Original Article

Efficacy and safety of sintilimab in combination with chemotherapy for recurrent extensive-stage small cell lung cancer: a real-world retrospective study

Jingyi Wang[1,2#], Shuzhi Liang[1#], Li Xu[1], Yi Kong[1], Nobuhiko Seki[3], Apar Kishor Ganti[4], Joel W. Neal[5], Jia Li[1], Fang Xu[1], Kang Li[1], Yan Xu[1], Lin Wu[1], Bolin Chen[1]

[1]The Second Department of Thoracic Oncology, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/Hunan Cancer Hospital, Changsha, China; [2]Department of Geriatrics, Respiratory Medicine, Xiangya Hospital, Central South University, Changsha, China; [3]Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; [4]Division of Oncology-Hematology, Department of Internal Medicine, VA Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, USA; [5]Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford, CA, USA

Contributions: (I) Conception and design: J Wang, L Wu, B Chen; (II) Administrative support: L Wu; (III) Provision of study materials or patients: S Liang, L Xu, Y Kong, J Li, F Xu, K Li, Y Xu; (IV) Collection and assembly of data: J Wang, S Liang; (V) Data analysis and interpretation: J Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Lin Wu, MD; Bolin Chen, MD. The Second Department of Thoracic Oncology, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/Hunan Cancer Hospital, Tongzipo Road 283, Changsha 410013, China. Email: wulin-calf@vip.163.com; chenbolin@hnca.org.cn.

Background: Immune checkpoint inhibitors (ICIs) no longer are approved for second-line or later treatment of extensive-stage small cell lung cancer (ES-SCLC), and have not been studied in combination with chemotherapy. Exploring the efficacy and safety of second-line or later immunotherapy for ES-SCLC is an urgent clinical question that needs to be addressed, and combination therapies are an important research direction. This study intended to investigate the efficacy and safety of the sintilimab in combination with chemotherapy as a second-line and beyond treatment option for ES-SCLC.

Methods: Medical records of patients who received treatment with sintilimab in combination with chemotherapy or chemotherapy alone as a second-line or beyond therapy were retrospectively analyzed. The study evaluated efficacy and safety. Indicators of efficacy included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Safety indicators included adverse events (AEs).

Results: This cohort comprised of 46 patients: 24 in the sintilimab combination chemotherapy group and 22 in the chemotherapy group. Chemotherapy received by both groups was either albumin-bound paclitaxel or irinotecan. Compared with the chemotherapy group, the sintilimab combination chemotherapy group had higher ORR and DCR (ORR: 37.5% *vs.* 9.1%, P=0.04; DCR: 75.0% *vs.* 40.9%, P=0.04), and significantly prolonged PFS and OS [median PFS (mPFS): 5.07 *vs.* 2.45 months, P=0.006; median OS (mOS): 14.43 *vs.* 10.34 months, P=0.009]. Also, there was no significant increase in the incidence of AEs in the sintilimab combination chemotherapy group, which was well tolerated by patients.

Conclusions: Sintilimab in combination with chemotherapy is superior to single-agent chemotherapeutic treatment as second-line or later therapy in ES-SCLC patients who have not received prior immunotherapy. These results need to be confirmed in future clinical trials.

Keywords: Small cell lung cancer (SCLC); immune checkpoint inhibitors (ICIs); sintilimab; immune-combination therapy

Submitted May 11, 2024. Accepted for publication Jun 20, 2024. Published online Jun 28, 2024.
doi: 10.21037/jtd-24-769
View this article at: https://dx.doi.org/10.21037/jtd-24-769

Introduction

Lung cancer is a malignant tumor with the second highest incidence rate (11.4%) and the highest mortality rate (18%) worldwide (1). Among the types of lung cancer, small cell lung cancer (SCLC) is a highly malignant pathologic type, accounting for about 14% of cases (2). Although SCLC is quite sensitive to chemotherapy and radiotherapy, it is likely to recur and metastasize, with a median overall survival (OS) for extensive-stage small cell lung cancer (ES-SCLC) of 8–13 months, and 5-year survival rate of only 2–4% (3). The improvement of the prognosis of SCLC patients is an urgent clinical issue. In recent years, immune checkpoint inhibitors (ICIs) have improved the prognosis of lung cancer. Programmed cell death ligand 1 (PD-L1) inhibitors combined with platinum-containing dual-agent chemotherapy have improved the prognosis of SCLC for the first time in more than 20 years. Atezolizumab (4,5) and durvalumab (6-8) are currently approved by the Food and Drug Administration (FDA), in combination with platinum based chemotherapy, for the first-line treatment of ES-SCLC.

Although SCLC is very sensitive to first-line treatment, the majority of ES-SCLC patients experience relapse and drug resistance after initial treatment; these patients have a median OS of only 7–9 months after receiving further chemotherapy (9,10). Based on early clinical trial data, programmed cell death 1 (PD-1) inhibitors nivolumab (11,12) and pembrolizumab (13,14) were approved for the subsequent treatment of ES-SCLC patients who relapsed after primary treatment. However, as data from subsequent phase III randomized trials did not show an improvement in OS, the FDA withdrew the indication for nivolumab or pembrolizumab for the subsequent treatment of patients with relapsed SCLC (15,16). No ICIs are currently approved for second-line or later treatment of ES-SCLC (17). Exploring the efficacy and safety of second-line or later immunotherapy for ES-SCLC is an urgent clinical question that needs to be addressed, and combination therapy is an important research direction (18,19). Herein, we conducted a real-world retrospective study to explore the efficacy and safety of the anti-PD-1 agent sintilimab in combination with chemotherapy as a second-line and beyond treatment option for ES-SCLC. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-769/rc).

Highlight box

Key findings

- In previously treated patients with extensive-stage small cell lung cancer (ES-SCLC), the sintilimab plus chemotherapy group had higher objective response rate and disease control rate and significantly prolonged progression-free survival and overall survival compared with the chemotherapy alone group.
- There was no significant increase in the incidence of adverse events in the sintilimab combination chemotherapy group, suggesting good tolerability by patients.

What is known, and what is new?

- No immune checkpoint inhibitors are currently approved for second-line or later treatment of ES-SCLC, particularly in combination with chemotherapy. This study investigated the efficacy and safety of sintilimab in combination with chemotherapy as a second-line and beyond treatment for ES-SCLC.
- Sintilimab, in combination with chemotherapy, is superior to single-agent chemotherapy as second-line or later therapy in ES-SCLC patients who have not received prior immunotherapy.

What is the implication, and what should change now?

- These results need to be confirmed in prospective clinical trials.

Methods

Patient enrollment and study design

This is a retrospective study screening patients with ES-SCLC treated between January 2018 and December 2022 at Hunan Cancer Hospital. The last follow-up and data collection were conducted in July 2023. The inclusion criteria were as follows: (I) age 18–75 years; (II) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2; (III) patients with histologic or cytologic diagnosis of ES-SCLC; (IV) receiving sintilimab combination chemotherapy or chemotherapy alone as second-line or later treatment, and in the case of second-line treatment, relapse within 6 months from the end of first-line treatment; (V) patients with at least 1 evaluable target lesion according to Response Evaluation Criteria

in Solid Tumors (RECIST, version 1.1) (20); and (VI) patients who had received at least 1 efficacy evaluation during treatment. The exclusion criteria were as follows: (I) patients with a pathologic diagnosis of non-small cell lung cancer (NSCLC) combined with SCLC; and (II) patients with prior treatment with ICIs. The outcome variables assessed in the study were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival, and adverse events (AEs).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Hunan Cancer Hospital (No. 202242) and individual consent for this retrospective analysis was waived.

Evaluation of efficacy and safety

ORR was defined as the proportion of patients who achieved complete response (CR) and partial response (PR) according to RECIST 1.1 criteria. DCR was defined as the proportion of patients who achieved CR, PR, and stable disease (SD) according to RECIST 1.1 criteria. PFS was defined as the time interval from the start of sintilimab combination chemotherapy or single-agent chemotherapy treatment initiation to disease progression or death from any cause, whichever occurred first, or, if no disease progression or death occurred, patients were censored at the date of the last imaging visit. OS was defined as the time interval between the start of treatment with sintilimab combination chemotherapy or single-agent chemotherapy and death from any cause, or if no death event occurred, patients were censored at the last date of the last follow-up visit. Treatment-related adverse events (TRAEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) (21).

Statistical analysis

All statistical analyses were performed by R (version 3.6.1; The R Foundation of Statistical Computing, Vienna, Austria), with a test level of α=0.05 and statistical significance at $P<0.05$ for two-tailed tests. We used the chi-square test or Fisher's exact test for the comparison of count data between groups and the Kaplan-Meier curve for the relationship between descriptive variables and survival. The log-rank test was used to compare the differences in survival between the two groups. The Cox proportional risk model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) to determine the survival differences.

Results

Baseline patient characteristics

We screened 274 patients with ES-SCLC treated at Hunan Cancer Hospital between January 2018 and December 2022 according to the illustrated process (*Figure 1*). Of these, 107 were on first-line treatment, 83 had received prior immunotherapy, and 38 had incomplete treatment records and were excluded. The final cohort comprised of 46 patients, including 24 patients in the group treated with sintilimab in combination with chemotherapy (sintilimab/chemotherapy) and 22 patients in the group receiving single-agent chemotherapy.

Table 1 demonstrates the baseline clinical characteristics of the two groups, which were comparable. In the sintilimab/chemotherapy group, 83.3% were male (20/24) and 29.2% (7/24) of patients were ≥65 years old. In the chemotherapy group, 86.4% were male (19/22) and 40.9% (9/22) of patients were ≥65 years old. The majority of patients in all groups had an ECOG PS score of 0–1. The prevalence of smoking was 83.3% (20/24) and 86.4% (19/22) in the sintilimab/chemotherapy and chemotherapy groups, respectively, whereas the proportion of patients with clinical stage IV at diagnosis, was 79.2% (19/24) and 86.4% (19/22), respectively. There was no significant difference in baseline metastatic sites between the two groups. In the sintilimab/chemotherapy group, 79.2% (19/24) of the patients received second-line treatment, and 20.8% (5/24) received third-line and beyond treatment, whereas all patients in the chemotherapy group received second-line treatment (P=0.05). In terms of choice of chemotherapeutic agent, 58.3% (14/24) and 59.1% (13/22) of patients in the sintilimab/chemotherapy and chemotherapy groups, respectively, received nano-albumin paclitaxel, whereas another 41.7% (10/24) and 40.9% (9/22) of patients received irinotecan, respectively.

Efficacy

ORR and DCR

ORR and DCR were significantly higher in the sintilimab/chemotherapy group compared with the chemotherapy group (ORR: 37.5% *vs.* 9.1%, P=0.04; DCR: 75.0% *vs.* 40.9%, P=0.04). When only those patients who received

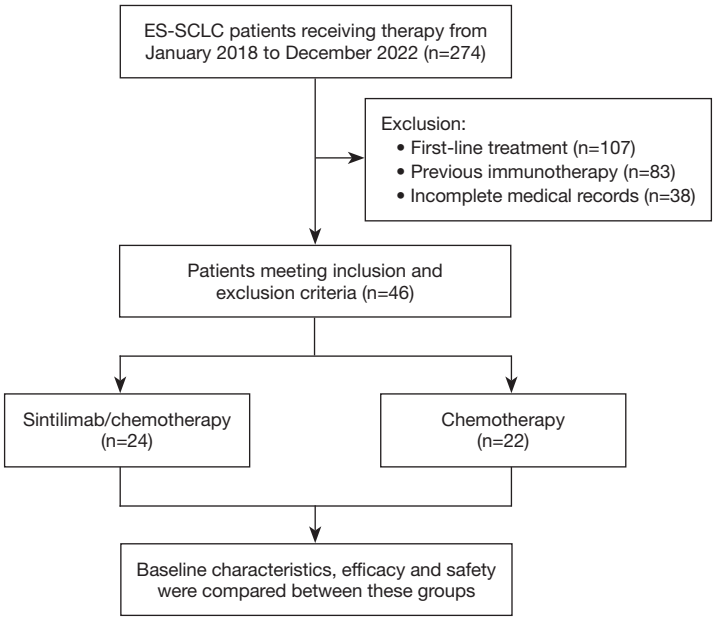

Figure 1 Flowchart of study design. ES-SCLC, extensive stage small cell lung cancer.

sintilimab in the second line were included, the ORR and DCR were higher in the sintilimab/chemotherapy group (ORR: 42.1% *vs.* 9.1%, P=0.03; DCR: 78.9% *vs.* 40.9%, P=0.03) (*Table 2*).

PFS and OS

The median survival follow-up time in this study was 33.63 months (95% CI: 24.12–43.14). PFS and OS were significantly prolonged in the sintilimab/chemotherapy group compared with the chemotherapy group [median PFS (mPFS): 5.07 *vs.* 2.45 months, P=0.006; HR =0.42, 95% CI: 0.22–0.79, P=0.007; median OS (mOS): 14.43 *vs.* 10.34 months, P=0.009; HR =0.43, 95% CI: 0.22–0.83, P=0.01] (*Figure 2A*,*2B*); PFS and OS were also longer in the sintilimab/chemotherapy group when restricted to second-line treatment (mPFS: 5.73 *vs.* 2.45 months, P=0.003; HR =0.36, 95% CI: 0.18–0.72, P=0.004; mOS: 15.47 *vs.* 10.34 months, P=0.01; HR =0.41, 95% CI: 0.21–0.84, P=0.02) (*Figure 3A*,*3B*). Cox multifactorial regression analyses also further determined that the sintilimab/chemotherapy combination compared to chemotherapy alone was an independent prognostic factor for improving PFS and OS in patients (*Tables 3*,*4*).

Safety

In the sintilimab/chemotherapy and chemotherapy groups, the number of patients who developed TRAEs was 18 (75.0%) and 14 (63.6%), and the incidence of grade ≥3 TRAEs was 12.5% (3/24) and 18.2% (4/22). The sintilimab/chemotherapy combination did not increase the TRAEs compared with chemotherapy significantly (*Table 4*). There were 2 patients (8.3%) in the sintilimab/chemotherapy group who experienced grade 1–2 treatment-related immune-related adverse events (irAEs), no patients had grade ≥3 treatment-related irAEs, and none of the patients discontinued treatment due to irAEs (*Table 5*).

Discussion

This study investigated the efficacy and safety of sintilimab plus chemotherapy as a second-line and later treatment for ES-SCLC. The results of the study showed that the addition of sintilimab to single agent chemotherapy improved efficacy, with observed higher ORR, DCR, PFS and OS in this group. There was no apparent difference between nab-paclitaxel and irinotecan. For patients with ES-SCLC who have not received prior immunotherapy, sintilimab in combination with chemotherapy appears to be a reasonable treatment option.

The National Comprehensive Cancer Network (NCCN) guideline (version 2.2023) (17) states that a rechallenge of the original regimen or a similar platinum-

Table 1 Baseline characteristics of patients

Characteristics	Sintilimab/chemotherapy (N=24), n (%)	Chemotherapy (N=22), n (%)	P value
Sex			>0.99
Male	20 (83.3)	19 (86.4)	
Female	4 (16.7)	3 (13.6)	
Age (years)			0.60
<65	17 (70.8)	13 (59.1)	
≥65	7 (29.2)	9 (40.9)	
ECOG PS			>0.99
0–1	22 (91.7)	21 (95.5)	
2	2 (8.3)	1 (4.5)	
Smoking histology			>0.99
Ever smoker	20 (83.3)	19 (86.4)	
Never smoker	4 (16.7)	3 (13.6)	
TNM stage			0.70
III	5 (20.8)	3 (13.6)	
IV	19 (79.2)	19 (86.4)	
Metastatic site			
Lung	3 (12.5)	5 (22.7)	0.45
Pleura	5 (20.8)	4 (18.2)	>0.99
Liver	6 (25.0)	6 (27.3)	>0.99
Bone	5 (20.8)	8 (36.4)	0.40
Brain	7 (29.2)	4 (18.2)	0.50
Adrenal gland	3 (12.5)	3 (13.6)	>0.99
Platinum-free interval (days)			>0.99
<90	11 (45.8)	10 (45.5)	
≥90	13 (54.2)	12 (54.5)	
Line of therapy			0.05
2	19 (79.2)	22 (100.0)	
≥3	5 (20.8)	0	
Selection of chemotherapy			>0.99
Albumin-bound paclitaxel	14 (58.3)	13 (59.1)	
Irinotecan	10 (41.7)	9 (40.9)	

ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis.

Table 2 ORR and DCR between the sintilimab/chemotherapy and chemotherapy group

Items	Sintilimab/chemotherapy (%)	Chemotherapy (%)	P value
ORR			
Total	37.5	9.1	0.04
Second-line	42.1	9.1	0.03
DCR			
Total	75.0	40.9	0.04
Second-line	78.9	40.9	0.03

ORR, objective response rate; DCR, disease control rate.

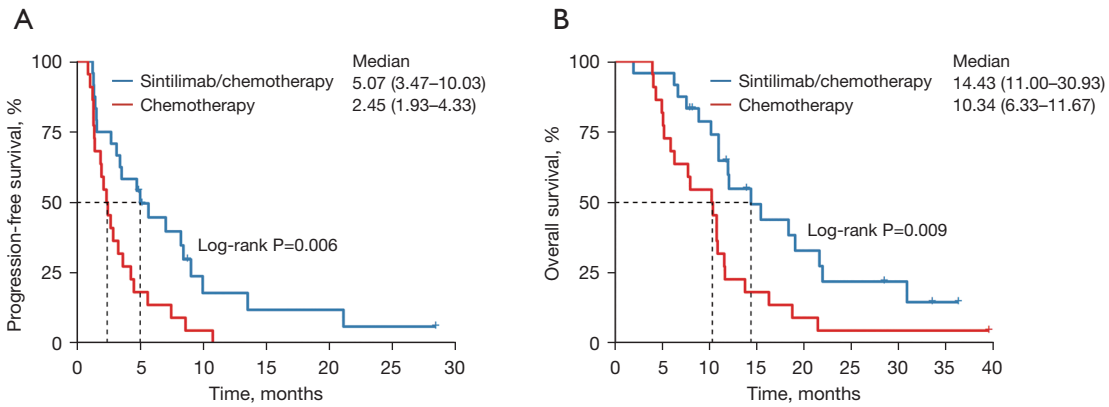

Figure 2 PFS and OS of patients with relapsed SCLC treated with sintilimab/chemotherapy (n=24) or chemotherapy (n=22) as the second-line treatment or later. (A) PFS of the sintilimab/chemotherapy or chemotherapy group as the second-line treatment or later. (B) OS of the sintilimab/chemotherapy or chemotherapy group as the second-line treatment or later. PFS, progression-free survival; OS, overall survival; SCLC, small cell lung cancer.

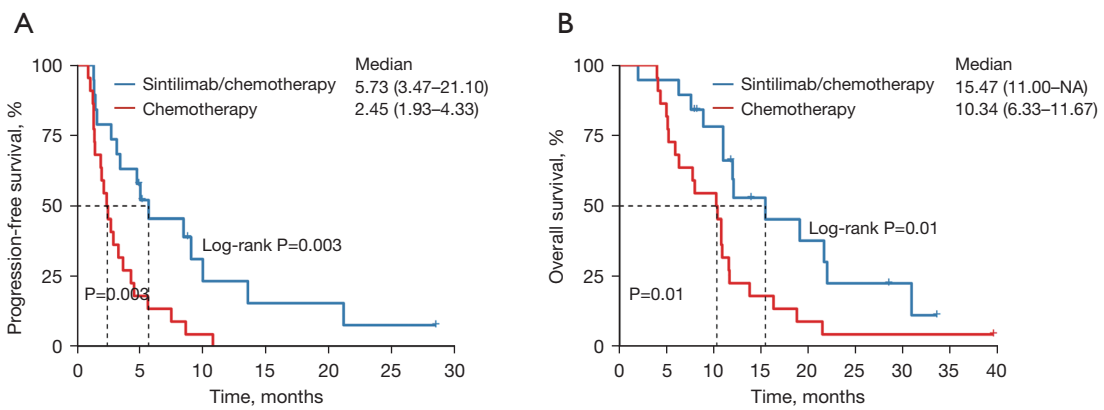

Figure 3 PFS and OS of patients with relapsed SCLC treated with sintilimab/chemotherapy (n=19) or chemotherapy (n=22) as the second-line treatment. (A) PFS of the sintilimab/chemotherapy or chemotherapy group as the second-line treatment. (B) OS of the sintilimab/chemotherapy or chemotherapy group as the second-line treatment. PFS, progression-free survival; OS, overall survival; SCLC, small cell lung cancer; NA, not applicable.

Table 3 Univariate and multivariate Cox regression analyses of clinical parameters on PFS between sintilimab/chemotherapy and chemotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Sex	Male *vs.* female	1.08 (0.48–2.46)	0.85	0.69 (0.29–1.66)	0.41
Age (years)	≥65 *vs.* <65	1.35 (0.68–2.67)	0.39	1.20 (0.55–2.62)	0.64
ECOG PS	2 *vs.* 0–1	2.43 (0.71–8.25)	0.16	2.32 (0.64–8.37)	0.20
Smoking history	Smoker *vs.* never smoker	1.08 (0.48–2.46)	0.85	0.69 (0.29–1.66)	0.41
TNM stage	IV *vs.* III	2.14 (0.89–5.16)	0.09	2.37 (0.87–6.46)	0.09
Treatment line	2 *vs.* ≥3	0.75 (0.29–1.93)	0.55	0.43 (0.13–1.38)	0.16
Chemotherapy	Irinotecan *vs.* albumin-bound paclitaxel	0.95 (0.50–1.79)	0.87	1.12 (0.54–2.32)	0.76
Therapeutic regimen	Sintilimab/chemotherapy *vs.* chemotherapy	0.42 (0.22–0.79)	0.008	0.34 (0.16–0.71)	0.004

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis.

Table 4 Univariate and multivariate Cox regression analyses of clinical parameters on OS between sintilimab/chemotherapy and chemotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Sex	Male *vs.* female	0.89 (0.37–2.14)	0.80	0.59 (0.23–1.51)	0.27
Age (years)	≥65 *vs.* <65	1.91 (0.96–3.82)	0.07	1.34 (0.61–2.96)	0.47
ECOG PS	2 *vs.* 0–1	1.62 (0.49–5.32)	0.43	3.03 (0.76–12.10)	0.12
Smoking histology	Smoker *vs.* never smoker	0.89 (0.37–2.14)	0.80	0.59 (0.23–1.51)	0.27
TNM stage	IV *vs.* III	1.37 (0.53–3.55)	0.52	1.14 (0.41–3.18)	0.81
Treatment line	2 *vs.* ≥3	1.37 (0.48–3.87)	0.55	0.59 (0.17–2.10)	0.41
Chemotherapy	Irinotecan *vs.* albumin-bound paclitaxel	0.90 (0.46–1.74)	0.74	0.76 (0.35–1.67)	0.49
Therapeutic regimen	Sintilimab/chemotherapy *vs.* chemotherapy	0.43 (0.22–0.83)	0.01	0.35 (0.15–0.82)	0.02

OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis.

based regimen is recommended as a subsequent treatment option if the disease-free interval is longer than 6 months and that rechallenge of the original regimen or a similar platinum-based regimen may be considered if the disease-free interval is at least 3–6 months. Other recommended regimens in this setting include topotecan, lurbinectedin, cyclophosphamide/doxorubicin/vincristine (CAV), docetaxel, etoposide, gemcitabine, irinotecan, nivolumab, paclitaxel, pembrolizumab, temozolomide, and vinorelbine (category 2A) (22).

Immunotherapy has greatly improved the prognosis of ES-SCLC. However, there are many patients with ES-SCLC in China who do not receive immunotherapy in the first line because it is more expensive compared to chemotherapy. Currently, only topotecan (23-25) and lurbinectedin (26,27) are approved by the FDA for second-line treatment of ES-SCLC, and the VEGFR inhibitor anlotinib (28,29) is approved by the National Medical Products Administration (NMPA) for third-line treatment of ES-SCLC. No ICIs have been approved by the FDA/NMPA for the second-line or later treatment of ES-SCLC, and exploring new options for the second-line or later treatment of ES-SCLC is an urgent clinical issue to be addressed.

Table 5 Adverse events of patients

Events	Grade	Sintilimab/chemotherapy (N=24), n (%)	Chemotherapy (N=22), n (%)	P value
TRAE	Any grade	18 (75.0)	14 (63.6)	0.61
	Grade 3–5	3 (12.5)	4 (18.2)	0.69
Nausea	Any grade	2 (8.3)	2 (9.1)	>0.99
	Grade 3–5	0	0	>0.99
Vomiting	Any grade	2 (8.3)	2 (9.1)	>0.99
	Grade 3–5	0	0	>0.99
Anemia	Any grade	9 (37.5)	11 (50.0)	0.58
	Grade 3–5	1 (4.2)	2 (9.1)	0.60
Leukopenia	Any grade	4 (16.7)	3 (13.6)	>0.99
	Grade 3–5	1 (4.2)	0	>0.99
Neutropenia	Any grade	3 (12.5)	2 (9.1)	>0.99
	Grade 3–5	1 (4.2)	1 (4.5)	>0.99
Thrombocytopenia	Any grade	0	2 (9.1)	0.22
	Grade 3–5	0	1 (4.5)	0.48
ALT/AST level increase	Any grade	4 (16.7)	3 (13.6)	>0.99
	Grade 3–5	0	0	>0.99
Treatment-related irAE	Any grade	2 (8.3)	N/A	N/A
	Grade 3–5	0	N/A	N/A
Hypothyroidism	Any grade	2 (8.3)	N/A	N/A
	Grade 3–5	0	N/A	N/A
Pneumonitis	Any grade	2 (8.3)	N/A	N/A
	Grade 3–5	0	N/A	N/A

TRAE, treatment-related adverse event; irAE, immune-related adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; N/A, not applicable.

The PASSION study (NCT03417985) is the first study to evaluate ICI (camrelizumab) in combination with anti-angiogenic agents (apatinib) in relapsed ES-SCLC. A total of 59 patients were enrolled in this study, and the ORR among the 47 patients in the QD cohort (camrelizumab Q3W + apatinib QD) was 34.0%, the DCR was 68.1%, and the mPFS and mOS were 3.6 and 8.4 months, respectively. However, the incidence of AEs was high, with 94.9% of patients experiencing a TRAE and 72.9% experiencing a grade 3 or higher TRAE (30). Another phase II study explored the safety and efficacy of toripalimab in combination with surufatinib for the second-line treatment of ES-SCLC. The 19 included evaluable patients had an ORR of 10.5%, a DCR of 94.7%, an mPFS of 2.96 months, and a mOS of 10.94 months (31). This combination regimen showed good antitumor activity and tolerable toxicity, which is important for enriching clinical treatment decisions in SCLC. Sintilimab plus anlotinib as second-line treatment or later for SCLC (NCT04055792) also showed good anti-tumor activity with manageable toxicity. A total of 42 patients were enrolled in the study, with an ORR of 56.8% and a DCR of 89.2%. The mPFS and mOS were 6.1 and 12.7 months, respectively (32). There are no clinical studies comparing the efficacy of sintilimab in combination with chemotherapy and sintilimab in combination with anlotinib. The results of this study suggest that sintilimab in combination with chemotherapy is also a viable second-line treatment option for patients with ES-SCLC and is

less expensive compared to sintilimab in combination with anlotinib.

A series of clinical studies have also explored the feasibility of immune-combination chemotherapy as a second-line and above treatment for patients with ES-SCLC. A phase II study (NCT02551432) enrolled 26 patients with ES-SCLC who had progressed on first-line platinum-based chemotherapy, to receive pembrolizumab in combination with paclitaxel. The ORR was 23.1%, the DCR was 80.7%, and the mPFS and mOS were 5.0 and 9.1 months, respectively (33). Another study (NCT03728361) used the combination of nivolumab and temozolomide in patients with ES-SCLC as a therapeutic option after progression on first-line chemo-immunotherapy (CIT), with an ORR of 30%, mPFS of 2.4 months, and mOS of 6.3 months (34).

There have been several real-world studies exploring the feasibility of ICIs in combination with anti-angiogenic drugs for the backline treatment of SCLC (35-37). Yu *et al.* compared PD-1/PD-L1 inhibitors in combination with anlotinib to paclitaxel as second-line and subsequent therapy for advanced SCLC. Their results showed that there was no significant difference in ORR between the two groups (15.0% *vs.* 8.9%, P=0.45), and the DCR was significantly higher in the combination therapy group than in the paclitaxel monotherapy group (80.5% *vs.* 54.5%, P=0.005), and the mPFS and mOS were also significantly prolonged (mPFS: 3.40 *vs.* 2.83 months, P=0.02; mOS: 8.20 *vs.* 5.87 months, P=0.048) (35). Another study, which included 28 patients with relapsed SCLC, showed that the PFS was significantly longer in the group receiving anlotinib in combination with PD-1 inhibitor than in patients treated with PD-1 inhibitor alone (mPFS: 5.0 *vs.* 3.0 months, P=0.005) (36).

There were no real-world studies exploring the use of ICI in combination with chemotherapy for second-line or later treatment in patients with ES-SCLC who have not received prior immunotherapy. In our study, the sintilimab combination chemotherapy group had better ORR, DCR, and significantly prolonged PFS and OS compared to the chemotherapy monotherapy group. Consistent with previous studies (30-35), no new safety issues were observed in this trial. In the sintilimab/chemotherapy group, the incidence of treatment-related irAEs was acceptable. The combination of sintilimab with chemotherapy did not significantly increase the incidence of TRAEs, suggesting that the combination regimen was well tolerated.

Sintilimab is an independently developed PD-1 inhibitor in China, and this study is the first to explore its efficacy and safety of this agent in combination with single agent chemotherapy for the treatment of relapsed ES-SCLC. On account of the improved affordability, this combination regimen is more accessible in Chinese SCLC patients. However, this study has some limitations. First, the study sample size was limited, which could lead to variability. Second, as this study was conducted retrospectively, TRAEs may have been underestimated despite chart review.

Conclusions

For patients with ES-SCLC who have not received prior immunotherapy, sintilimab in combination with chemotherapy in the second-line setting and beyond, is superior to chemotherapy monotherapy. It is well tolerated and may be a superior treatment strategy. However, the findings need further validation in randomized prospective trials.

Acknowledgments

The authors also appreciate the great support from Dr. Giulio Metro (Santa Maria della Misericordia Hospital, Italy) in improving the quality of this paper.

Funding: This research was funded by the Wu Jieping Medical Foundation (No. 320.6750.2020-10-81) to B.C., the National Key Clinical Specialty Scientific Research Project (No. Z2023098) to L.W., the Hunan Provincial Health High-Level Talent Scientific Research Project (No. R2023125) to L.W., the Science and Technology Innovation Program of Hunan Province (Nos. 2023SK4024 and 2021SK51121) to L.W., the Hunan Cancer Hospital Climb plan (No. ZX2020005-5) to L.W., and the Beijing Xisike Clinical Oncology Research Foundation (No. Y-2019Genecast-024) to L.W.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-769/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-769/dss

Peer Review File: Available at https://jtd.amegroups.com/

article/view/10.21037/jtd-24-769/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-769/coif). N.S. has obtained research grants from Eli Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Ono Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, Eisai, Shionogi, Daiichi Sankyo, and Boehringer Ingelheim; and has received speaking honoraria from Eli Lilly, AstraZeneca, MSD, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Ono Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, Daiichi Sankyo, Boehringer Ingelheim, Novartis, Kyowa Kirin, and Bristol Myers Squibb. A.K.G.'s institution has received grant funding for clinical trials from Apexigen, NEKTAR Pharmaceuticals, Merck, Pfizer, Boehringer Ingelheim, Poseida Inc. and Mirati Therapeutics. A.K.G. has received royalties from Oxford University Press; and consulting fees from Jazz Pharmaceuticals, AstraZeneca, Regeneron Pharmaceuticals, Sanofi Genzyme, Cardinal Health, Flagship Biosciences, Mirati Therapeutics, Beigene Ltd., G1 Therapeutics, Blueprint Medicines and Bayer; and honoraria for lectures from Paradigm Communications, Plexus Communications and MJH Life Sciences. A.K.G. also participated in data and Safety monitoring boards for YmAbs Therapeutics, and has administrative responsibilities (uncompensated) at Academic and Community Cancer Research United and International Association for the Study of Lung Cancer. J.W.N. reports research funding from Genentech/Roche, Merck, Novartis, Boehringer Ingelheim, Exelixis, Nektar Therapeutics, Takeda Pharmaceuticals, Adaptimmune, GSK, Janssen, AbbVie, and Novocure; and personal fees for consulting and advisory from AstraZeneca, Genentech/Roche, Exelixis, Takeda Pharmaceuticals, Eli Lilly and Company, Amgen, Iovance Biotherapeutics, Blueprint Pharmaceuticals, Regeneron Pharmaceuticals, Natera, Sanofi/Regeneron, D2G Oncology, Surface Oncology, Turning Point Therapeutics, Mirati Therapeutics, Gilead Sciences, AbbVie, Summit Therapeutics, Novartis, Novocure, Janssen Oncology and Anheart Therapeutics; and honoraria from CME Matters, Clinical Care Options CME, Research to Practice CME, Medscape CME, Biomedical Learning Institute CME, MLI Peerview CME, Prime Oncology CME, Projects in Knowledge CME, Rockpointe CME, MJH Life Sciences CME, Medical Educator Consortium, and HMP Education. B.C. reports that this research was funded by the Wu Jieping Medical Foundation (No. 320.6750.2020-10-81). L.W. reports that this research was funded by the National Key Clinical Specialty Scientific Research Project (No. Z2023098), the Hunan Provincial Health High-Level Talent Scientific Research Project (No. R2023125), the Science and Technology Innovation Program of Hunan Province (Nos. 2023SK4024 and 2021SK51121), the Hunan Cancer Hospital Climb plan (No. ZX2020005-5), and the Beijing Xisike Clinical Oncology Research Foundation (No. Y-2019Genecast-024), L.W. also received personal fees from AstraZeneca, Roche, Bristol-Myers Squibb, MSD, Pfizer, Lilly, Boehringer Ingelheim, Merck, Innovent, and Hengrui, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Hunan Cancer Hospital (No. 202242) and individual consent for this retrospective analysis was waived.

References

1. Chhikara BS, Parang K. Global Cancer Statistics 2022: the trends projection analysis. Chemical Biology Letters 2023;10:451.
2. Wang Q, Gümüş ZH, Colarossi C, et al. SCLC: Epidemiology, Risk Factors, Genetic Susceptibility, Molecular Pathology, Screening, and Early Detection. J Thorac Oncol 2023;18:31-46.
3. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
4. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage

Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
5. Liu SV, Reck M, Mansfield AS, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol 2021;39:619-30.
6. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-39.
7. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021;22:51-65.
8. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open 2022;7:100408.
9. Manzo A, Sforza V, Carillio G, et al. Lurbinectedin in small cell lung cancer. Front Oncol 2022;12:932105.
10. Zugazagoitia J, Paz-Ares L. Extensive-Stage Small-Cell Lung Cancer: First-Line and Second-Line Treatment Options. J Clin Oncol 2022;40:671-80.
11. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol 2020;15:426-35.
12. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-95.
13. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol 2017;35:3823-9.
14. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol 2020;15:618-27.
15. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331. Ann Oncol 2021;32:631-41.
16. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC). J Thorac Oncol 2018;13:1393-9.
17. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines® Insights: Non-Small Cell Lung Cancer, Version 2.2023. J Natl Compr Canc Netw 2023;21:340-50.
18. Moliner L, Zhang B, Lamberti G, et al. Novel therapeutic strategies for recurrent SCLC. Crit Rev Oncol Hematol 2023;186:104017.
19. Petty WJ, Paz-Ares L. Emerging Strategies for the Treatment of Small Cell Lung Cancer: A Review. JAMA Oncol 2023;9:419-29.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
21. Freites-Martinez A, Santana N, Arias-Santiago S, et al. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed) 2021;112:90-2.
22. Bernabé-Caro R, Chen Y, Dowlati A, et al. Current and Emerging Treatment Options for Patients With Relapsed Small-cell Lung Carcinoma: A Systematic Literature Review. Clin Lung Cancer 2023;24:185-208.
23. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-67.
24. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 2006;24:5441-7.
25. Ma S, He Z, Liu Y, et al. Sintilimab plus anlotinib as second or further-line therapy for extensive disease small cell lung cancer: a phase 2 investigator-initiated non-randomized controlled trial. EClinicalMedicine 2024;70:102543.
26. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol 2020;21:645-54.
27. Subbiah V, Paz-Ares L, Besse B, et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. Lung Cancer 2020;150:90-6.
28. Cheng Y, Wang Q, Li K, et al. OA13.03 Anlotinib as Third-Line or Further-Line Treatment in Relapsed

SCLC: A Multicentre, Randomized, Double-Blind Phase 2 Trial. J Thorac Oncol 2018;13:S351-S352.
29. Cheng Y, Wang Q, Li K, et al. 1738O - Overall survival (OS) update in ALTER 1202: Anlotinib as third-line or further-line treatment in relapsed small-cell lung cancer (SCLC). Abstract Book of the 44th ESMO Congress (ESMO 2019) 27 September–1 October 2019, Barcelona, Spain. Ann Oncol 2019;30:v711.
30. Fan Y, Zhao J, Wang Q, et al. Camrelizumab Plus Apatinib in Extensive-Stage SCLC (PASSION): A Multicenter, Two-Stage, Phase 2 Trial. J Thorac Oncol 2021;16:299-309.
31. Cheng Y, Shen L, Yu X, et al. 157P Surufatinib plus toripalimab in patients with advanced small cell lung cancer (SCLC) after failure of first-line systemic chemotherapy. Ann Oncol 2021;32:S1448-S1449.
32. Ma SX, He Z, Wang LL, et al. Sintilimab plus anlotinib as second or further-line therapy for small cell lung cancer: An objective performance trial. J Clin Oncol 2022;40:8516.
33. Kim YJ, Keam B, Ock CY, et al. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. Lung Cancer 2019;136:122-8.
34. Owen DH, Wei L, Benner B, et al. OA12.04 Efficacy of Nivolumab and Temozolomide in Extensive Stage Small Cell Lung Cancer after Chemo-Immunotherapy: A Phase 2 Trial. Abstracts from the 2022 World Conference on Lung Cancer. J Thorac Oncol 2022;17:S32-S33.
35. Yu L, Xu J, Qiao R, et al. Efficacy and safety of anlotinib combined with PD-1/PD-L1 inhibitors as second-line and subsequent therapy in advanced small-cell lung cancer. Cancer Med 2023;12:5372-83.
36. Zhang X, Zeng L, Li Y, et al. Anlotinib combined with PD-1 blockade for the treatment of lung cancer: a real-world retrospective study in China. Cancer Immunol Immunother 2021;70:2517-28.
37. Jiang Y, Zhang L, Zhu F, et al. Camrelizumab combined with anlotinib for the treatment of small cell lung cancer: a case report and literature review. Ann Palliat Med 2022;11:1135-46.

Cite this article as: Wang J, Liang S, Xu L, Kong Y, Seki N, Ganti AK, Neal JW, Li J, Xu F, Li K, Xu Y, Wu L, Chen B. Efficacy and safety of sintilimab in combination with chemotherapy for recurrent extensive-stage small cell lung cancer: a real-world retrospective study. J Thorac Dis 2024;16(6):3897-3908. doi: 10.21037/jtd-24-769