



Efficacy and safety of transarterial infusion of anti-PD-1 in the treatment of advanced or metastatic acral and mucosal melanomas

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ABSTRACT

This study aimed to evaluate the efficacy and safety of transarterial infusion of programmed cell death receptor-1 (PD-1) antibody therapy in advanced or metastatic acral and mucosal melanomas. Eleven patients with acral or mucosal melanoma were referred to the department of Internal Medicine-Oncology in Huazhong University of Science and Technology Union Shenzhen Hospital from January 2019 to August 2020. These patients received transarterial infusions of PD-1 antibody and intravenous infusions of albumin-bound paclitaxel. The median duration of follow-up was 8 months. The patients were treated with transarterial infusion of PD-1 antibody and intravenous infusion of albumin-bound paclitaxel. In study, we collected and recorded immunotherapy-related adverse events. The results showed that the response rate (RR) and the disease control rate (DCR) of the patients (seven with acral melanoma, four with mucosal melanoma) were 54.5 % and 90.9 %, respectively. No grade 3–4 adverse events or major complications were observed during the study. The median progression-free survival was 10 months. The transarterial infusion of PD-1 antibody has remission and control effects on acral and mucosal melanomas, which is important for the clinical care of these patients.

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Introduction

The global incidence of skin melanoma is increasing at a faster rate than any other type of cancer. It is the 15th most common cancer in the world. The incidence of skin melanoma varies widely between countries, and these different patterns are attributed to ethnic differences in skin phenotypes as well as differences in sun exposure (1). Although the incidence rate of melanoma in China is lower than that in Western countries, China has a high absolute number of cases due to its large population base, with incidence and mortality rates increasing rapidly each year. The pathological types and biological characteristics of melanoma in China are different from those in Western countries. In Western countries, skin melanoma is predominant, accounting for approximately 90 % of cases, while the acral and mucosa types are predominant in China, accounting for 41.8 % and 22.6 %, respectively (2-4). PD-1 antibody monotherapy has become the standard first-line therapy for advanced or metastatic cutaneous

melanoma, but the evidence for its clinical use in acral and mucosal melanomas is still limited. Some studies have shown that the response rates (RR) to anti-PD-1 therapy for acral and mucosal melanomas are lower than those for cutaneous melanomas (5,6). Therefore, we need to improve the therapeutic effect of the PD-1 antibody to delay the progression of these non-skin melanomas. Arterial perfusion provides a higher drug concentration than intravenous infusion (7). Some retrospective analyses show that intra-arterial infusion chemotherapy is more effective than intravenous chemotherapy in advanced or metastatic melanoma. However, clinical data regarding anti-PD-1 treatment by arterial perfusion are very rare (8-11). Therefore, this study aimed to evaluate the efficacy and safety of transarterial infusion of anti-PD-1 in the treatment of advanced or metastatic acral and mucosal melanomas, in order to develop reference values for the clinical treatment of these tumors.

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Materials and methods

Intervention process and data collection

The patients were treated with transarterial infusion of PD-1 antibody and intravenous infusion of albumin-bound paclitaxel at a dose of 260 mg/m² every 3 weeks for 12–18 weeks (4–6 cycles). After the end of this combined stage, PD-1 antibody could continue to be administered intravenously every 3 weeks until disease progression, the occurrence of unacceptable toxicity, or loss of follow-up. Imaging was carried out at baseline and every 6–9 weeks (2–3 cycles). We collected and recorded immunotherapy-related adverse events.

Statistical analysis

This study utilized a self-control case method. The data collection, statistics, and analysis involved in this experiment utilized SPSS18.0 software. The statistical charts were drawn by Microsoft office software.

Results

General information

A total of 11 melanoma patients were treated with transarterial infusion of PD-1 antibody between January 2019 and August 2020. The median age of the patients was 52 years (range 18–72), six of them were male, and their Eastern Cooperative Oncology Group performance scores were less than or equal to two. Seven of the patients were diagnosed with acral melanoma and four had mucosal melanoma. Two patients had metastatic melanoma with BRAF V600 mutation. The metastatic lesion sites included the liver, lung, distant lymph nodes, brain, bone, adrenal gland, and soft tissue. Five patients received PD-1 antibody as first-line therapy and six as at least second-line therapy (previously treated with immune checkpoint inhibitors). Nine patients received a transarterial infusion of pembrolizumab 200 mg fixed-dose, and two patients received toripalimab 240 mg fixed-dose. Arterial perfusion regions included metastases to the liver, lymph nodes, soft tissue, and adrenal gland (Table 1).

Tumor response after transarterial infusion of anti-PD-1 therapy

We evaluated the patients' clinical outcomes, including RR, DCR, and progression-free survival

Table 1. General information, demographic of study participants

Characteristic	N (%)
Age, median (range)	52(18-72)
Sex	
Male	6(54.5)
Female	5(45.5)
Tumor origin	
acral	7(63.6)
mucosa	4(36.4)
ECOG performance scale	
0	1(9.1)
1	8(72.7)
2	2(18.2)
BRAF-V600E/K	
/K	
Mutation	2(18.2)
Wild type	9(81.8)
LDH level	
Normal	10(90.9)
Elevated	1(9.1)
Location of metastasis	
Lung	5(45.5)
Liver	4(36.4)
Brain	1(9.1)
lymph nodes	10(90.9)
Bone	1(9.1)
Other ^a	6(54.5)
Lines of treatment	
1	5(45.5)
≥2	6(54.5)
Previous treatments	
Immune Checkpoint Inhibitors	6(54.5)
Targeted Therapy	3(27.3)
Chemotherapy	2(18.2)
Anti-PD-1 antibody	
Pembrolizumab 200mg	9(81.8)
Toripalimab 240mg	2(18.2)
Arterial perfusion region	
Liver	2(18.2)
lymph nodes	3(27.3)
soft tissue	7(63.6)
adrenal gland	1(9.1)

^a Other locations include the pancreas, spleen, adrenal gland and soft tissue.

(PFS) (Table 2 and Fig 1). The median duration of follow-up was 8 months. The disease control rate was 90.9 %. All 11 patients with measurable disease by

RECIST 1.1 criteria had tumor regression ranging from 23.09 % to 92.8 % (Fig 2). Among them, two patients were treated with radical surgery, and they are still receiving postoperative adjuvant treatment. One patient who refused radical surgery is currently undergoing anti-PD-1 maintenance therapy. An objective response with measurable disease was achieved in 10 of 11 patients, with six (54.5 %) achieving a partial response, and four (36.4 %) achieving stable disease as a best response (Fig 3).

In five patients (first-line treatment), the response rate (RR) and the disease control rate (DCR) were 60 % and 100 %, respectively. In six patients (second-line or later), the response rate (RR) and the disease control rate (DCR) were 50 % and 83 %, respectively, including those who received this treatment after progression on PD-1. The median overall PFS was 10 months. The median PFS as first-line treatment was 12 months, and as second-line (or higher) treatment was 9 months ($P=.41$). We concluded that transarterial infusion of anti-PD-1 antibody may be effective regardless, but clinical outcomes as front-line therapy are superior. In this study, no grade 3–4 adverse events or major complications were observed. The most frequent treatment-related grade 1–2 adverse events were rash and pruritus (36.4 %), cancer pain (27.3 %), neutropenia (27.3 %), and arthralgia (9.1 %). No patients discontinued anti-PD-1 therapy because of immune-related adverse events. There were no treatment-related deaths (Table 2).

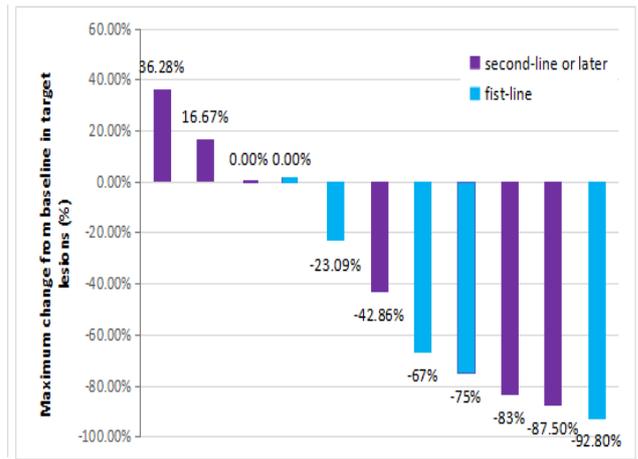
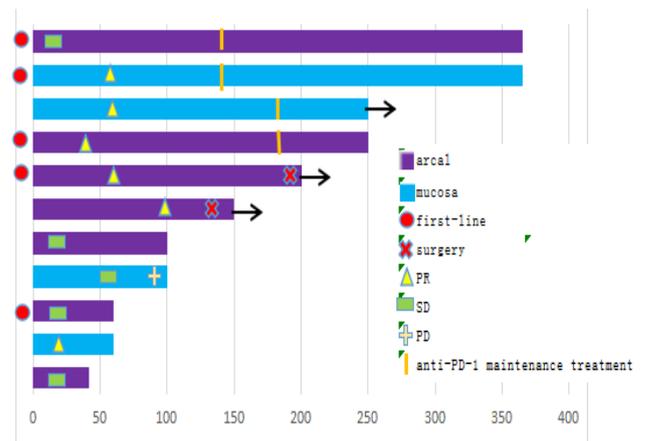


Figure 2. Changes in tumor burden in patients treated with transarterial infusion of PD-1 antibody



*arrow indicates the patient still on study

Figure 3. Patients' time to respond and current status

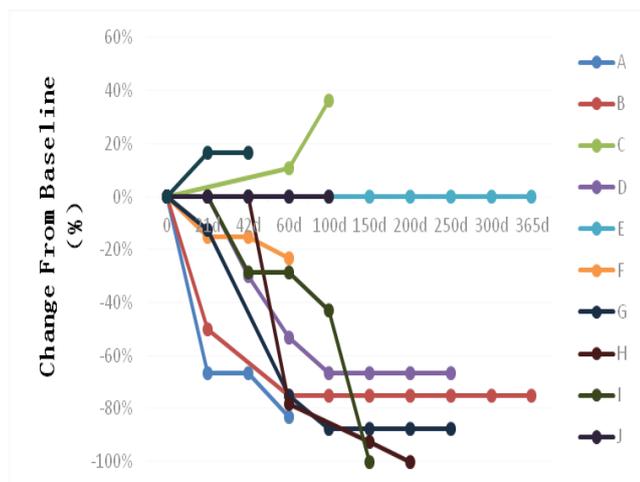


Figure 1. Change in target lesions over time-based on RECIST 1.1 criteria

Discussion

Acral and mucosal melanomas are extremely rare in Caucasians; however, they are the predominant melanoma subtypes in Asians and other non-Caucasian populations (12-14). In spite of advances in melanoma management, patients with acral and mucosal melanomas show limited benefit from current therapies (15,16) PD-1 antibody therapy is the first-line therapy for acral and mucosal melanoma, but there is little research on the clinical efficacy for these melanoma subtypes (17-20).

This study aimed to evaluate the efficacy and safety of transarterial infusion of PD-1 antibody therapy in advanced or metastatic acral and mucosal melanomas, and the conclusion is that the transarterial infusion of PD-1 antibody has remission and control effects on

acral and mucosal melanomas, which has importance for the clinical care of these patients. However, there are some inevitable limitations of this study. Due to the rarity of acral and mucosal melanomas, we only obtained 11 patients to participate in this experiment, which makes the representativeness of this study insufficient. In the future, we will endeavor to expand the sample size to make this research more representative

Ethical consideration

This study was approved by the ethics committee of Huazhong University of Science and Technology Union Shenzhen Hospital. All patients provided written informed consent prior to treatment.

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Interest conflict

The authors declare no conflict of interest.

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Ethics approval and consent to participate

Not applicable

Patient consent for publication

All authors agreed to publish the final manuscript.

Data availability statement

All authors confirm that the data and material are available.

Authors' contributions

Chen Qianqi and Zhou Qiming are responsible for **data collection, statistical analysis, writing articles**; Zhao Yan is responsible for **data collection**; Tang Yueqiang is responsible for the **statistical analysis**; Duan Jiangman and Fu Xiaohong are responsible for **clinical treatment**.

Abbreviations

DCR (disease control rate), PD-1 (programmed cell death receptor-1), PFS (progression-free survival) and RR (response rate)

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Table 2. Tumor response after transarterial infusion of anti-PD-1 therapy

Patient	Gender	Age	Tumor origin	Arterial perfusion regions	Combine cycles in this study	First-line treatment	Second-line treatment	Third-line treatment	Response	Adverse events
A	Male	72	mucosa	soft tissue metastasis	2	Dacarbazine+Lobaplatin+pembrolizumab	Paclitaxel+temozolomide+pembrolizumab	Treatment of this study ^b	PR	cancer pain (grade2)
B	Female	61	mucosa	soft tissue metastasis	4	Treatment of this study ^a	-	-	PR	Arthralgia (grade2)
C	Male	30	mucosa	Adrenal gland metastasis	3	Vimofine +pembrolizumab	Treatment of this study ^b	-	PD	rash and pruritus (grade2)
D	Female	61	acral	soft tissue metastasis	6	Treatment of this study ^b	-	-	PR	Neutropenia (grade2)
E	Male	57	acral	soft tissue metastasis	7	Treatment of this study ^b	-	-	SD	No
F	Male	52	acral	soft tissue metastasis	2	Treatment of this study ^b	-	-	SD	cancer pain (grade2)
G	Male	31	mucosa	liver and lymph node metastasis	6	HL-085(MERK inhibitor) clinical trial	Treatment of this study ^b	-	PR	Rash and pruritus (grade1)
H	Male	31	acral	soft tissue metastasi	5	Treatment of this study ^b	-	-	PR	Rash and pruritus (grade1) ; neutropenia (grade2)
I	Female	40	acral	lymph node metastasis	2	Vimofine +Corbidine	Pembrolizumab	Treatment of this study ^b	PR	Rash and pruritus (grade2) ; cancer pain (grade1)
J	Male	17	acral	liver and lymph node metastasis	4	Toripalimab+albumin bound paclitaxel	Treatment of this study ^a	-	SD	No
K	Female	61	acral	soft tissue metastasis	2	Pembrolizumab+albumin bound paclitaxel	Treatment of this study ^b	-	SD	Neutropenia (grade2)

a: transarterial infusion of toripalimab and intravenous infusion of albumin-bound paclitaxel

b: transarterial infusion of pembrolizumab and intravenous infusion of albumin-bound paclitaxel