New Clinical Applications-sintilimab Combined with Albumin-bound Paclitaxel/cisplatin in Treatment of Relapsed or Refractory ES-SCLC

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Research Article

New clinical applications-sintilimab combined with albumin-bound paclitaxel/cisplatin in treatment of relapsed or refractory ES-SCLC

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Abstract

Introduction: This study is aimed to evaluate the efficacy and safety of sintilimab combined with albumin-bound paclitaxel/ cisplatin as a second-line treatment in these patients with relapsed or refractory extensive-stage small cell lung cancer (ES-SCLC).

Methods and Materials: ES-SCLC patients received a second-line regimen of sintilimab combined with albumin-bound paclitaxel/cisplatin. Albumin-bound paclitaxel/cisplatin can be used for up to 6 cycles. Sintilimab use was not stopped until the disease progressed or untolerable side effects occurred. After 2 cycles of chemotherapy or when the patient's condition progressed significantly, computed tomography was rechecked to observe the clinical curative effect and adverse reactions.

Results: Totally 38 patients with recurrent SCLC were included for efficacy evaluation. The objective response rate and disease control rate were 26.3% and 84.2% respectively. The median PFS and OS were 6.5 months (95% CI: 3.8-7.8) and 10.8 months (95% CI: 8.5-16.2), respectively. The main

adverse reactions are bone marrow suppression, alopecia, peripheral neurotoxicity, muscle and joint pain, gastrointestinal reactions, and fatigue. The severe adverse reactions (grade 3-4) are mainly leukopenia (21.1%), neutropenia (21.1%) and decreased hemoglobin (7.9%). No significant correlation was found between PD-L1 expression and efficacy.

Conclusion: Sintilimab combined with albumin-bound paclitaxel/cisplatin has a positive effect on the treatment of ES-SCLC, and the adverse reactions are tolerable.

Keywords: Sintilimab, Paclitaxel/cisplatin, Safety, Efficacy, Small cell lung cancer

1. Introduction

Lung cancer is still the world's largest cause of cancer-related death, with a total 5-year survival rate of only 15%. Small cell lung cancer (SCLC) accounts for about 15%-20% of all lung cancer patients and is clinically featured by rapid growth and early distant metastasis[1, 2]. Newly-treated patients are sensitive to radiotherapy and chemotherapy, with the effective rate up to 60%-70%, but most patients will quickly develop acquired resistance and even die of recurrence. Combination of chemotherapy and radiotherapy can cure some limited-stage patients, but radiotherapy can only be used as an adjuvant treatment method for extensive-stage patients. The main treatment method still relies on chemotherapy, which can only relieve symptoms. The prognosis of patients is extremely poor and the mortality rate is very high. About two-thirds of SCLC patients are diagnosed at the extensive stage (ES) [3], and the median survival time of ES-SCLC patients is about 9.4-12.8 months, and the survival rate is between 5.2%-19.5% [4, 5]. However, almost all patients will suffer recurrence and metastasis within 1-2 years after standard first-line treatment. Therefore, many SCLC patients are facing second-line treatment. For sensitive relapsed SCLC patients, topoisomerase inhibitors are currently the only

second-line treatment approved in the US and the EU. The efficacy of therapeutic drugs is far lower than expected. Although the posterior treatments of recurrent SCLC have been discussed and summarized, the overall efficacy of various posterior treatments is not excellent [6]. Moreover, there is still no clear standard for the treatment of recurrent SCLC. Thus, it is particularly important to find an effective treatment.

At present, paclitaxel-based drugs are commonly used as the first-line drugs for non-small cell lung cancer and their efficacy has been generally recognized, but their efficacy in SCLC has been rarely studied. When paclitaxel chemotherapy was applied for some newly-treated SCLC patients, its total effective rate was significantly lower than that of etoposide/platinum-based combination chemotherapy [7]. Therefore, paclitaxel is usually given only when other drugs are ineffective, and the efficacy of paclitaxel alone in treatment of refractory SCLC is minimal. Hence, it may be necessary to combine paclitaxel with other drugs to improve the clinical benefit of the SCLC population. Recently, immune checkpoint inhibitors have shown activity in several solid tumors, including SCLC [8, 9]. The success of Impower133 and CASPIAN studies also standardizes SCLC to embark on a new journey of immunotherapy. Both studies show that immunotherapy combined with chemotherapy can bring survival benefits in the first-line treatment of SCLC, but both studies used anti-PD-L1 antibodies, and anti-PD-1 antibodies in SCLC. The research has failed. Sintilimab is a highly selective monoclonal antibody (mAb) that can block the interaction between programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1), thereby activating the function of effector T cells against tumor cells. The existing data indicate that cytotoxic chemotherapeutics can regulate PD-L1 expression on the surface of tumor cells. For example, doxorubicin downregulates PD-L1 expression on the surface of breast cancer cells both in vitro and in vivo, while paclitaxel and etoposide can upregulate PD-L1

expression [10, 11]. Albumin-bound paclitaxel is a type of nanoparticles made of solvent-based paclitaxel and human albumin through high-pressure vibration. Albumin-bound paclitaxel increases the dose of paclitaxel and shortens the infusion time. It can also raise paclitaxel concentration in the tumor interstitium and improve tumor resistance. This is because there is no allergic reaction, so no anti-allergic pretreatment is needed before medication. Therefore, the application of hormones is avoided, and almost no negative impact on immune checkpoints will occur. Given the advantages of albumin-bound paclitaxel and the possible predictive effect of PD-L1 expression in immunotherapy, we assume that albumin-bound paclitaxel, rather than topotecan/irinotecan, may have anti-inflammatory effects on SCLC. We designed this study to evaluate the efficacy and safety of sintilimab combined with albumin-bound paclitaxel/cisplatin in the treatment of relapsed or refractory ES-SCLC.

2. Materials and methods

Recurrent SCLC patients between January 2020 and April 2021 were selected. Main inclusion criteria were: 1) pathological confirmation of ES-SCLC; 2) disease progression during/after first-line treatment with etoposide combined with cisplatin or carboplatin; 3) age at 18-76 years; 4) Eastern Cooperative Oncology Group performance status (ECOG PS) being 0 or 1; 5) at least one measurable lesion according to the *Solid Tumor Response Evaluation Criteria* (RECIST) 1.1 [12]; 6) survival time > 3 months. Main exclusion criteria were: 1) interstitial lung diseases (e.g. idiopathic pulmonary fibrosis or organizing pneumonia) in the past 5 years; 2) suffering from or having evidence of severe autoimmunity requiring systemic immunosuppressive therapy; 3) active or uncontrolled brain metastases; 4) reception of treatment targeting PD-1, PD-L1 or PD-L2; 5) other malignant tumors that are progressing or need treatment. This study was approved by the Ethics Committees of the Hospital(2021-P2-112-01),and registered in chinese clinical trial registry (ChiCTR2100045074). All

patients signed informed consent.

All patients received a second-line treatment regimen of sintilimab combined with albumin-bound paclitaxel/cisplatin. The specific regimen is as follows: 200 mg of sintilimab on day 1, 130 mg/m^2 albumin-bound paclitaxel on day 1 and day 8, and 25 mg/m^2 cisplatin from day 1 to day 3, all through intravenous infusion and with every 21 days one cycle. Due to the accumulation of peripheral neuropathy toxicity and nephrotoxicity, white protein-bound paclitaxel/cisplatin can be used for up to 6 cycles. Sintilimab administration was continued until disease progression or intolerable side effects occurred.The primary endpoint is objective response rate (ORR). The secondary endpoints are disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety and biomarker analysis.

The specific evaluation criteria are as follows: to evaluate the efficacy of each patient every 2 cycles by using RECIST 1.1[12]. The possible therapeutic effects include (1) complete remission, (2) partial remission, (3) stable disease (in between partial remission and disease progression), and (4) disease progression. Complete remission means the target lesion disappears, and the pathological lymph node short diameter is reduced to <10 mm. Partial remission means the total measured diameter of the target lesion is reduced by 30% from the baseline. Disease progression means the sum of the long diameters of all target lesions increases by at least 20%, and the absolute value of the total diameter increase is more than 5 mm, or new lesions appear. Relevant equations include ORR = (N_{cr} + N_{pr}) / N_a × 100%, and DCR = (N_{cr} + N_{pr} + N_{sd}) / N_a × 100%, where N_{cr}, N_{pr}, N_a and N_{sd} are the numbers of complete remission cases, partial remission cases, all cases, and stable disease cases respectively. The efficacy of all patients was confirmed again after 4 weeks. Overall survival is defined from the day of treatment to the day of the last follow-up or death; PFS is defined from the day of treatment to the

day of determination of disease progression or death. The adverse reactions were recorded during treatment and classified into grades 1-4 (grades 3 and 4 are severe toxic reactions) by using the National Cancer Institute's *Commonly-Used Terminology Evaluation Standard for Adverse Events* 4.03. Serious adverse drug reactions are defined as any event that causes death, incapacity, or congenital abnormalities/birth defects or requires hospitalization or prolonged hospitalization.

Follow-up was conducted in outpatient clinics or by telephone. The deadline for follow-up was September 2020. All 38 patients were not lost to follow-up. The follow-up rate was 100%, and the median follow-up time was 13.7 months.

The representative formalin-fixed paraffin-embedded tissue blocks from each case were sent to IHC staining by using an anti-PD-L1 antibody DAKO22C3 pharmDx assay (Dako, Carpinteria, CA, USA). A certified pathologist determined the percentages of tumor cells showing different staining intensities. The PD-L1 expression was evaluated according to the intensity and ratio of membrane staining in tumor cells (no cytoplasmic staining). PD-L1 staining intensity is divided into four categories: no staining (0), weak (1+), moderate (2+) and strong (3+). If the expression intensity in ≥1% of tumor cells is ≥1+, the tumor cells are considered as positive for PD-L1[13].

Statistical analysis was performed on SPSS 23.0 (IBM, Chicago, IL, USA). The measured data obeying a normal distribution were expressed as mean ± standard deviation (x ± s) and compared using the independent sample t-test. The data that did not obey normality was expressed as the median (interquartile range) [M (P25, P75)] and compared using the rank sum test. The count data and the rank data were compared using the $\chi 2$ test and the rank sum test respectively. Survival data were compared by the Kaplan-Meier method.

3. Results

3.1 Patient characteristics

From January 2020 to April 2021, totally 38 ES-SCLC patients who progressed during or after treatment with etoposide/platinum were selected. The baseline characteristics of the patients are shown in Table 1. There are 5 females and 33 males. The age range is 48-76 years old, with a median age of 66.4 years. About 25 and 13 cases are ≤60 and > 60 years old respectively. Twelve cases of brain metastasis occurred at the time of diagnosis. There were 12, 12 and 5 cases of bone, dry and adrenal metastasis respectively. The patients were divided into a chemotherapy alone group (20 cases) and a radiotherapy + chemotherapy group (18 cases). Only 15 cases received preventive brain irradiation.

Table 1 Baseline Characteristics (n = 38)

Characteristics	No. of patients (%)
Age, median, years (range)	66.4 (48–76)
Gender	
Male	33(86.8)
Female	5(13.2)
Smoking	
Yes	27(71.1)
No	11(29.0)
ECOG performance status	
0	6(15.8)
1	32(84.2)
Previous chemotherapy	
Etoposide/platinum combination	38(100.0)
Previous radiotherapy	
Yes	18(47.4)
No	20(52.6)
Metastasis site	
Brain	12(31.6)
Bone	12(31.6)
Liver	12(31.6)
Adrenal	5(13.2)
PD-L1 immunohistochemistry	
Positive	7(18.4)
Negative	31(81.6)

3.2 Efficacy analysis

The efficacy and toxicity of all patients who received at least one course of sintilimab combined with albumin-bound paclitaxel/cisplatin were analyzed. The 38 patients completed totally 118 cycles of chemotherapy, with 1 to 6 cycles per person. Among them, 7 patients (20%) completed only 2 cycles, and 31 patients (80%) underwent more than 2 cycles, with a median number of 4 cycles. There was 1 case of CR (2.6%), 9 cases of PR (23.7%), 22 cases of SD (57.9%), and 6 cases of PD (15.8%) (Table 2), as shown in the waterfall chart (Figure 1). The ORR and DCR were 26.3% (10/38) and 84.2% (32/38), respectively, and the median values of PFS and OS time to remission were 6.5 months (95%CI: 3.8-7.8) (Figure 2A), 10.8 months (95%CI: 8.5-16.2) (Figure 2B) respectively.

Table 2. Best Overall Response.

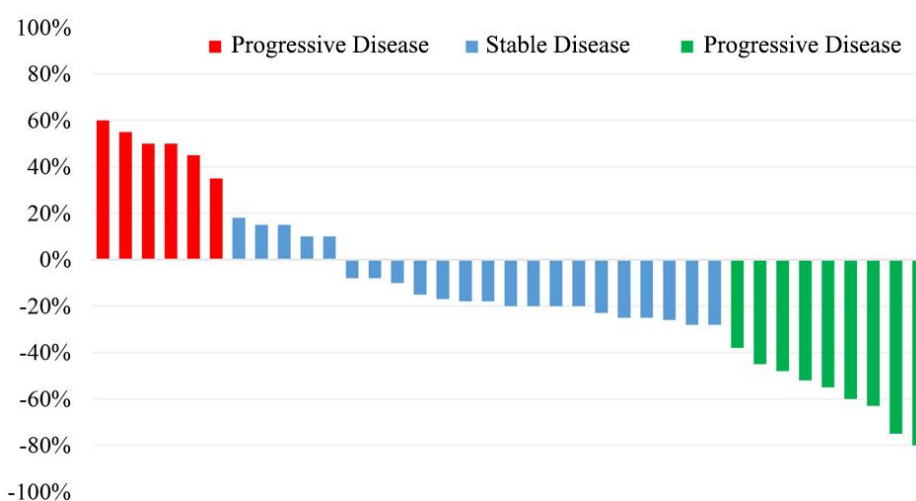| Response	No. of patients (%)
Best response	
Complete response (CR)	1(2.6)
Partial response (PR)	9(23.7)
Stable disease (SD)	22(57.9)
Progressive disease (PD)	6(15.8)
Objective response rate (ORR)	10(26.3)
Disease control rate (DCR)	32(84.2)

Figure 1. Waterfall plots of best percentage changes in the sum of the longest tumor diameter
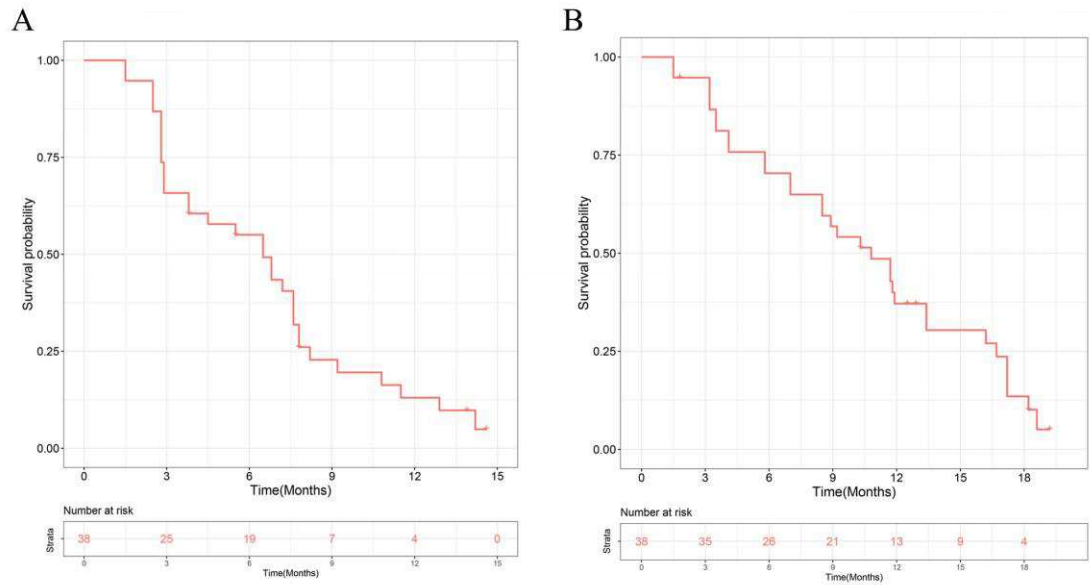
Figure 2. (A) Kaplan-Meier curve for progression-free survival. (B) Kaplan-Meier curve for overall survival.

3.3 Incidence of adverse reactions

About 86.8% (33/38) of the patients had adverse reactions. None of the patients discontinued treatment due to adverse reactions, and no treatment-related death occurred. The main adverse reactions were bone marrow suppression, hair loss, peripheral neurotoxicity, muscle and joint pains, gastrointestinal reactions, and fatigue. The main manifestations of bone marrow suppression were leukopenia (24 cases, 63.2%), neutropenia (23 cases, 60.5%) and hemoglobin reduction (14 cases, 36.8%). Among them, there were 8, 11, 6 and 2 patients with grade 1, 2, 3 and 4 myelosuppression, respectively. All patients got better after treatment with the granulocyte colony stimulating factor. For patients with severe neutropenia, the dose of albumin-bound paclitaxel was reduced. Two patients suffered severe muscle pains, mainly knee joint pain, which were improved after treatment with anti-inflammatory and analgesic drugs. Peripheral neurotoxicity was mainly manifested as numbness in the ends of the hands and feet, and gastrointestinal reactions were mainly manifested as nausea, vomiting and diarrhea, and were mainly grade 1-2. All patients were treated with sintilimab and

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albumin combined with paclitaxel/cisplatin chemotherapy. The overall regimen was well tolerated and

adverse reactions can be controlled, and no allergic reaction occurred during the treatment (Table 3).

Table 3. Summary of Adverse Events.

Adverse Event	All Grades (%)	Grade 3 or 4 (%)
Bone marrow suppression	27(71.1)	8(21.1)
Leukopenia	24(63.2)	8(21.1)
Neutropenia	23(60.5)	8(21.1)
Reduced hemoglobin	14(36.8)	3(7.9)
Hair loss	27(71.1)	3(7.9)
Peripheral neurotoxicity	14(36.8)	0(0)
Gastrointestinal reaction	21(55.3)	2(5.3)
Muscle joint pain	8(21.1)	0(0)
Fatigue	14(36.8)	0(0)
Rash	2(5.3)	0(0)
Fever	2(5.3)	0(0)

3.4 Relationships of molecular biomarkers with efficacy and survival

The expression of PD-L1, a potential molecular biomarker, was also analyzed to predict the

efficacy and survival of sintilimab combined with albumin and paclitaxel/cisplatin as the second-line

treatment of ES-SCLC patients. Seven patients (18.4%) had positive PD-L1 expression (including 1

case of strong positivity), and no significant correlation was found between PD-L1 expression and

ORR or PFS (23.5% vs. 27.1%, P= 0.459; 5.6 vs. 6.3 months, P = 0.897).

4. Discussion

The efficacy and adverse effects of sintilimab combined with albumin-bound paclitaxel- based

chemotherapy on recurrent SCLC were observed. Results showed that ORR was 26.3%, DCR was

84.2%, and median PFS was 6.5 months. Severe (grade 3-4) adverse reactions are mainly leukopenia

(21.1%) neutropenia (21.1%), hemoglobin reduction (7.9%), hair loss (7.9%), and muscle aches (5.3%).

These adverse reactions are controllable and can be resolved through active treatment. In general, the

chemotherapy regimen shows good clinical efficacy and tolerable adverse reactions in SCLC patients.

Before the immune era, there had been no major breakthrough in the treatment of SCLC and the prognosis of patients for nearly 30 years. The introduction of immune checkpoint inhibitors to SCLC treatment has brought new hope to improve the prognosis of SCLC. Two recent randomized controlled phase-3 clinical trials show that the addition of the immune checkpoint inhibitor Atezolizumab (IMpower-133 study) or Durvalumab (CASPIAN study) to first-line chemotherapy can significantly improve PFS and OS, and the program has been written in the major guidelines for SCLC treatment [14, 15]. Recently, many studies have been conducted on immune checkpoint inhibitors in the second-line and higher-line treatment of SCLC, but the results are not the same, especially in the case of single agent [16-18]. In the recent phase 3 clinical trial of CheckMate-331, the 569 patients who failed the platinum-containing regimen were randomly assigned to treatment with Nivolumab (a human IgG4 monoclonal antibody against PD-1; n = 284) or standard second-line chemotherapy (topotecan or amrubicin) (n = 285). Our results showed that with OS as the primary endpoint, Nivolumab did not significantly improve survival compared with standard chemotherapy (8.4 months [95%CI 7.0-10.0] vs. 7.5 months [95%CI 5.6–9.2]) after a median follow-up of 7.0–7.6 months. This confirms that at least in patients with relapsed SCLC, it is very challenging to completely give up chemotherapy and use immunotherapy alone. Based on the significant benefits of immunotherapy combined with chemotherapy in the first-line treatment of SCLC and combined with the results of immunotherapy alone in the second-line treatment, we designed a study on the application of immunotherapy combined with chemotherapy into recurrent SCLC. Immunotherapy and chemotherapy have a synergistic effect. For chemotherapy that kills tumor cells, more antigens are exposed and presented to the immune cells, activating the immune system to reidentify and kill tumor cells. It also can reduce the tumor volume,

improve the ratio of T cells to tumor cells, and make relatively more T cells infiltrate the tumor. In addition, chemotherapy can change the tumor barrier, increase T cell permeability, and reduce the tumor production of substances that inhibit T cells. At last, it is able to change the number of local suppressor T cells. The above effects of chemotherapy may further enhance the effect of immunotherapy, which is also the theoretical basis of immunotherapy combined with chemotherapy.

Although topotecan is still the only drug approved for relapsed SCLC patients so far, the response rate for sensitive patients is 7%–38%, and that for refractory patients is only 2%–7% [19]. A recent meta-analysis shows the clinical results of 1347 SCLC patients treated with Topotecan in 14 prospective trials. The objective tumor response rate and the 6-month OS rate are 5% and 37% in refractory patients, respectively, and are 17% and 57% in sensitive relapsed patients, respectively. These effective rates are far from the clinically effective level. demand. In vitro experiments show a certain correlation between p53 mutations (which occur in 75% to 90% of SCLC patients) and the efficacy of paclitaxel [20, 21]. For example, the absence of p53 in breast cancer indicates that paclitaxel is effective. Recently, the treatment of recurrent SCLC with paclitaxel-based regimens has been extensively reported, with a total effective rate of 20%-40%. Therefore, paclitaxel drugs show a certain prospect in recurrent SCLC. Considering the probable effect of hormone pretreatment on immunotherapy, we finally chose albumin combined with paclitaxel (a drug that does not require hormone pretreatment) combined with anti-PD-1 antibody, sintilimab and platinum for treatment of relapsed SCLC.

The efficacy of sintilimab combined with albumin, paclitaxel and platinum-based second-line treatment of relapsed ES-SCLC after etoposide/platinum therapy was compared with the KEYNOTE-158 study [22] and the KEYNOTE-028 study [17]. The PD-L1 positive ES-SCLC is

equivalent to the advanced SCLC. The ORR is 26.3%, which is higher than that of KEYNOTE-158 (18.7%) and lower compared with KEYNOTE-128 (33.3%). The median PFSs are 5.0, 2.0 and 1.9 months, respectively, and the median OSs are 9.1, 8.7 and 9.7 months respectively. Both KEYNOTE-158 [23] and KEYNOTE-028 [17] evaluated the effect of pembrolizumab as a single agent. KEYNOTE-028 only included PD-L1-positive SCLC patients, but most patients in our study were PD-L1-negative, while KEYNOTE-158 involved PD-L1-negative SCLC patients. The RR of monoclonal antibodies is only 6% [20]. Therefore, sintilimab combined with albumin, paclitaxel and platinum-based second-line treatment of relapsed ES-SCLC after etoposide/platinum-based treatment is of certain value.

PD-L1 expression has a certain value in predicting the efficacy of immune checkpoint inhibitors in non-small cell lung cancer and melanoma. A higher level of PD-L1 expression indicates a better efficacy. However, due to the heterogeneity of SCLC, the positive rate of PD-L1 expression varies among different studies. All current data are between 5% and 70%. In our study, the positive rate of PD-L1 is 18.4%, including 1 strong positive patient. We did not find a correlation between PD-L1 expression and the efficacy of immunotherapy.

There are several limitations. First, this is a single-arm study of second-line treatment, rather than a randomized trial, so it cannot be directly compared with other studies based on conventional second-line treatment. Therefore, the advantages of clinical benefit and toxicity compared with conventional treatment should be carefully explained. Second, the sample size of the study is small and the statistical power is low. Third, the small number of patients limits any conclusion based on biomarker analysis. In the study population, there are only 7 PD-L1-positive patients, which are not enough to ensure the use of PD-L1 as a predictive biomarker. Fourth, we have not obtained data from

the duration between enrollment and completion of platinum-etoposide treatment, and given the insufficient relapse-free interval, we cannot distinguish between refractory diseases without initial response and with drug-resistant relapse. In the future, we will design a large sample of randomized controlled studies to further verify our results.

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Authors' contributions

LH and LZ designed and performed the research, analyzed data, and wrote the manuscript; LL, JLH, YLL, LLS, and SCL participated in data preparation, analysis, and figure preparation. All the authors contributed to the review and revision of the manuscript, and all authors read and approved the final manuscript.

Competing interests

The authors have declared that no competing interests exist.

Availability of data and material

All data generated or analyzed during this study are included.

References

1. Gazdar, A.F., P.A. Bunn and J.D. Minna. 2017.Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 17: 725-737.

2. Subbiah, S., A. Nam, N. Garg, A. Behal, P. Kulkarni, and R. Salgia. 2020.Small Cell Lung Cancer from Traditional to Innovative Therapeutics: Building a Comprehensive Network to Optimize Clinical and Translational Research. J Clin Med. 9.

3. Tsoukalas, N., E. Aravantinou-Fatorou, P. Baxevanos, M. Tolia, K. Tsapakidis, and M.

Galanopoulos, et al. 2018.Advanced small cell lung cancer (SCLC): new challenges and new expectations. Ann Transl Med. 6: 145.

4. Kalemkerian, G.P. 2016.Small Cell Lung Cancer. Semin Respir Crit Care Med. 37: 783-796.

5. Mambetsariev, I., T. Mirzapoiazova, F. Lennon, M.K. Jolly, H. Li, and M.W. Nasser, et al. 2019.Small Cell Lung Cancer Therapeutic Responses Through Fractal Measurements: From Radiology to Mitochondrial Biology. J Clin Med. 8.

6. Koinis, F., A. Kotsakis and V. Georgoulias. 2016.Small cell lung cancer (SCLC): no treatment advances in recent years. Transl Lung Cancer Res. 5: 39-50.

7. Graziano, S.L., J.N. Herndon, M.A. Socinski, X. Wang, D. Watson, and E. Vokes, et al. 2008.Phase II trial of weekly dose-dense paclitaxel in extensive-stage small cell lung   cancer: cancer and leukemia group B study 39901. J Thorac Oncol. 3: 158-62.

8. Guo, H., Y. He, P. Chen, L. Wang, W. Li, and B. Chen, et al. 2020.Combinational immunotherapy based on immune checkpoints inhibitors in small cell   lung cancer: is this the beginning to reverse the refractory situation? J Thorac Dis. 12: 6070-6089.

9. Pacheco, J.M. 2020.Immunotherapy for extensive stage small cell lung cancer. J Thorac Dis. 12: 6212-6224.

10. Zhang, P., D.M. Su, M. Liang, and J. Fu. 2008.Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression   in breast cancer cells and promote PD-L1-mediated T cell apoptosis. Mol Immunol. 45: 1470-6.

11. Ghebeh, H., C. Lehe, E. Barhoush, K. Al-Romaih, A. Tulbah, and M. Al-Alwan, et al. 2010.Doxorubicin downregulates cell surface B7-H1 expression and upregulates its nuclear expression in breast cancer cells: role of B7-H1 as an anti-apoptotic molecule. Breast Cancer Res. 12: R48.

12. Nishino, M., D.M. Jackman, H. Hatabu, B.Y. Yeap, L.A. Cioffredi, and J.T. Yap, et al. 2010.New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced   non-small cell lung cancer: comparison with original RECIST and impact on assessment   of tumor response to targeted therapy. AJR Am J Roentgenol. 195: W221-8.

13. Roach, C., N. Zhang, E. Corigliano, M. Jansson, G. Toland, and G. Ponto, et al. 2016.Development of a Companion Diagnostic PD-L1 Immunohistochemistry Assay for Pembrolizumab Therapy in Non-Small-cell Lung Cancer. Appl Immunohistochem Mol Morphol. 24: 392-7.

14. Horn, L., A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, and M.J. Hochmair, et al. 2018.First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 379: 2220-2229.

15. Paz-Ares, L., M. Dvorkin, Y. Chen, N. Reinmuth, K. Hotta, and D. Trukhin, et al. 2019.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. 394: 1929-1939.

16. Antonia, S.J., J.A. López-Martin, J. Bendell, P.A. Ott, M. Taylor, and J.P. Eder, et al. 2016.Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 17: 883-895.

17. Ott, P.A., E. Elez, S. Hiret, D.W. Kim, A. Morosky, and S. Saraf, et al. 2017.Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From   the Phase Ib KEYNOTE-028 Study. J Clin Oncol. 35: 3823-3829.

18. Ready, N.E., P.A. Ott, M.D. Hellmann, J. Zugazagoitia, C.L. Hann, and F. de Braud, et al. 2020.Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol. 15: 426-435.

19. Eckardt, J.R., J. von Pawel, J.L. Pujol, Z. Papai, E. Quoix, and A. Ardizzoni, et al. 2007.Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 25: 2086-92.

20. Xu, J., C. Su, F. Zhao, J. Tao, D. Hu, and A. Shi, et al. 2018.Paclitaxel promotes lung cancer cell apoptosis via MEG3-P53 pathway activation. Biochem Biophys Res Commun. 504: 123-128.

21. Park, J.H., S.A. Park, Y.J. Lee, H.W. Park, and S.M. Oh. 2020.PBK attenuates paclitaxel-induced autophagic cell death by suppressing p53 in H460 non-small-cell lung cancer cells. FEBS Open Bio. 10: 937-950.

22. Marabelle, A., M. Fakih, J. Lopez, M. Shah, R. Shapira-Frommer, and K. Nakagawa, et al. 2020.Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 21: 1353-1365.

23. Gandhi, L., D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, and F. De Angelis, et al. 2018.Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 378: 2078-2092.
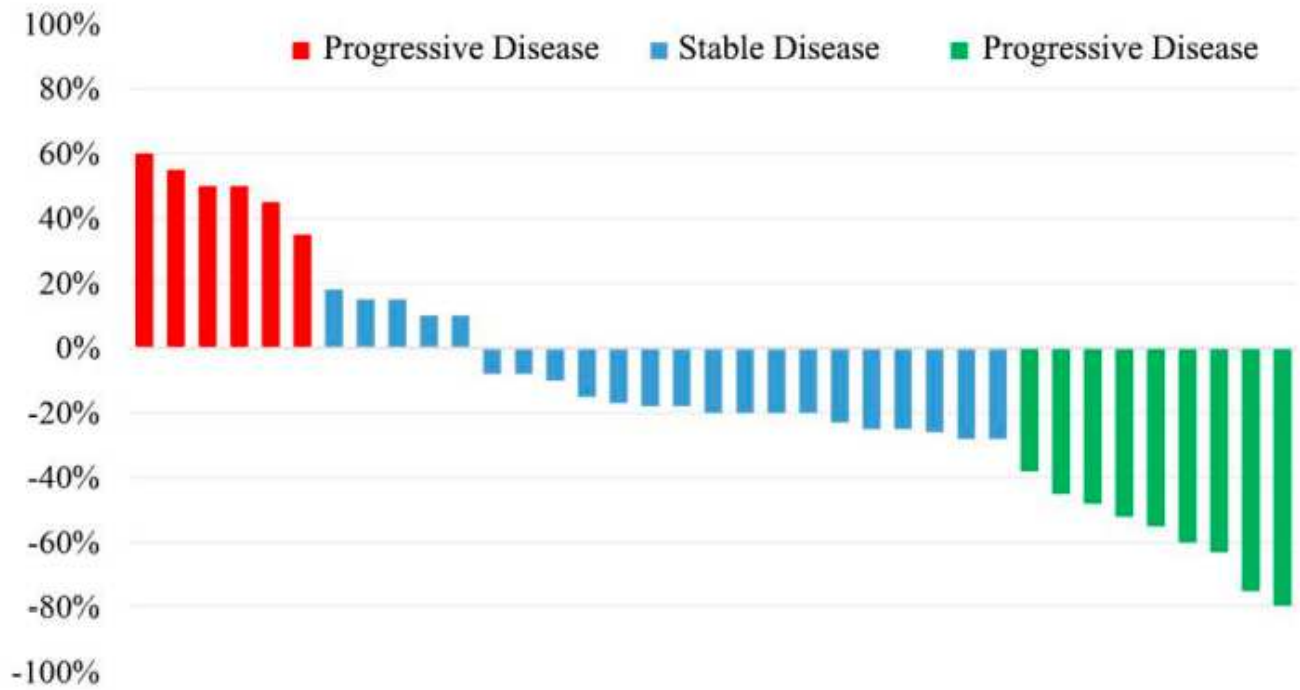
Figures

Figure 1

Waterfall plots of best percentage changes in the sum of the longest tumor diameter
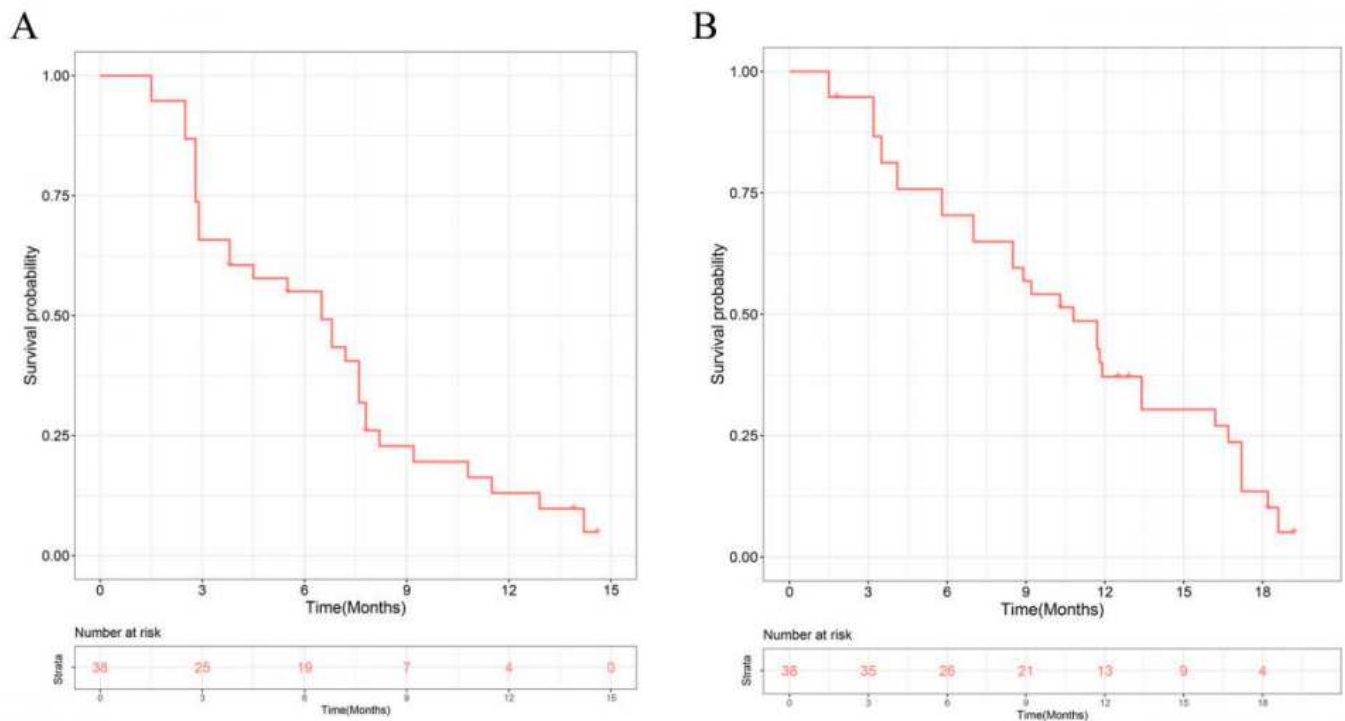
Figure 2

(A) Kaplan-Meier curve for progression-free survival. (B) Kaplan-Meier curve for overall survival