CASE REPORT

Tolerability and efficacy of IMpower133 regimen modified for dialysis patients with extensive-stage small cell lung cancer: Two case reports

Naokazu Watari | Kakuhiro Yamaguchi | Takeshi Masuda | Noriaki Ito
Shinjiro Sakamoto | Yasushi Horimasu | Shintaro Miyamoto | Taku Nakashima
Hiroshi Iwamoto | Kazunori Fujitaka | Hironobu Hamada | Noboru Hattori

Department of Respiratory Medicine, Hiroshima University Hospital, Hiroshima, Japan

Correspondence
Kakuhiro Yamaguchi, Department of Respiratory Medicine, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
Email: yamaguchikakuhiro@gmail.com

Abstract
The IMpower133 regimen, composed of atezolizumab/etoposide (VP-16)/carboplatin (CBDCA), is the standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC). However, the safety and efficacy of triplet therapy in patients receiving dialysis have not been sufficiently evaluated. Here, we report two cases of dialysis patients with ES-SCLC who received the modified IMpower133 regimen. Patient 1 was a 69-year-old man, and patient 2 was a 73-year-old man who received dialysis because of end-stage renal failure caused by diabetic nephropathy. Both patients received a modified IMpower133 regimen in the following order: atezolizumab (1200 mg/body) on Day 1, VP-16 (50 mg/m²) on days 1 and 3, and CBDCA (300 mg/m²) on day 1. Four hours of dialysis was performed 1 hour after completing the administration of CBDCA on Day 1 and 2 hours after completing the administration of VP-16 on Day 3. Both patients achieved a partial response (PR) and received atezolizumab maintenance therapy after four cycles of triplet therapy without uncontrollable adverse events. By modifying the dosage, the order of drugs, and the timing of dialysis, the IMpower133 regimen may be tolerable and effective for patients receiving dialysis.

KEYWORDS
adverse effects, dialysis, small cell lung carcinoma

INTRODUCTION
One of the standard first-line treatments for extensive-stage small cell lung cancer (ES-SCLC) has become a combination therapy of atezolizumab (an anti-programmed death ligand-1 [PD-L1] antibody), carboplatin (CBDCA), and etoposide (VP-16) because the IMpower133 trial has revealed that the addition of atezolizumab to CBDCA/VP-16 prolongs overall survival. However, the safety of this regimen has not been sufficiently elucidated in patients on dialysis. Herein, we report two cases of patients with ES-SCLC undergoing dialysis who received a modified IMpower133 regimen and achieved partial response (PR) with controllable adverse events.

CASE REPORTS
Two patients with ES-SCLC on dialysis because of chronic renal failure caused by diabetic nephropathy were treated with the modified IMpower133 regimen, which was administered in the order of atezolizumab (1200 mg/body) on Day 1, VP-16 (50 mg/m²) on Days 1 and 3, and CBDCA (300 mg/m²) on Day 1 (Table 1). Four hours of dialysis was performed 1 hour after completing the administration of CBDCA on Day 1 and 2 hours after completing the administration of VP-16 on Day 3. The dose and the order of CBDCA/VP-16 and the timing of dialysis were modified according to the previous reports analyzing the pharmacokinetics of these cytotoxic drugs in ES-SCLC patients on dialysis.
Patient 1 was a 69-year-old man and diagnosed with ES-SCLC (cT1cN3M1a stage IVA). His performance status (PS) was 0. Blood tests revealed that the progastrin-releasing peptide (ProGRP) levels were mildly elevated (Supporting Information Table S1). Contrast-enhanced computed tomography (CT) revealed a 20-mm-sized nodule in the lower left lobe and lymphadenopathy in the bilateral hilar, mediastinum, and right supraclavicular fossa (Figure 1(a) and Figure S1(A)). Therefore, we chose the modified IMpower133 regimen (Table 1). He experienced grade 3 neutropenia and grade 4 thrombocytopenia in the first cycle. Consequently, we reduced CBDCA to 240 mg/m² and used pegfilgrastim (3.6 mg) on day 5 from the second cycle. However, in the second and third cycles, he experienced grade 3 anemia. Therefore, VP-16 was reduced to 40 mg/m² in the fourth cycle. After three cycles of chemotherapy, the patient achieved PR (Figure 1(b)). In all, he received four cycles of chemotherapy followed by maintenance therapy with atezolizumab. After two cycles of atezolizumab, he was diagnosed with progressive disease because of an increased primary lesion and mediastinal lymph node metastasis.

Patient 2 was a 73-year-old man and diagnosed with ES-SCLC (cT2aN1M1b stage IVA). His PS was 1. Blood tests showed elevated ProGRP levels (Supporting Information Table S2). Contrast-enhanced CT showed an 80-mm-sized mass in the upper left lobe (Figure 1(b) and Figure S1(B)). Head magnetic resonance imaging revealed a 40-mm-sized mass with edema in the left frontal lobe. After stereotactic radiotherapy (39 Gy/13 in fractions) for brain metastasis, the modified IMpower133 regimen was administered (Table 1). Considering that his PS was 1 and that moderate to severe hematological toxicity was observed in patient 1, CBDCA was reduced to 240 mg/m², and VP-16 was decreased to 40 mg/m². In the first cycle, hospitalization was required for febrile neutropenia. From the second cycle, CBDCA was reduced to 210 mg/m². After two cycles of chemotherapy, the patient achieved PR (Figure 1(b)). He received four cycles of chemotherapy and maintenance therapy with atezolizumab for 4 months.

### Table 1. Comparison of the IMpower133 regimen with a modified regimen for dialysis patients

| Drug sequence | Drug | Solution | Dosing time |
|---------------|------|----------|-------------|
| **A. IMpower133 regimen** |      |          |             |
| Day 1         | 1    |          |             |
|               | 2    | Atezolizumab (1200 mg/body) | Saline solution 100 mL | 10 min |
|               | 3    |          |             |
|               | 4    | Granisetron 3.0 mg + dexamethasone 6.6 mg | Saline solution 100 mL | 15 min |
|               | 5    | CBDCA (AUC: 5) | 5% glucose solution 250 mL | 60 min |
|               | 6    | VP-16 (100 mg/m²) | Saline solution 500 mL | 60 min |
|               | 7    |          |             |
| Day 2         | 1    | Granisetron 3.0 mg + dexamethasone 6.6 mg | Saline solution 100 mL | 15 min |
|               | 2    | VP-16 (100 mg/m²) | Saline solution 500 mL | 60 min |
|               | 3    |          |             |
| Day 3         | 1    | Granisetron 3.0 mg + dexamethasone 6.6 mg | Saline solution 100 mL | 15 min |
|               | 2    | VP-16 (100 mg/m²) | Saline solution 500 mL | 60 min |
|               | 3    |          |             |
| **B. Modified IMpower133 regimen for dialysis patients** |      |          |             |
| Day 1         | 1    |          |             |
|               | 2    | Atezolizumab (1200 mg/body) | Saline solution 100 mL | 10 min |
|               | 3    |          |             |
|               | 4    | Granisetron 3.0 mg + dexamethasone 6.6 mg | Saline solution 100 mL | 15 min |
|               | 5    | VP-16 (100 mg/m²) | 5% glucose solution 250 mL | 60 min |
|               | 6    | CBDCA (300 mg/m²) | 5% glucose solution 250 mL | 60 min |
|               | 7    |          |             |
| Dialysis (4 h) 1 h after CBDCA administration |      |          |             |
| Day 2         | 1    | Granisetron 3.0 mg + dexamethasone 6.6 mg | Saline solution 100 mL | 15 min |
|               | 2    | VP-16 (50 mg/m²) | 5% glucose solution 250 mL | 60 min |
|               | 3    |          |             |
| Dialysis (4 h) 2 h after VP-16 administration |      |          |             |
DISCUSSION

This paper demonstrates that a combination therapy composed of atezolizumab/VP-16/CBDCA can be safely and effectively administered to dialysis patients with ES-SCLC. Monotherapy of anti-PD-1/PD-L1 antibodies, including atezolizumab, has been reported to be safely administered to dialysis patients for several types of cancers, as shown in Table 2. Additionally, the dose and the administration schedule of CBDCA/VP-16 were modified according to the previous reports analyzing the pharmacokinetics of these cytotoxic drugs in ES-SCLC patients on dialysis. Although the dose of CBDCA/VP-16 and the timing of dialysis were different, Imaji et al. reported that atezolizumab/VP-16 (40 mg/m² on day 1, 2, and 3)/CBDCA (area under the concentration-time curve = 5 on day 1) could be administered to dialysis patients with ES-SCLC, as seen in this report. Therefore, the modified IMpower133 regimen can be a treatment option in patients with ES-SCLC on dialysis.

Atezolizumab binds to PD-L1 and inhibits the interaction between PD-1 on T cells and tumor-bearing PD-L1, followed by enhanced antitumor immune responses. Although T cell function is generally impaired in dialysis patients, the objective response rate of anti-PD-1/PD-L1 antibody was 22.6% in 53 dialysis patients with various cancers (Table 2). This is comparable to that of anti-PD-

FIGURE 1  Clinical course of the chest CT findings. (a) Clinical course of the chest CT findings in patient 1. (a),(c) Chest CT on admission showed a 20-mm-sized nodule in the lower left lobe. Lymphadenopathies were found in the bilateral hilar region and mediastinal region. (b),(d) Chest CT after three cycles of modified IMpower133 regimen showed that all lesions were decreasing in size. (b) Clinical course of the chest CT findings in patient 2. (a) Chest CT on admission showed an 80-mm-sized mass in the left hilar region. (b) After two cycles of modified IMpower133 regimen, chest CT showed that the mass in the left hilar region decreased in size. CT, computed tomography.
In conclusion, the IMpower133 regimen can be a treatment option in patients with ES-SCLC on dialysis by modifying the doses, orders of drugs, and timing of dialysis, although further investigations are needed.

ACKNOWLEDGMENTS
We would also like to thank Editage for carefully proofreading the manuscript.

ORCID
Kakuhiro Yamaguchi https://orcid.org/0000-0002-9117-1934
Takeshi Masuda https://orcid.org/0000-0003-3557-0049

REFERENCES
1. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220–9. https://doi.org/10.1056/NEJMoa1809064
2. Inoue A, Saijo Y, Kikuchi T, Gomi K, Suzuki T, Maemondo M, et al. Pharmacokinetic analysis of combination chemotherapy with carboplatin and etoposide in a small cell lung cancer patient undergoing hemodialysis. Ann Oncol. 2004;15:515-21. https://doi.org/10.1093/annonc/mdh008
3. Takezawa K, Okamoto I, Fukuoka M, Nakagawa K. Pharmacokinetic analysis of carboplatin and etoposide in a small cell lung cancer patient undergoing hemodialysis. J Thorac Oncol. 2008;3:1073–5. https://doi.org/10.1097/JTO.0b013e318183af89
4. Jain J, Stein J, Garje R. Evaluation of checkpoint inhibitors in cancer patients with end-stage renal disease on hemodialysis: case series and review of the literature. J Immunother. 2020;43:244–51. https://doi.org/10.1097/JIT.0000000000000327
5. Imaji M, Fujimoto D, Kato M, Tanaka M, Furuta K, Yamamoto N. Chemotherapy plus atezolizumab for a patient with small cell lung cancer under haemodialysis: a case report and review of literature. Respiril Case Rep. 2021;9:e00741. https://doi.org/10.1002/rcr2.741
6. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol. 2008;3:1526-33. https://doi.org/10.2215/CJN.00950208

7. Zhao B, Zhao H, Zhao J. Efficacy of PD-1/PD-L1 blockade monotherapy in clinical trials. Ther Adv Med Oncol. 2020;12:1–22. https://doi.org/10.1177/1758835920937612

8. Chan KK, Bass AR. Autoimmune complications of immunotherapy: pathophysiology and management. BMJ. 2020;369:m736. https://doi.org/10.1136/bmj.m736

9. Hall KH, Liu Y, Jiang C, Harvey RD. New and worsening long-term immune-related adverse events with PD-1/PD-L1 pathway agents in patients with cancer. Pharmacotherapy. 2020;40:133–41. https://doi.org/10.1002/phar.2354

10. Centanni M, Moes DJAR, Trocóniz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet. 2019;58:835–57. https://doi.org/10.1007/s40262-019-00748-2

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

**How to cite this article:** Watari N, Yamaguchi K, Masuda T, Ito N, Sakamoto S, Horimasu Y, et al. Tolerability and efficacy of IMpower133 regimen modified for dialysis patients with extensive-stage small cell lung cancer: Two case reports. Thorac Cancer. 2021;12:2956–60. https://doi.org/10.1111/1759-7714.14166