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Effect of pembrolizumab on T lymphocyte subsets in patients with advanced oral cancer and its therapeutic effect

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Abstract

Background: The aim of this study is to investigate changes of peripheral blood lymphocyte subsets before and after treatment with pembrolizumab for advanced oral cancer and its clinical sig-nificance.

Methods: 32 patients with advanced oral cancer who received pembrolizumab treatment were selected as observation group, 30 healthy people during the same period were selected as control group. Before treatment and in cycles 1, 2, 3 and 4 after treatment, fluid cytometry was used to detect changes in levels of lymphocyte subsets in peripheral blood of patients.

Results: $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ indexes of patients with advanced oral cancer before treatment were significantly lower than those in control group ($P < .05$), $CD8^+$ level was significantly increased ($P < .05$); After 1 cycle of pembrolizumab treatment, there was no significant difference in changes of lymphocyte subsets compared with before immunotherapy; After 2 and 3 cycles of treatment, $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ values were higher than before the treatment ($P > .05$), $CD8^+$ index was slightly lower than before treatment ($P < .05$); After fourth cycle of treatment, $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ values were significantly improved compared to before treatment ($P < .05$), $CD8^+$ index was significantly lower than before treatment ($P < .05$); In treatment process of patients with stable disease (SD)/partial response (PR), the $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ values of fourth cycles were higher than before treatment ($P < .05$), $CD8^+$ index was lower than before treatment ($P < .05$); During treatment of progressive disease (PD) patients, changes of lymphocyte subsets in fourth cycles were not significantly different from those before treatment ($P > .05$). This article shows through analysis that expression of programmed cell death ligand 1 (PD-L1) and pathological types have no obvious influence on effect of immunotherapy. Multi-factor analysis shows that it is more meaningful to observe the changes of $CD3^+$, $CD4^+$ and $CD8^+$ at the same time to predict effect of immunotherapy.

Conclusion: Pembrolizumab can regulate changes of T lymphocyte subsets in patients with advanced oral cancer, improve immune status of patients, there is no obvious adverse reaction. Monitoring changes of lymphocyte subsets during treatment can predict effect of immunotherapy.

Abbreviations: CR = complete Response, MHC = major histocompatibility complex, PD = progressive disease, PD = progressive disease, PD-1 = Programmed death 1, PD-L1 = programmed cell death ligand 1, PR = partial response, PR = Partial response, RECIST = Response Evaluation Criteria in Solid Tumors, ROC = receiver operating characteristic, SD = stable disease.

Keywords: advanced oral cancer, immunotherapy, pembrolizumab, t lymphocyte

1. Introduction

Oral cancer is a general term for malignant tumors occurring in the oral cavity, most of which are squamous cell carcinoma, namely the so-called mucous membrane mutation.[1] Oral cancer is also one of the more common malignant tumors of the head and neck.[2] Surgery is still the main means of treatment, while radiotherapy and chemotherapy are usually used as adjuvant therapy.[3,4] If there is no cervical lymph node metastasis in early oral cancer, surgery alone or radiotherapy is effective. Middle and late oral cancer, more suitable for the use of surgery and radiation therapy. Oral cancer is a preventable disease associated with behavioral and lifestyle factors, including tobacco and alcohol.[5] The occurrence and development of advanced oral cancer are closely related to cellular immunity, adaptive immunity and innate immunity of the host,

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The authors of this work have nothing to disclose

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among which cellular immunity dominated by T lymphocytes plays an important role in the antitumor immune response.[6] Immune suppression of tumor microenvironment reduces the infiltration of lymphocytes, leading to immune dysfunction of the body and conducive to the immune escape of tumor cells. Therefore, changes in lymphocyte subsets can be used to monitor and judge the disease and prognosis of tumor patients.[7] Immunotherapy has become an additional option for systemic cancer treatment, And often the better choice.[8] Programmed death 1 (PD-1) is expressed in activated T cells, B cells and bone marrow cells.[9] Under normal circumstances, The binding of PD-1 and its ligand (programmed cell death ligand 1, PD-L1) antagonizes the major histocompatibility complex (major histocompatibility complex, MHC) -CD3-mediated T cell activation pathway. Prevent tissue damage and inflammation caused by overactivation of T cells, Therefore, tumor cells can avoid the killing effect of T cells through high expression of PD-L1.[10] PD-1 inhibitors, combined with immune checkpoints, can reactivate the immune response of T cells and inhibit immunosuppressive regulatory T cells,[11] and further activate the host immune system to recognize, attack and eradicate tumor cells, which has been considered as a promising and effective strategy in clinical therapy.[12] Therefore, this study analyzed the changes of peripheral blood lymphocyte subsets in patients with advanced oral cancer treated with Pembrolizumab and in patients with different therapeutic effects during treatment, to discuss the effects of pembrolizumab treatment on peripheral blood lymphocyte subsets in patients with advanced oral cancer.

2. Methods

2.1. Patients and ethics

A total of 30 cases of advanced oral cancer (stage IV) treated with line II single drug using PD-1 immunosuppressant Pembrolizumab were selected as the observation group from December 20, 2020 to December 21, 2021 in the Fourth Hospital of Hebei Medical University. And the type of study design is double-blind.

Inclusion criteria: patients with advanced oral cancer treated with Pembrolizumab.

Exclusion criteria: patients with diseases of immune system and blood system. Patients with recent obvious infection. Cancer patients with no measurable lesions. Exclude participants who disagree; Exclusion of vulnerable groups, such as pregnant women; Exclude those with poor physiological condition; Exclude those taking contraindicated drugs.

This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. Written informed consent was obtained from all patients.

2.2. Parameters in the research

All cases in this study were clearly diagnosed by pathology, and PD-1 expression was positive in all patients with advanced oral cancer in this study. At the same time, 30 healthy persons were selected as the control group, The study parameters and the occurrence of complications of patients in the 2 groups were recorded. Based clinical information of patients were classed according to sex (Male/Female), age (<60/≥60), smoking status (Never smoked/ Keep smoking)

2.3. Evaluation criteria

According to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guideline, the efficacy Criteria are: complete Response (CR): All the target lesions disappeared completely; Partial response (PR): the sum of diameters of all measurable target lesions was ≥ 30% below baseline; Stable disease (SD): the total diameter of lesions at baseline has a decreasing trend but does not meet the standard of PR, or it has increased but does not meet the evaluation standard of progressive disease (PD); PD: The total diameter of the target lesions increases by 20% over baseline or new lesions appear. The efficacy evaluation of all patients in this study was based on image data and efficacy evaluation criteria.

2 mL of venous blood was collected from all patients, and deTA-K2 anticoagulation was used to detect peripheral blood lymphocyte subsets. All collection operations are completed by experienced laboratory technicians.

2.4. Statistical methods

SPSS 24.0 and GraphPad Prism 8.4.3 were used for statistical analysis of experimental data. Counting data were expressed by χ^2 test, measurement data were expressed by Mean ± standard deviation (Mean ± SD), comparison was performed by T test, and multiple factor analysis was performed by Logistic regression. $P < .05$ was considered statistically significant.

3. Results

3.1. Basic information of the patients

There were 16 male patients and 14 female individuals. In addition, all patients included 22 cases with age < 60 years old, and 8 cases with age ≥ 60years old. And there were 10 individuals Never smoked, and 20 cases Keep smoking. The difference between control group and observation group was statistically significant ($P < .05$). (Table 1)

The lymphocyte subsets of the observation group were compared with those of the control group before pembrolizumab treatment

The $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ indexes of 30 patients with advanced oral cancer in observation group were significantly decreased before treatment compared with control group ($P < .05$). $CD8^+$ level was significantly increased ($P < .05$). At the same time, the difference of lymphocyte subsets between smokers and nonsmokers was not statistically significant ($P > .05$). It can be seen that patients with advanced oral cancer are in a state of immunosuppression, and their immune function is lower than that of healthy controls.

3.2. The changes of lymphocyte subsets in observation group before and after treatment

The lymphocyte subsets of 30 patients in observation group were compared before and after immunotherapy for 1 cycle. The results showed that although the values of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were increased after 1 cycle, $CD8^+$ index was slightly decreased after 1 cycle, but the differences were not statistically significant ($P > .05$). After 2 and 3 cycles of treatment, the values of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were higher than

Table 1

Clinical characteristics of patients.

Characteristics		Control group	Observation group	*P*
Sex	Male	16	20	0.292
	Female	14	10	
Age	≥60	8	10	0.573
	<60	22	20	
Smoking status	Never smoked	10	20	0.010*
	Keep smoking	20	10	

*$P < .05$.

Table 2

Changes of lymphocyte subsets after 1, 2, 3 and 4 cycles of immunotherapy.

Group	Treatment period	CD4⁺ (%)	CD8⁺ (%)	CD4⁺/CD8⁺ (%)	CD3⁺ (%)
Observation group	Before the treatment	31.38 ± 6.88	36.16 ± 9.06	0.66 ± 0.28	53.28 ± 12.16
	T1	32.88 ± 10.66	32.06 ± 8.33	0.78 ± 0.38	59.16 ± 17.96
	T2	35.80 ± 7.67	29.86 ± 7.06	0.98 ± 0.46	62.06 ± 13.36
	T3	36.68 ± 9.96	28.77 ± 6.18	1.15 ± 0.58	65.56 ± 15.33
	T4	38.96 ± 8.43	26.96 ± 8.18	1.33 ± 0.66	68.68 ± 12.76

T: Cycles

those before treatment ($P > .05$), and the differences were not statistically significant, CD8⁺ index decreased compared with before treatment ($P < .05$), the difference was statistically significant; After 4 cycles of treatment, the values of CD3⁺, CD4⁺ and CD4⁺/CD8⁺ were significantly improved compared with those before treatment ($P < .05$), and CD8⁺ index was significantly decreased compared with those before treatment ($P < .05$). After 4 cycles of treatment, peripheral blood lymphocyte subsets were significantly improved. There was no statistical significance in the changes of lymphocyte subsets after the second cycle and third of treatment compared with the first cycle of treatment ($P > .05$). The changes of lymphocyte subsets after the fourth cycle of treatment were statistically significant compared with those after the first cycle of treatment ($P < .05$) (Table 2). There was no significant difference in lymphocyte subsets after the 4th cycle of treatment compared with the 2nd cycle and 3rd of treatment ($P > .05$). In this paper, changes of CD3⁺ and CD8⁺ are represented by changes in the variation chart (Fig. 1).

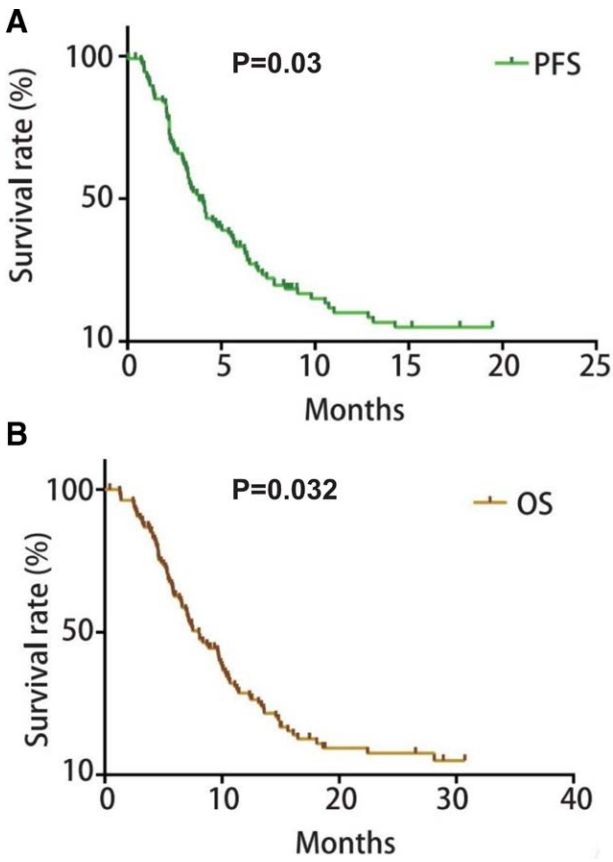

Figure 1. The change trend of patients' CD3⁺(A) and CD8⁺(B) T lymphocyte subsets during immunotherapy, T briefly represents the period; response means SD/PR, nonresponse means PD. The abscissa represents time (months) and the ordinate represents survival rate (%).$P < .05$.

3.3. The effect of pembrolizumab and the changes of T lymphocyte subsets in observation group were observed

In the observation group of 32 patients with advanced oral cancer, 24 patients achieved SD and PR after the fourth cycle of pembrolizumab treatment, accounting for 75% of the total number of patients. 8 patients achieved PD, accounting for 25% of the total number of patients observed. The results showed as follows: After the 4th cycle of immunotherapy, the values of CD3⁺, CD4⁺, CD4⁺/CD8⁺ in SD/PR patients were higher than before treatment ($P < .05$), and CD8⁺ index was lower than before treatment ($P < .05$). Lymphocyte subsets of patients with PD showed no significant difference after treatment ($P > .05$), as shown in Table 3. There was no significant difference in the therapeutic effect of immunotherapy between patients with positive PD-L1 expression and patients with negative PD-L1 expression ($P > .05$). (Table 3)

3.4. The ROC curve of CD3⁺/CD4⁺/CD8⁺ T lymphocyte after the fourth cycle of immunotherapy

The receiver operating characteristic (ROC) curve results showed that the specificity and sensitivity of immunotherapy to CD3⁺/CD4⁺/CD8⁺ T lymphocytes were high after the fourth cycle. And CD3⁺, CD4⁺, CD8⁺ lymphocytes could predict the immunotherapy effect. CD3⁺ (AUC = 0.788); CD4⁺ (AUC = 0.810); CD8⁺ (AUC = 0.716); CD3⁺, CD4⁺, CD8⁺ (AUC = 0.968). (Fig. 2)

4. Discussion

Oral cancer is creating an alarming situation worldwide. It is a global concern and one of the most common cancers worldwide. Most oral malignancies are squamous cell carcinoma,[13] the clinical manifestations and therapeutic outcomes of advanced oral cancer can negatively affect the quality of life of patients. In the diagnosis, treatment and survival of patients with advanced oral cancer, their physical function, appearance and mental health may be impaired.[14] The prevention and treatment of tumor has always been an important direction of medical research. In recent years, breakthroughs have been made in the elimination and killing of tumor cells by mobilizing the body's immune system through immunotherapy.[15] The immune system of human body mainly includes natural immunity, acquired immunity composed of humoral immunity and cellular immunity, among which cellular immunity is considered as the main way of antitumor immunity. Massive infiltration of lymphocytes is the core of the antitumor response of cellular immunity, and also the cytological basis for the effect of immunotherapy.[16] Therefore, the monitoring of lymphocyte subsets has important guiding significance for the prevention, diagnosis and judgment of drug efficacy of tumor. Subsets of lymphocytes can be divided into T lymphocytes, B lymphocytes and natural killer (NK) cells according to their surface markers and biological characteristics. Among them, T lymphocyte subsets are the main immune response forms of lymphocyte subsets. The unique molecular marker of T lymphocytes is CD3, which exists on the surface of all T lymphocytes and can be further divided into CD4⁺ T cells and CD8⁺ T

Table 3

Changes in the relationship between lymphocyte subsets after the 4 cycle of immunotherapy.

curative effect		CD3⁺ (%)	CD4⁺ (%)	CD8⁺ (%)	CD4⁺/CD8⁺ (%)
PR/SD		73.64 ± 7.94	41.72 ± 6.01	25.06 ± 1.28	1.17 ± 0.49
	t	6.82	7.25	5.1	6.71
	P	0.00	0.00	0.00	0.00
PD		53.89 ± 13.22	30.71 ± 9.67	22.43 ± 6.04	1.99 ± 0.60
	t	0.12	0.15	0.32	0.82
	P	0.91	0.88	0.76	0.44

PD = progressive disease, PR = partial response, SD = stable disease.

cells. CD4⁺ helper/inducer T cells play a central role in the antitumor immune process. The cytokines secreted by T cells not only have a positive enhancing effect on cellular immunity, but also promote the proliferation of B cells, which is conducive to the production of antibodies and assist humoral immunity to play an antitumor role. CD8⁺ T cells have 2 phenotypes: one is CD8⁺/CD28⁺, which has cytotoxic effect, and the other is CD8⁺/CD28⁺, which has inhibitory effect.[17] Studies have shown[18] that CD8⁺ T cells not only have certain cytotoxic effects on antigen presenting cells, but also produce inhibitory cytokines that can negatively inhibit the expression of CD4⁺ T lymphocytes and inhibit humoral and cellular immunity. Therefore, the increase of CD8⁺ T cells provides conditions for the proliferation and metastasis of tumor cells.

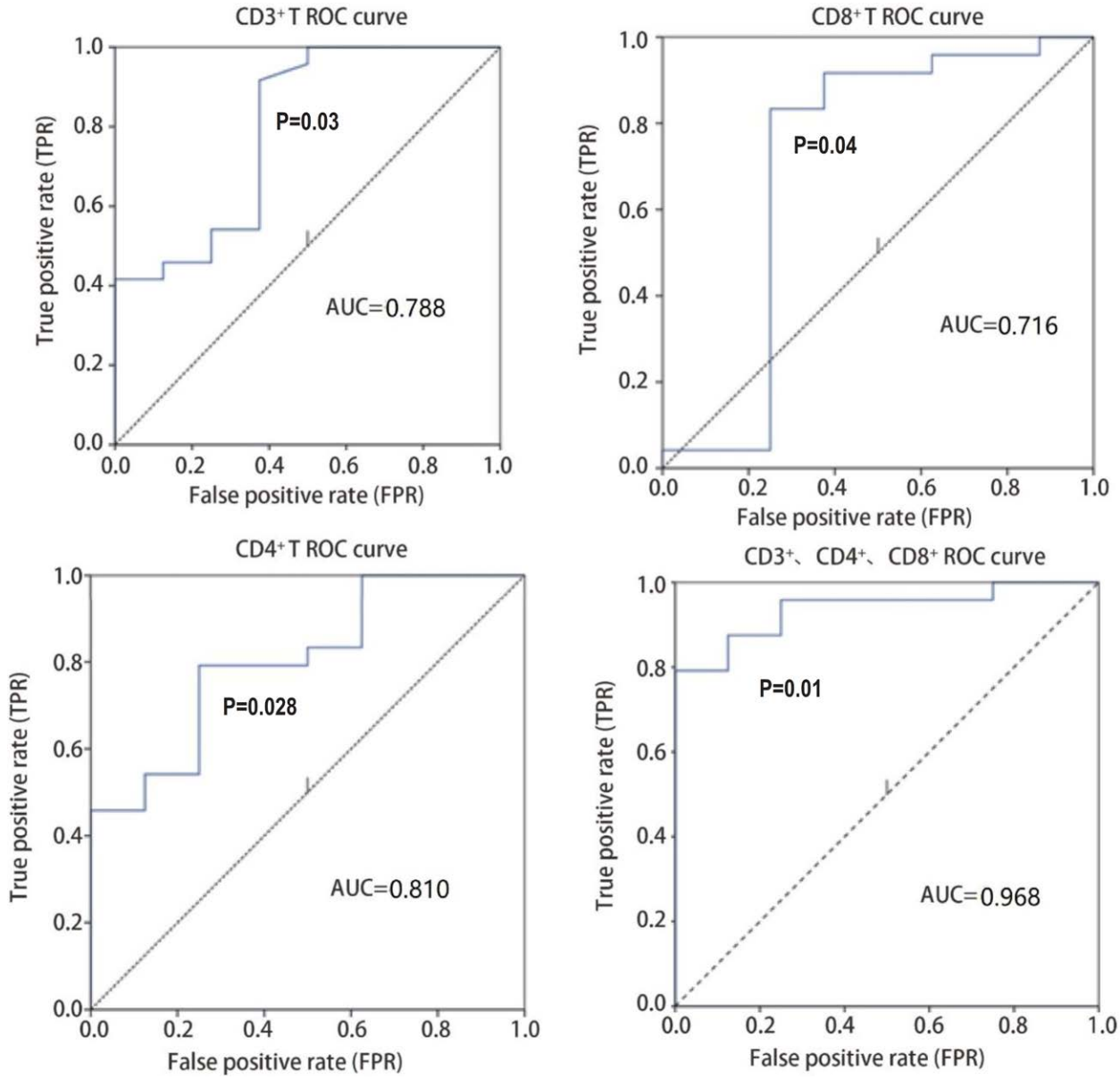

Figure 2. The ROC curve of CD3⁺/CD4⁺/CD8⁺ T lymphocyte after the fourth cycle of immunotherapy. ROC: receiver operating characteristic curve. The abscissa represents false positive rate (FPR) and the ordinate represents true positive rate (TPR). $P < .05$.

Under normal circumstances, the ratio of $CD4^+/CD8^+$ is in a relative balance to maintain the normal immune response of the body. When the ratio decreases, it indicates that the cellular immune function of the body decreases, and the killing effect on tumor cells is weakened, so that the body of the patient is in the immunosuppression state.

In this study, compared with the healthy control group, the counts of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ indexes in the observed tumor patients were significantly decreased before treatment, and $CD8^+$ T lymphocyte levels were significantly increased, which was consistent with the results of Yan and Shanshan Wu 's study.[19,20] The changes of T lymphocyte subsets indicate that the cellular immunity of patients with malignant tumor is in immunosuppression state, and the number of positive immune cells decreases while negative immune cells increase. The rapid decline of cellular immune function in vivo and the overexpression of immunosuppressive factors lead to the formation of immunosuppressive microenvironment, which creates conditions for immune escape and malignant proliferation of tumor cells. The results of this study also showed that the indexes of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ increased significantly after Pembrolizumab treatment, and the indexes of $CD8^+$ T cells decreased significantly after Pembrolizumab treatment, suggesting that pembrolizumab may alleviate the immune suppression state of the body to a certain extent. It can positively regulate the immune system, promote the activation of immune cells and enhance the antitumor effect of the body. At the same time, there was no statistical difference in lymphocyte subsets in the first cycle of treatment compared with before treatment, In the second cycle, only $CD8^+$ changes were statistically significant, and the difference in the fourth cycle was statistically significant, which may be related to the slow onset of immunotherapy.

At the same time, this study also compared the changes of lymphocyte subsets in SD/PR patients whose efficacy evaluation was achieved by pembrolizumab with those in PD patients. It was found that in the fourth cycle after treatment, the effect was as good as the lymphocyte subsets of SD/PR patients. However, there was no significant difference in lymphocyte subsets of PD patients after treatment compared with those before treatment ($P > .05$). Results suggest that advanced oral cancer patients accept palmer show bead a fight after treatment, patients with curative effect good immune suppression condition significantly improved, T lymphocyte infiltration, antitumor immune inhibiting cell number also fell, enhance the body's antitumor immune response, is conducive to the prognosis of patients with tumor and survival. The immune function of patients who did not respond well to the treatment was not effectively restored. At the same time, by comparing the efficacy of patients with different expression of PD-L1 and different pathological types, it was found that the expression of PD-L1 and pathological types had no obvious influence on the efficacy of immunotherapy. Through univariate and multivariate analysis, regular detection of T lymphocyte subsets in immunotherapy patients has certain value in predicting curative effect. And this study provides a certain degree of reference value for studying the changes of lymphocyte and cellular immunity in the process of malignant tumor. No obvious adverse reactions were observed in all patients in the observation group.

4.1. Study limitations

Whether lymphocyte subsets can be used as a predictor of immunotherapy efficacy remains to be verified. The sample size of the observation group was relatively limited, so in order to further verify the results, clinical data should be continuously collected, summarized and analyzed in the process of clinical work. nonhomogenous groups of participants, influence of additional confounding and co-factors, as well as the impact of PD-1 inhibitors on lymphocytes profile in general were avoided whenever possible.

In conclusion, pembrolizumab can regulate the changes of lymphocyte subsets in patients with advanced oral cancer, improve the immune status of the body, and provide important reference value for judging the immune status of the body and predicting the effect of immunotherapy. Therefore, regular monitoring of the changes of lymphocyte subsets in patients, combined with the analysis of immune-related factors when conditions permit, can provide a reference for the selection of treatment plan and prognosis of patients. In this study, patients were only followed up to the 4th cycle of immunotherapy, and only the changes of lymphocyte subsets in the 4th cycle of the observation group were statistically significant compared with those before treatment ($P < .05$).

Correction

When originally published, the ending date of the observation group in the Methods section was incorrect. It originally appeared as December 21, 2020 and has been corrected to December 21, 2021.

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