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SHORT REPORT

Atezolizumab plus carboplatin and etoposide in small cell lung cancer patients previously treated with platinum-based chemotherapy

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Summary
Although immune checkpoint inhibitors have improved the survival of small cell lung cancer (SCLC) patients, their efficacy in SCLC patients who relapsed after systemic chemotherapy is unclear. This retrospective study aimed to investigate the utility of treatment with atezolizumab plus carboplatin and etoposide in SCLC patients previously treated with platinum-based chemotherapy. We retrospectively screened consecutive eight SCLC patients who received atezolizumab plus carboplatin and etoposide after platinum-based chemotherapy. We evaluated the efficacy of this treatment and its association with programmed cell death-ligand 1 (PD-L1) expression. Three and five patients had sensitive relapse and refractory relapse for first-line platinum-based chemotherapy, respectively. The overall response rate and disease control rate was 37.5% and 75.0%, respectively. Median progression-free survival was 4.0 months. Out of three patients who achieved clinical response, two patients had refractory relapse for first-line platinum-based chemotherapy. No patient exhibited PD-L1 expression. Atezolizumab plus carboplatin and etoposide therapy was effective in SCLC patients with sensitive and refractory relapse and might be a second-line treatment option for SCLC patients previously treated with platinum-based chemotherapy.

Keywords Small cell lung cancer · Immune checkpoint inhibitor · PD-L1 · Chemotherapy

Introduction

Small cell lung cancer (SCLC) comprises approximately 15% of all lung cancer cases and has rapid progression [1]. Despite high sensitivity of SCLC to chemotherapy and radiotherapy, most patients experience relapse within a year of treatment [2]. Recently, immune checkpoint inhibitors have been used as a new treatment strategy in various malignancies [3]. Addition of anti-programmed cell death-ligand 1 (PD-L1) antibodies including atezolizumab and durvalumab to platinum-based chemotherapy showed clinical benefits for untreated advanced SCLC patients [4, 5]. However, the efficacy of immune checkpoint inhibitors in SCLC patients who relapsed after systemic chemotherapy is unclear. This retrospective study evaluated the efficacy of atezolizumab plus carboplatin and etoposide in SCLC patients who were previously treated with platinum-based chemotherapy.

Patients and methods

We retrospectively examined consecutive SCLC patients who were treated with atezolizumab plus carboplatin and etoposide at Kurume University Hospital between October 2019 and March 2020. Eight patients were previously treated with platinum-based chemotherapy. In this study, we defined sensitive relapse in patients who had relapse for more than 90 days after completion of first-line platinum-based chemotherapy and refractory relapse as those who had relapse for during or less than 90 days after completion of first-line chemotherapy.

The sections were mounted onto slides and incubated with anti-rabbit monoclonal antibody against PD-L1 (Cell Signaling Technology, Danvers, MA, USA) for immunohistochemical (IHC) analysis using a BenchMark XT slide staining system (Ventana Automated Systems, Inc., Tucson, AZ,

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USA). For PD-L1 IHC analysis, each specimen should contain more than 100 viable malignant cells, and the percentage of stained malignant cells in the entire area of the tumor (tumor proportion score; TPS) was determined.

Overall response rate (ORR) was defined as the proportion of patients who achieved a complete or partial response according to the Response Evaluation Criteria in Solid Tumors (ver. 1.1). Disease control rate (DCR) was defined as the percentage of patients who achieved complete response, partial response, and stable disease. Stable disease was defined as maintenance between a 30% reduction and a 20% increase of tumor size over six weeks or longer. Progression-free survival (PFS) was defined as the period from the start of treatment to the date of disease progression or death due to any cause. We followed the provisions of the Declaration of Helsinki and obtained study approval from the Institutional Review Board of Kurume University Hospital.

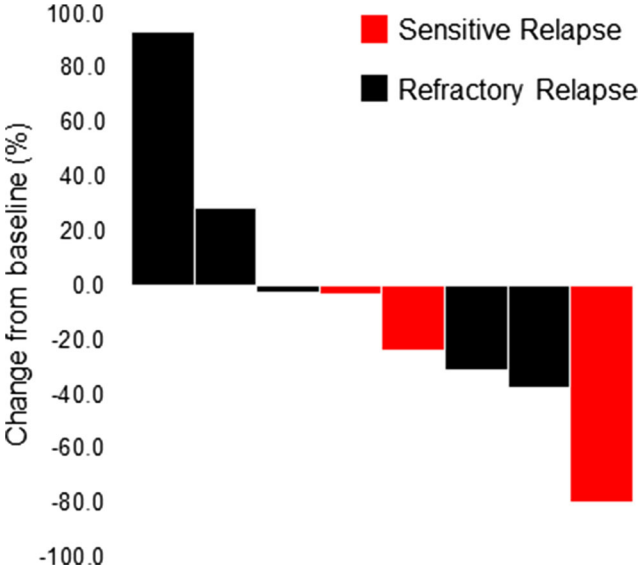

Fig. 1 Waterfall plot of tumor responses from the baseline

Results

The characteristics of the enrolled patients are shown in Table 1. All patients received platinum-based chemotherapy as a first-line treatment. Atezolizumab plus carboplatin and etoposide therapy was used as the second-line, third-line, and fourth-line therapy in one, three, and four patients, respectively. Three and five patients had sensitive and refractory relapse for first-line platinum-based chemotherapy, respectively.

The waterfall plot of response to atezolizumab plus carboplatin and etoposide is shown in Fig. 1. The ORR and DCR were 37.5% and 75.0%, respectively. Median PFS was 4.0 months. Out of three patients who achieved clinical response, two patients had refractory relapse for first-line platinum-based chemotherapy.

Among all patients, adequate tumor samples containing abundant tumor cells were available in seven patients. No patient exhibited PD-L1 expression.

Discussion

The option of second-line or further treatment in SCLC has been limited. Amrubicin and topotecan are standard chemotherapy regimens as monotherapy lead to relapse [2, 6]. In SCLC patients with sensitive relapse, combination chemotherapy with cisplatin, etoposide, and irinotecan (PEI) had better survival than topotecan in randomized phase III trial [7]. However, the PEI schedule is less convenient and has more frequent severe hematological toxicity than topotecan. Therefore, the use of PEI is limited for the treatment of relapsed SCLC.

Results of preliminary phase III clinical trials of treatment with immune checkpoint inhibitors for non-small-cell lung cancer have suggested that PD-L1 expression can predict treatment response [8]. However, PD-L1 expression has not been considered a predictive marker for the efficacy of immune checkpoint inhibitors in SCLC. A phase III clinical trial

Table 1 Patients' characteristics and treatment efficacy

Case	Age	Sex	PS	Treatment line	Relapse style after 1st-line therapy	PD-L1 expression	Efficacy	PFS(months)
Case 1	59	Female	1	4th	Refractory	Negative	PD	0.9
Case 2	68	Male	0	5th	Sensitive	N.A.	PR	4.6
Case 3	66	Male	2	4th	Refractory	Negative	PD	1.5
Case 4	64	Male	1	2nd	Sensitive	Negative	SD	4.0
Case 5	63	Female	0	3rd	Refractory	Negative	PR	5.0
Case 6	70	Male	0	4th	Sensitive	Negative	SD	4.8
Case 7	44	Male	0	3rd	Refractory	Negative	PR	N.R.
Case 8	69	Male	2	3rd	Refractory	Negative	SD	1.0

PS, performance status; PD-L1, programmed cell death ligand-1; N.A., not applicable; PR, partial response; SD, stable disease; PD, progressive disease; N.R., not reach

reported that PD-L1 expression was not associated with the efficacy of immune checkpoint inhibitors [4, 5]. In our study, patients, in whom PD-L1 expression could be analyzed, had negative expression for PD-L1. Thus, PD-L1 expression might not be a biomarker for atezolizumab plus carboplatin and etoposide in second-line or later treatment for relapsed SCLC patients.

In clinical practice, re-challenge treatment with platinum-based chemotherapy has been used conventionally in patients with relapsed SCLC. Although the significance of re-challenge platinum-based chemotherapy has been controversial, several studies reported that it might have clinical benefits for patients with SCLC and sensitive relapse. In this study, all enrolled patients received prior platinum-based chemotherapy, and atezolizumab plus carboplatin and etoposide treatment was effective in SCLC patients with sensitive and refractory relapse.

Several studies investigated the efficacy of anti-PD-1/PD-L1 inhibitors in SCLC relapse after platinum-based chemotherapy and reported that the ORR and DCR of anti-PD-1/PD-L1 inhibitor monotherapy were 2.3–33.0% and 21.0–33.0%, respectively [9]. Although the present study included a relatively small number of patients, the ORR and DCR in our cohort were higher than those reported in previous studies. Therefore, the antitumor effect of immunotherapy can be increased by combining it with platinum-based chemotherapy.

Our study had some limitations. The number of patients analyzed in this study was relatively low, and the data were collected retrospectively. Additionally, the follow-up time was too short to analyze the survival data. Therefore, further prospective clinical trials are warranted to clarify the efficacy of atezolizumab plus carboplatin and etoposide treatment in SCLC patients with relapse.

In conclusion, our study findings showed that treatment with atezolizumab plus carboplatin and etoposide was effective in SCLC patients with sensitive and refractory relapse and therefore can be considered a treatment option for second-line or further treatment in SCLC patients who have received platinum-based chemotherapy.

Authors' contributions HI, KA: Concept and design, HI, KA, NM, TT: Care of patients, acquisition of data, HI, AK: Analysis and interpretation of data, HI, KA: Writing the original draft, HI, KA, AK, NM, TT, TH: Review and editing the manuscript.

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Compliance with ethical standards

Conflict of interest Dr. Ishii reports grants and personal fees from Boerhinger-Ingelheim, personal fees from Ono Pharmaceutical, personal fees from Chugai Pharmaceutical, personal fees from Astra Zeneca, outside the submitted work. Dr. Azuma reports personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from MSD Oncology, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Chugai Pharma, outside the submitted work. Dr. Kawahara has nothing to disclose. Dr. Matsuo reports personal fees from Boerhinger-Ingelheim, personal fees from Chugai Pharmaceutical, outside the submitted work. Dr. Tokito reports personal fees from Ono Pharmaceutical, personal fees from MSD Oncology, personal fees from Chugai Pharmaceutical, personal fees from Astra Zeneca, outside the submitted work. Dr. Hoshino reports grants from GSK Japan, grants from Novartis Pharmaceuticals Japan, grants from Chugai Pharmaceutical Co. Ltd., outside the submitted work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the declaration of Helsinki and ethical standards of the institutional research committee.

Consent to participate Patient samples (anonymized) were taken as part of routine clinical care.

Consent for publication Patient samples (anonymized) were taken as part of routine clinical care.

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