen[2], Lang Chen[1], Hui Gong[3]

Departments of [1]Dermatology, [2]Oncology, Hainan Hospital of Traditional Chinese Medicine, Haikou, Hainan Province, China; [3]Department of Medical Oncology, Hu'nan Academy of Traditional Chinese Medicine Affiliated Hospital, Changsha, Hu'nan Province, China. [*]Equal contributors and co-first authors.

Received January 11, 2021; Accepted February 9, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Objective: To investigate the clinical application value of Pembrolizumab (PEM) in the treatment of advanced cutaneous malignant melanoma (ACMM). Methods: The data of 56 patients with ACMM were retrospectively analyzed. According to the treatment methods, they were divided into a control group (30 cases) and an observation group (26 cases). Patients in the control group were given chemotherapy with Temozolomide (TEM), and patients in the observation group were treated with PEM on the basis of the treatment provided to the control group. The short-term therapeutic efficacy, long-term survival rate and the incidence of adverse reactions were compared between the two groups. Results: After treatment, the short-term clinical effective rate was higher in the observation group than that in the control group (P<0.05). In addition, the survival time in the observation group was longer than that in the control group (P<0.001); and the one-year survival rate was higher in the observation group (53.85% vs. 40.00%, P>0.05). No statistical difference was found in the incidence of adverse reactions between the two groups (P>0.05). Conclusion: PEM can improve the short-term clinical effective recovery rate, long-term survival time and prognosis survival rate of patients with cutaneous malignant melanoma, with no increased incidence of drug-related adverse reactions. It is relatively safe and worthy of front-line clinical promotion and application.

Keywords: Advanced cutaneous malignant melanoma, Pembrolizumab, chemotherapy, clinical efficacy, adverse reaction

Introduction

The skin is the largest tissue organ of the human body, and it functions in the role of immunity against infection, prevention of sunburn and high temperature, heat preservation and water storage [1, 2]. However, when exposed to sunlight and radioactive substances for a long time, the skin may be at risk for cancerization [3, 4]. In terms of age and gender, the incidence of cutaneum carcinoma is higher in males than that in females, which also gradually increases with age [5, 6]. In China, the incidence of cutaneum carcinoma is also on the rise along with environmental factors, lifestyle changes and the aggravation of an aging society [7].

Melanoma is a common pathological type of cutaneum carcinoma, and its clinical characteristics include a high degree of malignancy, strong aggressiveness and high mortality [8]. At present, melanoma patients who have missed the opportunity for surgery can only rely on comprehensive treatment including chemotherapy and immunotherapy. This comprehensive treatment achieves certain clinical effects, but it fails to meet the expected therapeutic value for patients [9]. The combination of immune checkpoint drugs such as Pembrolizumab (PEM), a PD-1 antibody drug, has achieved a good therapeutic effect in the treatment of malignant tumors, and it can improve the clinical treatment efficiency and survival cycle of patients with advanced melanoma. There is still a lack of relevant retrospective controlled trial studies [10]. Based on this, this study retrospectively analyzed the clinical data of patients with advanced melanoma who received treatment, and explored the effect of PEM on the clinical therapeutic efficiency and survival related aspects, so as to provide more

clinical evidence-based data for the treatment of advanced melanoma.

Materials and methods

General information

The data of 56 patients with advanced cutaneous malignant melanoma (ACMM) admitted to our hospital from January 2016 to December 2018 were retrospectively analyzed. According to the clinical treatment methods, they were divided into the control group (30 cases) and observation group (26 cases). This study was approved by the Ethics Committee of our hospital.

Inclusion criteria: 1) The diagnosis of melanoma was confirmed by preoperative local cell biopsy or postoperative pathology, and the results met the relevant diagnostic criteria [11]. 2) Patients were aged between 20 and 70 years old; 3) Patients had no previous history of surgery and chemoradiotherapy; 4) The expected survival time of patients were more than two months.

Exclusion criteria: 1) Patients with clinical stage I-II; 2) Patients with other tissue tumors; 3) Patients with Karnofsky (KPS) score <60 [12]. 4) Patients with dysfunction of major organs, such as the heart, liver and kidney; 5) Patients with previous immune system diseases; 6) Patients with systemic infection or cachexia.

Methods

Temozolomide (TEM; Jiangsu Tasly Diyi Pharmaceutical Co., Ltd., China) was used for chemotherapy in both groups. The main drug regimens were as follows: Patients received TEM (200 mg/m^2/day) orally for five consecutive days, every 28 days, or TEM (75 mg/m^2/day) orally for three weeks, every four weeks. The observation group was given additional dose of 2 mg/kg PEM (Merck & Co., Inc., USA) once a day, every three weeks. In light of the experience of previous studies considering the toxic side effects of chemotherapy drugs, after 6-8 weeks of TEM treatment and clinical benefit, patients were treated with PEM maintenance therapy [13]. Objective efficacy was evaluated after two cycles of treatment.

Outcome measures

Primary outcome measures: 1) Clinical effective rate: According to American efficacy evaluation standard of solid tumor, it is divided into four grades: complete response, partial response, stable disease and progressive disease. Clinical effective rate = Number of (complete response + partial response) cases/total number of cases *100%. 2) Total survival time: From the first day of combined treatment to the day of first onset of progressive disease or death from any cause [14].

Secondary outcome measures: 1) Drug treatment-related toxic side effects are classified as mild, moderate, high and life threatening according to the standards of the World Health Organization. 2) Clinically relevant adverse reactions were recorded and compared between the two groups, including skin problems, gastrointestinal reactions and changes in related hematological indicators (transaminase elevation and leukopenia) [15].

Statistical analysis

SPSS 22.0 statistical analysis software was used to analyze all the data. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and independent t test was used for inter-group comparison. Count data were expressed as case/percentage (n/%); comparison of inter-group rates was determined by chi-square test. Kaplan-Meier method was applied to draw the survival curve, and the difference between groups was detected by Log-rank test. P<0.05 was defined as statistically significant.

Results

Comparison of general information

There was no statistical difference between the two groups in the general information, including gender, age, lesion site and clinical stage (all P>0.05), and as such the two groups were comparable. See **Table 1**.

Comparison of clinical effective rate

It showed that the clinical effective rate of the observation group was higher than that of the control group (P<0.05), preliminarily indicating

Table 1. Comparison of general information

Group	Control group (n=30)	Observation group (n=26)	t/χ^2	P
Gender (male/female)	20/10	15/11	0.172	0.678
Age (years)	48.9±3.5	47.9±3.5	1.029	0.308
Lesion site (n)			0.611	0.737
Skin	11	9		
Acra	12	8		
Mucosa	6	7		
Other	1	2		
Clinical stage (n)			0.068	0.794
III stage	24	19		
IV stage	6	7		

Table 2. Comparison of clinical effective rate (n)

Group	Clinical effectiveness				Total effective rate (n, %)
	Complete response	Partial response	Table disease	Progressive disease	
Control group (n=30)	7	6	11	6	13 (43.33)
Observation group (n=26)	9	10	3	4	19 (70.38)
χ^2			3.890		
P			0.049		

that PEM can improve the clinical effectiveness of chemotherapy drugs in the treatment of advanced melanoma. See **Table 2**.

Comparisons of the survival period and the one-year survival rate

The total survival time of the two groups was 9.98±0.57 months (CI: 8.856-11.103), and the observation group showed a longer average survival period (11.32±0.59 months vs. 6.69± 0.29 months, P<0.001). This illustrated that PEM could improve the survival time of patients with advanced melanoma (**Figures 1**, **2**). Moreover, compared with the control group, the observation group showed a slightly higher one-year survival rate (14/26 vs. 12/30, P=0.443).

Comparisons of toxic side effects

The results showed that there was no statistical significance in the grade of related toxic side effects or the incidence of related clinical complications in the two groups (all P>0.05). This indicated that PEM did not increase the incidence of adverse reactions during treatment, meaning it is relatively safe clinically. See **Tables 3**, **4**.

Discussion

Melanoma is a malignant tumor originating from melanocytes in the skin tissue, with no specific clinical manifestations at first (the main manifestation is similar to the appearance, size, color and associated touch of a nevus). However, a relevant non-invasive examination fails to obtain an accurate diagnosis, and biopsy is also unable to accurately distinguish pigmented nevus tissue and early pigmented tumor; therefore, patients often miss optimal treatment measures and seek comprehensive treatment [16].

The results of this study showed that the clinical effective rate of TEM treatment for advanced melanoma in the control group was 43.33%, which was related to the mechanism of the strong tumor killing effect of chemotherapy drugs, so as to obtain the clinical effect of inhibiting tumor lesion growth. However, some studies have confirmed that the complete remission rate of TEM in the treatment of melanoma is close to 20%, and about 60% of the total clinical response rate can be achieved under conventional standardized treatment with sufficient amounts [17]. The effective rate of this study was lower than that of previous

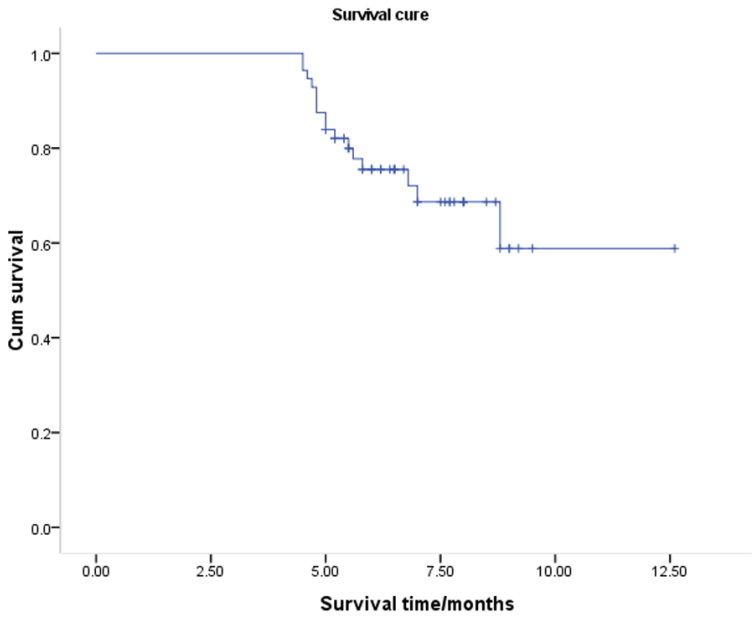

Figure 1. Survival cycle chart of all patients.

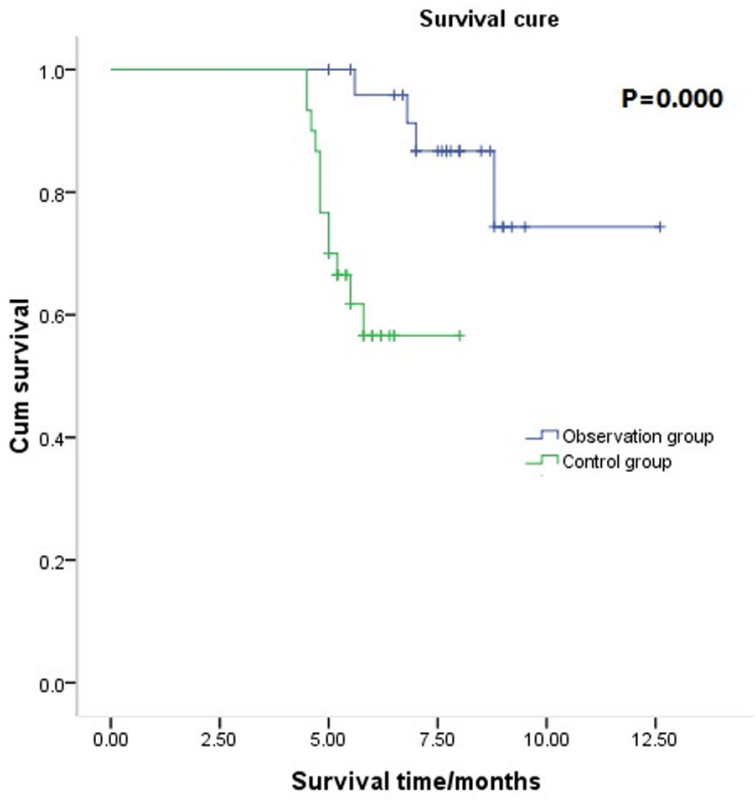

Figure 2. Comparison of survival cycles.

results, which may be related to the general characteristics and small sample size in the included patients of this study. Moreover, the non-specificity of chemotherapy drugs leads to large toxic side effects on the body, which not only increases patients' discomfort during the treatment, but also reduces the safety of medical treatment. Therefore, better clinical treatment effects and reduced related treatment complications are current research hotspots of melanoma treatment [18].

Basic studies have confirmed the close correlation between the function of the immune system and the occurrence and development of tumors. Relevant literature has also verified that the receptor ligand of the immune detection point carried on the surface of tumor cells can reduce the killing effect of immune cells on tumors [19]. This study showed that the survival cycle, clinical effective rate and one-year survival rate in the observation group were higher than those in the control group after the combination of PEM. It may be related to the elimination of the negative regulation effect of such targets on T cell activity by PEM and the enhancement of the killing effect of T cells on tumors. The results of this study were consistent with previous research conclusions that PD-1 monoclonal antibody (PD-1 mAb) could improve the clinical effective rate and clinical survival cycle of patients with advanced melanoma [20].

The toxic side effects of drugs and clinical adverse reactions are important components of drug evaluation. The results of this study found that the addition of PEM did not increase the toxic side effects and adverse reactions in patients, indicating that PEM is relatively safe in the treat-

Table 3. Comparison of toxic side effects (n)

Group	Toxic and side effects			
	Mild	Moderate	High	Life threatening
Control group (n=30)	4	3	3	0
Observation group (n=26)	3	5	2	0
χ^2	0.843			
P	0.656			

Table 4. The occurrence of drug-related adverse reactions (n)

Group	Adverse reactions			
	Skin problems	Gastrointestinal reactions	Transaminase elevation	Leukopenia
Control group (n=30)	4	2	2	2
Observation group (n=26)	3	3	2	2
χ^2	0.343			
P	0.952			

ment of melanoma and can be applied in clinic. Similar conclusions have been found in previous studies [21].

This study also has some limitations. First of all, it was a single-center study with a small sample size; therefore, the clinical effect of PD-1 mAb in the treatment of advanced melanoma needs to be further confirmed by multi-center large-sample studies. In addition, the clinical data collected in this study was simultaneous, and prospective or nested case studies are needed to determine the efficacy. Last but not least, the clinical efficacy evaluation of PEM alone in the treatment of advanced melanoma is also an important supplement to improve the treatment of melanoma with PD-1 mAb.

In conclusion, PEM combined with TEM can increase the therapeutic effectiveness of advanced melanoma patients and increase the survival cycle, with no increased related toxic side effects of clinical treatment, which is worthy of clinical promotion.

Acknowledgements

This work was supported by The Natural Science Foundation of Hainan Province (817338) and Hainan Province in 2019-2021 Provincial Key Subject Construction Project of Traditional Chinese Medicine (The Oncology Department) (S100111.401).

Disclosure of conflict of interest

None.

Address correspondence to: Hui Gong, Department of Medical Oncology, Hu'nan Academy of Traditional Chinese Medicine Affiliated Hospital, No.58 Lushan Road, Changsha 410000, Hu'nan Province, China. Tel: +86-15973208619; E-mail: gonghui3g5d@163.com

References

[1] Wang J, Kaplan MH and Yang K. ResTORing barrier function in the skin. J Allergy Clin Immunol 2020; 145: 111-113.
[2] Solano F. Metabolism and functions of amino acids in the skin. Adv Exp Med Biol 2020; 1265: 187-199.
[3] Garrubba C and Donkers K. Skin cancer. Jaapa 2020; 33: 49-50.
[4] Peate I. Skin cancer. Br J Healthcare Assistants 2019; 13: 78-84.
[5] Leiter U, Keim U and Garbe C. Epidemiology of skin cancer: update 2019. Adv Exp Med Biol 2020; 1268: 123-139.
[6] Apalla Z, Lallas A, Sotiriou E, Lazaridou E and Ioannides D. Epidemiological trends in skin cancer. Dermatol Pract Concept 2017; 7: 1-6.
[7] Li J, Wang B, Deng Y, Shi W, Jian D, Liu F, Huang Y, Tang Y, Zhao Z, Huang X, Li J and Xie H. Epidemiological features of rosacea in Changsha, China: a population-based, cross-sectional study. J Dermatol 2020; 47: 497-502.
[8] Paulson KG, Lahman MC, Chapuis AG and Brownell I. Immunotherapy for skin cancer. Int Immunol 2019; 31: 465-475.
[9] Lowe MC and Kudchadkar RR. Neoadjuvant therapy for melanoma. Surg Oncol Clin N Am 2020; 29: 445-453.
[10] Bhatia S and Thompson JA. PD-1 blockade in melanoma. J Am Med Assoc 2016; 315: 1573-1575.

[11] Dinehart MS, Dinehart SM, Sukpraprut-Braaten S and High WA. Immunohistochemistry utilization in the diagnosis of melanoma. J Cutan Pathol 2020; 47: 446-450.
[12] Larsen FU, Wilhjelm JK and Nielsen ES. Remission of a perimyocardial melanoma? Metastasis with pembrolizumab treatment. JACC Case Rep 2019; 1: 5-8.
[13] Alimohammadi E, Bagheri SR, Sadeghsalehi A, Rizevandi P, Rezaie Z and Abdi A. Prognostic factors in patients with glioblastoma multiforme: focus on the pathologic variants. Acta Neurol Belg 2020; 120: 1341-1350.
[14] Ahmed FS, Dercle L, Goldmacher GV, Yang H, Connors D, Tang Y, Karovic S, Zhao B, Carvajal RD, Robert C, Maitland ML, Oxnard GR and Schwartz LH. Comparing RECIST 1.1 and iRECIST in advanced melanoma patients treated with pembrolizumab in a phase II clinical trial. Eur Radiol 2020; 1: 10.
[15] Liu YJ, Zhu GP and Guan XY. Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma. Oral Oncol 2012; 48: 554-559.
[16] O'Neill CH and Scoggins CR. Melanoma. J Surg Oncol 2019; 120: 873-881.
[17] Kiyohara E, Tanemura A, Nishioka M, Yamada M, Tanaka A, Yokomi A, Saito A, Sakura K, Nakajima T, Myoui A, Sakurai T, Kawakami Y, Kaneda Y and Katayama I. Intratumoral injection of hemagglutinating virus of japan-envelope vector yielded an antitumor effect for advanced melanoma: a phase i/iia clinical study. Cancer Immunol Immunother 2020; 69: 1131-1140.
[18] Smith N, Finn M, Segars L, Burns E and Menser M. Melanoma and medical education: knowledge and sun safety practices amongst medical students. Our Dermatol Online 2018; 9: 11-14.
[19] Schrom KP, Kim I and Baron ED. The immune system and pathogenesis of melanoma and non-melanoma skin cancer. Adv Exp Med Biol 2020; 1268: 211-226.
[20] Munhoz RR and Postow MA. Clinical development of PD-1 in advanced melanoma. Cancer J 2018; 24: 7-14.
[21] Ramelyte E, Schindler SA and Dummer R. The safety of anti PD-1 therapeutics for the treatment of melanoma. Expert Opin Drug Saf 2017; 16: 41-53.