


CASE REPORT

Atezolizumab in combination with carboplatin and etoposide for heavily treated small cell lung cancer

Nobutaka Kataoka, Yusuke Kunitatsu, Yusuke Tachibana, Takumi Sugimoto, Izumi Sato, Nozomi Tani, Yuri Ogura, Kazuki Hirose & Takayuki Takeda 

Department of Respiratory Medicine, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

Keywords

Atezolizumab; carboplatin; etoposide; retreatment; small cell lung carcinoma.

Correspondence

Takayuki Takeda, Department of Respiratory Medicine, Japanese Red Cross Kyoto Daini Hospital, 355-5, Haruobi-cho, Kamanza-dori, Marutamachi-agaru, Kamigyo-ku, Kyoto 602-8026, Japan.

Tel: +81 75 231 5171

Fax: +81 75 256 3451

Email: dyckw344@yahoo.co.jp

Received: 12 June 2020;

Accepted: 8 July 2020.

doi: 10.1111/1759-7714.13588

Thoracic Cancer **11** (2020) 2740–2742

Abstract

Atezolizumab was the first immune checkpoint inhibitor (ICI) to be introduced as a first-line treatment option for extensive-stage small cell lung cancer (ES-SCLC), in combination with carboplatin and etoposide (CE) chemotherapy. However, SCLC treatment options after progression to first-line chemotherapy are limited, warranting the readministration of previously used drugs. In combination with atezolizumab, CE readministration may theoretically be effective, based on two tentative mechanisms: its additive and synergistic effects on cytotoxic chemotherapy. The additive effect is based on the IFCT-1603 trial in which the Kaplan-Meier estimates of both progression-free survival (PFS) and overall survival (OS) in the atezolizumab group exhibited a tail plateau in the selected population. Conversely, an anti-PD-L1 antibody synergistic effect on platinum compounds was assessed in a preclinical study, which was reinforced by clinical data. Thus, atezolizumab in combination with CE may be a treatment option in heavily treated patients. Here, we describe the first case of a heavily treated ES-SCLC patient treated with chemoimmunotherapy, resulting in a partial response and a durable PFS.

Key points

Significant findings of the study and what this study adds: CE readministration with atezolizumab may be effective based on two tentative mechanisms. Additive and synergistic effects of atezolizumab on CE have been previously suggested via a clinical trial and preclinical study, respectively. This is reflected in the current case in clinical settings.

Introduction

The introduction of immune checkpoint inhibitors (ICIs) has revolutionized the treatment strategy of non-small cell lung cancer (NSCLC) without an oncogenic driver mutation. Atezolizumab, a humanized monoclonal anti-programmed death ligand 1 (PD-L1) antibody, was the first ICI to be introduced as an extensive stage small cell lung cancer (ES-SCLC) first-line treatment, in combination with carboplatin and etoposide (CE) chemotherapy (IMpower133 trial). In the IMpower133 trial, atezolizumab and CE exhibited a significant improvement over the placebo group, in both overall survival (OS) and progression-free survival (PFS).¹ After progression to first-line treatment, the remaining options are limited to

amrubicin, irinotecan, and topotecan therapy. Sometimes, this scarcity leads to the readministration of previously used drugs in heavily treated patients.

Readministration of CE in combination with atezolizumab has not previously been reported. Here, we describe an ES-SCLC patient in whom atezolizumab plus CE showed a partial response after disease progression, following the second readministration of CE.

Case report

A 60-year-old male ES-SCLC patient had been previously diagnosed (cT4N3M1a [PUL], stage VIA) 35 months

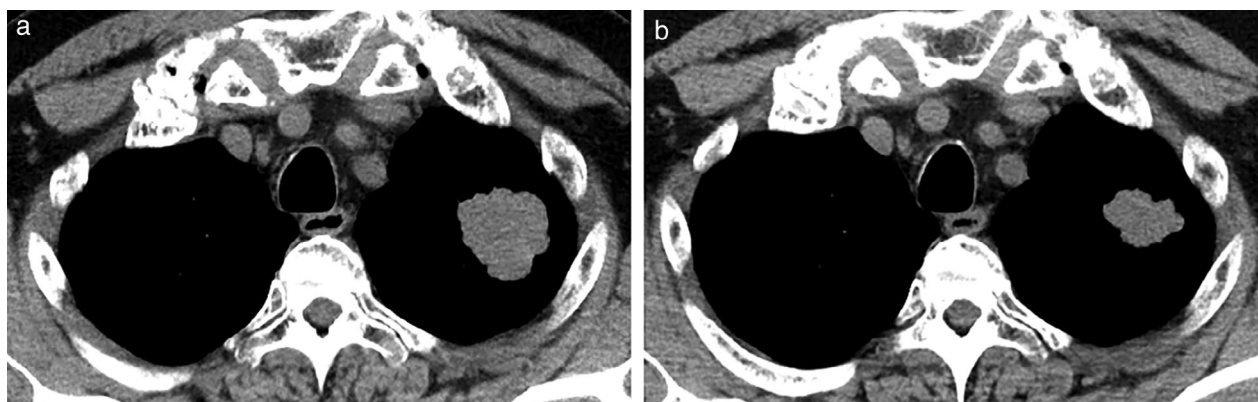


Figure 1 Chest computed tomography in axial slices (a) before; and (b) after three cycles of chemoimmunotherapy induction with atezolizumab, carboplatin, and etoposide. The primary site located at S¹+²a of the left upper lobe shrunk after treatment, exhibiting a partial response in coronal slices (not shown).

before the start of this study, and had been treated with the following regimens and response evaluations: CE for four cycles with a partial response (PR) and a time to progression (TTP) of nine months, CE rechallenge as a sensitive relapse for four cycles with stable disease (SD) and a TTP of nine months, amrubicin for six cycles with SD, and a TTP of six months with brain metastasis as a progressive disease (PD) site treated using stereotactic radiosurgery (SRS), irinotecan for six cycles with SD and a TTP of six months, and CE rechallenge for the third time administration for two cycles with PD and a TTP of two months.

After three months of treatment holiday following PD with third time CE, atezolizumab and CE were administered, which resulted in a PR after three cycles at the primary site (Fig 1) and in SD with a limited tumor shrinkage

of brain metastasis (Fig 2). After four cycles of induction treatment, atezolizumab continuation maintenance therapy was followed for two cycles, and the response remained durable for five months with an ongoing regimen without any immune-related adverse events.

Discussion

SCLC is the most aggressive and devastating lung cancer type, which progresses rapidly. However, ES-SCLC treatment strategies have not changed over the past two decades,² in contrast with NSCLC.

SCLC has diverse tumor suppressor gene targets, and mutations or functional alterations in *TP53*, *RB1*, and *MYC* families genes³ pose potential targeted therapies via

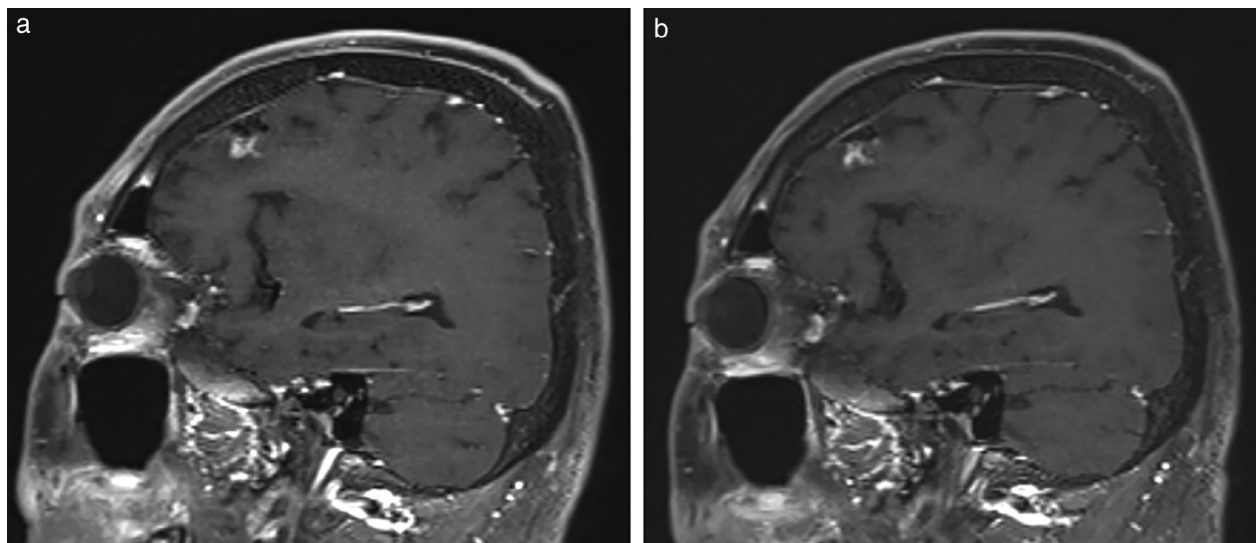


Figure 2 Brain enhanced magnetic resonance imaging (a) before; and (b) after four cycles of chemoimmunotherapy induction with atezolizumab, carboplatin, and etoposide. The shrinkage of brain metastasis after four induction therapies was limited, with a stable disease.

cellular apoptotic pathway. However, these have not been established as standard SCLC therapies, possibly due to the high sensitivity of SCLC which has previously been reported to initial platinum doublet chemotherapy with OS for 9.3 to 12.8 months,^{4–6} which hampers targeted therapies to show superior or noninferior effects over the pre-existing standard platinum doublet chemotherapy. Therefore, the role of targeted therapies in SCLC may be limited.

Conversely, SCLC frequently develops paraneoplastic syndromes through its potentially high immunogenicity, such as Lambert-Eaton myasthenic syndrome and limbic encephalitis, or paraneoplastic cerebellar degeneration via several antibodies affecting the neuromuscular junction and central nervous system, respectively.⁷ The potential high immunogenicity of SCLC has been considered a theoretical basis for the introduction of ICIs in SCLC treatment.

Under such circumstances, the IMpower133 trial confirmed atezolizumab and CE efficacy as an ES-SCLC first-line treatment.¹ However, chemoimmunotherapy efficacy on ES-SCLC is limited in chemotherapy-naïve ES-SCLC, and its effect on previously treated ES-SCLC has not been explored.

The documented efficacy of CE readministration in combination with atezolizumab in the current case may be based on two tentative theories: the additive and synergistic effects of atezolizumab on cytotoxic chemotherapy. The additive effect of atezolizumab in the current case is better understood, as CE readministration immediately before the current treatment resulted in PD. Atezolizumab monotherapy in patients treated with first-line platinum-etoposide chemotherapy has previously demonstrated efficacy (IFCT-1603 trial), in which the response rate and median PFS were 2.3% and 1.4 months, respectively.⁸ Although the IFCT-1603 trial resulted in a negative result, Kaplan-Meier estimates of both PFS and OS in the atezolizumab group exhibited a tail plateau, suggesting that there is a selected population who may benefit from SCLC second-line atezolizumab monotherapy. Conversely, anti-PD-L1 antibody synergistic effect on cytotoxic chemotherapy is based on the cancer-immunity cycle model.⁹ Cytotoxic chemotherapy may accelerate the release of neoantigen, which is a key element of the priming phase in the cancer-immunity cycle, and changes the immune status from “immune desert” to “immune inflamed” where an ICI can exert its power more effectively.¹⁰ The synergistic effect of anti-PD-L1 antibody on platinum compounds has been assessed in a preclinical study using an NSCLC model, which was reinforced by clinical data elucidating PD-L1 expression changes in the tumor obtained before and after neoadjuvant platinum-doublet chemotherapy.¹¹ The PD-L1 expression in SCLC¹² is relatively low compared with NSCLC, which may also be a limitation of the proposed synergistic mechanism.

Chemoimmunotherapy efficacy on brain metastasis may have been limited due to previous SRS, which decreased

viable tumor cells, compared to the primary site. However, chemoimmunotherapy in heavily treated ES-SCLC may also be effective for brain metastases without SRS.

Considering the above-mentioned mechanism and atezolizumab and CE efficacy observed in this case, an atezolizumab-containing regimen may be a treatment option in cases without exposure to anti-PD-L1 antibodies.

Disclosure

The authors declare no conflicts of interest.

References

- Horn L, Mansfield AS, Szczesna A *et al.* First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018; **379**: 2220–9.
- Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. *Transl Lung Cancer Res* 2018; **7**: 69–79.
- George J, Lim JS, Jang SJ *et al.* Comprehensive genomic profiles of small cell lung cancer. *Nature* 2015; **524**: 47–53.
- Fukuoka M, Furuse K, Saijo N *et al.* Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst* 1991; **83**: 855–61.
- Noda K, Nishiwaki Y, Kawahara M *et al.* Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; **346**: 85–91.
- Hanna N, Bunn PA Jr, Langer C *et al.* Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006; **24**: 2038–43.
- Pelosof LC, Gerber DE. Paraneoplastic syndromes: An approach to diagnosis and treatment. *Mayo Clin Proc* 2010; **85**: 838–54.
- Pujol JL, Greillier L, Audigier-Valette C *et al.* A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: results from the IFCT-1603 trial. *J Thorac Oncol* 2019; **14**: 903–13.
- Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. *Immunity* 2013; **39**: 1–10.
- Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature* 2017; **541**: 321–30.
- Fournel L, Wu Z, Stadler N *et al.* Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer. *Cancer Lett* 2019; **464**: 5–14.
- Schultheis AM, Scheel AH, Ozretić L *et al.* PD-L1 expression in small cell neuroendocrine carcinomas. *Eur J Cancer* 2015; **51**: 421–6.