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Effect of external washing with self-made Xiaofeng Jiedu powder on expressions of serum inflammatory cytokines in patients with cutaneous adverse events induced by programmed cell death protein 1 inhibitor

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Wide application of programmed cell death protein 1 (PD-1) inhibitor for tumor treatment has led to increased immune-related adverse events (irAEs), particularly cutaneous irAE. In this study, we assessed the effects of external washing with self-made Xiaofeng Jiedu powder on the expressions of serum inflammatory cytokines in patients with cutaneous adverse events (AEs) induced by PD-1 inhibitor. Fifty-six tumor patients with cutaneous AEs induced by PD-1 inhibitor were randomly divided into observation and control groups (n=28). The control group underwent routine treatment with PD-1 inhibitor and oral administration with cetirizine, while the observation group received PD-1 inhibitor and soaking and fumigation by Xiaofeng Jiedu powder in the affected skin once in the morning and once in the evening. The levels of serum interleukin-6 (IL-6), IL-10, and immunoglobulin E (IgE) were detected before and after treatment. After treatment, the disease control rate of the observation group was higher than that of the control group (P <0.05), and the observation group also had higher objective response rate [71.4% (20/28) *vs.* 28.6% (8/28), P <0.05]. The levels of serum IL-6 and IgE in the observation group were lower than those of thecontrol group, whereas the level of IL-10 in the former was significantly higher (P <0.05). Xiaofeng Jiedu powder exerts evident therapeutic effects on PD-1 inhibitor-induced cutaneous AEs.

Keywords: PD-1 inhibitor, Traditional Chinese medicine, Tumor

Programmed cell death ligand-1 (PD-L1) overexpressed on the surface of tumor cells can bind programmed cell death protein 1 (PD-1) mainly expressed on activated T cells. Then T cells are inactivated, thus enabling cancerous cells to escape normal immune monitoring[1]. However, the binding between PD-1 and PD-L1 can be blocked by the anti-PD-1 and its ligand PD-L1 in immune checkpoint inhibitors, which inhibits the negative signal transmission and restores the activity of T cells, thus modulating immune monitoring, enhancing immune recognition, and killing cancerous cells.

As PD-1 inhibitor has been widely applied, increasingly more immune-related adverse events (irAEs) have caused concern[2]. Among them, the incidence rate of the most common cutaneous irAE is as high as 34%. In severe cases, cutaneous maculopapules with severe itching, chapping, and even induced infections are found in large areas. After the discontinuance of PD-1 inhibitor, skin symptoms still endure several months, which threatens the quality of life of patients. Moreover, inflammatory cytokines, IL-6, IL-10 and immunoglobulin E (IgE), markedly rose in the peripheral blood of patients with cutaneous irAEs[3]. Nonetheless, it has been manifested that cutaneous irAEs induced by PD-1 monoclonal antibody are probably positive prognostic factors[4]. which show a better survival benefit or a higher objective response rate (ORR), and drug discontinuance may cause loss of an opportunity of obtaining potential clinical benefits. Hence, the way to alleviate PD-1 inhibitor-induced cutaneous AEs safely and effectively and improve patients' quality of life may become another hot topic in future studies.

Traditional Chinese medicine displays uniqueness in theory and advantages in treating skin diseases. In this study, we elaborated the pathogenesis of cutaneous AEs triggered by immunotherapy and treated PD-1 inhibitor induced cutaneous AEs by external washing with a self-made traditional Chinese medicine, Xiaofeng Jiedu powder. We compared the the expression levels of IL-6, IL-10 and IgE in serum of patients before and after treatment with Xiaofeng Jiedu powder, and further tried to understand the mechanism by which Xiaofeng Jiedu powder alleviated PD-1 inhibitor-induced cutaneous AEs.

Methodology

General data

This study has been approved by the ethics committee of our hospital, and written informed consent has been obtained from all patients. The sample size was determined based on pre-experiment results. A total of 56 tumor patients with PD-1

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inhibitor-induced cutaneous AEs admitted to the Oncology Department of Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang from September 2019 to November 2021 were included. They were randomly divided into a control group (n=28) and an observation group (n=28). The control group included 16 males and 12 females aged 45-80 years old, with an average age of (59.4±3.6) years old, an average weight of (61.35±4.53) kg, and an average course of disease of (3.25±0.61) years. As for underlying diseases, there were 21 cases of hypertension, 11 cases of diabetes and 12 cases of coronary heart disease. In terms of the type of tumors, there were 8 cases of lung cancer, 5 cases of liver cancer, 4 cases of gastric cancer, 4 cases of esophageal cancer, 3 cases of bladder cancer and 4 cases of breast cancer. The observation group consisted of 18 males and 10 females at the age of 42-78 years old, with (58.6±3.3) years old on average, the weight of (60.55±3.89) kg on average, and the disease course of (2.98±0.81) years on average. In terms of underlying diseases, there were 17 cases of hypertension, 10 cases of diabetes and 15 cases of coronary heart disease. Based on tumor classification, there were 6 cases of lung cancer, 6 cases of liver cancer, 3 cases of rectal cancer, 3 cases of gastric cancer, 5 cases of oesophageal cancer, 3 cases of ovarian cancer and 2 cases of breast cancer. No evident differences were found in general data, such as gender and age, between the two groups of patients (P >0.05).

Inclusion and exclusion criteria

Inclusion criteria: Patients aged ≥18 years old, those with tumors manifested as Grade I-III skin toxicity and Grade IV skin toxicity without skin infections after treatment with PD-1 inhibitors; those with at least one target tumor lesion that met the immune-related Response Evaluation Criteria In Solid Tumors (irRECIST); those who agreed to take contraceptive measures during treatment and within 120 d after the last administration of PD-1 inhibitor; and those who were clear-minded and able to communicate smoothly with medical staff.

Ex*clusion criteria*: Patients with unconsciousness due to severe dysfunction of major organs; or those who were unable to communicate effectively due to other reasons before enrolment; those with a medical history of autoimmune diseases, interstitial pneumonia, radiation pneumonia, HIV infection, *etc*., that needed maintenance treatments with corticosteroids and immunosuppressants, female patients in the gestation period or lactation period, or those who were considered by researchers to be unsuitable to participate in this study for any other reasons except the inclusion criteria and exclusion criteria.

Diagnostic criteria

Grading criteria of skin toxicity caused by PD-1 inhibitor: According to the grading criteria of immunotherapy-induced toxicity in the European Society of Oncology (ESMO) immunotherapy guidelines[5], cutaneous AEs can be divided into four grades as follows: Grade I: Rashes cover <10% of body surface area (BSA) with or without symptoms; Grade II: Rashes cover 10-30% of BSA with or without symptoms, limiting the activities of daily living; Grade III: Rashes cover >30% of BSA, with or without symptoms, limiting the activities of daily living; and Grade IV: Rashes cover 30% of BSA, accompanied by infections or other complications, which require hospitalized treatment in the intensive care unit.

Treatment methods

The control group was treated with PD-1 inhibitor and orally took 10 mg of cetirizine [Dawnrays Pharmaceutical (Holdings) Limited, Suzhou, China, NMPN: H19980014] once every night for one week. The observation group was treated with PD-1 inhibitor and Xiaofeng Jiedu powder. In detail, Xiaofeng Jiedu powder was decocted to 250 mL and mixed evenly with 2000 mL of warm water (35-45ºC) by stirring. Then the affected skin was soaked and fumigated once in the morning and once in the evening for one week. Prescription: 15 g of Periostracum cicadae, 20 g of Schizonepeta, 15 g of Radix Saposhnikoviae, 15 g of *Kochia scoparia*, 15 g of Cortex phellodendri, 10 g of *Rheum officinale*, 20 g of Radix Sophorae flavescentis, 15 g of Lonicerae japonicae flos, 15 g of Radix Arnebiae, and 10 g of Semen persicae were basic ingredients. Dialectical addition and subtraction: For patients with maculopapular rashes and obvious itching accompanied by desquamation and fading mainly caused by wind pathogens, 10 g of *Lumbricus* and 15 g of nidus vespae were added. For patients with plasma exudation in the skin and skin blisters mainly caused by damp-heat toxins, 10 g of *Coptis chinensis*, 15 g of *Sanguisorba officinalis* and 10 g of Artemisiae scopariae Herba were added. For patients with redness, pain, ulceration and molting mainly induced by heat toxins, 30 g of Violae yedoensis Herba, 15 g

of Forsythiae Fructus and 5 g of borneol were added. For patients with rough, dry and dark purple skin mainly due to stasis toxins, 15 g of *Salvia miltiorrhiza*, 15 g of *Angelica sinensis* and 10 g of *Carthamus tinctorius* were added. All traditional Chinese medicine drugs were provided by the Traditional Chinese Medicine Pharmacy, Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang.

In the 6^{th} and 12^{th} weeks after treatment, the target lesions were scanned by imaging, and then reviewed every nine weeks. Afterwards, the irRECIST was adopted to evaluate the imaging effect. The relevant survival data of all the patients included were obtained by regular follow-up every twelve weeks until they died or the study was terminated.

Response rate analysis of rashes treated with traditional Chinese medicine drugs

The response rate of rashes was compared between the two groups of patients. For traditional Chinese medicine drugs, rash response rate = cases of complete response (CR) + cases of partial response (PR)/all cases treated.

Duration analysis of rash alleviation by traditional Chinese medicine drugs

The duration was recorded as the time interval from the discontinuance of traditional Chinese medicine drugs to the recurrence or aggravation of rashes. If the rashes did not recur, the duration was recorded as the time interval from the discontinuance of traditional Chinese medicine drugs to 3 months after the last PD-1 inhibitor treatment.

Survival analysis

The survival data of patients included the ORR, disease control rate (DCR) and overall survival (OS). ORR is the percentage of CR and PR cases in all cases in the same group, and the DCR is the percentage of cases of CR, PR, and stable disease (SD) in all cases in the same group. The overall survival (OS) is defined as the period from the beginning of the treatment with PD-1 inhibitor to the date of death due to any causes. The OS of patients was obtained by acquiring electronic doctor's advice and records of the course of disease, or contacting the family members of the patients by phone. The ratio of loss to follow-up was controlled within 10%.

Measurement of serum inflammatory cytokines

A total of 10 mL of peripheral blood samples were collected from patients in each group1 d before treatment and 2 weeks after treatment, respectively, and centrifuged to obtain serum. Subsequently, ELISA was carried out to examine the levels of IL-6, IL-10 and IgE according to the instructions of corresponding kits (Thermo Fisher Scientific, USA).

Clinical efficacy evaluation criteria

With RECIST 1.1 as the reference standard[6], the efficacy of drugs in alleviating the PD-1 inhibitor-induced skin toxicity was evaluated as follows: CR: All skin toxicities disappear. PR: The skin toxicity has been degraded by at least 1 grade, but the lesion does not completely disappear. Progressive disease (PD): The skin toxicity has been upgraded by at least 1 grade, or the symptoms have not been alleviated. SD: The skin toxicity has been effectively controlled, and some symptoms have been alleviated. Besides, there is neither sufficient degrading of cutaneous AEs to qualify for PR nor sufficient upgrading to qualify for PD.

The efficacy of immunotherapy for malignant tumors was evaluated using the irRECIST as follows: CR: All target lesions disappear, and the short diameter of all pathological lymph nodes (including target and non-target nodules) must be reduced to less than 10 mm. PR: The sum of target lesion diameters is reduced by at least 30% compared with the baseline level. PD: Compared with the lowest level, the total tumor load is increased by ≥20% and the absolute value by at least 5 mm, non-target lesion progression appears, or malignant lesions appear, and irPD patients need to be re-evaluated after at least four weeks to confirm the progression of the disease. SD: There is neither sufficient reduction of target lesions to qualify for PR nor sufficient increase to qualify for PD, and the minimum value of the sum of diameters can be used as a reference in research. New lesions do not really mean progression. The longest diameter of the new lesion was included in the baseline tumor load and measured in this study.

Observation of other Adverse events (AEs)

In the treatment process, whether vomiting, leukopenia, thrombocytopenia, hypothyroidism, and other AEs occurred was observed.

Statistical analysis

SPSS 26.0 software was employed for statistical analysis. The measurement data were represented as($\bar{x} \pm s$), and the count data were expressed as the number of cases and percentage. The data in line with normal distribution were detected by the '*t*' test. The

χ^2 test was conducted for comparison between groups, and the Kaplan-Meier method was utilized to plot survival curves. P <0.05 represented that the difference was statistically significant.

Results and Discussion

Short-term efficacy on cutaneous AEs

The objective response rate (ORR) was 28.6% (8/28) in the control group and 71.4% (20/28) in the observation group, displaying a statistically significant difference (χ^2=10.286, P=0.001). DCR of the observation group [92.9% (26/28)] was higher than that of thecontrol group [60.7% (17/28)], with a statistically significant difference (χ^2=8.114, P=0.004) (Table 1).

Table 1 — Short-term efficacy on PD-1 inhibitor-induced cutaneous AEs

Group	CR (%)	PR (%)	PD (%)	SD (%)	ORR	DCR
Control (n=28)	0 (0.0)	8 (28.6)	11 (39.3)	9 (32.1)	28.6%	60.7%
Observation (n=28)	0 (0.0)	20 (71.4)	2 (7.1)	6 (21.5)	71.4%	92.9%
χ^2					10.286	8.114
P					0.001	0.004

[P<0.05 indicates statistically significant differences. AE: Adverse event; CR: complete response; DCR: disease control rate; ORR: objective response rate; PD: progressive disease; PD-1: programmed cell death protein 1; PR: partial response; SD: stable disease]

Life Table[a]

Interval start time	0	6	12	18	24
Number entering interval	56	56	39	24	2
Number withdrawing during interval	0	9	7	18	1
Number exposed to risk	56.000	51.500	35.500	15.000	1.500
Number of terminal events	0	8	8	4	1
Proportion terminating	0.00	0.16	0.23	0.27	0.67
Proportion surviving	0.00	0.84	0.77	0.73	0.33
Cumulative proportion surviving at end of interval	1.00	0.84	0.65	0.48	0.16
SE of cumulative proportion surviving at end of interval	0.00	0.05	0.07	0.09	0.19
Probability density	0.000	0.026	0.032	0.029	0.000
SE of probability density	0.000	0.008	0.010	0.013	0.000
Hazard rate	0.00	0.03	0.04	0.05	0.00
SE of hazard rate	0.00	0.01	0.01	0.03	0.00

[a, The median survival time is 23.31]

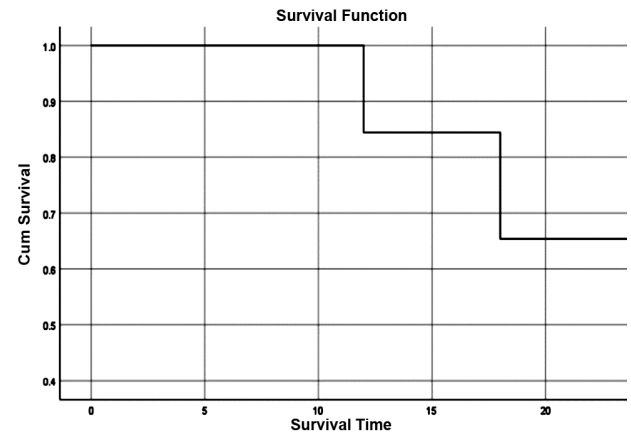

Fig. 1 — Survival analysis results of PD-1 inhibitor treatment at different time periods. [The median shown by the survival analysis was 23.31. PD-1, Programmed cell death protein 1]

Long-term efficacy of PD-1 inhibitor

All the patients underwent at least twocycles of treatment and were followed up until November 30th, 2021. Data were collected every six months. The survival rates of patients treated with PD-1 inhibitor in different time periods are shown in Fig. 1, and the median shown by the survival analysis was 23.31. Moreover, the survival analysis of 58 patients treated with PD-1 inhibitor in different time periods revealed that the survival of patients receiving the treatment for more than one year was longer than that of patients treated for one year (P <0.05) (Fig. 2).

Levels of serum IL-6, IL-10 and IgE before and after treatment

No evident differences were found in the levels of serum IL-6, IL-10 and IgE between the two groups before treatment (P >0.05). The levels of serum IL-6 and IgE declined remarkably but the level of IL-10 markedly rose after treatment compared with those before treatment in both groups. Additionally, the observation group had significantly lower levels of serum IL-6 and IgE and a higher level of IL-10 than those of the control group (P <0.001) (Table 2).

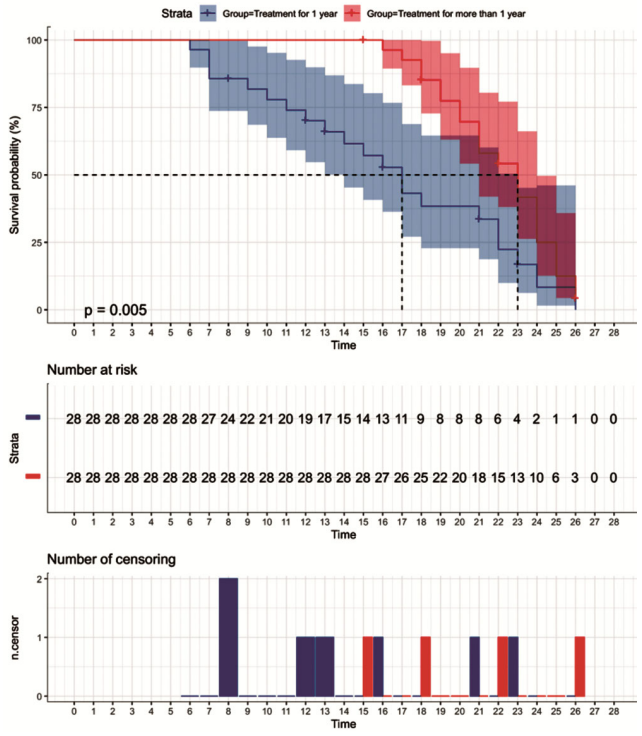

Fig. 2 — Survival curve of PD-1 inhibitor at different time periods. [The survival of patients receiving the treatment for more than one year was longer than that of patients treated for one year. PD-1, Programmed cell death protein 1]

Table 2 — Levels of serum IL-6, IL-10 and IgE in patients with PD-1 inhibitor-induced cutaneous AEs before and after treatment ($\bar{x}\pm$ s, n=56)

Group	n	IL-6/(pg·mL^{-1})		IL-10/(ng·L^{-1})		IgE (IU/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	28	119.54±4.59	80.34±3.41*	9.62±2.72	16.87±2.56*	256.21±63.89	211.43±57.38*
Observation	28	120.12±4.78	63.21±3.56*	9.58±2.64	30.56±3.34*	247.64±57.97	165.54±60.51*
t (intergroup)		0.617	10.135	0.525	12.372	0.701	15.373
P		0.502	<0.001	0.387	<0.001	0.566	<0.001

[*P <0.05 *vs.* before treatment in the same group. AE, Adverse event; IgE, Immunoglobulin E; IL, Interleukin; PD-1, Programmed cell death protein 1]

Table 3 — Incidence of other adverse events (AEs)

Group (n=28)	Vomiting (n)	Leukopenia (n)	Thrombocytopenia (n)	Hypothyroidism (n)	Total
Control	2 (7.1%)	2 (7.1%)	2 (7.1%)	1 (3.6%)	7 (25.0%)
Observation	2 (7.1%)	2 (7.1%)	1 (3.6%)	1 (3.6%)	6 (21.4%)

Other Adverse events (AEs)

In the control group, there were 7 cases of other AEs, including 2 cases of vomiting, 2 cases of leukopenia, 2 cases of thrombocytopenia and 1 case of hypothyroidism, showing an incidence rate of AEs of 25.0%. In the observation group, there were 6 cases of other AEs, including 2 cases of vomiting, 2 cases of leukopenia, 1 case of thrombocytopenia and 1 case of hypothyroidism, with an incidence rate of AEs of 21.4%. The incidence rate of other AEs had no statistically significant difference between the two groups (Table 3).

According to the latest data of the World Health Organization in 2021, cancers are the first or second leading cause of deaths before the age of 70 years old in 112 countries, and the burden brought by cancer incidence and mortality rates have been rapidly increasing all over the world[7]. In-depth research on tumorigenesis in recent years has revealed the crucial function of immune escape, which pushes the anti-tumor immunotherapy research towards a higher stage[8]. Immune checkpoint inhibitors can not only remove immunosuppression and enhance the anti-tumor effect of T cells by blocking the negative regulatory signal of T cells, but also may result in the imbalance of immune tolerance owing to the abnormally enhanced normal autoimmune responses, showing autoimmune-like inflammatory responses when involving normal tissues[9]. PD-1 inhibitor has been proven to be a safe, effective, and broad-spectrum treatment method for malignancies in numerous clinical trials[10-12]. In the present study, the comparison among different periods of treatment with PD-1 inhibitor revealed that the survival of patients treated with PD-1 inhibitor for more than one year was significantly longer than that of patients treated with PD-1 inhibitor for one year. Nevertheless, as the clinical data of patients treated with PD-1 inhibitor accumulate, PD-1 inhibitor-induced AEs gradually emerge. Hence, the diagnosis, management and methods to reduce AEs and their influences are also worthy of attention.

As the most common irAEs, cutaneous AEs show an incidence rate of as high as 34%. In severe cases, cutaneous maculopapules appear with severe itching, chapping and even infections in large areas, and skin symptoms can endure several months after the discontinuance of PD-1 inhibitor, which threatens the patients' quality of life[13]. Meanwhile, patients with cutaneous AEs have a higher response rate to immunotherapy, and drug discontinuance may cause a loss of an opportunity of obtaining potential clinical benefits. Based on the basic theory of traditional Chinese medicine and clinical symptoms, the research grouptreated PD-1 inhibitor-induced cutaneous AEs by external washing with a self-made traditional Chinese medicine, Xiaofeng Jiedu powder, achieving significant outcomes. Although PD-1 inhibitor-induced cutaneous AEs have no counterparts in Chinese medicine, its manifestations accord with the skin symptoms caused by drug toxicity. In Traditional Chinese medicine, this disease can always be triggered by congenital intolerance and internal drug toxicity, whose pathogenesis has an intimate relation to the invasion of wind-pathogens. The invasion of wind-pathogens heats the blood, leading to bleeding. Then drug toxicity invades the blood-heat body of patients, triggering fire toxins, which are manifested on the surface of the skin and attack the internal organs. Besides, the damp-heat body is invaded by drug toxicity, making the damp-heat in the body accumulate and steam in the skin. Long-term attack by drug toxicity burns blood, causing both qi and yin injuries as well as skin dystrophy. Otherwise, chronic illness makes yin fluid exhausted and causes the non-attachment and floating of yang, which triggers serious and critical diseases. The treatment of the disease mainly focuses on

clearing away heat and expelling wind, promoting diuresis and detoxification.

In the prescription of Xiaofeng Jiedu powder, Schizonepeta dispels pathogenic wind, detoxicates and disperses pathogenic wind, promotes eruption, and eliminates sores, and Radix Saposhnikoviae can remove pathogenic wind and dampness. The combination of the two can increase the efficacy of dispelling pathogenic wind and promoting eruption. Kochia Scoparia can clear away heat and dampness, dispel wind and relieve itching. Cortex Phellodendri clears away heat and dampness and purges fire to remove toxins, and its combination with Radix Sophorae Flavescentis can enhance the efficacy of clearing away heat and dampness. *Rhubarb officinale* purges heat, removes blood stasis, cools blood, removes toxins and relax bowels. Flos Lonicerae japonicae have strong heat-clearing ability and detoxification ability, Radix Arnebiae can clear away heat, cool blood, remove toxins and promote eruption. Besides, Semen Persicae can promote blood circulation, remove blood stasis, and relax bowels, and Periostracum Cicadae can disperse wind-heat, stop spasm, and strengthen the antipruritic effect of the whole prescription. Modern research has demonstrated that Radix Saposhnikoviae, Periostracum Cicadae, Cortex Phellodendri, Radix Sophorae Flavescentis and *Rhubarb officinale* exhibit different pharmacological effects including anti-inflammation, immune regulation, and anti-tumor effects, and also have potential antiallergic effects. In the present study, the observation group had ORR of 71.4% and DCR of 92.9%, displaying significantly better effects than those of the control group.

Suppressing the inflammatory response in the affected area is a vital approach to the treatment of PD-1 inhibitor-induced cutaneous AEs, and the level of serum inflammatory cytokines turns out to be a sensitive biological index for evaluating the severity of inflammatory responses[14]. IL-6, a cytokine participating in natural immune defense[15], has close relevance to antibodies produced by B cells. It is produced by fibroblasts, keratinocytes, endothelial cells, and T lymphocytes, and can be synthesized by monocytes and macrophages after antigen activation. In the case of skin injury, the expression of IL-6 messenger RNAs is raised in the skin, and the up-regulated IL-6 acts on dendritic cells[16]. IL-10 is a pleomorphic anti-inflammatory cytokine with various phenotypic effects[17]. Initially, IL-10 was found to be a product of the process of T helper 2 cells inhibiting the activation of T helper 1 cells. Now it has been recognized that IL-10 can be produced by almost all kinds of activated immune cells, including B cells, mastocytes, granulocytes (such as neutrophils, basophils and eosinophils), macrophages, dendritic cells and multiple T cell subsets[18]. Additionally, IL-10 primarily displays anti-inflammation, inhibition, or self-regulation effects, and it is also an effective negative feedback regulator, which influences the control and decomposition of T cell subsets. This immunosuppression can be widely found at the cellular and humoral levels, and IL-10 mainly resists the potentially destructive inflammatory responses in the following aspects: (i) It suppresses the antigen presentation of dendritic cells; and (ii) it inhibits the macrophage activation and infiltration of injured sites, so as to reduce the expression of pro-inflammatory cytokines[19]. IL-10 is regarded as a post-transcriptional regulator at the cellular level, which inhibits the messenger RNA-stabilizing protein HuR. Furthermore, IL-10 can also enhance the phagocytosis of bacteria and remove apoptotic cells[20].

IgE is a type of antibody in circulation with the lowest concentration in blood, but all epithelial tissues contain resident cells binding to IgE antibodies. In addition, it has high affinity to its receptor FceRI, and basophils and mastocytes carry numerous FceRI receptors[21]. When local inflammatory responses occur in the skin, the circulating IgE level shows an obvious elevation. The enhancement of serum IgE relies on local exposure. After the inflammation is alleviated, there are only a small number of mastocytes in the skin, and about 2% IgE-containing basophils of all $CD45^+$ leukocytes. When inflammatory responses disappear, the number of basophils becomes larger, and then it is decreased with the extinction of inflammatory responses[22]. In this study, the levels of serum IL-6 and IgE after treatment declined compared with those before treatment in both groups, and these levels ofthe observation group significantly decreased compared with those of the control group. However, the level of serum IL-10 after treatment rose remarkably in comparison with that before treatment in both groups, and it was significantly raised in the observation group compared to that in the control group. The above results indicated that Xiaofeng Jiedu powder can effectively relieve PD-1 inhibitor-induced inflammatory responses in the skin.

Conclusion

The current study has clearly demonstrated that Xiaofeng Jiedu powder can improve the clinical efficacy and relieve symptoms and signs of patients with PD-1 inhibitor-induced inflammatory responses in the skin. Our analysis suggests that its mechanism is probably associated with the reduction of inflammatory responses and regulation of immune functions. Nevertheless, this study still has limitations, such as small sample size and failure to follow-up and observe the recurrence of disease in patients.

Conflicts of interest

Authors declare no competing interests.

References

1 Fameli A, Nardone V, Shekarkar Azgomi M, Bianco G, Gandolfo C, Oliva BM, Monoriti M, Saladino RE, Falzea A, Romeo C & Calandruccio ND, PD-1/PD-L1 immune-checkpoint blockade induces immune effector cell modulation in metastatic non-small cell lung cancer patients: A single-cell flow cytometry approach. *Front Oncol*, 12 (2022) 911579.

2 Holstead RG, Kartolo BA, Hopman WM & Baetz TD, Impact of the development of immune related adverse events in metastatic melanoma treated with PD-1 inhibitors. *Melanoma Res*, 31 (2021) 258.

3 Waldron JL, Schworer SA & Kwan M, Hypersensitivity and immune-related adverse events in biologic therapy. *Clin Rev Allergy Immunol*, 62 (2021) 413.

4 Sibaud V, Dermatologic Reactions to Immune Checkpoint Inhibitors: Skin Toxicities and Immunotherapy. *Am J Clin Dermatol*, 19 (2018) 345.

5 Luchini C, Bibeau F, Ligtenberg MJ, Singh N, Nottegar A, Bosse T, Miller R, Riaz N, Douillard JY, Andre F & Scarpa A, ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Ann Oncol*, 30 (2019) 1232.

6 Schwartz LH, Seymour L, Litière S, Ford R, Gwyther S, Mandrekar S, Shankar L, Bogaerts J, Chen A, Dancey J & Hayes W, RECIST 1.1 - Standardisation and disease-specific adaptations: Perspectives from the RECIST Working Group. *Eur J Cancer*, 62 (2016) 138.

7 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA & Jemal A, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 68 (2018) 394.

8 Walsh SR, Simovic B, Chen L, Bastin D, Nguyen A, Stephenson K, Mandur TS, Bramson JL, Lichty BD & Wan Y, Endogenous T cells prevent tumor immune escape following adoptive T cell therapy. *J Clin Invest*, 129 (2019) 5400.

9 Klempner SJ, Fabrizio D, Bane S, Reinhart M, Peoples T, Ali SM, Sokol ES, Frampton G, Schrock AB, Anhorn R & Reddy P, Tumor Mutational Burden as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors: A Review of Current Evidence. *Oncologist*, 25 (2020) e147.

10 Xia W, Chen H, Chen D, Ye Y, Xie C & Hou M, PD-1 inhibitor inducing exosomal miR-34a-5p expression mediates the cross talk between cardiomyocyte and macrophage in immune checkpoint inhibitor-related cardiac dysfunction. *J Immunother Cancer*, 8 (2020) e001293.

11 Kooshkaki O, Derakhshani A, Safarpour H, Najafi S, Vahedi P, Brunetti O, Torabi M, Lotfinejad P, Paradiso AV, Racanelli V & Silvestris N, The Latest Findings of PD-1/PD-L1 Inhibitor Application in Gynecologic Cancers. *Int J Mol Sci*, 21 (2020) 5034.

12 Wu Q, Jiang L, Li SC, He QJ, Yang B & Cao J, Small molecule inhibitors targeting the PD-1/PD-L1 signaling pathway. *Acta Pharmacol Sin*, 42 (2021) 1.

13 Dang YC, Kong QT, Wang Z & Sang H, Cutaneous adverse events in lung cancer patients on the therapy based on PD-1/PD-L1 inhibitors: A prospective observational cohort study. *Curr Probl Cancer*, 47 (2023) 100934.

14 Chen L & Shen Z, Tissue-resident memory T cells and their biological characteristics in the recurrence of inflammatory skin disorders. *Cell Mol Immunol*, 17 (2020) 64.

15 Ibrahim ML, Lu C, Klement JD, Redd PS, Yang D, Smith AD & Liu K, Expression profiles and function of IL6 in polymorphonuclear myeloid-derived suppressor cells. *Cancer Immunol Immunother*, 69 (2020) 2233.

16 Ma L, Chen Y, Gong Q, Cheng Z, Ran C, Liu K & Shi C, Cold atmospheric plasma alleviates radiation-induced skin injury by suppressing inflammation and promoting repair. *Free Radic Biol Med*, 204 (2023) 184.

17 Shi J, Shi S, Xie W, Zhao M, Li Y, Zhang J, Li N, Bai X, Cai W, Hu X & Hu D, IL-10 alleviates lipopolysaccharide induced skin scarring via IL-10R/STAT3 axis regulating TLR4/NF-κB pathway in dermal fibroblasts. *J Cell Mol Med*, 25 (2021) 1554.

18 Steen EH, Wang X, Balaji S, Butte MJ, Bollyky PL & Keswani SG, The Role of the Anti-Inflammatory Cytokine Interleukin-10 in Tissue Fibrosis. *Adv Wound Care* (New Rochelle), 9 (2020) 184.

19 Chen L, Zhang L, Zhang H, Sun X, Liu D, Zhang J, Zhang Y, Cheng L, Santos HA & Cui W, Programmable immune activating electrospun fibers for skin regeneration. *Bioact Mater*, 6 (2021) 3218.

20 Walter MR, The molecular basis of IL-10 function: from receptor structure to the onset of signaling. *Curr Top Microbiol Immunol*, 380 (2014) 191.

21 van Splunter M, Liu L, van Neerven RJJ, Wichers HJ, Hettinga KA & de Jong NW, Mechanisms Underlying the Skin-Gut Cross Talk in the Development of IgE-Mediated Food Allergy. *Nutrients*, 12 (2020) 3830.

22 Hayes MD, Ward S, Crawford G, Seoane RC, Jackson WD, Kipling D, Voehringer D, Dunn-Walters D & Strid J, Inflammation-induced IgE promotes epithelial hyperplasia and tumour growth. *Elife*, 9 (2020) e51862.