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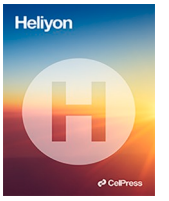

Clinical efficacy of Camrelizumab combined with first-line chemotherapy in extensive-stage small-cell lung cancer

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ABSTRACT

Objective: Exploring the clinical efficacy of camrelizumab in combination with first-line chemotherapy in patients with extensive-stage small-cell lung cancer (ES-SCLC).
Methods: The clinical data of 35 patients with ES-SCLC who received camrelizumab combined with EC or EP regimen in First Teaching Hospital of Tianjin University of Traditional Chinese Medicine from January 2020 to January 2023 were retrospectively analyzed. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were OS, ORR and DCR. SPSS 25.0 software was used for statistical analysis, Kaplan-Meier curve and Log-Rank test analysis, and survival curve was drawn.
Results: The median PFS of 35 patients with SCLC was 7.4 months (95 % CI 6.75–9.81 months), . and the median OS was 12.5 months (95% CI,11.71-16.90 months). The ORR and DCR were 65.7 % and 74.3 %, respectively. Adverse events (AEs) were mainly concentrated in grade 1–2, and the probability of occurrence of grade 3 or above was low. Reactive Cutaneous Capillary Endothelial Proliferation (RCCEP) was the most common, followed by nausea &vomit and anemia. The other common AEs included abnormal thyroid function, decreased neutrophil count, skin rash and leucopenia.
Conclusion: Camrelizumab in combination with first-line chemotherapy regimens prolonged OS and PFS in SCLC patients and showed efficacy and safety in real-world data.

1. Introduction

Lung cancer is of high morbidity and mortality. SCLC, as a high-grade lung neuroendocrine tumor, is characterized by high malignancy, invasiveness, and poor prognosis, and its incidence accounts for about 15 % of lung cancers [1,2]. Prior to the advent of immunotherapy, etoposide plus platinum-based drugs had been the standard first-line treatment option with limited efficacy [3]. In recent years, the continuous exploration of immune checkpoint inhibitors has cracked the dilemma of SCLC treatment [4–6]. The

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Abbreviations

extensive-stage small-cell lung cancer (ES-SCLC)
overall survival (OS)
progression-free survival (PFS)
immune checkpoint inhibitors (ICIs)
Eastern Cooperative Oncology Group (ECOG)
Reactive Cutaneous Capillary Endothelial Proliferation (RCCEP)
Complete Response (CR)
Stable Disease (SD)
Partial Response (PR)
Progressive Disease (PD)
Disease Control Rate (DCR)
Objective Response Rate (ORR)
Etoposide and Carboplatin/Cisplatin (EP/EC)
Adverse events (AEs)

PD-L1 inhibitors combined with chemotherapy regimens represented by the IMpower133 and CASPIAN studies have successfully opened up a new era of SCLC immunotherapy [7–9]. Serplulimab combined with chemotherapy group achieved a median OS of 15.9 months [10], which became the first PD-1 inhibitor with highly breakthrough efficacy in the first-line treatment of ES-SCLC that has brought a new dawn for SCLC patients.

Although PD-L1 monoclonal antibodies have shown some promise in SCLC patients, OS prolongation is only about 2 months. PD-1 monoclonal antibodies, represented by Pembrolizumab and Nivolumab, have not yet provided a definite survival effect in SCLC patients [11,12]. Most of the current clinical studies have focused on PD-L1 inhibitors combined with first-line chemotherapy regimens, while relatively few studies related to PD-1 treatment for SCLC still need to be supplemented by actual data on efficacy and safety.

Camrelizumab is a novel humanized immunoglobulin G4 monoclonal antibody, which can promote and stimulate T cells, effectively kill tumor cells, and prolong the survival cycle of NSCLC patients in combination with chemotherapy [13,14]. However, there is a lack of research evidence on its applicability to the treatment of SCLC patients. Some existing literature reports the promise and potential shown by camrelizumab in small cells. PASSION study [15] on camrelizumab for ES-SCLC demonstrated that patients with sensitive and drug-resistant relapses could benefit from its use, with an OS of up to 8.4 months. In another non-randomized trial [16], apatinib plus camrelizumab showed positive results in the maintenance phase of untreated ES-SCLC. A retrospective comparative cohort study showed longer PFS was observed in PD-1 inhibitor-treated patients, and better PFS may have been achieved with camrelizumab compared with other ICIs [17], and these clinical studies provide us with new directions for SCLC treatment. Therefore, in order to further clarify the efficacy and safety of camrelizumab, we decided to conduct this retrospective study to investigate whether camrelizumab, as a PD-1 inhibitor, could provide a benefit for the survival of SCLC patients.

2. Materials and methods

2.1. Research subjects

In this study, a total of 239 SCLC patients were screened from January 2020 to January 2023. According to the inclusion and exclusion criteria, a total of 35 patients were included, and the others were excluded.

Inclusion criteria : (1) Patients aged 18–75 years (2) Patients with SCLC confirmed by histology or cytopathology (3) At least one measurable objective lesion, assessed using RECIST version 1.1 criteria (4) Patients with clinical stage -IV (5) ECOG score of 0–1 (6) Good function of the hematopoietic system and important organs such as heart, lung, liver and kidney (7) The expected survival time of the patient was more than 3 months. All patients were treated with 4 cycles of camrelizumab in combination with EC/EP prior to enrollment, and were given the usual baseline symptomatic treatment with no other immunosuppressive agents.

Exclusion criteria: (1) incomplete pathological diagnostic data (2) history of other malignancies (3) history of psychiatric disease (4) history of non-infectious pneumonia requiring glucocorticoids (5) autoimmune diseases, infectious diseases (6) allergy to drugs (7) severe liver and kidney dysfunction (8) female patients in pregnancy and lactation. (9) SCLC patients on non-first-line platinum-based agents or other PD-1/-PD-L1 inhibitors.

2.2. Study regimen

Each patient received 4 cycles of camrelizumab combined with EC/EP. EC protocol: etoposide 100 mg/m^2 IV infusion, day 1–3, carboplatin 0.3 g/m^2 IV infusion, day 1 or EP protocol: etoposide 100 mg/m^2 IV infusion, day 1–3, cisplatin 25 mg/m^2 IV infusion, day 1–3. A 21-day regimen with 4 cycles until disease progression, death, or intolerable toxicity. Camrelizumab for Injection (200 mg/pc), 200 mg ivgtt q3w.

2.3. Study endpoints and assessment

The primary endpoint was PFS, and secondary endpoints included OS, objective response rate (ORR), and disease control rate (DCR) (all of which were assessed by an independent radiology review board and investigators using RECIST version 1.1). Safety was assessed using Common Terminology Criteria 4.0 for Adverse Events.

2.4. Statistical methods

Excel was used to establish the clinical data database of patients, and SPSS 25.0 software was used for statistical analysis. Kaplan-Meier curve and Log-Rank test were used for analysis. The data were recorded by Excel, the count data were expressed as ratio or constituent ratio, the measurement data were described by mean ± standard deviation or quartile, and the count data were described by frequency. $P < 0.05$ indicated statistical significance. Survival curves were plotted using GraphPad Prism 9.0 software.

3. Results

3.1. Patient baseline characteristics

A total of 35 ES-SCLC patients were included in the study, and all patients received the treatment regimen of camrelizumab combined with etoposide and carboplatin/cisplatin (EP/EC). The baseline characteristics of the patients are shown in Table 1. The median age was 63 years (range 40–85 years). Smoking and former smoking accounted for 74.3 % of patients The physical status score of the Eastern Cooperative group was 0 (37.1 %) or 1 (62.9 %). The *t*-test and chi-square test were used to compare the general data such as gender, average age, smoking status, and ECOG score status between the two groups, and there was no significant difference ($P > 0.05$).

3.2. Study results

3.2.1. PFS and OS

The primary endpoint was PFS, and the secondary end points were OS, ORR, and DCR. mPFS time of all patients was 7.4 months (95 % CI, 6.75–9.81 months) (Fig. 1) and the mOS was 12.5 months (95% CI,11.71-16.90 months) (Fig. 2).

3.3. Efficacy evaluation

In terms of efficacy evaluation, of the 35 patients, no patient achieved CR, 23 (65.7 %) patients were in PR, 3 (8.6 %) patients had SD, and 9 (25.7 %) patients experienced PD, the ORR was 65.7 % and the DCR was 74.3 %.

3.4. Adverse reactions

From the statistical results, it was found that the adverse reactions of camrelizumab combined with etoposide and carboplatin/

Table 1
Baseline patient characteristics.

Characteristic	N = 35
Median age(range)-year	63 (40–85)
Age (years), n (%)	
≥65	19 (54.3/%)
< 65	16 (45.7 %)
Sex, n (%)	
Male	20 (57.1 %)
Female	15 (42.9 %)
Smoking status, n (%)	
former smoking	12 (34.3 %)
Never smoking	9 (25.7 %)
smoking	14 (40.0 %)
ECOG status score, n (%)	
0	13 (37.1 %)
1	22 (62.9 %)
Distant metastatic site(s), n=(%)	
Liver	4 (11.4 %)
Bone	9 (25.7 %)
Brain	17 (48.6 %)
lymph node	26 (74.3 %)
Lung	8 (22.6 %)
pancreas	4 (11.4 %)

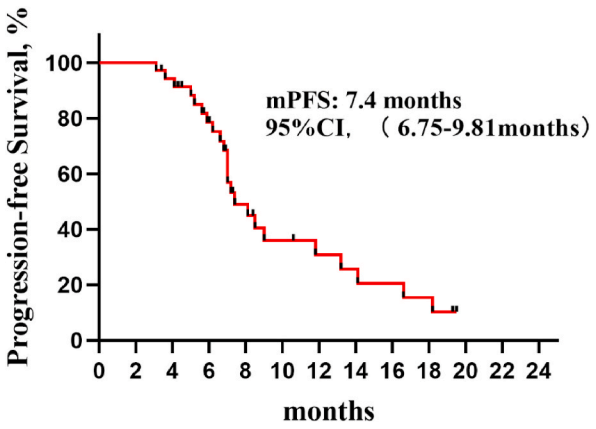

Fig. 1. PFS survival curve of patients with ES-SCLC treated with Camrelizumab combined with first-line chemotherapy
mPFS of all patients was 7.4 months (95 % CI, 6.75–9.81 months) (Fig. 1); progression-free survival (PFS); CI, confidence interval.

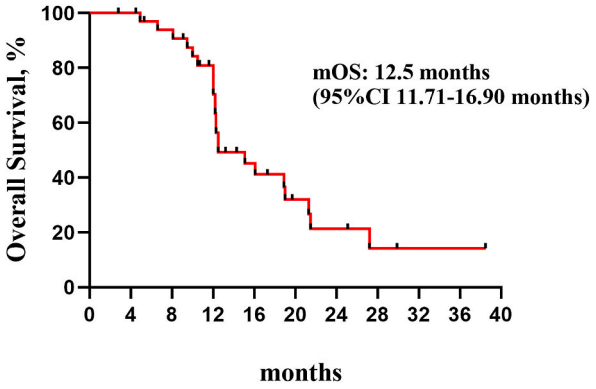

Fig. 2. OS survival curve of patients with ES-SCLC treated with Camrelizumab combined with first-line chemotherapy mOS of all patients was 12.5 months (95% CI,11.71-16.90 months) (Fig.2). overall survival (OS); CI, confidence interval

cisplatin in the treatment of SCLC were mainly grade 1–2, and the probability of adverse events above grade 3 was low (Table 2). The common symptoms were RCCEP (37.1 %), anemia (25.7 %), abnormal thyroid function (17.1 %), nausea and vomiting (28.6), leucopenia (11.4 %). Other adverse events (AEs) included Neutropenia and lymphopenia. Adverse reactions are safe and controllable.

4. Discussion

The treatment modalities of SCLC are limited, and immunotherapy has gradually emerged and achieved certain effects in the

Table 2
Treatment-related adverse events.

	Patients who experienced treatment-related adverse events, No. (%) n = 35	
	Grade 1-2	Grade≥3
RCCEP	13 (37.1)	2 (5.7)
Anemia	9 (25.7)	2 (5.7)
Decreased platelet count	4 (11.4)	1 (2.8)
Nausea &Vomit	10 (28.6)	1 (2.8)
Abnormal thyroid function	6 (17.1)	0
Decreased white blood cell count	5 (14.3)	2 (5.7)
Leucopenia	4 (11.4)	3 (8.6)
Decreased neutrophil count	6 (17.1)	1 (2.8)
Skin rash	5 (14.3)	0
Lymphopenia	2 (5.7)	1 (2.8)
Neutropenia	2 (5.7)	3 (8.6)

treatment of a variety of tumors [18,19]. Immune checkpoint inhibitors have effectively improved the survival prognosis of patients by activating the activity of body immune cells and improving the tumor microenvironment. Currently, immune-combination chemotherapy has become a standard first-line treatment option for ES-SCLC, and PD-L1 inhibitors represented by atezolizumab and durvalizumab have demonstrated promising activity [20,21]. The ASTRUM-005 study, on the other hand, made serplulimab the first PD-1 monoclonal antibody to obtain positive OS results for first-line treatment of ES-SCLC, with a median overall survival (OS) exceeding 15.8 months [10], opening a new chapter in PD-1 inhibitor immunotherapy for SCLC. Data from the RATIONALE-312 study were presented at the 2023 WCLC Congress, the median OS of first-line treatment of ES-SCLC with Tislelizumab + EP amounted to 15.5 months (vs. 13.5 months for chemotherapy, with a HR 0.75, $P = 0.0035$) and a median PFS of 4.8 months (vs. chemotherapy 4.3 months, HR 0.63, $P < 0.0001$), which provided a significant survival benefit for patients and is expected to be another option for first-line immunotherapy for ES-SCLC.

Although many studies have demonstrated the efficacy of immunosuppressive agents in SCLC, not all of them have achieved satisfactory results. As far as PD-1 inhibitors are concerned, the OS of KEYNOTE-604 did not reach statistical significance, which may be related to the more severe disease of the enrolled population. Not coincidentally, the difference in OS of patients in the ECOG-ACRIN EA5161 study also failed to achieve positive results, but PFS as the primary study endpoint also proved the feasibility and efficacy of PD-1 in SCLC. Therefore, there is an urgent need to explore new combination therapy options to benefit more SCLC patients.

SCLC is highly aggressive and has a poor prognosis, the high mutational load of SCLC tumors can generate a large number of potential tumor-specific antigens. As one of the humanized *anti*-PD-1 monoclonal antibodies, camrelizumab has a high affinity for binding to programmed cell death protein-1 on the surface of T cells, releasing antigens and activating the body's anti-tumor immune response, thus achieving anti-tumor effects [22,23]. Compared with other PD-1 inhibitors, the half inhibitory concentration of camrelizumab is 3.0 nmol/L, which is lower than that of other PD-1 inhibitors. Camrelizumab has a higher occupancy rate of PD-1 receptor in vivo, and the anti-tumor effect is more obvious [24]. Studies have shown that camrelizumab has been used to treat patients who have failed platinum-based chemotherapy and have high expression of programmed cell death protein-1 ligand with significant tumor suppression [25,26].

This study sought to further evaluate the efficacy of camrelizumab and showed that the addition of the PD-1 inhibitor camrelizumab mPFS to the first-line chemotherapy regimen resulted in an effective improvement PFS. Results showed that 35 patients had mPFS and mOS of 7.4 months and and 12.5 months, suggesting that patients with extensive-stage SCLC may benefit from camrelizumab. Although camrelizumab has not yet been included in SCLC indications, it has shown promising activity overall compared to some of the current studies.

Several studies have now demonstrated the activity and potential of camrelizumab in SCLC. In a retrospective study of camrelizumab as a novel third-line or post-third-line treatment for small-cell lung cancer, patients had an OS of 10 months, a PFS of 4 months, and an ORR of 41.7 %, a result that demonstrates the potential benefit of camrelizumab in patients with SCLC with an overall manageable safety profile. Of note, the median PFS in the third-line or post-third-line subgroup of patients was 7 months (12 % CI: 12.88–10.0 months) [27]. PASSION study [15] reported a synergistic anticancer effect of camrelizumab in combination with apatinib in ES-SCLC, with an ORR of 34 % (95 % CI: 20.9–49.3), with a median PFS and median OS of 3.6 and 8.4 months, respectively, and an overall manageable safety profile. In a non-randomized clinical trial, IP/IC plus camrelizumab had comparable objective remission rates compared to EP/EC plus a PD-L1 inhibitor, while PFS performed even better at 10.25 months, a result of the PFS in our study but whose OS was not yet mature [16]. RCCEP and were also the most common adverse reactions, which was consistent with those in our study, but IP/IC in combination with camrelizumab had a higher incidence of neutropenia than EP/EC in combination with a PD-L1 inhibitor, which may have been induced due to 6 cycles of chemotherapy in this cohort. In this retrospective study, the related adverse reactions caused by camrelizumab combined with chemotherapy were mainly grade 1–2, and the most important manifestation was reactive capillary endothelial hyperplasia, which is worthy of attention. Other adverse events such as anemia, abnormal thyroid function, nausea and vomiting were common adverse events, and the safety was generally controllable.

Based on the observation and analysis of clinical case data, we explored the role of camrelizumab in ES- SCLC in an attempt to find a new means of treatment for patients with ES-SCLC. However, as a retrospective nominal study, there are certain limitations, including the small sample size of the included observation population, the lack of a longer follow-up period, and the results are likely to be overestimated. The fact that camrelizumab has no currently approved indications in SCLC, which are important factors affecting the results of this study. Therefore, follow-up studies with larger sample sizes, longer follow-up times, and higher levels of quality, as well as various clinical trials, are needed to provide more evidence of the safety and effectiveness of camrelizumab in the treatment of ES-SCLC.

5. Conclusion

In this real-world data, the combination of camrelizumab and EC/EP chemotherapy regimen showed promising activity in SCLC patients, which also provided new support for the exploration of PD-1 inhibitor combined with chemotherapy. Larger samples and longer follow-up are still needed to confirm the efficacy of this regimen in the future.

Submission declaration

We confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal.

Consent for publication

Not applicable.

Clinical trial registration

Not applicable.

Code availability

Not applicable.

Permission to reproduce material from other sources

Not applicable.

Patient consent statement

Not applicable.

Ethical statement

Review and/or approval by an ethics committee was not needed for this study because the study was a retrospective study.

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Data availability statement

The data and supportive information are available within the article. Data associated with the study has not been deposited into a publicly available repository, it will be made available on request from the corresponding author.

CRediT authorship contribution statement

Dou Zhang: Writing - review & editing, Writing - original draft, Conceptualization. **Fanming Kong:** Writing - review & editing, Writing - original draft, Conceptualization. **Fangfang Gao:** Writing - review & editing, Supervision. **Longhui Li:** Data curation. **Yangyueying Liang:** Data curation. **Minghui Yu:** Data curation. **Lu Zhao:** Data curation. **Na Wang:** Data curation. **Yingjie Jia:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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