Intermittent administration of atezolizumab with combined carboplatin and etoposide therapy for patients with extensive-disease small cell lung cancer

TAKESHI TSUDA[1*], HISAO IMAI[2*], YOSHIAKI NAGAI[3], YUKIHIRO UMEDA[4], AYAKO SHIONO[2], JUN SHIIHARA[3], OU YAMAGUCHI[2], ATSUTO MOURI[2], KYOICHI KAIRA[2], TAMOTSU ISHIZUKA[4], HIROKAZU TANIGUCHI[1] and HIROSHI KAGAMU[2]

[1]Division of Respiratory Medicine, Toyama Prefectural Central Hospital, Toyama, Toyama 930-8550; [2]Department of Respiratory Medicine, International Medical Center, Saitama Medical University, Hidaka, Saitama 350-1298; [3]Department of Respiratory Medicine, Jichi Medical University, Saitama Medical Center, Saitama, Saitama 330-8503; [4]Third Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Eiheiji, Fukui 910-1193, Japan

Received September 19, 2022; Accepted January 16, 2023

DOI: 10.3892/ol.2023.13696

Abstract. To the best of our knowledge, no published reports have examined the significance of additional immune checkpoint inhibitors in treating malignancies, including lung cancer. Therefore, the present study aimed to examine the efficacy and feasibility of adding atezolizumab to carboplatin and etoposide combination chemotherapy for small cell lung cancer with extensive disease (ED-SCLC). The present retrospective analysis examined 16 patients with ED-SCLC who received the addition of atezolizumab to carboplatin and etoposide therapy during treatment at four institutions between August 2019 and September 2020. The effectiveness of treatment was evaluated based on tumor response, survival time and adverse events. Within the study cohort, there were 14 males (87.5%) and 2 females (12.5%), with a median age of 73.5 years (range, 62-79 years); 7 patients had a performance status (PS) of 0-1 (43.8%) and 9 had a PS of 2-3 (56.3%). The median follow-up period was 12.1 months. The overall response rate, median progression-free survival time and median overall survival time were 75.0%, 5.3 and 13.0 months, respectively. Regarding the frequency of hematological adverse events, the occurrence of grade ≥3 adverse events was observed, including decreased neutrophil (56.3%), white blood cell (50.0%) and platelet (43.8%) counts, as well as febrile neutropenia (12.5%). Although 1 patient developed grade 3 pneumonitis as a serious adverse event, no treatment-related deaths were observed. Despite the aforementioned hematological toxicities, the addition of atezolizumab to carboplatin and etoposide therapy during treatment demonstrated favorable efficacy and acceptable toxicity in ED-SCLC. Thus, adding atezolizumab to carboplatin and etoposide combination chemotherapy may be a treatment option for ED-SCLC.

Correspondence to: Dr Hisao Imai, Department of Respiratory Medicine, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
E-mail: m06701014@gunma-u.ac.jp

*Contributed equally

Abbreviations: CI, confidence interval; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; ED, extensive disease; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PPS, post-progression survival; PR, partial response; PS, performance status; SCLC, small cell lung cancer; SD, stable disease; TNM, Tumor-Node-Metastasis

Key words: atezolizumab, carboplatin, etoposide, ICI, SCLC

Introduction

Small cell lung cancer (SCLC) accounts for ~14% of all lung cancer cases (1). Until recently, the standard first-line treatment for patients with SCLC with extensive disease (ED-SCLC) was platinum and etoposide combination chemotherapy. Despite a median patient survival time of ~10 months, there has been no significant improvement in overall survival (OS) time for over 2 decades (2,3). ED-SCLC is a malignant disease with an objective response rate (ORR) of 44-78% for first-line treatment, a median progression-free survival (PFS) time of 4.3-5.7 months, a median OS time of 7.5-10.9 months and a 5-year survival rate of only 2.8% (3,4).

Atezolizumab, a programmed death ligand 1 inhibitor, was studied in the IMpower133 trial in combination with carboplatin and etoposide therapies (5,6). The trial determined that median PFS and OS times were significantly more favorable in patients who received atezolizumab with carboplatin and etoposide than in patients who received a placebo with carboplatin and etoposide (5.2 vs. 4.3 months and 12.3 vs. 10.3 months, respectively). However, the IMpower133 trial was a study of a cohort of patients with a favorable performance status (PS) of 0-1 (7), and there was no investigation for a PS of 2. Furthermore, the trial was designed for patients with

preserved organ function and no autoimmune diseases or other complications under favorable conditions. Thus, to the best of our knowledge, there are currently no published studies on the addition of immune checkpoint inhibitors (ICIs) in patients with poor PS, organ dysfunction or complications.

There have been two phase III trials that included patients with a PS of 3, and these patients may be eligible for chemotherapy if the therapeutic effect on SCLC can improve PS (8,9). A phase III trial (JCOG9702) of carboplatin and etoposide versus split cisplatin (cisplatin administered in divided doses) and etoposide in patients aged ≥70 (PS, 0-2) and <70 (PS, 3) years showed more grade 3/4 thrombocytopenia in patients given carboplatin and etoposide (56 vs. 16%, respectively; P<0.01), but ORR (73 vs. 73%, respectively) and OS time (median 7.1 vs. 6.9 months, respectively, in the subgroup analysis of patients with PS 3 <70 years) were similar (10). Therefore, PS could be improved with cytotoxic drug chemotherapy, and even if treatment is initially started with carboplatin and etoposide for the first cycle due to complications, ICIs can be intermittently added during the sequential course of carboplatin and etoposide chemotherapy. However, the efficacy and feasibility of starting carboplatin and etoposide at the beginning of first-line chemotherapy and adding atezolizumab during the treatment course in patients with ED-SCLC with a poor PS or complications during the initial cycle of carboplatin and etoposide have not been investigated. Furthermore, to the best of our knowledge, no reports have examined the significance of additional ICIs in malignancies other than lung cancer. Therefore, the present investigation aimed to examine the efficacy and feasibility of carboplatin and etoposide as treatment options at the beginning of therapy with atezolizumab administered during the treatment course in patients with ED-SCLC.

Materials and methods

Patients. The present retrospective study assessed the clinical records of patients diagnosed with ED-SCLC who received atezolizumab in addition to carboplatin and etoposide combination therapy for SCLC between August 2019 and September 2020 in four institutions (Toyama Prefectural Central Hospital, Toyama, Japan; International Medical Center, Saitama Medical University, Saitama, Japan; Jichi Medical University, Saitama Medical Center, Saitama, Japan; and University of Fukui, Fukui, Japan). The inclusion criteria were: i) Cytological or histopathological diagnosis of stage III/IV SCLC without curative radiotherapy or postoperative recurrence; ii) first-line chemotherapy with carboplatin and etoposide; and iii) addition of atezolizumab during carboplatin and etoposide combination therapy. Key exclusion criteria were: i) A history of previous treatment with immune-checkpoint blockade therapies; and ii) having no measurable lesions to assess tumor shrinkage efficacy. The pathological stage was evaluated based on the Tumor-Node-Metastasis (TNM) classification of the Union for International Cancer Control, eighth edition (11). The Eastern Cooperative Oncology Group (ECOG)-PS scale scores range from 0-4, where low scores indicate a good general condition and high scores signal a poor prognosis (7). A PS of 0 indicated the best general condition and a PS of 4 indicated the poorest general condition. Before therapy, all patients underwent systematic evaluation and standardized staging procedures. The clinical stage was assigned according to the results of physical examination, chest X-ray, thoracic and abdominal computed tomography (CT), brain CT or magnetic resonance imaging, and bone scintigraphy or ^{18}F-fluorodeoxyglucose positron emission tomography to evaluate the TNM stage. Aspiration cytology and/or biopsy as part of the clinical staging procedure was performed as needed. Data were extracted from the medical records of eligible patients. Data from some patients (7 patients) who received atezolizumab plus carboplatin and etoposide were used in a previously reported analysis (12). The present study was approved by the Institutional Review Board of the International Medical Center of Saitama Medical University (Hidaka, Japan; approval no. 2021-113). All procedures complied with the ethical standards of the institutional and/or national research committee and the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards. As this was a retrospective study, the requirement for informed consent was waived.

Evaluation of treatment and response. None of the patients in the cohort had previously received ICIs, including atezolizumab, carboplatin or combination etoposide chemotherapy. Each patient was administered up to six cycles of carboplatin [area under the curve (AUC) of 3.5-5 min/mg/ml; intravenous injection on day 1 of each cycle] and etoposide (60-100 mg/m^2 body surface area; intravenous injection on days 1-3 of each cycle), followed by atezolizumab maintenance every 3 weeks. Atezolizumab (fixed dose of 1,200 mg, intravenous injection on day 1 of each cycle) was added to the carboplatin and etoposide therapy based on the attending physician's decision. Granulocyte colony-stimulating factor was administered as a prophylaxis against neutropenia at the discretion of the attending physician. Treatment was terminated when disease progression or irreversible toxicity was observed, or when the patient withdrew consent to chemotherapy. When treatment failure occurred with the combination of atezolizumab with carboplatin and etoposide therapy, subsequent chemotherapy with a cytotoxic drug or best supportive care alone was performed at the discretion of the treating physician.

Radiographic tumor responses were evaluated in line with the best overall response and maximum tumor shrinkage according to the Response Evaluation Criteria for Solid Tumors, version 1.1 (13). Treatment-related toxicities were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) (14).

Statistical analysis. PFS time was calculated from the first day of carboplatin and etoposide combination chemotherapy until progressive disease (PD) or death for any reason. OS time was calculated from the first day of carboplatin and etoposide combination chemotherapy until death or censored on the day of the last consultation. Post-progression survival (PPS) time was calculated as the period from PD to death or censored on the date of the last consultation or follow-up. PFS and OS times were evaluated using the Kaplan-Meier method. All statistical analyses were performed using JMP statistical software, version 11.0, for Windows (SAS Institute, Inc.).

Table I. Baseline patient characteristics (n=16).

Characteristic	Value
Sex, n	
Male	14
Female	2
Age, years	
Median	73.5
Range	62-79
Disease stage, n	
III	1
IV	15
Postoperative recurrence	0
ECOG-PS at first administration of carboplatin + etoposide, n	
0	3
1	4
2	5
3	4
4	0
Smoking status, n	
Yes	16
No	0
Histology, n	
Small cell carcinoma	16
Combined small cell carcinoma	0
History of postoperative adjuvant chemotherapy, n	
Yes	0
No	16
Intracranial metastases at initial treatment, n	
Yes	6
No	10
Liver metastases at initial treatment, n	
Yes	5
No	11
Bone metastases at initial treatment, n	
Yes	6
No	10
Cycle at addition of atezolizumab, n	
2	10
3	3
4	2
5	1
ECOG-PS at addition of atezolizumab, n	
0	2
1	13
2	1
3	0
4	0
Number of cycles carboplatin + etoposide (+ atezolizumab) administered	
Median	4
Range	1-6
Number of cycles of atezolizumab maintenance therapy administered	
Median	2.5
Range	0-15
Starting dose, n	
CBDCA (AUC 5) + etoposide (100 mg/m^2)	10
CBDCA (AUC 5) + etoposide (80-99 mg/m^2)	1
CBDCA (AUC 4) + etoposide (80-99 mg/m^2)	3
CBDCA (AUC 5) + etoposide (<80 mg/m^2)	1
CBDCA (AUC 3.5) + etoposide (<80 mg/m^2)	1
With or without G-CSF prophylaxis, n	
Yes	14
No	2
Prior radiotherapy, n	
Yes	1
No	15
Reason for addition of atezolizumab to carboplatin + etoposide[a], n	
Poor PS	7
Due to complications of immune disease	4
Concurrent with radiotherapy	2
Due to the extensive tumor	1
Elderly	1
Due to complications of pneumothorax	1
Steroid treatment for adverse events[b], n	
Yes	3
No	13
Continuing administration of atezolizumab at data cutoff, n	
Yes	1
No	15

[a]Excluding atezolizumab maintenance therapy; [b]excluding topical agents. PS, performance status; ECOG-PS, Eastern Cooperative Oncology Group-PS; CBDCA, carboplatin; AUC, area under the curve; G-CSF, granulocyte-colony stimulating factor.

Results

Patient backgrounds. A total of 98 patients were screened who received atezolizumab with carboplatin and etoposide combination chemotherapy. Atezolizumab was added from the middle course of carboplatin and etoposide therapy in 16 patients, who were evaluated in the present analysis. The patient selection diagram is shown in Fig. S1. The characteristics of the 16 patients are listed in Table I and detailed clinical information for each patient is presented in Table II. The median age of all patients was 73.5 years (range, 62-79 years), and 14 patients (87.5%) were male. Stage III disease was observed in 1 patient, and stage IV in 15 patients. ECOG-PS at the first administration of carboplatin and etoposide was 0,

Table II. Detailed list of individual patients.

Patient	Age, years	Sex	Smoking history, BI index	Stage	PS at initiation of CE	Cycle no. at addition of atezolizumab	Reason for addition	PS at addition of atezolizumab	Total CE administration cycles	Best overall response	PFS, months	OS, months	Death event	irAE	No. of subsequent-treatment lines
1	78	M	1040	IVB	1	4	Elderly	1	4	PR	5.8	24.4	Yes	-	2
2	76	F	560	IVB	2	4	Poor PS (PS 2)	1	4	PR	5.4	8.7	Yes	-	1
3	66	F	860	IVA	1	2	Concurrent with palliative radiotherapy	1	4	PR	10.4	22.3	No	Hypothyroidism grade 2	1
4	63	M	630	IVB	2	2	Poor PS (PS 2)	1	2	PD	0.8	2.3	No	-	1
5	75	M	1480	IVA	0	2	Complications of immune disease (untreated hyperthyroidism)	0	4	PR	2.6	11.3	Yes	-	1
6	72	M	2400	IVA	1	3	Complications of immune disease (ILD)	1	4	PR	4.9	7.0	Yes	Pneumonitis grade 3	0
7	75	M	1080	IIIA	0	3	Complications of immune disease (ILD)	0	4	PR	14.3	14.3	No	Adrenal insufficiency grade 2, skin rash grade 1	On maintenance therapy at data cut-off
8	65	M	1800	IVA	3	2	Poor PS (PS 3)	2	6	SD	4.4	6.6	Yes	-	1
9	72	M	520	IVB	2	2	Extensive tumor	1	4	PR	11.2	12.9	No	-	1
10	74	M	1120	IVB	2	2	Poor PS (PS 2)	1	2	PR	2.0	2.0	Yes	-	0
11	73	M	2120	IVB	2	5	Poor PS (PS 2)	1	4	PR	8.0	21.9	Yes	-	3
12	75	M	1560	IVB	3	2	Poor PS (PS 3)	1	3	PR	5.3	14.0	Yes	-	1
13	74	M	1650	IVB	3	3	Poor PS (PS 3)	1	4	PR	7.4	12.9	No	-	0
14	79	M	2400	IVB	3	2	Concurrent with palliative radiotherapy	1	4	SD	7.8	10.0	Yes	-	0
15	70	M	960	IVA	0	3	Complications of pneumothorax	1	4	PR	3.1	13.0	Yes	-	1
16	62	M	1260	IVB	1	2	Complications of immune disease (RA)	1	4	PD	2.7	4.5	Yes	-	1

BI, Brinkman index; PS, performance status; CE, carboplatin and etoposide; PFS, progression-free survival; OS, overall survival; irAE, immune-related adverse event; ILD, interstitial lung disease; PR, partial response; SD, stable disease; PD, progressive disease; RA, rheumatoid arthritis; M, male; F, female.

1, 2 and 3 in 3, 4, 5 and 4 patients, respectively. Meanwhile, ECOG-PS in patients with the addition of atezolizumab was 0, 1 and 2 in 2, 13 and 1 patient, respectively. The number of cycles with atezolizumab addition was 2, 3, 4, and 5 in 10, 3, 2 and 1 patient, respectively. The median number of carboplatin and etoposide (plus atezolizumab) administration cycles was 4 (range, 1-6). The most common doses of carboplatin and etoposide were AUC 5 mg/min/ml and 100 mg/m^2, respectively (n=10; 62.5%). Only 1 patient received palliative radiotherapy before atezolizumab administration. The most common reason for adding atezolizumab to carboplatin and etoposide therapy was poor PS, followed by complications from autoimmune diseases.

Treatment efficacy. Treatment response results are shown in Table III. The median follow-up period was 12.1 months (range, 1.9-24.3 months). Although a complete response was not achieved in any patient, a partial response (PR) was observed in 12 patients, stable disease (SD) in 2 and PD in 2. The response and disease control rates were 75.0% [95% confidence interval (CI), 50.0-90.2] and 87.5% (95% CI, 62.7-97.7), respectively. The median PFS and OS times were 5.3 months (95% CI, 2.6-7.8 months) and 13.0 months (95% CI, 6.9-24.3 months), respectively (Fig. 1). All 11 deaths in the study were directly attributable to SCLC events. The swimmer plot shown in Fig. 2 shows the duration of carboplatin and etoposide treatment, the duration of atezolizumab plus carboplatin and etoposide treatment, and the duration of PPS of atezolizumab plus carboplatin and etoposide after PD in all 16 patients. Long-term survivors with a median survival time of ≥13.0 months tended to have a longer PPS after adding atezolizumab to carboplatin and etoposide therapy, with PPS accounting for more than one-half of the survival period, except for 1 patient who remained on atezolizumab maintenance therapy. All patients achieved a PR.

Toxicity. Treatment-related adverse events were assessed in all 16 patients (Table IV). Adverse events of any grade were observed in all 16 patients, and an adverse event that led to discontinuation of treatment (pneumonia grade 3) occurred in 1 patient. The most common treatment-related adverse event was hematological toxicity. The most frequent adverse events of any grade were decreased platelet count (n=15; 93.8%), anemia (n=14; 87.5%), decreased white blood cell count (n=11; 68.8%), and decreased neutrophil count (n=10; 62.5%). The incidence of immune-related adverse events was generally low. In 1 patient with a grade ≥3 adverse event, a diagnosis of grade 3 pneumonitis was seen as a serious enough adverse event to discontinue treatment. The patient received prednisolone (0.5 mg/kg) and died of the primary disease. No deaths due to the combination of carboplatin and etoposide (plus atezolizumab) were observed during the study period.

Subsequent treatments. Among the 15 patients who developed PD, 11 received subsequent-line chemotherapy. The most common second-line chemotherapy was amrubicin monotherapy. A total of 5 patients did not receive subsequent treatment for PD after first-line treatment and were treated with the best supportive care alone. The subsequent treatments administered beyond PD are listed in Table SI.

Table III. Treatment response.

Treatment response	Value
Complete response, n	0
Partial response, n	12
Stable disease, n	2
Progressive disease, n	2
Not evaluated	0
Response rate, % (95% CI)	75.0 (50.0-90.2)
Disease control rate, % (95% CI)	87.5 (62.7-97.7)

CI, confidence interval.

Discussion

The efficacy and feasibility of the therapeutic option of adding atezolizumab during carboplatin and etoposide treatment in patients with SCLC has remained to be determined. In the present study, atezolizumab was added to carboplatin and etoposide therapy during treatment, and this revealed favorable efficacy with no new safety concerns in patients with SCLC. This outcome suggests its tolerability in patients with SCLC with problems, such as a poor PS and immune disease complications, at the start of the initial treatment. The efficacy of treatment in the patients enrolled in the present analysis was comparable to that of the atezolizumab plus carboplatin and etoposide arm of the phase III IMpower133 trial (5). Furthermore, the ORR was comparable, while median PFS and OS times in the present study were slightly shorter than those from the atezolizumab plus carboplatin and etoposide clinical practice data in our previous study, which were 73.8%, 5.4 and 15.9 months, respectively (15). The results of the present study suggest that this treatment efficacy is comparable to the conventional results of atezolizumab with carboplatin and etoposide therapy from the first cycle of treatment and may be a sufficient option for clinical practice. Thus, the feasibility of these treatments is considered adequate. It should be emphasized that the novelty of the present study is the clinical significance of intermittent addition of atezolizumab to carboplatin and etoposide therapy during treatment since some concern prevented their initial combination.

Detailed data from the patients are presented in Table II and Fig. 2. In the cohort, 7 of the 16 patients received atezolizumab from an intermittent cycle of carboplatin and etoposide due to a PS of 2-3. Of these patients, 6 improved to a PS of 1, and 1 improved from a PS of 3 to a PS of 2. Therefore, atezolizumab was added to the therapy. There were 4 patients with autoimmune diseases who did not receive atezolizumab at the beginning of carboplatin and etoposide therapy. However, their autoimmune diseases varied widely, and 1 patient with interstitial pneumonia (patient 6) developed drug-induced interstitial pneumonitis after receiving atezolizumab. However, the treatment choice of starting additional doses of atezolizumab after the subsequent cycle is at the discretion of the treating physician and is inconsistent, as shown in Table II. Additionally, in a small number of patients, it is difficult to determine whether there is a survival benefit from adding atezolizumab to the

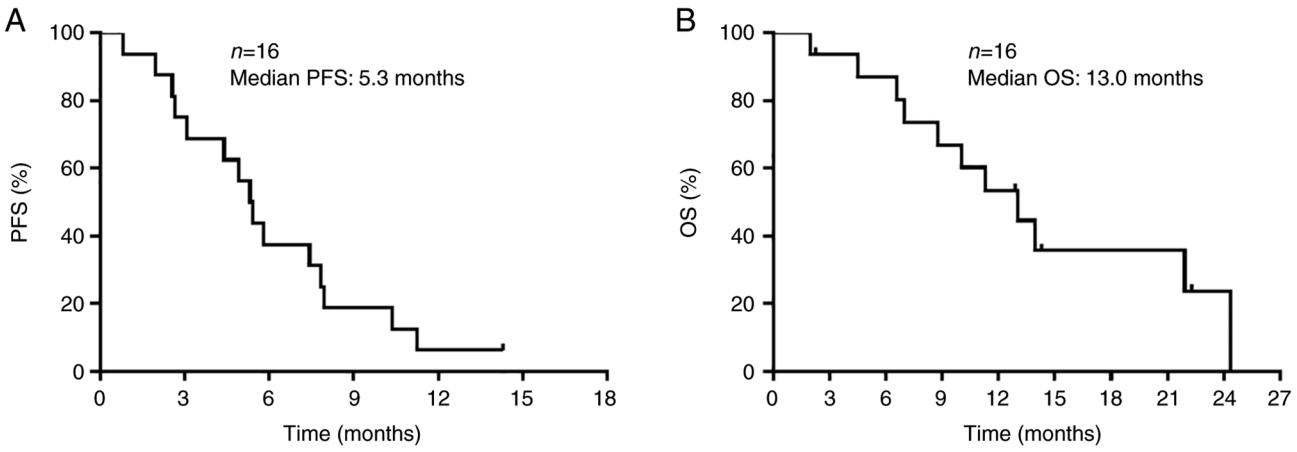

Figure 1. Kaplan-Meier survival curves. (A) PFS of patients with SCLC after adding atezolizumab to carboplatin and etoposide combination therapy during the treatment cycle. The median PFS time was 5.3 months (95% CI, 2.6-7.8 months). (B) OS of patients with SCLC after adding atezolizumab to carboplatin and etoposide combination therapy during the treatment cycle. The median OS time was 13.0 months (95% CI, 6.9-4.3 months). CI, confidence interval; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

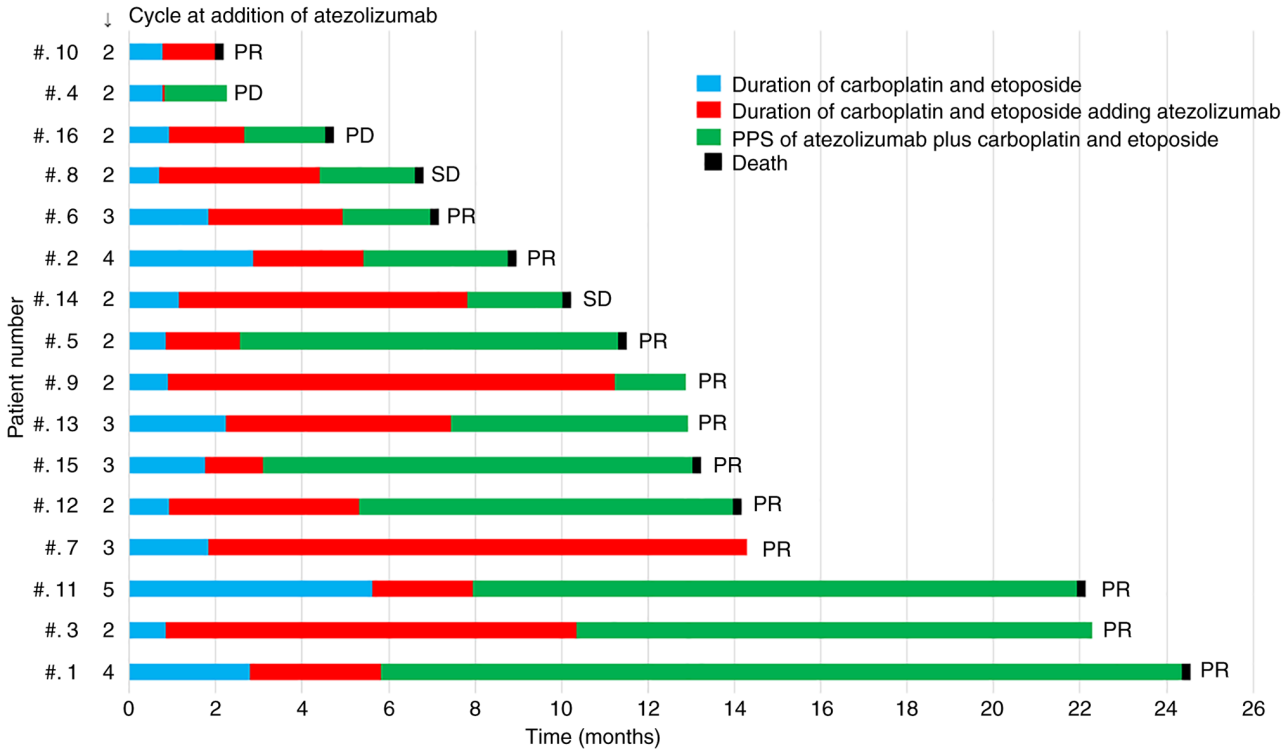

Figure 2. Swimmer chart showing the treatment duration of carboplatin and etoposide, the treatment duration of atezolizumab plus carboplatin and etoposide, and the duration of PPS of atezolizumab plus carboplatin and etoposide after disease progression in the 16 patients. The cycle in which atezolizumab was added and the best overall response in each patient are shown. The numbers (#) correspond to the patient numbers in Table II. PD, progressive disease; SD, stable disease; PR, partial response; PPS, post-progression survival.

combination of carboplatin and etoposide for various reasons during drug therapy. However, all 6 long-term survivors, with a median survival of ≥13 months, achieved a PR and a PS of 0-1 at the beginning of atezolizumab administration. Of these 6 patients, PPS after PD with atezolizumab plus carboplatin and etoposide combination therapy represented more than one-half of the OS time period. These patients received at least one line of anticancer agent therapy as a subsequent treatment, except for 1 patient who continued atezolizumab maintenance therapy at the data cut-off. Of the 6 patients, 4 started with additional atezolizumab after the third cycle. Additionally, all patients with SD or PD had a below median OS time, and 2 patients with PD had a poor OS time of <5 months. A patient with PR (patient 10) died of cerebral infarction and had a short OS time of 2.0 months. Based on the aforementioned data, long-term OS time can be expected even in patients who start combination therapy with carboplatin and etoposide, if the addition of atezolizumab is considered even in the latter half of the combination therapy and if PPS, which accounts for more than half of the OS time period, is controlled.

Table IV. Adverse events.

Adverse event	Any grade, n (%)	Grade ≥3, n (%)
Led to discontinuation	1 (6.3)	1 (6.3)
Led to death	0 (0.0)	0 (0.0)
Treatment-related[a]		
White blood cell decreased	11 (68.8)	8 (50.0)
Neutrophil count decreased	10 (62.5)	9 (56.3)
Anemia	14 (87.5)	3 (18.8)
Platelet count decreased	15 (93.8)	7 (43.8)
Febrile neutropenia	2 (12.5)	2 (12.5)
Immune-related[b]		
Pneumonitis	1 (6.3)	1 (6.3)
Skin rash	1 (6.3)	0 (0.0)
Hypothyroidism	1 (6.3)	0 (0.0)
Adrenal insufficiency	1 (6.3)	0 (0.0)

[a]Treatment-related adverse grade ≥3 events reported in ≥1 patient; [b]immune-related adverse events reported in ≥1 patient.

Regarding safety, the addition of atezolizumab during carboplatin and etoposide treatment was well managed in the current population. However, the percentage of patients who exhibited hematological toxicities, such as decreased neutrophil, white blood cell and platelet count, was higher in the patients in the present study than in the IMpower133 study (5). Furthermore, hematological toxicity was somewhat higher than that in our previously reported cohort, starting with atezolizumab plus carboplatin and etoposide chemotherapy (15). It is possible that hematologic toxicity was slightly higher in this population due to poor PS or other reasons that would have prevented the administration of atezolizumab from the first cycle. These perceptions suggest that the toxicity signal from the addition of atezolizumab during the carboplatin and etoposide treatment period may be feasible in patients with SCLC who have some problems at the beginning of initial therapy.

Although the combination of atezolizumab plus carboplatin and etoposide has recently become a standard treatment choice for patients with ED-SCLC in good general condition, such as a good PS, good organ function and no comorbidities, the efficacy and feasibility of atezolizumab to carboplatin and etoposide treatment for patients with SCLC with any problems at the beginning of initial treatment have not been evaluated. The present analysis demonstrated that treatment with atezolizumab in combination with carboplatin and etoposide therapy has a favorable effect in any untreated patients with ED-SCLC who have problems at the start of first-line treatment. While previous phase III trials on ICIs, such as atezolizumab and durvalumab in combination with platinum and etoposide, have focused on patients with a good PS (PS, 0-1) and enrolled patients with strict eligibility criteria, such as lack of palliative radiotherapy or absence of complications of autoimmune or interstitial lung diseases (5,16), the patients in the present study not only had a poor PS, but were also heterogeneous in their population characteristics (i.e., patients included those with autoimmune diseases, elderly patients and patients who had started concurrent radiotherapy). However, the efficacy and safety results of this analysis suggest that the addition of atezolizumab to carboplatin and etoposide therapy may be a treatment option for such patients.

There are some limitations to the present analysis. Firstly, the current study was retrospective with a small sample size. Therefore, it is an exploratory study and cannot be definitive. Although it does suggest a possible treatment option, further validations are needed to evaluate the clinical efficacy and feasibility of the findings. Secondly, the treatment strategy of starting carboplatin and etoposide at the beginning of initial treatment and adding atezolizumab during the treatment cycle is largely at the discretion of the physician according to the policy of each institution. Similarly, the physician decides whether to reduce, delay or skip chemotherapeutic agents. These decisions of individual physicians and institutions are undeniably subject to selection bias, which is an inherent s of retrospective analyses. It is necessary to interpret the present results cautiously, as this bias may have affected the effectiveness of the treatment.

The results of the present study demonstrate that adding atezolizumab to carboplatin and etoposide therapy during the treatment cycle may be a tolerable therapeutic option with favorable efficacy for patients with SCLC with any problems at the start of initial treatment. The present study may therefore provide a new direction in the treatment strategy for patients with any problems at the beginning of the initial treatment cycle. However, this is a small retrospective study, and further validation in clinical practice is needed.

Acknowledgements

The authors would like to thank Ms. Kyoko Nakagawa (International Medical Center, Saitama Medical University, Saitama, Japan), Dr Kosuke Hashimoto (International Medical Center, Saitama Medical University, Saitama, Japan), Dr Yu Miura (International Medical Center, Saitama Medical University, Saitama, Japan), Dr Fuyumi Nishihara (International Medical Center, Saitama Medical University, Saitama, Japan) and Dr Kunihiko Kobayashi (International Medical Center, Saitama Medical University, Saitama, Japan) for their assistance in preparing the manuscript.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

TT and HI designed the study. YN, YU, AS, JS, OY, AM, HT, TI and HK were responsible for the acquisition of data, and HI and KK performed the analysis and interpretation of data. TT,

HI and KK prepared and wrote the original draft of the manuscript. YN, YU, AS, JS, OY, AM, HT, TI and HK reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. TT, HI and KK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

All procedures complied with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. The study design was approved by the Institutional Ethics Committee of The International Medical Center, Saitama Medical University (Hidaka, Japan; approval no. 2021-113). The requirement of written informed consent was waived by the ethics committee of Saitama Medical University due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Barta JA, Powell CA and Wisnivesky JP: Global epidemiology of lung cancer. Ann Glob Health 85: 8, 2019.
2. Byers LA and Rudin CM: Small cell lung cancer: Where do we go from here? Cancer 121: 664-672, 2015.
3. Farago AF and Keane FK: Current standards for clinical management of small cell lung cancer. Transl Lung Cancer Res 7: 69-79, 2018.
4. Schabath MB, Nguyen A, Wilson P, Sommerer KR, Thompson ZJ and Chiappori AA: Temporal trends from 1986 to 2008 in overall survival of small cell lung cancer patients. Lung Cancer 86: 14-21, 2014.
5. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, *et al*: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379: 2220-2229, 2018.
6. Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, Garassino MC, De Castro Carpeno J, Califano R, Nishio M, *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 39: 619-630, 2021.
7. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol 5: 649-655, 1982.
8. Girling DJ: Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: A stopped multicentre randomised trial. Medical research council lung cancer working party. Lancet 348: 563-566, 1996.
9. Souhami RL, Spiro SG, Rudd RM, de Elvira MC, James LE, Gower NH, Lamont A and Harper PG: Five-day oral etoposide treatment for advanced small-cell lung cancer: Randomized comparison with intravenous chemotherapy. J Natl Cancer Inst 89: 577-580, 1997.
10. Okamoto H, Watanabe K, Kunikane H, Yokoyama A, Kudoh S, Asakawa T, Shibata T, Kunitoh H, Tamura T and Saijo N: Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer 97: 162-169, 2007.
11. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, *et al*: The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 11: 39-51. 2016.
12. Imai H, Nagai Y, Minemura H, Tsuda T, Yamada Y, Wasamoto S, Kishikawa T, Shiono A, Shiihara J, Yamaguchi O, *et al*: Efficacy and safety of amrubicin monotherapy after atezolizumab plus carboplatin and etoposide in patients with relapsed small-cell lung cancer. Invest New Drugs 40: 1066-1079, 2022.
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
14. National Cancer Institute: CTCAEv 5.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed January 4, 2023.
15. Shiono A, Imai H, Wasamoto S, Tsuda T, Nagai Y, Minemura H, Yamada Y, Kishikawa T, Umeda Y, Takechi H, *et al*: Real-world data of atezolizumab plus carboplatin and etoposide in elderly patients with extensive-disease small-cell lung cancer. Cancer Med 12: 73-83, 2022.
16. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Özgüroğlu M, Ji JH, *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 394: 1929-1939, 2019.