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Real-world data on immunotherapy combined with chemotherapy in elderly patients with extensive-stage small cell lung cancer

Ke Zhao[1,2], Shuangqing Lu[2], Jiling Niu[2], Hui Zhu[2], Yaru Tian[1,2*] and Jinming Yu[1,2*]

Abstract

Background Immunotherapy combined with chemotherapy has shown good results in the treatment of extensive-stage small cell lung cancer (ES-SCLC), but there are fewer clinical studies on elderly ES-SCLC patients. This study was aimed to evaluate the efficacy and safety of immunotherapy in combination with chemotherapy in elderly patients with ES-SCLC.

Methods Elderly patients with ES-SCLC who were 70 years of age or older and were diagnosed at Shandong Cancer Hospital from May 20, 2020, to February 24, 2023, were included in this study. Overall survival (OS) and progression-free survival (PFS) were calculated via the Kaplan–Meier method and compared via the log-rank test. In addition, the Cox regression model was used to analyze prognostic factors.

Results A total of 135 patients were included in this study; 82 patients were in the immunotherapy combined with chemotherapy (IO + ChT) group, and 53 patients were in the chemotherapy alone (ChT-alone) group. The median overall survival (mOS) for the entire patient cohort was 12.89 months, whereas the median progression-free survival (mPFS) was 7.21 months. There was a significant difference in mPFS (8.26 months vs. 6.59 months, $P=.02$) and no statistically significant difference in mOS (14.20 months vs. 11.44 months, $P=.14$) between the IO + ChT and ChT-alone groups. The incidence of grade ≥ 3 adverse events in the IO + ChT group was not significantly different from that in the ChT-alone group. Moreover, we did not observe grade ≥ 3 immune-related adverse reactions. The univariate multifactorial analysis demonstrated that the absence of liver metastases at baseline and in female patients were favorable prognostic factors for OS, and the addition of immunotherapy was a favorable prognostic factor that improved overall survival in elderly patients with ES-SCLC. Subgroup analyses indicated that adding immunotherapy provided a survival benefit for patients with baseline brain metastases and baseline liver-free metastases.

Conclusion Immunotherapy combined with chemotherapy can provide a survival benefit, and the addition of immunotherapy does not result in significant toxicity in elderly patients. The results of this study have important clinical implications for the future treatment of elderly patients with ES-SCLC.

Keywords Immunotherapy, Elderly patient, Extensive-stage small cell lung cancer (ES-SCLC), Toxicity

*Correspondence:
Yaru Tian
sdtianyr@163.com
Jinming Yu
sdyujinming@163.com

[1]Shandong University Cancer Center, Cheeloo College of Medicine, Shandong University, Jinan 250117, Shandong, China
[2]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences, Jinan 250117, China

Introduction

Lung cancer is one of the most prevalent cancers and a significant contributor to cancer-related mortality (accounting for 18.4% of all cancer-related deaths). Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers and is characterized by rapid growth, extensive metastasis, and a relatively short survival period [1, 2]. At the time of diagnosis, approximately 70% of patients have extensive-stage SCLC (ES-SCLC). The prognosis of ES-SCLC is very poor, with a median overall survival (OS) of 7.5–10.9 months and a 5-year OS rate of only 2.8% [3]. The advent of immune checkpoint inhibitors ushered in a qualitative increase in the treatment of ES-SCLC [4]. Consequently, since then, immunotherapy in combination with chemotherapy has become the standard first-line treatment option for ES-SCLC [5]. This is evidenced by the results of several phase III trials, including Impower133, CASPIAN, ASTRUM-005, and CAPSTONE-1. In IMpower133, compared with chemotherapy alone, atezolizumab plus chemotherapy prolonged overall survival (OS) by two months (12.3 months vs. 10.3 months, HR, 0.70; 95%CI, 0.54 to 0.91; $P=.0069$). Progression-free survival (PFS) was extended by 0.9 months (5.2 vs. 4.3 months, HR, 0.77; 95% CI, 0.62 to 0.96; $P=.02$) [6]. However, Impower133 had a relatively small percentage of elderly patients, with only 10% of participants over 75 years of age [4]. In another study, CASPIAN, OS continued to improve in the durvalumab plus chemotherapy group, with OS prolonged by 2.7 months compared with that in the chemotherapy alone group (13.0 months vs. 10.3 months, HR 0.73; 95% CI 0.59–0.91; $P=.0047$) [7]. In summary, these clinical trials revealed that the addition of immune checkpoint inhibitors (ICIs) to chemotherapy in ES-SCLC patients (regardless of patient age) improved their survival. However, these clinical trials included a small proportion of elderly patients and involved high or variable treatment doses [4].

In the context of a significantly aging global population, the incidence of cancer has been gradually increasing in the elderly population [8]. With an increase in the proportion of elderly patients among all SCLC cases over the past four decades. Approximately half of all patients with SCLC patients are older than 70 [9]. Elderly patients have relatively poorer physical function, decreased liver and kidney function, impaired immune function, decreased bone marrow regeneration, more difficult treatment courses, and more comorbidities. Therefore, elderly patients are often excluded from clinical trials [10]. According to the 2001–2010 U.S. National Cancer Institute study, only approximately 25% of patients aged 65–74 years and less than 10% of patients aged 75 years or older were enrolled in clinical trials. Consequently, more research is needed to select more appropriate treatments for these patients and to provide more significant survival benefits [11]. Therefore, we conducted this retrospective study to evaluate the safety and efficacy of immunotherapy combined with chemotherapy for the treatment of elderly patients with ES-SCLC. In addition, we analyzed the treatment efficacy in elderly ES-SCLC patients with baseline brain metastases and liver metastases.

Patients and methods

Patients

We included and analyzed the records of elderly patients (≥70 years old) with ES-SCLC who received immunotherapy combined with chemotherapy at Shandong Cancer Hospital from May 20, 2020, to February 24, 2023. Elderly patients were defined as those aged ≥70 years. All patients underwent a physical examination, chest and abdominal computed tomography (CT), cranial computed tomography (CT) or magnetic resonance imaging (MRI), bone scanning, and positron emission tomography (PET-CT) before treatment to evaluate the patient's pretreatment TNM stage, 33 of these patients underwent PET-CT to clarify staging. Each patient underwent a rigorous and thorough examination before inclusion in the study. The electronic medical records of the mobile phone patients were also maintained, and they were regularly followed up for disease progression.

There are two methods of staging SCLC, American Joint Committee on Cancer (AJCC) 8th edition cancer staging system or the American Legion staging system. Veterans Administration Lung Study Group (VALG) categorizes SCLC into limited and extensive stages. Patients with distant metastases were defined as ES-SCLC according to TNM staging. In this study TMN staging was used. All patient procedures conformed to the Declaration of Helsinki and the International Guidelines for Quality Management Practices in Drug Clinical Trials.

Treatments

In this study, patients were treated with EP or PD-1 (serplulimab/tislelizumab)/PD-L1 (durvalumab/atezolizumab) inhibitors in combination with EP every 21 days. Serplulimab fixed dose 4.5 mg/kg, tislelizumab fixed dose 200 mg, durvalumab fixed dose 1500 mg and atezolizumab fixed dose 1200 mg, all administered intravenously on day 1 of each cycle until disease progression, death, unacceptable toxicity. Cisplatin (area under the curve of 4–5 min mg/ml, intravenous injection on day 1 of each cycle), and etoposide (80–100 mg/m^2 body surface area, intravenous injection on days 1 through 3 of each cycle). 92 patients received 4–6 cycles of chemotherapy and 43 patients received >6 or <4 cycles of chemotherapy. During the course of treatment, clinicians adjusted the doses of the drug according to the occurrence of adverse events

and tolerance of the patient, and patients who could not tolerate the standard dosage were given a reduction of the doses to 80% or 90%.

After first-line treatment, 112 patients experienced disease progression, including 63 patients in the IO + ChT group and 49 patients in the ChT-alone group. Among the 63 patients in the IO + ChT group, 27 patients received IO as second-line therapy, 6 patients received anlotinib as second-line therapy, 3 patients received chest radiotherapy, and 2 patients received radiotherapy for brain metastases. Among the 49 patients in the ChT-alone group, 10 patients received salvage IO, 7 patients were treated with anlotinib, 15 patients received chest radiotherapy, and 5 patients received radiotherapy to treat brain metastasis.

Assessments of response and toxicity

Patients were followed until the follow-up cutoff date or patient death, with tumor imaging performed at baseline, tumor status evaluated every 2 cycles for 4–6 cycles from the start of initial treatment, and efficacy evaluated every 3 months after the treatment period. This efficacy was evaluated according to the Criteria for the Evaluation of Solid Tumor Efficacy, version 1.1, and categorized as progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR). We also assessed efficacy using version 1.1 of the Immunotherapy-based Solid Tumor Efficacy Evaluation Criteria 1.1 (iRECIST), and there was no difference between the two.

Adverse reactions were recorded and graded throughout the treatment period and 30 days after the end of treatment, and the immune-related adverse reactions in the IO + ChT group were analyzed. Toxic reactions were mainly focused on hematologic toxicity (myelosuppression, anemia, thrombocytopenia), hepatorenal toxicity, cardiotoxicity, and gastrointestinal reactions and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

The primary study endpoints were overall OS and PFS of the patients. OS was defined as the time from the date of pathological diagnosis to the date of death from any cause or the date of last known follow-up. PFS was defined as the time from the date of pathological diagnosis to the date of disease progression in the chest or distant lesions, the date of death from any cause, or the date of last known follow-up. The secondary endpoints included OS, PFS, and adverse events (AEs) in the different subgroups of the baseline transfer. AEs, including any adverse events that occurred during treatment, such as hematologic toxicity, gastrointestinal toxicity, and hepatorenal toxicity, were assessed in all patients.

Statistical analysis

The K-square test was used to assess differences in baseline characteristics and adverse events between the two groups. The Kaplan–Meier method was used to calculate OS and PFS. The log-rank test was employed to compare the disparities in the survival curves between the two groups. Estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for PFS and OS were determined via stratified Cox proportional risk models. Additionally, we performed univariate analyses via Cox proportional risk models to identify possible prognostic predictors. All variables showing significant correlations and trends ($P < .05$) were included in multivariate models to identify associations between OS and various clinical characteristics. To ascertain the correlation between clinical baseline characteristics and OS and PFS, all reported P values were two-sided with a 95% confidence interval (CI). Statistical significance was defined as occurring at a P value of < 0.05. SPSS statistical software version 27.0 (IBM Corporation) and Prism software version 8.02 (GraphPad) were used for these statistical analyses.

Results

Patient characteristics

From May 20, 2020, to February 24, 2023, approximately 847 SCLC patients were diagnosed at Shandong Cancer Hospital, 235 of whom were aged 70 years and above. Only a few elderly patients received first-line chemotherapy or chemotherapy combined with immunotherapy because of their general physical condition and poor drug tolerance. Therefore, a total of 147 elderly patients (≥ 70 years old) with extensive-stage SCLC who were first diagnosed and first treated were enrolled in this study, and 12 patients (8.16%) were lost to follow-up because they refused to be informed of their status during follow-up. This resulted in a follow-up rate of 91.8%. Ultimately, 135 fully eligible patients were enrolled in this study. The screening flowchart is presented in Fig. 1. After follow-up through June 14, 2024, the median follow-up time for all patients was 23.54 months (range 18.30–28.78 months). The median age of the entire patient cohort was 73 years, with a range of 70 to 86 years. Among the 135 patients, 116 (85.9%) were male, and 19 (14.1%) were female. The patients were categorized into two groups on the basis of the first-line treatment modality. The ChT-alone group consisted of 53 patients (39.3%), whereas the IO + ChT group consisted of 82 patients (60.7%). The patient characteristics are shown in Table 1, which categorizes patient characteristics according to first-line treatment modality. The distributions of all variables except treatment modality did not differ significantly between the two groups. Forty-three (31.85%) patients (IO + ChT group, 30 patients; ChT-alone group, 13 patients) were initially diagnosed with liver metastases, and 38 (28.15%)

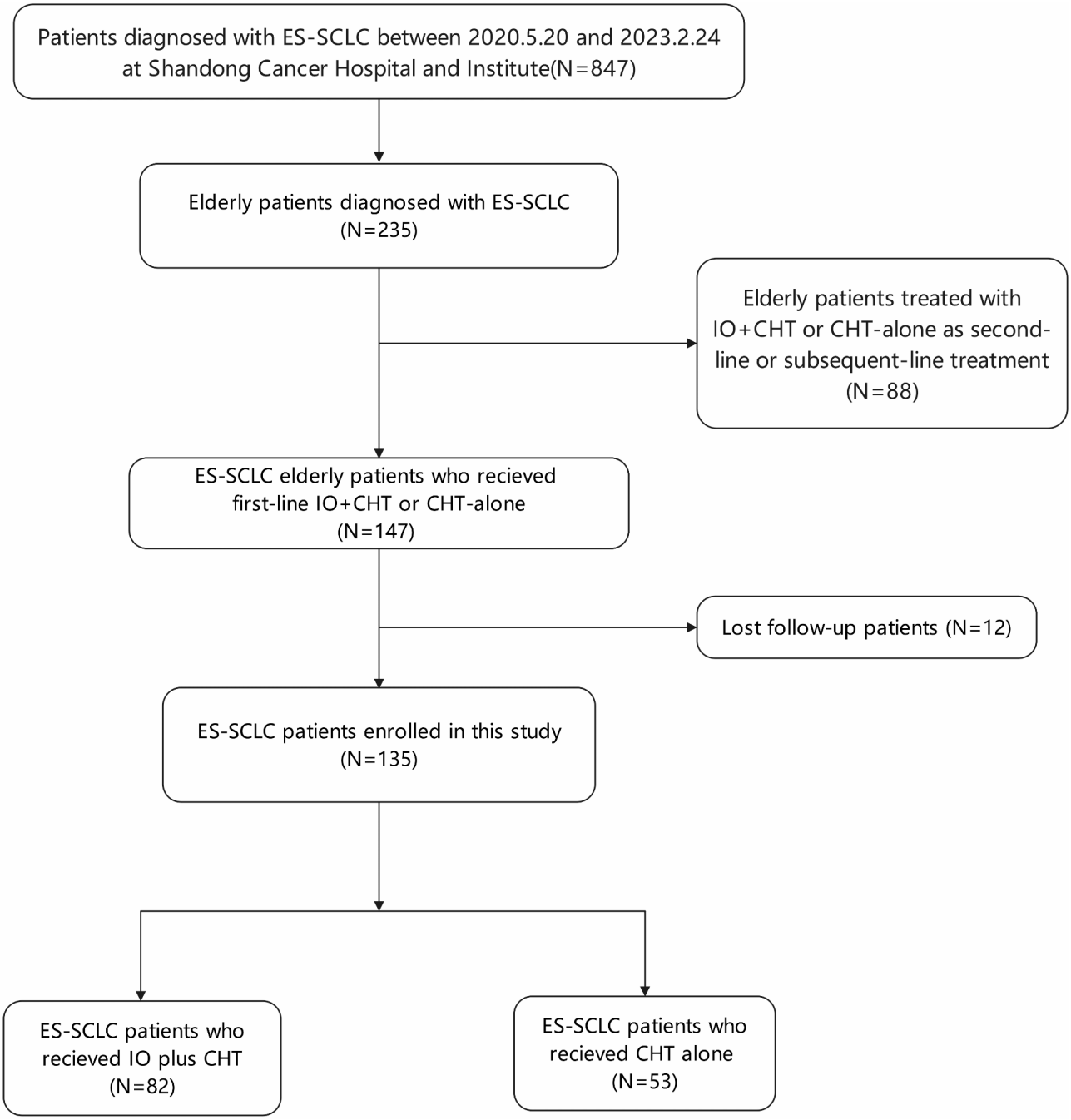

Fig. 1 Flowchart of the screening procedure. ChT indicates chemotherapy; IO, immunotherapy; ES-SCLC, extensive-stage small-cell lung cancer

patients (IO + ChT group, 22 patients; ChT-alone group, 16 patients) were diagnosed with brain metastases.

Treatment response

In the entire cohort, the objective response rate (ORR) was 60.0%, and the disease control rate (DCR) was 84.4%. The treatment response of the patient group is shown in Table 2. A total of 1, 54, and 20 patients in the IO + ChT group achieved CR, PR, and SD, respectively, whereas 7 patients developed PD. In total, 4, 22, and 13 patients in the ChT-alone group achieved CR, PR, and SD, respectively, while 14 patients developed PD. The ORRs were 67.1% and 49.1% (P=.048), and the DCRs were 91.5% and 73.6% (P=.007). There was a statistically significant difference in the ORR and DCR.

Table 1 Baseline patient characteristics

Characteristics	IO + ChT (*n* = 82)	ChT-alone (*n* = 53)	*P*
Age(years)			
Median	73	74	
Range	70–82	70–86	
Sex			
Male	70(85.4)	46(86.8)	0.8159
Female	12(14.6)	7(13.2)	
KPS score			
≥ 80	73(89.0)	47(88.7)	0.9503
<80	9(11.0)	6(11.3)	
Smoking status			
Never	30(36.6)	16(30.2)	0.4438
Former or Current	52(63.4)	37(69.8)	
Hypertensive			
No	54(65.9)	34(64.2)	0.8393
Yes	28(34.1)	19(35.8)	
Diabetes			
No	71(86.6)	45(84.9)	0.7840
Yes	11(13.4)	8(15.1)	
CHD			
No	67(81.7)	47(88.7)	0.2751
Yes	15(18.3)	6(11.3)	
Cerebral infarction			
No	77(93.9)	46(86.8)	0.1563
Yes	5(6.1)	7(13.2)	
ILD、COPD			
No	52(63.4)	22(41.5)	0.0125
Yes	30(36.6)	31(58.5)	
Liver metastasis			
No	52(63.4)	40(75.5)	0.1420
Yes	30(36.6)	13(24.5)	
Bone metastasis			
No	61(74.4)	32(60.4)	0.0895
Yes	21(25.6)	21(39.6)	
Brain metastasis			
No	60(73.2)	37(69.8)	0.6717
Yes	22(26.8)	16(30.2)	
ChT cycles			
>6	4(4.9)	3(5.7)	0.0015
4–6	65(79.3)	27(50.9)	
<6	13(15.9)	23(43.4)	

Abbreviations: IO, immunotherapy; ChT: chemotherapy; CHD, coronary heart disease; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; KPS, Karnofsky Performance Status

Survival

Among all 135 patients, 23 patients had no progression, and 112 patients experienced disease progression, including 49 patients in the ChT-alone group and 63 patients in the IO + ChT group. The median OS for the entire population was 12.89 months, and the median PFS was 7.21 months (Fig. 2A and B). The median OS was 11.44 months (95% CI, 9.47–13.41) in the ChT-alone group and 14.20 months (95% CI, 11.64–16.76) in the IO + ChT group (Fig. 3A). The median PFS was 6.59 months (95% CI, 5.12 ~ 8.06) in the ChT-alone group and 8.26 months (95% CI, 6.90 ~ 9.63) in the IO + ChT group (Fig. 3B). The Kaplan–Meier (KM) curves revealed a clear trend toward a difference in OS between the two groups, with the IO + ChT group prolonging their OS by 2.76 months compared with the ChT-alone group; however, there was no statistically significant difference in the *P* value (*P* = .14). There was a statistically significant difference in PFS between the two groups (*P* = .02). Of the 63 patients who progressed in the IO + ChT group, 27 of

Table 2 Treatment response

	Total($n=135$)	IO + ChT($n=82$)	ChT-alone($n=53$)	*P*
Response rate, %				
Cnmplete response	5(3.7)	1(1.2)	4(7.5)	
Partial response	76(56.3)	54(65.9)	22(41.5)	
Stable disease	33(24.4)	20(24.4)	13(24.5)	
Progressive diease	21(15.6)	7(8.5)	14(26.4)	
Response rate, %(95%CI)	60.0	67.1	49.1	0.048
Disease control rate, %(95%CI)	84.4	91.5	73.6	0.007

Abbreviations: IO, immunotherapy; ChT, chemotherapy

Comparison between IO + ChTgroup and ChT-alone group

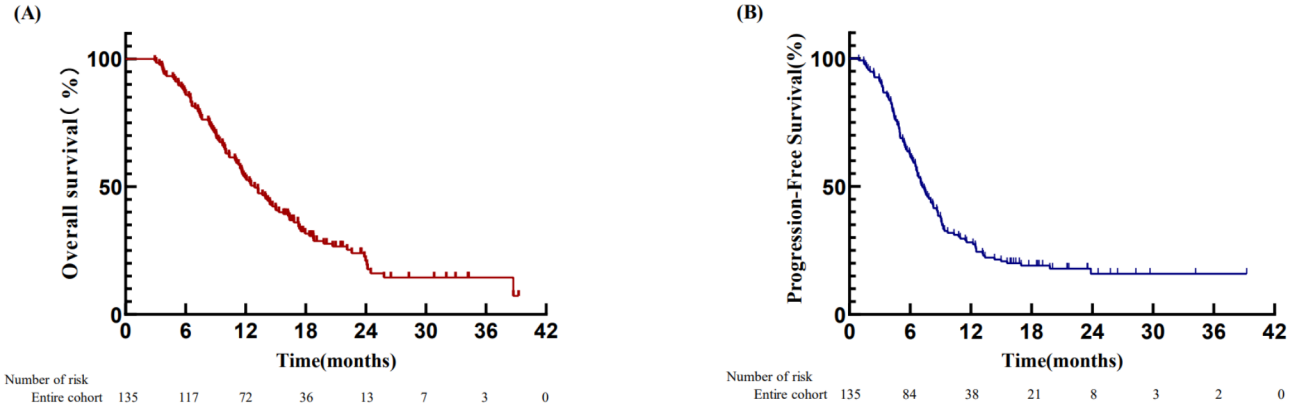

Fig. 2 **(A)** OS in the entire cohort. **(B)** PFS in the entire cohort. OS, overall survival; PFS, progression-free survival

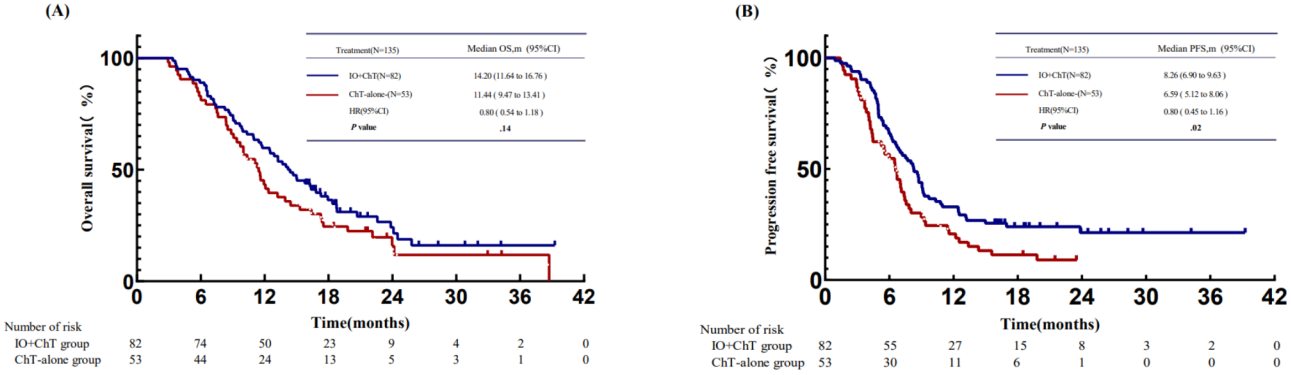

Fig. 3 Kaplan-Meier graphs of OS **(A)** and PFS **(B)** for IO + ChT versus ChT-alone. ChT indicates chemotherapy; IO, immunotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

them continued immunotherapy in the second line, 25 patients did not change their immunotherapy regimen. The mOS in the 2 L-ICIs group was longer than that in the 2 L-non-ICIs group (13.67months vs. 10.33 months, HR,0.57, $P=.027$) (Supplemental Fig. 1).

Survival analysis of subgroups

The population of ES-SCLC patients with different baselines was further analyzed. Among the total 135 patients, 43 had baseline liver metastases, and 92 had no liver metastases. Among the 92 elderly patients without baseline liver metastases, 52 were in the IO + ChT group, and 40 were in the ChT-alone group, with a disease control rate of 98.1% in the IO + ChT group and 75.0% in the ChT-alone group. Compared with those in the ChT-alone group, patients in the IO + ChT group had a significant improvement in survival (median PFS, 9.12 vs. 6.72 months; HR, 0.50; 95% CI, 0.32–0.81; $P<.01$. However, there was no significant difference in median OS (16.36 vs. 11.57 months; HR, 0.69; 95% CI, 0.43–1.11; $P=.13$) between the two groups (Fig. 4A and B). Among 43 patients with baseline liver metastases, OS (9.9 vs. 10.00 months; HR, 0.878; 95% CI, 0.402–1.921; $P=.745$) and PFS (5.425 vs. 6.490 months; HR, 1.096; 95% CI,

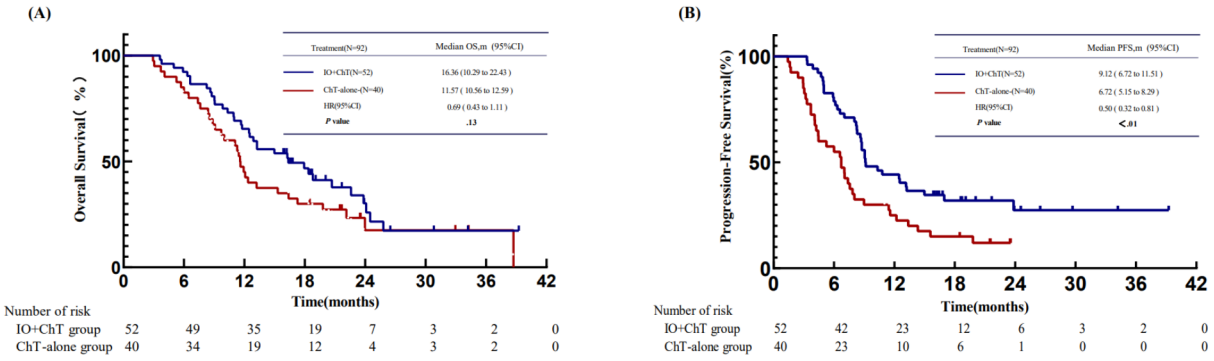

Fig. 4 Kaplan-Meier graphs of **(A)** OS and **(B)** PFS in patients without baseline liver metastases who received IO + ChT versus ChT-alone. ChT indicates chemotherapy; IO, immunotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

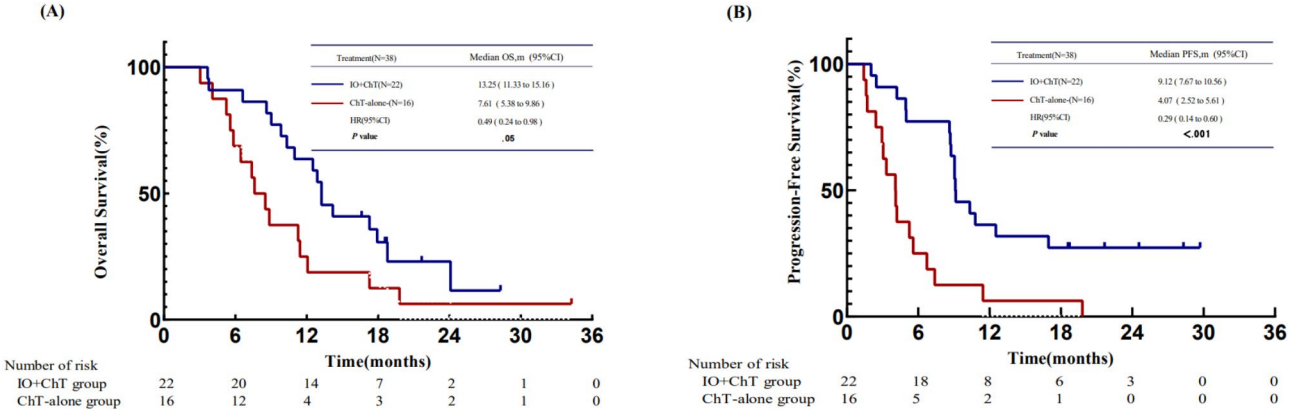

Fig. 5 Kaplan-Meier graphs of **(A)** OS and **(B)** PFS in patients with baseline brain metastases who received IO + ChT versus ChT-alone. ChT indicates chemotherapy; IO, immunotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

0.562–2.138; P=.787) did not significantly differ between the IO + ChT group and the ChT group.

Among the total 135 patients, 38 had baseline brain metastases, and 97 did not. Among the 38 elderly patients with baseline brain metastases, 22 were in the IO + ChT group, and 16 were in the ChT-alone group, with a disease control rate of 90.9% in the IO + ChT group compared with 50.0% in the ChT-alone group. Patients in the IO + ChT group had a significant survival benefit (median PFS, 9.12 vs. 4.07 months; HR, 0.29; 95% CI, 0.14– 0.60; P<.001; median OS 13.25 vs. 7.61 months; HR, 0.49; 95% CI, 0.24–0.98; P=.05.) compared with patients in the ChT-alone group (Fig. 5A, B). The median OS (14.00 vs. 14.43 months; HR, 0.94; 95% CI, 0.55–1.60; P=.82) and median PFS (7.12 vs. 7.11 months; HR, 1.14; 95% CI, 0.72–1.80; P=.58) of patients without brain metastases at baseline did not significantly differ between the IO + ChT group and the ChT-alone group.

The percentage of these 38 patients with brain metastases who received brain radiotherapy was 28.95%, 22 of them received chemotherapy combined with immunotherapy, of which 7 received brain radiation therapy and 15 did not receive brain radiation therapy, with a median OS of 13.25 months vs. 13.25 months for both groups, P=.41 (Supplemental Fig. 2).

Notably, when OS was analyzed, all subgroups except the diabetic patients and the two subgroups with more than 6 chemotherapy cycles benefited from chemotherapy combined with immunization. However, this difference was significant only in the brain metastasis subgroup. (Fig. 6)

Through subgroup survival analyses, we found that the addition of immunotherapy improved survival in patients with no liver metastases at baseline and those with brain metastases at baseline.

Prognostic factors

In addition, we evaluated the effects of different variables on survival via univariate and multivariate Cox models. Univariate analysis revealed that patient sex, Karnofsky Performance Status (KPS) score at diagnosis, smoking status, baseline liver metastasis status, and baseline bone metastasis status were significant prognostic factors for OS. However, only patient sex and baseline liver

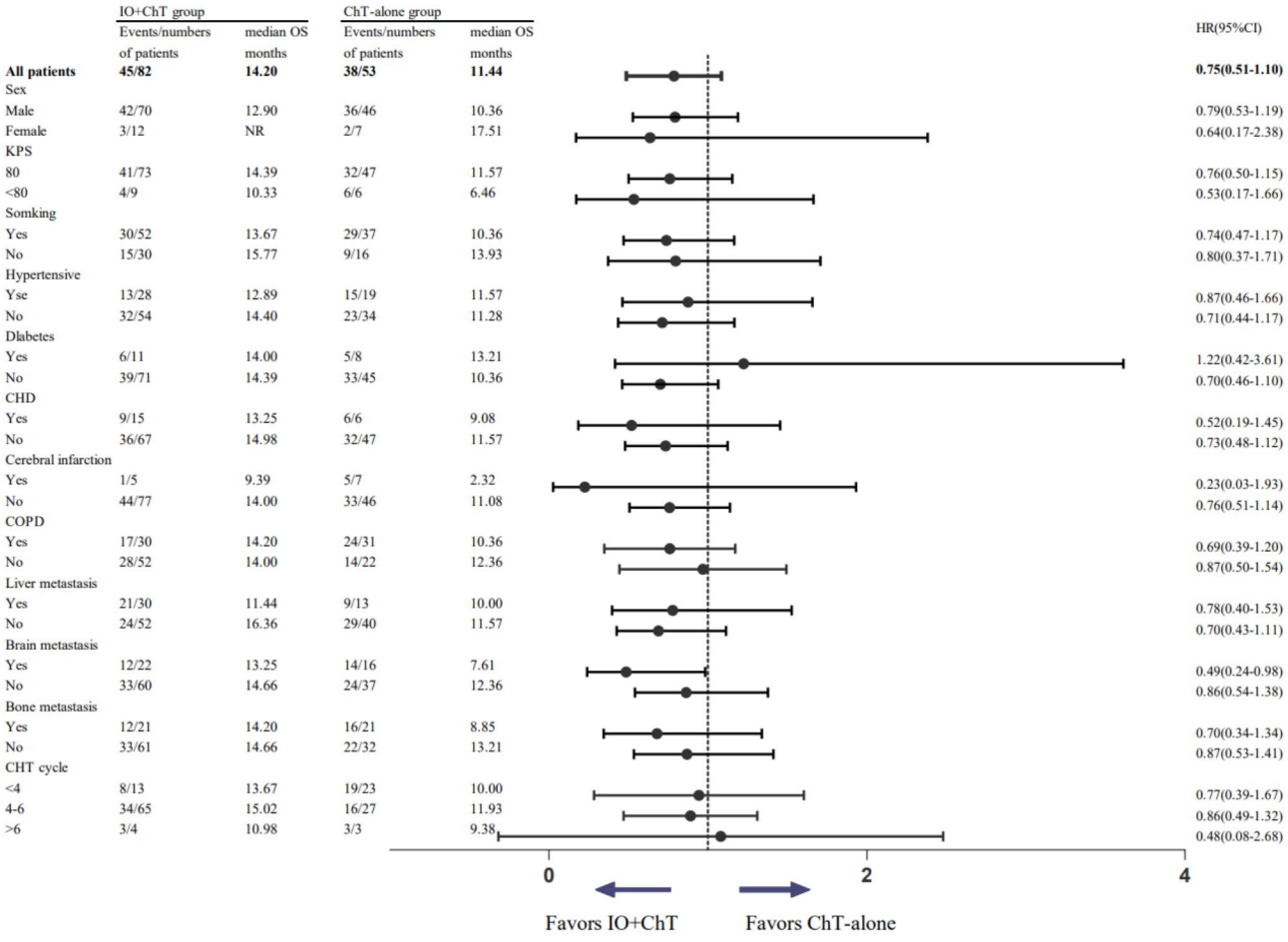

Fig. 6 Forest plot of OS subgroup analysis. ChT indicates chemotherapy; IO, immunotherapy CI, confidence interval; HR hazard ratio

metastasis were included in the multivariate analysis, which demonstrated that the absence of baseline liver metastases (HR, 0.523; 95% CI, 0.326–0.828; P=.007) was a favorable prognostic factor for OS. In contrast, male sex (HR, 2.783; 95% CI, 1.231–66.295; P=.014) was an unfavorable prognostic factor for OS (Table 3).

Toxicities

All 135 patients were evaluated for treatment-emergent adverse events, and the toxicities are shown in Table 4. The most common treatment-emergent adverse event was hematologic toxicity-anemia, with 76 (92.7%) patients in the IO + ChT group experiencing any grade of anemia and 6 (7.3%) patients experiencing grade 3 or higher anemia; 42 (79.2%) patients in the IO + ChT group experienced any grade of anemia, and 2 patients (3.77%) presented with grade 3 or higher anemia. The incidence rates of hemoglobin toxicity and gastrointestinal toxicity in the two groups were significantly different, the incidence rates of anemia, vomiting and diarrhea in IO + ChT group were significantly greater than those in the ChT-alone group (92.68%, 79.25%, P=.022; 53.66%, 75.47%, P=.011; 2.44%, 11.32%, P=.033, respectively). The incidence rates of the remaining toxicity reactions were not significantly different. However, among the adverse reactions of grade ≥ 3 and above, the incidence rates of the two groups were not significantly different, which shows that combination immuno-chemotherapy may increase the incidence of anemia and gastrointestinal reactions but does not increase the risk of severe toxicity.

Notably, in the IO + ChT group, we did not observe grade 3 or higher immune-related adverse reactions. There were 5 cases of grade 1 immune pneumonia and 1 case of grade 2; 23 cases of grade 1 immune cardiac injury and 1 case of grade 2; and 13 cases of grade 1 immune thyroid dysfunction. This finding shows that adding immunotherapy to the elderly patient population is safe.

Discussion

This study investigated the safety and efficacy of IO + ChT in the treatment of elderly patients with ES-SCLC, which is highly valuable for guiding the clinical application of immunotherapy in elderly patients. The results of the

Table 3 Univariate and multivariate analyses of factors influencing overall survival of all patients

	Univariate analysis			Multivariate analysis		
Variable	***P***	**HR**	**95%CI**	***P***	**HR**	**95%CI**
Sex						
Male	.005	2.647	1.334–5.253	.014	2.783	1.231–6.295
Female						
KPS score						
≥80	.007	0.601	0.341–1.057	.478	0.786	0.405–1.527
<80						
Smoking status						
Never	.025	0.611	0.397–0.929	.799	1.068	0.642–1.779
Former or Current						
Hypertensive						
No	.377	0.837	0.564–1.242	.317	0.790	0.479–1.255
Yes						
Diabetes						
No	.529	1.939	0.689–2.066	.361	1.320	0.728–2.393
Yes						
CHD						
No	.080	0.645	0.395–1.054	.197	0.696	0.401–1.207
Yes						
Cerebral infarction						
No	.424	1.344	0.652–2.770	.568	1.252	0.578–2.714
Yes						
ILD、COPD						
No	.210	0.782	0.532–1.148	.930	1.019	0.672–1.544
Yes						
Liver metastasis						
No	.020	0.62	0.415–0.927	.007	0.523	0.326–0.828
Yes						
Bone metastasis						
No	.008	0.572	0.380–0.862	.082	0.682	0.444–1.049
Yes						
Brain metastasis						
No	.131	0.725	0.471–1.101	.129	0.676	0.408–1.120
Yes						
IO						
Yes	.142	0.748	0.508–1.102	.050	0.658	0.433–0.999
No						

Abbreviations: IO, immunotherapy; CHD, coronary heart disease; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary; HR, hazard ratio; CI, Confidence interval; KPS, Karnofsky Performance Status

present study show that combination immuno-chemotherapy shows promising efficacy in primary-treated elderly patients with ES-SCLC, and by analyzing the adverse events, the statistically significant adverse reaction, i.e., anemia, can be avoided to some extent by active prevention. Subgroup analyses showed that patients with baseline non-liver metastases as well as baseline brain metastases could significantly benefit from chemoimmunotherapy. Univariate multifactorial analysis showed that female and baseline non-liver metastases were favorable prognostic factors.

In the overall population enrolled in this study, compared with chemotherapy alone, chemoimmunotherapy prolonged mOS by 2.76 months (HR, 0.80; 95% CI, 0.54–1.18; P=.14) and mPFS by 1.67 months (HR, 0.80; 95% CI, 0.45–1.16; P=.02). Although there was no statistically significant difference in the median OS time, Kaplan–Meier curves revealed a discernible trend between the two groups, indicating that the combination of chemotherapy and immunotherapy resulted in a more favorable survival profile than did chemotherapy alone. The 1-year and 2-year OS rates in the IO + ChT group were 60.24% and 9.64%, respectively, whereas the 1-year and 2-year OS rates in the ChT-alone group were 42.31% and 7.69, respectively, with a significant difference between the two groups. The findings of this study indicate that

Table 4 Adverse event

	IO + ChT (*n* = 82)				ChT (*n* = 53)				Chi-square test	
Adverse event	**Any grade**	**%**	**Grade ≥ 3**	**%**	**Any grade**	**%**	**Grade ≥ 3**	**%**	***P* (Any grade)**	***P* (Grade ≥ 3)**
Treatment related										
Decreased leukocyte count	56	68.20	16	19.51	33	62.26	6	11.32	.470	.678
Decreased neutrophil count	55	67.07	30	36.59	38	71.70	17	32.08	.571	.776
Decreased red blood cell count	76	92.68	6	7.31	42	79.25	2	3.77	.022	.537
Decreased platelet count	36	43.90	9	10.96	22	41.51	4	7.55	.784	.488
Decreased lymphocyte count	65	79.27	18	21.95	38	71.70	12	22.64	.312	.765
Transaminase increase	1	1.22	0	0	4	7.55	0	0	.057	/
Creatinine increase	2	2.44	0	0	1	1.89	0	0	.832	/
Nausea or vomiting	44	53.66	0	0	40	75.47	0	0	.011	/
Diarrhea	2	2.44	0	0	6	11.32	0	0	.033	/
Constipation	31	37.80	0	0	25	47.17	0	0	.281	/

Abbreviations: IO, immunotherapy; ChT, chemotherapy

immunotherapy administered in conjunction with chemotherapy is a safe and manageable first-line treatment for elderly patients with ES-SCLC.

In a retrospective study of atezolizumab plus carboplatin and etoposide in elderly patients with ES-SCLC, 65 patients were included. 36 and 29 patients were aged ≥ 70 and < 70 years, respectively. There was no significant difference in both the mPFS (5.5 months vs. 4.9 months, $p = .18$) and the mOS (15.4 months vs. 15.9 months, $p = .24$) between the elderly group and the non-elderly group [12]. Demonstrates that chemoimmunotherapy can provide a survival benefit for elderly patients.

In light of the lack of statistical significance in OS between the two groups, an analysis of subsequent therapy was conducted. This evaluation revealed that 112 elderly patients in the two groups progressed following first-line treatment, with 63 patients in the IO + ChT group and 49 patients in the ChT-alone group. After disease progression, patients received different second-line therapy, including immunotherapy (27 patients in the IO + ChT group and 10 patients in the ChT-alone group), targeted therapy, radiotherapy, and chemotherapy.

A series of second-line therapy can improve the OS of the ChT-alone group. This would result in no statistically significant difference in outcomes when ultimately comparing the median OS of the IO + ChT group to that of the ChT-alone group. In the ChT-alone group, 49 patients had PD, of which 15 patients received thoracic radiotherapy (TRT). A phase 3 randomized CREST trial enrolled patients with ES-SCLC who responded to initial chemotherapy and randomly assigned them to receive TRT or no TRT. TRT significantly improved 2-year OS (13% vs. 3%, $P = .004$) and mPFS (4 months vs. 3 months, $P = .001$) [13]. A meta-analysis of the Jeremic and CREST trials have also shown that thoracic radiotherapy improved OS (HR 0.81, $P = .014$) and PFS (HR 0.74, $P < .001$) [14].And 17 patients were treated with a combination immunotherapy regimen with anlotinib in the subsequent therapy. In a phase II non-randomized controlled trial, the mPFS of sintilimab combined with anlotinib for second-line and above ES-SCLC reached 6.1 months, and the 6-month and 12-month PFS rates were 54.1% and 31.7%, respectively, with significant clinical efficacy and a manageable safety profile [15]. These subsequent therapies improved survival in the ChT-alone group.

63 patients in the IO + ChT group continued second-line therapy after progression. An analysis of their adverse reactions revealed that the hematologic adverse reactions in this patient population were obvious, with leukopenia in 44 (69.8%), neutropenia in 45 (71.4%), anemia in 57 (90.5%), thrombocytopenia in 27 (42.9%), and lymphopenia in 48 (76.2%) patients. In addition, 36 (51.7%) patients developed significant gastrointestinal reaction, which affected the treatment compliance and continuity of the elderly patients, thus affecting the survival time of the immunochemotherapy group. Meanwhile, the phenomenon of immune senescence, which is observed in elderly patient populations, has been the subject of much speculation. It has been postulated that aging influences the immune system and that intrinsic differences in the immune system of elderly individuals may affect the efficacy and toxicity of cancer immunotherapy. The number of immune cells is known to change with age. Specifically, there is an increase in virtual memory T cells and a loss of primitive T cells. These findings reveal that the efficacy of tumor immunotherapy in elderly cancer patients is suboptimal [16]. Moreover, it can be reasonably deduced that the basic physical condition of older patients is worse than that of younger people, that their condition is more severe, and that their prognosis is relatively poorer. Alternatively, the overall condition of the patients included in this analysis may have been more severe, which is related to the prognosis of SCLC. In the Keynote-604 study, the median OS of the pembrolizumab combined with EP group was not significantly different from that of the placebo group ($P = .164$). Notably, patients with more severe

disease were included in the analysis [17]. Based on these analyses, new clinical decisions are provided for chemoimmunotherapy to be considered for older patients with better physical tolerance.

To further investigate the populations in which combination immuno-chemotherapy specifically works, we reanalyzed the characteristics of the enrolled patients and found that, in patients without baseline liver metastases, the IO + ChT group had significantly prolonged median PFS compared with the ChT-alone group (9.12 vs. 6.72 months; HR, 0.50; 95% CI, 0.32–0.81; P <.01). The median OS (16.36 vs. 11.57 months; HR, 0.69; 95% CI, 0.43–1.1; P =.13) was prolonged by 4.79 months, and although the P value was not statistically significant, the trend of the two significantly differed from the KM curve up to 24 months. The reason for the lack of difference in survival in the later period was the intolerable toxicity of immunotherapy in elderly patients or the occurrence of immunoresistance induced by long-term immunotherapy. Why did the group of patients without liver metastases at baseline show a more significant survival advantage, and how do liver metastases affect immunologic efficacy in elderly patients? These questions remain to be addressed. In a retrospective analysis exploring the impact of liver metastases on the survival of patients with SCLC, a total of 23,678 patients were included. Liver metastasis was found to be the most common site of distant metastasis in SCLC. Among patients with a single metastasis, patients with brain or bone metastasis had a longer OS, with a median OS of 5–7 months, and patients with liver metastasis had an OS of 3 months (all P values < 0. 001), and among patients with multiple metastases, the OS was 4 months for SCLC patients with liver metastases and 6 months for those without liver metastases (P =.017). The results of this study revealed that liver metastases were the worst prognostic factor for patients with ES-SCLC [18]. These findings indicate that patients with liver metastases themselves have a lower survival expectancy. Some mouse model studies in which researchers first induced tumor formation in mice and then induced liver metastases have shown that mice without liver metastases respond to the PD-1 drug; however, when liver metastases occur, these mice do not respond to the PD-1 drug, and the researchers repeated the study with another model of lung metastases, thereby confirming that systemic resistance to immunotherapy is highly dependent on liver metastases. In the absence of liver metastases, there were many $CD8^+$T cells in the primary tumor lesions, but in the liver metastasis group, there was a large reduction in immune T cells. The activation of immune cells is not affected by liver metastasis. However, liver metastasis "siphons off" many immune T cells, resulting in a systemic reduction in T cells and the formation of an "immune desert" [19]. Interestingly, in one study, liver metastases were found to be an independent predictor of immunotherapy response. Cancer liver metastases have been shown to regulate T-cell clearance by macrophages, thereby limiting immunotherapeutic efficacy. In mice, activated T cells from the circulation are depleted in patients with liver metastases, resulting in a significant reduction in activated immune cells in the systemic body and the apoptosis of activated T cells in the liver, with monocyte-derived macrophages interacting with FasL + CD11b + F4/80 + monocytes. This process leads to a systemic immune desert, systemic depletion of immune cells, and greatly reduced immunotherapy efficacy, resulting in reduced tumor lesion killing. This mechanism corresponds to the initiation of a systemic immunosuppressive mechanism [20]. In this study, the researchers used mice with liver metastases. They directly irradiated the liver tumors, a therapy that stops T-cell death. As T cells are restored, the immune checkpoint inhibitor PD-1 activates the immune system, which in turn generates an immune response that achieves the same efficacy as that in patients with nonliver metastases [20]. The main cause of death in cancer patients is metastasis, and the liver is one of the most common organs where metastasis occurs. In Nature's latest Cancer Metastasis Atlas, the liver ranks second to the brain in terms of the metastasis of breast cancer, and therefore, it is essential to reverse the suppression of liver metastasis in patients by administering immunotherapy [21].

Assessing the subgroup of patients with brain metastases, we concluded that elderly patients with baseline brain metastases had a significant survival benefit with immunotherapy combined with chemotherapy compared with those receiving chemotherapy alone. Median OS (13.25 vs. 7.61 months; HR, 0.49; 95% CI, 0.24–0.98; P =.05), median PFS (9.12 vs. 4.07 months; HR, 0.29; 95% CI, 0.14–0.20; P <.001). In the OAK study reported by Gadgeel et al., in which brain metastases were present in 14% of patients, ICIs demonstrated superior survival and safety compared to that with docetaxel, with OS rates of 16.0 and 11.9 months for both (HR = 0.74; CI: 0.49–1.13), and this study further demonstrated that treatment with ICIs significantly reduced the likelihood that patients would present with new intracranial lesions (HR = 0.38, 95% CI: 0.16–0.91) [22]. These findings were similar to the results of our study.

Ultimately, our prognostic analysis revealed that female patients without baseline liver metastases had significantly improved OS. The significant survival benefit of the immunotherapy combined with chemotherapy in the population of patients without a baseline absence of liver metastases was mentioned in the above analysis. Immunotherapy combined with chemotherapy yielded more favorable outcomes in female patients than in male patients, and we believe that perhaps the female patients

included in this study were in better physical condition than the male patients were and that perhaps the female patients were more adherent to the treatment, which led to this indirect result. It is also possible that the sample size was too small because only 14.1% of the patients in that sample were female.

Elderly patients are frail and have more comorbidities; moreover, they receive poorer social support and have a relatively lower tolerance level for various drugs than younger patients do. For the same treatment regimen, elderly patients have a greater risk of toxicity than younger patients do. In a clinical trial evaluating the efficacy and feasibility of atezolizumab administered in combination with chemotherapy in elderly patients with ES-SCLC, atezolizumab in combination with etoposide and carboplatin showed good efficacy and acceptable toxicity despite hematologic toxicity (neutropenia) [12]. Changes in the immune system associated with aging in elderly individuals may affect the efficacy of immunotherapy. However, on the basis of the existing data and clinical application results, the application of immunotherapy in elderly patients is still feasible. Moreover, in this study, although chemotherapy combined with immunotherapy increased the incidence of various adverse reactions, only hemoglobin reduction and gastrointestinal reactions were significantly different; the other indicators did not significantly differ, and the prophylactic use of blood-boosting drugs and antiemetic drugs reduced the incidence of adverse reactions.

There are several limitations in the current analysis. First, this was a retrospective study with a small sample size that lacks representativeness, which may not be representative of the entire population elderly ES-SCLC patients. And limits causal reasoning and may introduce selection bias. A more extensive prospective study is needed to prove the clinical feasibility and safety of this therapy. Second, the patients' immunotherapy and chemotherapy regimens were affected by various factors, such as adverse reactions, and patients with liver metastasis have a reduced tolerance to drugs, which may have led to a decrease in treatment regularity or dosage reduction. Moreover, the population of this study included elderly patients, and elderly patients inevitably have poor compliance, all of which may affect the final results, which is an inherent limitation of retrospective studies.

In conclusion, our real-world data suggest that combination immuno-chemotherapy provides a survival benefit in the elderly ES-SCLC patient population and can be considered a feasible treatment option. This study suggests a new way of considering follow-up treatment for elderly ES-SCLC patients. To further clarify the efficacy of chemo-immunotherapy, a future large-scale prospective study of combination immuno-chemotherapy in the elderly ES-SCLC patient population is necessary.

Conclusion

This study revealed that chemotherapy combined with immunotherapy (a PD-1/L1 inhibitor) can improve progression-free survival in elderly patients with ES-SCLC. Despite some toxicity, prophylaxis can be used to mitigate side effects. This study demonstrated that combination immuno-chemotherapy is safe and manageable in the elderly ES-SCLC population. This study adds to the data from IMpower133, AUSRUM-005, CASPLAN, and other clinical trials in elderly patients (≥ 70 years) and provides new ideas and clinical evidence for the first-line treatment of elderly patients with ES-SCLC.

Abbreviations

SCLC Small-cell lung cancer
ES-SCLC Extensive-stage small-cell lung cancer
PFS Progression-free survival
OS Overall survival
VALG Veterans Administration Lung Study Group
TNM Tumor node metastasis classification
ICIs Immune checkpoint inhibitors
CT Computed tomography
MRI Magnetic resonance imaging
PET-CT Positron emission tomography computed tomography
AJCC American Joint Committee on Cancer
IO Immunotherapy
ChT Chemotherapy
EP Rtoposide + cisplatin
PD-1 Programmed death 1
PD-L1 Programmed cell death 1 ligand 1
PD Progressive disease
SD Stable disease
PR Partial response
CR Complete response
iRECIST Immunotherapy-based Solid Tumor Efficacy Evaluation Criteria
AEs Adverse events
KM Kaplan–Meier
HRs Hazard ratio
CIs Confidence intervals
ORR Objective response rate
DCR Disease control rate
KPS Karnofsky Performance Status
TRT Thoracic radiotherapy

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

K Zhao: Conceptualization, data organization, data analysis, formal analysis, writing the first draft, agreement on article results and conclusions.S Lu: Provided guidance on data analysis, critically revised and reviewed the content structure of the article, and concurred with the results and conclusions of the article. J Niu: Agreed with article results and conclusions and critically edited and reviewed the article.H Zhu: Conceptualization, fundraising, project management, writing review and editing.Y Tian: The article was critically edited and reviewed for content, logic, and formatting,

and the results and conclusions were agreed upon.J Yu: Agreed with article results and conclusions and critically edited and reviewed the article.All authors read and approved the final version.

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Data availability
All the data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author.

Declarations

Ethics approval and consent to participate
Study was approved by the institutional review board of Shandong Cancer Hospital and Institute and was performed in accordance with the Declaration of Helsinki. Given the study's retrospective nature and the use of de-identified data, the Shandong Cancer Hospital and Institute provided a waiver for the requirement of written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Completing interest
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