EJMO

DOI: 10.14744/ejmo.2023.42506
EJMO 2023;7(3):265–269

Research Article

Short-Term Efficacy and Safety of Camrelizumab-Based Treatment for Refractory or Metastatic Oesophageal Squamous Cell Carcinoma

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Abstract

Objectives: To evaluate the shortterm efficacy and safety of camrelizumab in combination with apatinib for refractory or metastatic oesophageal squamous cell carcinoma.

Methods: We retrospectively reviewed the medical records of 30 patients with refractory or metastatic oesophageal squamous cell carcinoma treated with camrelizumab in combination with apatinib at a single institution. The shortterm efficacy was evaluated according to the RECIST. The safety was evaluated by the CTCAE.

Results: Among all 30 patients, the ORR and DCR were 27% (8/30) and 63% (19/30), respectively. CR was achieved in 0% (0/30) of patients, PR in 27% (8/30), SD in 36% (11/30), and 37% (11/30) experienced PD. The median PFS interval was 3.7 (95% CI: 2.48–3.88) months, and the median OS outcome was not reached.

Conclusion: Our study reveals that camrelizumab in combination with apatinib is a promising therapy for patients with refractory or metastatic ESCC. This combination has a high response rate and favourable clinical safety.

Keywords: Apatinib, camrelizumab, efficacy, oesophageal squamous cell carcinoma, safety

Cite This Article: *Yuan Y, Han L, Feng Y, Li X. Short-Term Efficacy and Safety of Camrelizumab-Based Treatment for Refractory or Metastatic Oesophageal Squamous Cell Carcinoma. EJMO 2023;7(3):265–269.*

In East Asia, especially China, approximately 90% of oesophageal cancers are squamous cell carcinoma (ESCC).[1] According to statistical data,[2] China has the 5th-highest ESCC prevalence and mortality rate, accounting for up to 55% of cases worldwide. Approximately 70% of patients are initially diagnosed at an advanced stage, and radical surgery is not an option. For nearly 20 years, there was no significant improvement in the treatment of refractory or metastatic ESCC, and there was no standard second-line treatment available. The median survival time was approximately 5 months.[3] In recent years, with the development of biological immunotherapy, multiple immune checkpoint inhibitors (ICIs) have been approved for the management of a variety of cancers.[4] The efficacy and safety of ICIs for ESCC as second-line therapy were tested in several randomized controlled phase 3 trials,[5] and pembrolizumab and nivolumab have already been approved by the FDA for the treatment of ESCC. Compared with chemotherapy, ICIs have better safety and tolerability. However, information concerning camrelizumab,[6] an ICI developed in China, is very limited in ESCC. Thus, we reviewed 30 patients with refractory or metastatic ESCC who were treated at a single institution to evaluate the short-term efficacy and safety of camrelizumab in combination with apatinib.

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Submitted Date: August 04, 2023 **Accepted Date:** September 05, 2023 **Available Online Date:** October 06, 2023

Methods

Patients

We carried out a retrospective study of 30 patients with refractory or metastatic ESCC who received camrelizumab in combination with apatinib as a second-or subsequent-line treatment. All of the patients were diagnosed at a single institution. The diagnostic criteria were based on histopathological analysis (the World Health Organization, 2004). Patients' clinical characteristics and details regarding their therapies were retrieved from archived medical records. This study was approved by the institutional subcommittee and ethics committee. Institutional Review Board (IRB) approval and informed patient consent were obtained.

Responses and Toxicity

The best response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST v1.1). The objective tumour responses recorded were complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate (DCR) was defined as the sum of objective responses and stabilization rates (CR + PR + SD). Treatmentrelated adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Statistical Analysis

Both progressionfree survival (PFS) and overall survival (OS) rates were assessed in all patients. The KaplanMeier method was used for survival estimations. SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Patient Characteristics

The patients' characteristics are presented in Table 1. Thirty patients had a median age of 63 years (range: 56–80 years), comprising 22 men and 8 women. Disease onset often presented as dysphagia, abdominal pain or discomfort, weight loss, poor appetite, nausea and vomiting. None of the patients experienced perforation prior to treatment. All patients had a performance status (PS) of 0-1. Routine laboratory tests, such as blood and biochemical tests, were typically within normal limits. The diagnosis was made on the basis of an endoscopic biopsy. Macroscopically, the most commonly involved site was the middle oesophagus, followed by the upper oesophagus and lower oesophagus.

All patients received camrelizumab in combination with apatinib as second-line(18) or further-line(12) treatment. Camrelizumab was administered once at a dose of 200 mg. One treatment cycle consisted of 14 days. Apatinib was administered at a dose of 425 mg once daily. One treatment cycle consisted of 28 days.

Table 1. Baseline characteristics

Characteristics	No (%)
Gender	
Male	22(73)
Women	8 (27)
Median age (range)	60 (56-80)
ECOG performance status	
0	9 (430)
1	21 (70)
Lymphocyte count	
Normal	18 (60)
Lymphocyte-rich	7(23)
Lymphocyte-poor	5 (17)
Staging	
III	7 (23)
IV	23 (77)
Histologic grade	
G1	0 (0)
G2	14 (47)
G3	9 (30)
Gx	7 (23)
Previous therapies	
Radiotherapy	14 (47)
Chemotherapy	30 (100)
Lines of salvage therapy	
Second-line	18 (60)
Further-line	12 (40)

Short-Term Efficacy

Before the end follow-up, the best response was available for all patients. The ORR and DCR were 27% (8/30) and 63% (11/30), respectively. CR was achieved in 0% (0/30) of patients, PR in 27% (8/30), SD in 36% (11/30), and 37% (11/30) patients experienced PD.

Safety

The patients' treatment-related AEs are summarized in Table 2. All patients experienced at least one treatment-related AE. The most common treatment-related AEs were fatigue, cutaneous reactive capillary endothelial proliferation (RCEP) and hypertension, followed by pyrexia. For most patients, the adverse events were tolerable and were relieved by appropriate supportive care without dose adjustment. No patients experienced serious treatment-related AEs resulting in treatment interruption. Two patients experienced apatinib-related grade 3 hypertension leading to permanent dose reduction, but none showed grade 4 toxicities. No treatment-related deaths occurred.

Table 2. Summary of treatment related AEs

AE	n (%)	
	Grade 1-2	Grade 3-4
Fatigue	13 (43)	-
RCEP	10 (33)	-
Hypertension	9 (30)	2 (7)
Pyrexia	6 (20)	-
Haematologic toxicity		
Leucopenia	7 (23)	1(0.3)
Anaemia	9 (30)	-
Hand-foot syndrome	4 (13)	-
Abnormal liver function	5 (17)	-
Cough	2 (7)	-

Survival Analysis

The median followup time was 187 days (range 1–317). The median PFS rate was 3.7 (95% CI: 2.48–3.88) months, and the median OS rate was not reached. The survival curves are shown in Figure 1.

Discussion

Refractory or metastatic ESCC is a lethal disease with poor prognosis. For patients for whom first-line chemotherapy or radiotherapy fails, few treatment options are available, and more effective therapies are urgently needed. Irinotecan-based chemotherapy, commonly administered alone or in addition to fluoropyrimidine, is the main treatment available, which has a disappointing ORR of 12.8% and a poor average OS time of 5 months.[7] Additionally, a high incidence of AEs is reported with these therapies, and many patients cannot withstand the severe adverse events. Effective therapies associated with fewer adverse events are urgently needed.

In recent years, the treatment of tumours has entered a new era with the development of immunotherapy. The efficacy of ICIs is related to PD-L1 expression in tumour cells. Preclinical studies have demonstrated that ICIs activate T lymphocytes. Activated T lymphocytes help to inhibit cancer growth and improve cancer patient survival rates. Clinical studies have shown that PD-L1 expression is an important biomarker to identify patients who will most likely benefit from ICIs, and the higher the expression of PD-L1 is, the better the efficacy of ICIs will be in cancer patients.[8] Interestingly, a large proportion of ESCC patients have a high positive rate of PD-L1 expression.[9,10] Therefore, oesophageal squamous cell carcinoma patients may be more likely to benefit from ICIs. Several trials have been initiated to evaluate the efficacy and safety of ICIs in ESCC patients. Based on the results of several preclinical and clinical studies,[11,12] two ICIs (pembrolizumab and nivolumab) have already been approved by the FDA for the second-line treatment of ESCC. According to the results of other studies, pembrolizumab and nivolumab have the same or better efficacy as chemotherapy with better safety and tolerability. KEYNOTE-590 was a phase 3 trial to investigate pembrolizumab in combination with chemotherapy versus chemotherapy alone as the first-line treatment for oesophageal cancers. In the ITT population, pembrolizumab in combination with chemotherapy led to significantly longer OS and PFS times than chemotherapy alone, regardless of PD-L1 CPS status (CPS ≥1 or CPS ≥10). The ORR was also improved in this subpopulation. In addition, grade 3–5 TRAE rates were similar between the two groups. Camerizumab, an ICI developed in China, has been tested mainly for the treatment of classical Hodgkin lymphoma,[13] and data on the use of this drug for refractory or metastatic ESCC are lacking. We chose the dose level (200mg Q2W) mainly based

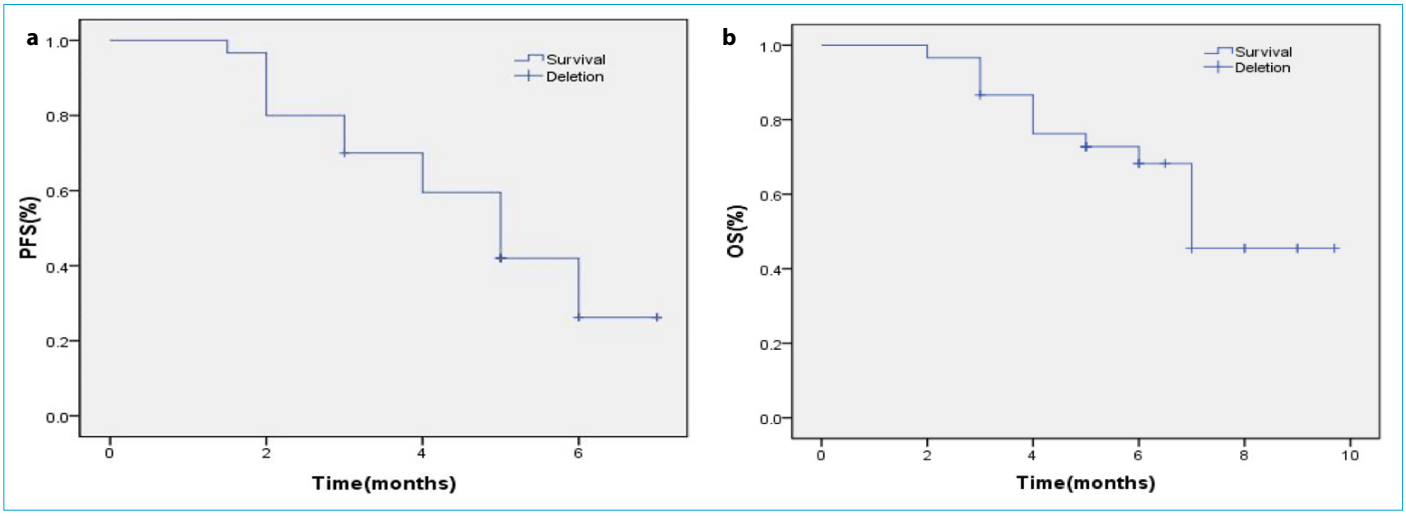

Figure 1. Survival curves for the entire population of 30patients. Progression-free survival (PFS; **a**) and overall survival (OS; **b**).

on the PK and toxicity properties of camrelizumab given in previous phase 1 study.[6] The study consisted of an initial dose-escalation and subsequent expansion phase. During dose-escalation, patients were treated with camrelizumab at a fixed dose of 60mg every 2 weeks, with escalation to 200mg and 400 mg. Receptor occupancy persisted for≥28 days with the 200 and 400 mg doses, but declined to 50% at the end of day 28 with the 60 mg dose. Receptor occupancy remained high at steady state in patients receiving repeated infusions (once every 2 weeks) of the 200 and 400 mg doses, with receptor occupancy at the trough concentration after the first infusion of treatment cycle 5 of 67, 77 and 76% for the 60, 200 and 400 mg doses, respectively. In our study, camrelizumab-based therapy achieved an ORR of 41% and a DCR of 83% in 12 patients with refractory or metastatic ESCC when used as a second- or further-line treatment. The median PFS time was 3.7 months. Both response and survival data were comparable to the results[14] reported for salvage chemotherapies.

Although both pembrolizumab and nivolumab achieved durable responses in previous studies, the ORRs of monotherapy were less than 20%, highlighting that monotherapy with ICIs is insufficient for most patients. In contrast to a previous study, eight patients received camrelizumab in combination with apatinib in our study. Many previous studies[15,16] have demonstrated that synergistic effects can be achieved between antiangiogenic agents and immunotherapy. The theoretical basis for this is that antiangiogenic agents can induce prolonged vessel normalization, thereby reducing tumour hypoxia and acidosis and improving the anticancer activity of infiltrating immune cells. Apatinib, a small molecular antiangiogenic agent, has been proven to improve the survival of patients with metastatic gastric cancer. The results of several clinical studies[17] have indicated that apatinib has potential as a therapeutic agent for patients with ESCC. Thus, we conducted this retrospective analysis to investigate the efficacy of camrelizumab in combination with apatinib for the treatment of refractory or metastatic ESCC as salvage treatment. In our study, the ORR for 30 patients who received camrelizumab in combination with apatinib was 27%, and the DCR was 63%. Notably, these rates are higher than those achieved by monotherapy with pembrolizumab or nivolumab.

In addition to the increased efficacy of camrelizumab in combination with apatinib, the safety of this combination was consistent with previous reports for component monotherapies. In our study, adverse events were tolerable for most patients, and no patient experienced serious treatment-related AEs resulting in treatment interruption, highlighting that the tolerability of camrelizumab was likely unaffected by apatinib.

In conclusion, we have shown that camrelizumab in combination with apatinib is a promising therapy for patients with refractory or metastatic ESCC. Furthermore, this combination was safe and well tolerated. However, as the number of patients in our study is extremely limited, largerscale, prospective, randomized clinical studies are needed in the future.

Disclosures

Ethics Committee Approval: This study was approved by Xuzhou Central Hospital Ethics Committee (Date: 9/7/2020, Number: XZEC-2020-097).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – X.L., Y.Y.; Design – X.L., Y.Y.; Supervision – X.L., Y.F.; Materials – L.H., Q.M.; Data collection &/or processing – Y.F., Q.M.; Analysis and/or interpretation – Q.M.; Literature search – Q.M., Y.F.; Writing – Y.Y., X.L; Critical review – X.L., Y.Y.

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