European Review for Medical and Pharmacological Sciences 2024; 28: 659-667

Clinical efficacy and adverse reactions analysis of PD-1/PD-L1 inhibitors in advanced esophageal squamous cell carcinoma

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Abstract. – OBJECTIVE: The aim of this study was to investigate the clinical efficacy and associated adverse reactions of Programmed Death Receptor-1 (PD-1)/PD-L1 inhibitors in the management of patients with advanced esophageal squamous cell carcinoma (ESCC).

PATIENTS AND METHODS: In this retrospective study, 54 patients with advanced ESCC treated with PD-1/PD-L1 inhibitors in our hospital from January 2021 to January 2023 were identified as the research subjects. Using propensity score matching at a 1:1 ratio, patients only receiving chemotherapy were recruited as controls. The clinical effectiveness of PD-1/PD-L1 was evaluated by comparing the objective response rate (ORR) and disease control rate (DCR). Progression-free survival (PFS) and overall survival (OS) were analyzed for treatment outcome assessments. Adverse events (AEs) between the two groups were recorded and compared.

RESULTS: Patients treated with PD-1/PD-L1 inhibitors had a higher rate of ORR (33.33%) and disease control (85.19%), compared to controls with an objective response rate of 20.37% and a disease control rate of 59.26%. The two groups showed similar ORR results, while the incorporation of PD-1/PD-L1 inhibitors resulted in significantly increased DCR when compared to the controls. The median OS was 22 months (95% CI: 1,629 months) for the control group and 31 months (95% CI: 28NA) for the study group, suggesting OS benefits offered by PD-1/PD-L1 inhibitor treatment (HR=0.479, 95% CI: 0.284, 0.809). The median PFS was 15 months (95% CI: 1,223 months) for the control group and 23 months (95% CI: 1,926) for the study group, indicating more PFS benefits provided by PD-1/PD-L1 inhibitors (HR=0.662, 95% CI: 0.436, 1.005). Adverse events and their severity were recorded during patient follow-up, and no grade 5 adverse events were reported in either group. The incidence of grade 3 or higher adverse events between the two groups was similar, while PD-1/PD-L1 inhibitors appeared to significantly reduce the incidence of gastrointestinal reactions in patients.

CONCLUSIONS: PD-1/PD-L1 inhibitors integrated with chemotherapy provide significant benefits in the management of patients with advanced ESCC without increasing adverse events.

Key Words:
Esophageal Squamous Cell Carcinoma, Programmed Death Receptor-1, Chemotherapy, Survival Curves.

Introduction

Esophageal cancer (EC) is the seventh most common malignancy and the sixth leading cause of cancer death globally. As a primary histological subtype of EC, esophageal squamous cell carcinoma (ESCC) accounts for 90% of all EC cases in China[1]. Esophageal cancer is mostly managed through surgical resection, radiotherapy, chemotherapy, and immune therapy, and esophagectomy stands as the treatment of choice. However, the prognosis of patients remains poor despite surgical resection with curative intent, with a 5-year survival following esophagectomy of only 20-40%[2]. Patients with locally advanced EC are exposed to a high risk of recurrence and metastasis after mere surgical interventions, which only achieve an R0 resection of 50%[3].

Immune escape of tumors is a critical process during tumor survival and progression. Programmed death receptor-1 (PD-1) is a crucial immune inhibitory molecule, which can be specifically bound by PD-1 inhibitors, resulting in a relieved immune suppression regulation on T lymphocytes, to restore their abilities of tumor cell killing[4]. PD-L1 inhibitors can preempt the binding of the PD-L1 on tumor cells to the PD-1 on lymphocytes by proactively binding to the PD-L1 on tumor cells, thus restoring the immune function of the body and eliminating

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tumor cells[5]. Immune therapy based on PD-1/PD-L1 has become the new standard treatment for second-line therapy in the advanced ESCC[6]. Neoadjuvant therapy with PD-1/PD-L1 has shown[7,8] excellent efficacy and good tolerability in various cancers such as lung cancer, melanoma, and colorectal cancer. It has been reported[9] that PD-1 inhibitors provide a new viable alternative for the second-line treatment in advanced ESCC, and the integration of PD-1 inhibitors with chemotherapy also demonstrates[10] significant benefits in first-line treatment.

This study investigates the clinical efficacy and associated adverse reactions of PD-1/PD-L1 inhibitors in treating patients with advanced ESCC.

Patients and Methods

Participants

This study is a retrospective analysis of the treatment methods, and clinical outcomes of unresectable advanced ESCC patients admitted to our hospital from January 2020 to January 2023. A total of 54 patients treated with a combination of synchronous chemotherapy and PD-1/PD-L1 inhibitor therapy were included in the study group. Patients treated with chemotherapy matched 1:1 using propensity score matching, served as the controls.

Inclusion and Exclusion Criteria

Inclusion criteria

(1) Age between 18 and 80 years, regardless of gender.
(2) Pathologically confirmed ESCC.
(3) At least one measurable lesion based on the Response Evaluation Criteria In Solid Tumors (RECIST v1.1).
(4) Primary tumor is unresectable.
(5) No prior treatment with radiotherapy, chemotherapy, immunotherapy, targeted therapy, or anti-angiogenic therapy.
(6) ECOG performance status (PS) score of 0-1.
(7) Expected survival time of more than 6 months.

Exclusion criteria

(1) Unable to undergo immunotherapy or chemotherapy due to poor overall condition.
(2) Immunodeficiency or autoimmune diseases.
(3) Abnormal liver or kidney function or organic damage to other organs.
(4) Concomitant other malignancies.
(5) Incomplete clinical data or lack of follow-up information.

Treatment Protocol

The control group received chemotherapy. For patients in relatively good condition, platinum-based chemotherapy combined with paclitaxel was administered every 21 days as one treatment cycle. For patients with poor health status, single-agent chemotherapy with paclitaxel, platinum, or tegafur-gimeracil-oteracil was adopted, with a specific regimen of paclitaxel + platinum/paclitaxel/tegafur-gimeracil-oteracil every 21 days. The study group, on the basis of chemotherapy, integrated PD-1/PD-L1 inhibitor immunotherapy, including camrelizumab and sintilimab, with a treatment cycle of every 21 days. The dosage was determined based on the patient's body surface area. Specifically, it included paclitaxel + platinum-based agents/paclitaxel/tegafur-gimeracil-oteracil + camrelizumab/sintilimab, administered every 21 days.

In case of chemotherapy-related adverse reactions such as pain, vomiting, or severe mucositis, corticosteroid therapy was administered accordingly based on the clinical judgment of the physician. The specific medication plan was 5 mg of dexamethasone administered intravenously on the first day of chemotherapy.

Clinical Efficacy

All patients underwent CT scans to assess treatment efficacy every two treatment cycles. The RECIST[11] 1.1 was used to evaluate disease progression through radiographic assessment. The RECIST 1.1 criteria involve comparing the sum of the longest diameters of the target lesions (SLD) in radiographic images taken after treatment to assess the presence or absence of non-target lesions and to determine treatment efficacy. The efficacy was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR indicates the disappearance of all target lesions, and any pathological lymph nodes must have a short axis of less than 10 mm. PR indicates that the SLD is reduced by less than 30% compared to the baseline. PD indicates an increase in the SLD by at least 30%, with an absolute increase of at least 5 mm or the appearance of any new tumor lesions. SD indicates that neither PR

nor PD criteria were met. For patients evaluated with CR, PR, and SD, the original treatment regimen was continued, while for patients evaluated with PD, alternative regimens were considered for continuation of treatment. The best ORR and DCR of patients were recorded[12].

Outcome Measures

All patients were followed up until September 30, 2023, and the follow-up time, progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) were recorded. PFS refers to the time from the start of treatment to disease progression. OS refers to the time from the start of treatment to death for any reason. ORR refers to the proportion of patients who achieved CR and PR among all patients. DCR refers to the proportion of patients who achieved CR, PR, and SD among all patients. AEs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, a common grading system for adverse reactions in cancer treatment and served as an important indicator for evaluating the safety of neoadjuvant treatment. AEs include bone marrow suppression, leukopenia, neutropenia, anemia, fatigue, thrombocytopenia, gastrointestinal reactions, skin toxicity, and liver and kidney function damage. When patients experienced severe treatment-related adverse events, the current treatment regimen was discontinued, and complications were properly treated.

Statistical Analysis

Statistical analysis was conducted using SPSS 24.0 software (IBM Corp., Armonk, NY, USA), and figures were generated using the R language. Continuous variables were expressed as mean ± standard deviation (±s), and the independent samples *t*-test was used for inter-group comparison. Categorical variables were expressed as percentages (%), and the Chi-square test was used to compare differences between groups. Kaplan-Meier curves were used to evaluate patient PFS and OS. All tests were two-tailed, and a significance level of $\alpha=0.05$ was used as the threshold for determining statistical significance.

Results

Baseline Patient Profiles

In the control group, the average age was 62.36±12.05 years, BMI was 22.96±5.33, with 14 male and 40 female patients. ECOG scores were 1 in 33 cases and 2 in 21 cases. Endoscopic classifications identified 32 cases of protruding type, 14 cases of ulcerative type, and 8 cases of stenotic type. TNM staging consisted of 11 cases of stage III, 20 cases of stage IVa, and 23 cases of stage IVb. There were 10 cases in the cervical segment and 44 cases in the thoracic segment. In the study group, the average age was 64.19±14.23 years, BMI was 24.05±5.83, with 16 male and 38 female patients. ECOG scores were 1 in 39 cases and 2 in 15 cases. Endoscopic classifications included 38 cases of protruding type, 11 cases of ulcerative type, and 5 cases of stenotic type. TNM staging consisted of 9 cases of stage III, 17 cases of stage IVa, and 28 cases of stage IVb. There were 17 cases in the cervical segment and 37 cases in the thoracic segment. The two groups were well-balanced in terms of basic characteristics, indicating comparability ($p>0.05$), as presented in Table I.

Clinical Efficacy

All patients underwent CT examination to assess treatment outcomes after every two cycles of treatment, and the best clinical efficacy was recorded. In the control group, there were 11 cases of PR, 21 cases of SD, and 22 cases of PD. The ORR was 20.37% (11/54), and the DCR was 59.26% (32/54). In the study group, there were 18 cases of PR, 28 cases of SD, and 8 cases of PD. The ORR was 33.33% (18/54), and the DCR was 85.19% (46/54). The two groups showed similar ORR results, while the incorporation of PD-1/PD-L1 inhibitors resulted in significantly increased DCR when compared to the controls ($p<0.05$), as shown in Table II.

Survival Analysis

The shortest follow-up time was 2 months, the longest was 36 months, and the median follow-up time was 22 months. Kaplan-Meier analysis showed that the median OS was 22 months (95% CI: 1629 months) for the control group and 31 months (95% CI: 28NA) for the study group, suggesting a strong association between PD-1/PD-L1 inhibitor treatment and improved OS (HR=0.479, 95% CI: 0.284, 0.809), as depicted in Figure 1. Kaplan-Meier analysis demonstrated that the median PFS was 15 months (95% CI: 1,223 months) for the control group and 23 months (95% CI: 1,926) for the study group, indicating that PD-1/PD-L1 inhibitor treatment provided more PFS benefits (HR=0.662, 95% CI: 0.436, 1.005), as illustrated in Figure 2.

Table I. Baseline patient profiles.

Factors	Control group	Study group	t/χ^2	p
N	54	54		
Age ($\bar{x} \pm s$, years old)	62.36 ± 12.05	64.19 ± 14.23	0.721	0.472
BMI ($\bar{x} \pm s$, kg/m^2)	22.96 ± 5.33	24.05 ± 5.83	1.075	0.313
Gender (Male/Female)			0.185	0.667
Male	14	16		
Female	40	38		
ECOG			1.500	0.221
0	33	39		
1	21	15		
Endoscopic classification			1.567	0.457
Protruding type	32	38		
Ulcerative type	14	11		
Stenotic type	8	5		
TNM stage			0.933	0.627
III	11	9		
IVa	20	17		
IVb	23	28		
Location			2.420	0.120
Cervical segment	10	17		
Thoracic segment	44	37		

Body mass index (BMI), Electrocorticography (ECOG).

Adverse Event Analysis

The most common adverse reactions were gastrointestinal symptoms, including nausea and constipation. The two groups reported 11 cases of grade 3 or above adverse events (p>0.05), which significantly improved after symptomatic treatment. No grade 5 adverse events were reported in either group. The use of PD-1/PD-L1 inhibitors appeared to significantly reduce the incidence of gastrointestinal reactions in patients (Table III).

Discussion

With population aging and changes in lifestyle, the incidence of ESCC has presented a rising trend[13]. Esophageal squamous cell carcinoma features a poor global prognosis, with a 5-year survival recorded of 19% in the United States, 12.4% in Europe, and 20.9% in China[14]. Currently, the standard treatment for advanced ESCC is chemotherapy that involves platinum-based agents, 5-fluorouracil, and taxanes. However, the treatment outcomes following chemotherapy remain poor, with an ORR of 35-62%, a PFS of 2.5-6.2 months, and an OS of 7.6-11.1 months[15].

Table II. Clinical efficacy (n).

	Control group	Study group	χ^2	p
N	54	54		
CR	0	0		
PR	11	18		
SD	21	28		
PD	22	8		
ORR	11	18	2.310	0.129
DCR	32	46	9.046	0.003

Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR), disease control rate (DCR).

Elevated levels of multiple immune checkpoints are significantly correlated with the epithelial-mesenchymal transition status of ESCC patients and are one of the markers of tumor metastasis[16]. PD-1/PD-L1 are critical immune checkpoint molecules that cause immune escape of tumor cells. Leone et al[17] reported that immune checkpoint inhibitors have consistent benefits in reducing the risk of death in ESCC patients, depending on the PD-1 combined positive score status. Blocking PD-1/PD-L1 can re-activate the cytotoxic T cells to eliminate tumor cells and is of clinical significance in immunotherapy[18]. For advanced ESCC patients with objective remission or stable disease ≥6 months, B cells in the tumor microenvironment were significantly associated with longer PFS and OS[19]. Existing research has identified a negative correlation between over-expression of PD-L1 and ESCC survival. Akutsu et al[20] showed that the concentration of PD-L1 in peripheral blood of patients with

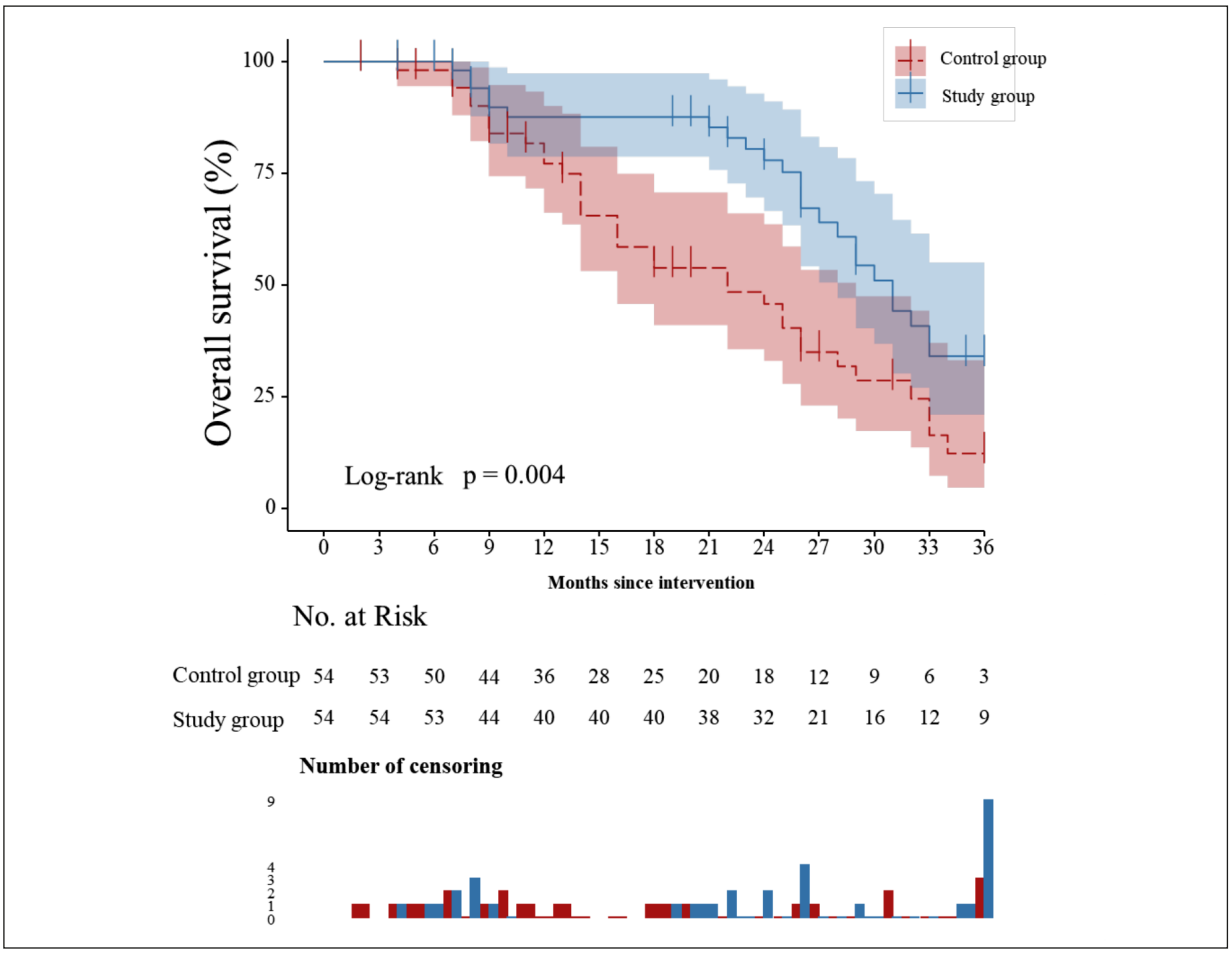

Figure 1. Kaplan-Meier curve for overall survival.

advanced ESCC was higher, indicating that the increase in PD-L1 concentration indicated the progression and survival rate of ESCC patients. The expression of PD-L1 in ESCC and adjacent immune cells is under 50% and is strongly associated with tumor stage, lymphatic metastasis, and distant metastasis[21].

In the present study, PD-1/PD-L1 inhibitors, camrelizumab and sintilimab, achieved an ORR of 33.33% and a DCR of 85.19%, as compared to the highest ORR of 20.37% and DCR of 59.26% in the controls. The two groups showed similar ORR results, while the incorporation of PD-1/PD-L1 inhibitors resulted in significantly increased DCR when compared to the controls. A meta-analysis[22] including 5 RCT with a total of 2,962 advanced ESCC patients showed that compared with the chemotherapy group, the ORR, and DCR of advanced ESCC patients in the immunochemotherapy based on PD-1/PD-L1 group were increased by 2.05 times and 1.54 times, respectively. Another meta-analysis[23], including 16 RCTs with a total of 9,304 advanced ESCC patients, showed that compared with chemotherapy, patients treated with PD-1/PD-L1 inhibitors had significantly improved OS, but there was no significant improvement in PFS. Moreover, a meta-analysis[24] of 17 phases 2/3 randomized controlled trials, with 12,312 patients, suggested that for males, Asians, and those with esophageal primary, PD-L1 positive tumors, and squamous cell carcinoma, immune checkpoint inhibitors improve OS without significantly increasing the side effects. Taken together, there was a strong association between PD-1/PD-L1 inhibitor treatment and more benefits in OS and PFS.

Camrelizumab is a novel PD-1/PD-L1 inhibitor developed in China and has been employed in the management of various malignancies, such as refractory classical Hodgkin lymphoma and gastric or gastroesophageal junction adenocarcinoma[25,26]. The research found that camreli-

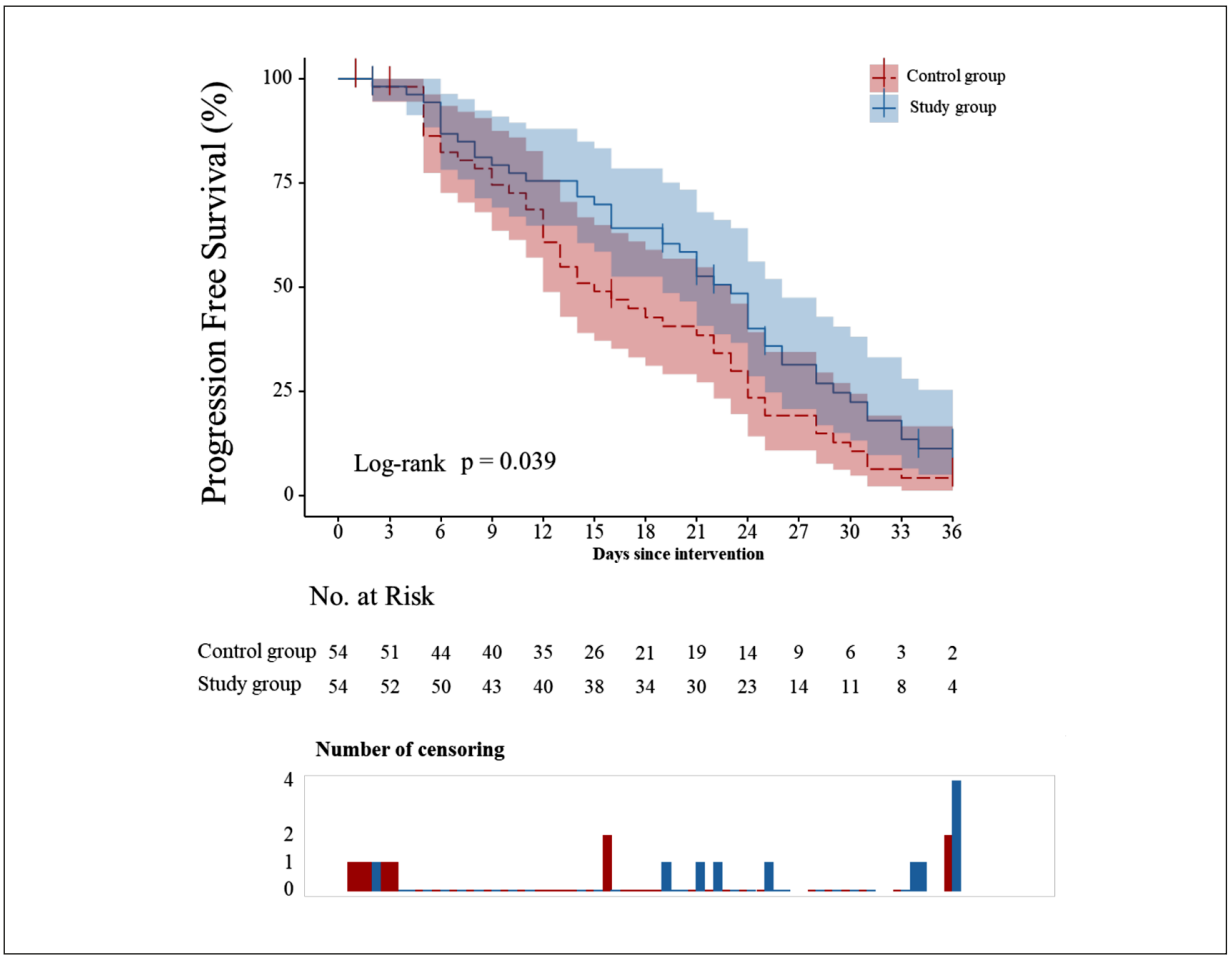

Figure 2. Kaplan-Meier curve for progression-free survival.

Table III. Comparison of adverse events.

	Control group (n = 54)	Study group (n = 54)
GI (all/Gr 3,4)		
Diarrhea	17/1	7/2
Constipation	26/3	11/5
Nausea	23/3	15/1
Vomiting	13/0	7/0
Skin rash (all/Gr 3,4)	22/2	11/1
Mucositis (all/Gr 3,4)	24/1	23/0
Pneumonitis (all/Gr 3,4)	10/0	9/1
Hepatitis (all/Gr 3,4)	4/0	3/0
AKI (all/Gr 3,4)	5/0	6/1
Endocrine (all/Gr 3,4)	0/0	2/0
Leukopenia (all/Gr 3,4)	16/1	12/0
Anemia (all/Gr 3,4)	22/2	18/0
Thrombocytopenia (all/Gr 3,4)	13/1	5/0
Fatigue (all/Gr 3,4)	14/0	13/0

Acute kidney injury (AKI).

zumab, used for neoadjuvant chemotherapy, has achieved an ORR of 90.5%, a DCR of 100%, an R0 resection of 100%, and a pathological complete response (pCR) of 25% in 20 patients with locally advanced ESCC after esophagectomy. Sintilimab is a PD-L1 inhibitor. In the ORIENT-15 study[27], sintilimab integrated with chemotherapy provided significant overall survival benefits for patients irrespective of the expression levels of PD-L1, with a mOS of 16.7 months *vs.* a mOS of 12.5% obtained in the placebo group. KEYNOTE-590[28] provided a basis for the use of PD-1/PD-L1 inhibitors in advanced esophageal cancers. Its mid-term analysis results revealed that pembrolizumab, in addition to chemotherapy, resulted in a prolongation in OS of more than 5 months for ESCC patients with PD-L1 combined positive score (CPS)≥10, and the overall survival for the overall ESCC population was extended by nearly 3 months.

Gastrointestinal reactions were the most common adverse events, followed by leukopenia, anemia, and thrombocytopenia. It has been reported[29] that in advanced ESCC Asian patients from RATIONALE-302 (NCT03430843), compared with the single-agent chemotherapies (paclitaxel, docetaxel, or irinotecan) group, the symptoms of gastroesophageal reflux in the tislelizumab group were improved at week 12 after treatment. Furthermore, compared with patients treated with investigator-selected chemotherapy, the fatigue symptoms and physical function of patients with advanced or metastatic ESCC treated with tislelizumab were maintained after 12 weeks of treatment[30]. Similarly, in this study, compared with patients receiving chemotherapy alone, patients given PD-1/PD-L1 inhibitors with chemotherapy had significantly reduced gastrointestinal adverse reactions such as nausea, vomiting, and diarrhea. This study corroborated that patients with advanced ESCC have a good tolerance to immunotherapy regimens.

Although the results of this study are encouraging, the following limitations should be taken into account. First, the sample is small, with only 54 ESCC patients. However, despite the small number of patients, our findings are consistent with previous reports on the effectiveness of PD-1/PD-L inhibitors in the treatment of ESCC. Secondly, this study only provided PD-1/PD-L inhibitors and the effectiveness of ESCC treatment, but there was no investigation of the mechanism.

Conclusions

PD-1/PD-L1 inhibitors integrated with chemotherapy provide significant benefits in the management of patients with advanced ESCC without increasing adverse events. In future studies, we should conduct a multicenter study including more samples to explore the effectiveness of PD-1/PD-L inhibitors on ESCC patients and their exact mechanism.

Conflict of Interest

The authors declare that they have no conflict of interests.

Acknowledgements

We thank the members of The First People's Hospital of Shang Qiu for helpful discussions. We apologize to the scientists whose work could not be cited due to space limitations.

Authors' Contribution

Yuan Liu conceived the structure of the manuscript. Lanlan Wang did the experiments and made the figures. Yingxia Xie reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding

The study was funded by Henan Medical Science and Technology Research Program Project: Clinical Safety Study of PD-l/PD-L1 Inhibitors Based on the Real World CHPS System, LHGJ20210992.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This study was conducted in accordance with the ethical provisions of the Helsinki Declaration. The study was approved by the Ethics Committee of Shangqiu First People's Hospital. The acceptance number of the Ethics Committee is HS2021007.

Informed Consent

All patients signed the informed consent form.

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