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PREDICTIVE VALUE OF RCCEP IN THE OUTCOME OF PATIENTS WITH ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA TREATED WITH CAMRELIZUMAB

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Abstract: To evaluate the predictive value of reactive cutaneous capillary endothelial proliferation (RCCEP) in the treatment outcome of patients with first-diagnosed advanced esophageal squamous cell carcinoma (ESCC) treated with camrelizumab in combination with chemotherapy. This is a single-center, retrospective, observational study of 76 patients who were first diagnosed with advanced ESCC and received Camrelizumab combination chemotherapy at our institution from January 2021 to December 2022, and were compared between those who had and those who did not have an RCCEP response to determine the predictive value of an RCCEP response for treatment outcomes in this patient population.The overall survival (OR) of patients with RCCEP response was 15.08 ± 6.35 months, which was better than that of patients without RCCEP response of 10.55 ± 4.68 months, and the difference was statistically significant (P=0.001). Twenty-eight cases (77.78%) of the patients who experienced partial response (PR), while the overall response rate (ORR) was 77.78%; while among the patients who did not experienced RCCEP response, only five cases (12.50%) experienced PR, and the ORR was 12.50%, which were statistically different in both cases (P<0.001; P<0.001). There was no difference in the occurrence of treatment-related adverse events between the two groups. Meanwhile, 88.89% of RCCEP patients experienced grade I response, 11.11% experienced grade II response, and no grade III-V response occurred. 66.67% of RCCEP patients showed red-nevus-like.The occurrence of RCCEP suggests therapeutic efficacy in patients with advanced ESCC treated with camrelizumab in combination with chemotherapy, indicating the prognostic value, and may serve as a potential predictor of treatment outcome in this patient population.

Keywords: Esophageal Squamous Cell Carcinoma; Reactive cutaneous capillary endothelial proliferation; Camrelizumab; Immune-related adverse events; Advanced esophageal carcinoma

1 PREAMBLE

In 2020, it is estimated that there will be more than 19.3 million new cancer cases and more than 10 million new cancer deaths in the world, and esophageal cancer has become one of the major cancers threatening human health, accounting for 3.1 percent of new cancer cases and 5.5 percent of new cancer deaths[1, 2]. The histological subtype of Esophageal carcinoma (EC) shows varying incidence depending on regional differences, although in some Western populations, the incidence of adenocarcinoma has surpassed that of squamous carcinoma. Esophageal Squamous Cell Carcinoma (ESCC) remains the dominant sub type in Asian populations[3-5]. With the optimization of surgical modalities and treatment strategies, although EC-related mortality and 5- year overall survival (OS) have improved, patients with advanced ESCC have an OS of only 8-11 months, and the prognosis remains poor[3, 6, 7].

Patients with EC are usually already advanced or metastasized at the time of diagnosis, and the current recommended first-line treatment for such advanced or metastasized ESCC is chemotherapy[8]. However, multiple prospective clinical studies have shown that overall survival remains low in patients receiving chemotherapy[9]. In recent years, Programmed cell death protein (PD-1) and Programmed cell death protein ligand 1(PD-L1) has shown remarkable efficacy and great promise in the treatment of a variety of cancers[10-13]. In the ATTRACTION-03 clinical trial,

Nivolumab for advanced ESCC showed prolonged OS (10.9 vs. 8.4 months) and a lower incidence of grade III or IV adverse events (18% vs. 63%) in the Nibolumab group compared with chemotherapy[14]. At the same time, immunotherapy combined with chemotherapy showed better outcomes in a variety of tumor types. The ESCORT study has demonstrated that in patients with advanced or metastatic ESCC, Camrelizumab combined with chemotherapy significantly improves overall survival and progression-free survival compared with placebo-plus chemotherapy[8].

Although immune-related adverse events (irAE) during immunotherapy have been shown to predict immunotherapy outcomes, few studies have been conducted in advanced ESCC. Especially reactive cutaneous capillary endothelial proliferation(RCCEP), which is a common occurrence of immune-related adverse events[15, 16]. Therefore, we conducted this retrospective study to evaluate the prognostic value of RCCEP in patients receiving Camrelizumab in combination with chemotherapy for advanced ESCC.

2 METHODS OF STUDY

2.1 Clinical Data

This study was a single-center, retrospective, observational study. The protocol was approved by the Institutional Review Board of our hospital, which waived the need for informed consent because it was a retrospective study. All methods were carried out in accordance with the Helsinki Principles. A total of 76 patients with advanced Esophageal Squamous Cell Carcinoma (ESCC) who were first diagnosed in our hospital between January 2021 and December 2022 and received Camrelizumab combined with chemotherapy were selected as the study subjects.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: Meet the diagnostic criteria for advanced esophageal cancer, clinical stage III b-IV; The pathological types were squamous cell carcinoma; Aged 30-80 years old; Have not had any previous treatment; Camrelizumab combined with chemotherapy was chosen; Patients were conscious and able to communicate normally. Exclusion criteria: other serious diseases, such as cardiovascular and cerebrovascular diseases; Combined with consciousness or cognitive impairment; Allergic reactions and contraindications to the drugs in this study; Patients with concurrent autoimmune disease or a history of chronic autoimmune disease; And a history of previous tumors other than esophageal cancer.

2.3 Methods

Control group: All patients agreed to receive and use the regimen recommended by the Clinical Oncology Collaborative Committee of the Chinese Anti-Cancer Association (CSCO) guidelines, mainly platinum combined with paclitaxel or fluorouracil or docetaxel. Observation group: On the basis of control group, patients received immunotherapy combined with Camrelizumab. Usage and dosage:Camrelizumab injection 200mg+250ml0.9% sodium chloride solution, intravenous infusion, 60min(90min for the first time), a treatment cycle of 3 weeks, a total of 2 cycles of treatment (clinical efficacy evaluation every 2-3 cycles, patients without disease progression continue to receive the next course of treatment).

2.4 Outcome Measures

(1) survival: overall survival (OS), which refers to the time from the start of treatment to the last follow-up or death from any cause; (2) anti-tumor effect: refer to the RECIST efficacy evaluation criteria (2000) to determine the anti-tumor effect of the patient. overall response rate (ORR)= complete response (CR)+ partial response (PR); stable disease (SD); progressive disease (PD); (3) treatment-related adverse reactions: nausea; Fatigue; Vomiting; Fever; Gastrointestinal reactions; Leukopenia; thrombocytopenia;(4) reactive cutaneous capillary endothelial proliferation (RCCEP) grade: Grade I (maximum nodule diameter ≤10 mm, with or without rupture and bleeding); Grade II (nodule maximum diameter >10 mm, with or without rupture and bleeding); Grade II (diffuse nodules throughout the body that may be complicated by skin infection); Grade IV (systemic and multiple nodules, and life-threatening); And Grade V

(death). RCCEP remission refers to regression of all RCCEP lesions. At the same time, according to the shape of RCCEP occurrence, it is divided into; Red nevus shape; Pearl-like; Mulberry; Patchy; Tumour-like.

2.5 Statistical Methods

SPSS 23.0 statistical software was used for analysis, measurement data were represented by($\bar{x} \pm s$), and T-test was performed; Counting data were represented by frequency and rate, and P<0.05 indicated statistical difference.

3 RESULTS

3.1 General Data Comparison

The mean age of patients with RCCEP reaction was 63.25 ± 9.40, and the mean age of patients without RCCEP reaction was 65.20 ± 8.23, with no statistical difference. Among the patients with RCCEP reaction, 32 (88.89%) were treated with paclitaxel + cisplatin combined with carrellizumab (Camrelizumab), and 4 (11.11%) were treated with docetaxel + cisplatin combined with Camrelizumab; Among the patients with no RCCEP response, 22 (55.00%) were treated with paclitaxel + cisplatin combined with Camrelizumab, and 18 (45.00%) were treated with docetaxel + cisplatin combined with Camrelizumab, with statistical differences (P<0.001; P<0.001). No statistically significant difference was found in other patients' general data, as shown in Table 1.

Table 1. Clinical characteristics of patients

	RCCEP(n=36)	Non-RCCEP (n=40)	P
age	63.25 ± 9.40	65.20 ± 8.23	0.338
Gender,male	35 (97.22)	35 (87.50)	0.117
BMI, kg/m2	22.14 ± 2.25	21.53 ± 4.65	0.468
ECOG rating			
0	26 (72.22)	30 (75.00)	0.784
1	10 (27.78)	8 (20.00)	0.426
2	0 (0)	2 (5.00)	0.174
Transfer parts			
lung	1 (2.78)	2 (5.00)	0.619
liver	0 (0)	1 (2.50)	0.340
bone	1 (2.78)	0 (0)	0.289
other	0 (0)	1 (2.50)	0.340
Treatment mode			
TP+Cam	32 (88.89)	22 (55.00)	0.001
DP+Cam	4 (11.11)	18 (45.00)	0.001

Note: Eastern Cooperative Oncology Group (ECOG) score; TP, Paclitaxel + cisplatin; DP,docetaxel + cisplatin; Cam, carelizumab; Metrological data were expressed with ($\bar{x} \pm s$) ; Counting data is expressed in frequency and rate.

3.2 Treatment-Related Adverse Reactions were Compared between the Two Groups

Treatment-related adverse reactions occurred: nausea, fatigue, vomiting, fever, gastrointestinal reactions, leukopenia, thrombocytopenia and hyperthyroidism, and there were no statistical differences between the two groups, as shown in Table 2.

Table 2. Comparison of treatment-related adverse reactions between the two groups

	RCCEP(n=36)	Non-RCCEP (n=40)	P
Nausea	9 (25.00)	5 (12.50)	0.160
Fatigue	5 (13.89)	7 (17.50)	0.666
Vomiting	5 (13.89)	6 (15.00)	0.891
Fever	3 (8.33)	5 (12.50)	0.555
Gastrointestinal reactions	4 (11.11)	6 (15.00)	0.617
Hyperthyroidism	1 (2.78)	1 (2.50)	0.940
Leukopenia	2 (5.56)	3 (7.50)	0.733
Thrombocytopenia	1 (2.78)	0 (0)	0.289

Note: Measurement data are represented by($\bar{x} \pm s$) ; Counting data is expressed in frequency and rate.

3.3 Comparison of Treatment Outcomes between the Two Groups

It was found in Table 3 that the overall survival of patients with RCCEP reaction was 15.08 ± 6.35 months, which was better than 10.55 ± 4.68 months without RCCEP reaction, and the difference was statistically significant (P=0.001). There were no patients with complete response in either group. A total of 28 patients (77.78%) with RCCEP response had partial response, which was better than 5 patients (12.50%) without RCCEP response, and the difference was statistically significant (P<0.001). Disease progression occurred in 1 case (2.78%) with RCCEP reaction, and in 3 cases (7.50%) without RCCEP reaction, with no statistical difference (P=0.357). It can be observed by follow-up CT that the length and thickness of follow-up CT with RCCEP reaction were 3.52 ± 2.07cm and 0.98 ± 0.48cm, respectively, which were smaller than those without RCCEP reaction (4.87 ± 1.67cm; 1.54 ± 0.70cm), the difference was statistically significant (P=0.002; P<0.001).

Table 3. Comparison of treatment outcomes between the two groups

	RCCEP(n=36)	Non-RCCEP (n=40)	P
Lifetime			
Overall survival,OS	15.08 ± 6.35	10.55 ± 4.68	0.001
Complete remission,CR	0 (0)	0 (0)	
Partial remission,PR	28 (77.78)	5 (12.50)	<0.001
Disease stable,SD	7 (19.44)	32 (80.00)	<0.001
Disease progression,PD	1 (2.78)	3 (7.50)	0.357
Objective response rate,ORR	28 (77.78)	5 (12.50)	<0.001
CT(before treatment)			
Length,cm	5.84 ± 2.14	5.39 ± 1.87	0.335
Thickness,cm	1.73 ± 0.85	1.68 ± 0.62	0.766
CT(Last follow-up)			
Length,cm	3.52 ± 2.07	4.87 ± 1.67	0.002
Thickness,cm	0.98 ± 0.48	1.54 ± 0.70	<0.001

Note: Measurement data are indicated by($\bar{x} \pm s$) ; Counting data is expressed in frequency and rate.

3.4 RCCEP Response

Among the 36 patients with RCCEP reaction, 32 patients (88.89%) had grade I reaction, 4 patients (11.11%) had grade II reaction, and no patients had grade III-V reaction. According to the morphological observation of RCCEP reaction, a total of 24 patients (66.67%) showed red nevus, 5 patients (13.89%) showed pearl, 1 patient (2.78%) showed mulberry, 4 patients (11.11%) showed patellar and 2 patients(5.56%) showed nodular. Among the 36 patients with RCCEP, 1 (2.78%) had oral mucosal lesions, 2 (5.56%) had conjunctival lesions, and 1 (2.78%) had nasal mucosal lesions.

4 DISCUSS

Esophageal carcinoma (EC) is a malignant tumor occurring in the esophageal epithelium with various etiology and can be caused by alcohol abuse, smoking, bad diet and other factors. China is one of the countries with high incidence of esophageal cancer in the world[17]. In China, the most common subtype of Esophageal Squamous Cell Carcinoma (ESCC), and EC because of the early clinical symptoms are not obvious, usually when the doctor is already in the late stage or metastasis, the prognosis is poor, 5-year survival rate is only 15%-25%[18]. In the past, the first-line treatment for advanced EC is mainly the use of systemic chemotherapy containing fluorouracil and platinum drugs, but the traditional chemotherapy has poor efficacy, large side effects, and the after-line treatment after chemotherapy failure is not good[19]. In recent years, with a large number of clinical studies on PD-1/PD-L1 treatment of a variety of tumors, and achieved gratifying results, but also for the treatment of advanced EC has brought opportunities and challenges.

A number of clinical trials at home and abroad have confirmed that immunotherapy in patients with advanced or metastatic EC, compared with traditional chemotherapy, can bring better safety and effectiveness for patients. In addition to being effective on tumor cells, Immune checkpoint inhibitors (ICIs) may also cause autoimmune toxicity and immune-related adverse events (irAE)[20-22]. Although the exact mechanism of irAE is unknown, autoantibody stimulation, overactivation of T cells and increased cytokine levels may explain this phenomenon[21, 23]. Although irAE is an adverse drug reaction, several studies have found that the occurrence of irAE may be associated with better clinical outcomes[24]. IrAE is an immune reaction involving multiple organs in the whole body, especially the skin reaction. Reactive cutaneous capillary endothelial proliferation (RCCEP) is the irAE with the highest incidence during Camrelizumab treatment[15, 25, 26]. The objective of this study was to explore the predictive value of RCCEP in treatment outcomes of patients with first diagnosed advanced ESCC treated with Camrelizumab combined with chemotherapy.

In a study of RCCEP, Camrelizumab may promote vascular proliferation by activating CD4+T cells and increasing the release of cytokine IL-4, thereby stimulating macrophage differentiation and releasing VEGF-A[15]. In this study, the incidence of RCCEP was 47.37%(36/76). However, in one nasopharyngeal carcinoma patient receiving Camrelizumab combined with apatinib, the incidence of RCCEP was only 12.1%(4/33), and Apatinib, as a VEGFR 2 inhibitor, was considered to be related to the inhibition of RCCEP by blocking downstream proteins after Apatinib binding to VEGF[27]. These results suggest that RCCEP may not be appropriate for predicting the occurrence of RCCEP in all tumors treated with Camrelizumab, as other agents may affect the occurrence[28] of RCCEP. Meanwhile, in the present study, RCCEP occurred mainly in the skin of the head, face and trunk and was mainly red nevus (66.67%). Among all the grades of RCCEP, 88.89%(32/36) were in grade I patients and 11.11%(4/36) were in grade II patients. No III-V RCCEP was observed, and no RCCEPrelated death events were observed. Most RCCEP usually did not require special management, and most lesions resolved spontaneously within 2 months of discontinuation of Camrelizumab. When nodules need to be treated, the ruptured and bleeding nodules should be stopped and mupirocin ointment should be administered to prevent infection; In patients with larger nodules, some may also be surgically removed. Of the 36 patients who developed RCCEP, 1 had oral mucosal lesions, 2 conjunctival lesions, and 1 nasal mucosal lesions. No mucosal lesions of the trachea or digestive tract (esophagus and gastrointestinal tract) were observed, and therefore none of the patients was at risk of hemoptysis or gastrointestinal bleeding.

Several studies have shown that the occurrence of cutaneous irAE can predict the efficacy of PD-1/PD-L1 in some tumors[16, 29]. Also, in our study, we found that the group that developed an RCCEP response had an increased overall

survival relative to the group that did not develop an RCCEP response (15.08 ± 6.35 months vs. 10.55 ± 4.68 months). In terms of antitumor effect, although there was no difference between the two groups in patients with complete response, the RCCEP group had better partial response and objective response rate than the group without RCCEP response. In addition, in a study of Camrelizumab for hepatocellular carcinoma, patients who responded to RCCEP had a higher rate of objective response than those who did not respond to RCCEP (19.3% vs. 5.6%)[16, 29]. This suggests that patients who respond to RCCEP during Camrelizumab therapy may have a better prognosis.Therefore,RCCEP may be a clinical indicator for predicting the efficacy of Camrelizumab.

In conclusion, RCCEP can predict the outcome of advanced ESCC patients treated with Camrelizumab combined with chemotherapy to some extent, but it needs to be confirmed by larger prospective clinical trials. At the same time, more monitoring and follow-up of patients with RCCEP should be conducted to prevent the occurrence of severe and life-threatening RCCEP.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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