Received: 11 August 2021 | Accepted: 9 September 2021

DOI: 10.1111/1759-7714.14166

CASE REPORT

WILEY

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

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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/m^2) on days 1 and 3, and CBDCA (300 mg/m^2) 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 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.[1] 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/m^2) on Days 1 and 3, and CBDCA (300 mg/m^2) 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.[2,3]

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	–	Saline solution 100 mL	10 min
	2	Atezolizumab (1200 mg/body)	Saline solution 250 mL	60 min
	3	–	Saline solution 100 mL	10 min
	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/m^2)	Saline solution 500 mL	60 min
	7	–	Saline solution 100 mL	10 min
Day 2	1	Granisetron 3.0 mg + dexamethasone 6.6 mg	Saline solution 100 mL	15 min
	2	VP-16 (100 mg/m^2)	Saline solution 500 mL	60 min
	3	–	Saline solution 100 mL	10 min
Day 3	1	Granisetron 3.0 mg + dexamethasone 6.6 mg	Saline solution 100 mL	15 min
	2	VP-16 (100 mg/m^2)	Saline solution 500 mL	60 min
	3	–	Saline solution 100 mL	10 min
B. Modified IMpower133 regimen for dialysis patients				
Day 1	1	–	Saline solution 50 mL	10 min
	2	Atezolizumab (1200 mg/body)	Saline solution 250 mL	60 min
	3	–	Saline solution 50 mL	10 min
	4	Granisetron 3.0 mg + dexamethasone 6.6 mg	Saline solution 100 mL	15 min
	5	VP-16 (50 mg/m^2)	5% glucose solution 250 mL	60 min
	6	CBDCA (300 mg/m^2)	5% glucose solution 250 mL	60 min
	7	–	Saline solution 50 mL	10 min
		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
Day 3	1	Granisetron 3.0 mg + dexamethasone 6.6 mg	Saline solution 100 mL	15 min
	2	VP-16 (50 mg/m^2)	5% glucose solution 250 mL	60 min
	3	–	Saline solution 50 mL	10 min
		Dialysis (4 h) 2 h after VP-16 administration		

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/m^2 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/m^2 in the fourth cycle. After three cycles of chemotherapy, the patient achieved PR (Figure 1 (a)). 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/m^2, and VP-16 was decreased to 40 mg/m^2. In the first cycle, hospitalization was required for febrile neutropenia. From the second cycle, CBDCA was reduced to 210 mg/m^2. 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.

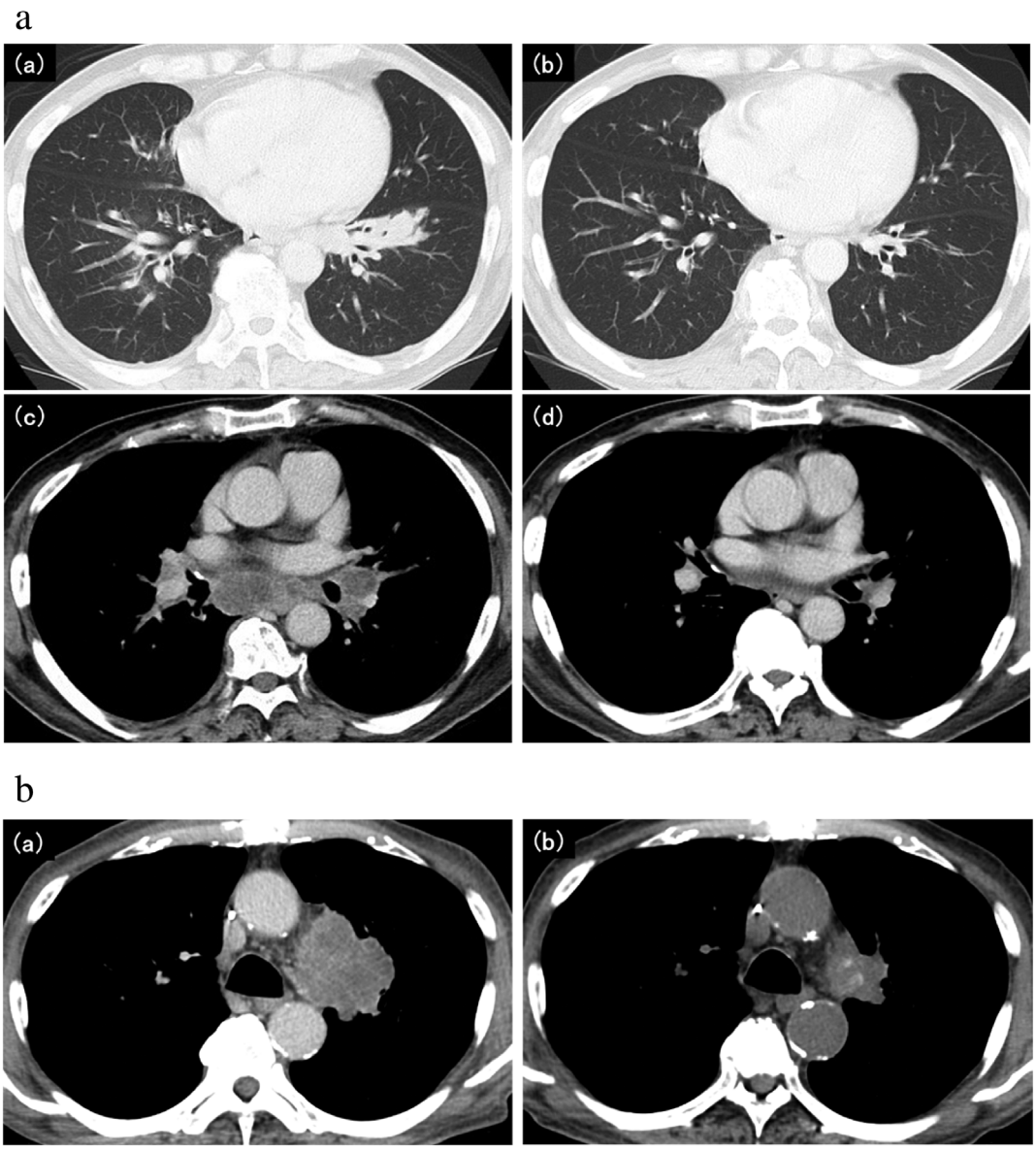

FIGURE 1 Clinical course of the chest CT findings. (a) Clinical course of the chest CT findings in patient 1. (a),(c) Chest CT on admission showed a 20-mm-sized nodule in the lower left lobe. Lymphadenopathies were found in the bilateral hilar region and mediastinal region. (b),(d) Chest CT after three 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

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.[4] 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.[2,3] Although the dose of CBDCA/VP-16 and the timing of dialysis were different, Imaji et al.[5] reported that atezolizumab/VP-16 (40 mg/m^2 on dayd 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,[6] the objective response rate of anti-PD-1/PD-L1 antibody was 22.6% in 53 dialysis patients with various cancers (Table 2).[4] This is comparable to that of anti-PD-

TABLE 2 Summary of prior studies in patients undergoing dialysis treated with an immune checkpoint inhibitor

Immune checkpoint inhibitors	Malignancy	Tumor response	Adverse events
ATE	Urothelial carcinoma: 3 cases, genitourinary cancer: 1 case, lung cancer: 1 case	PR: 1 case SD: 1 case PD: 3 cases	G1 pruritis (1/5), G1 asthenia (1/5), G1 nausea (1/5), G1 dysgeusia (1/5), G1 constipation (1/5), none (4/5)
NIVO	Renal cell carcinoma: 18 cases, genitourinary cancer: 3 cases, melanoma: 2 cases, urothelial carcinoma: 1 case, squamous cell lung cancer: 1 case, Merkel cell carcinoma: 1 case	PR: 7 cases SD: 12 cases PD: 6 cases NA: 1 case	G2 rash (1/26), G2 pneumonitis (1/26), G3 pneumonitis (1/26), G3-4 myocarditis (1/26), G4 encephalitis (1/26), none (14/26)
PEM	Melanoma: 4 cases, head and neck cancer: 3 cases, cutaneous squamous cell cancer: 2 cases, genitourinary cancer: 2 cases, retroperitoneal sarcoma: 2 cases, urothelial carcinoma: 2 cases, angiosarcoma of thigh: 1 case, cholangiocarcinoma: 1 case, hodgkin lymphoma: 1 case, lung cancer: 1 case, renal cell carcinoma: 1 case, squamous cell lung cancer: 1 case	CR: 1 case PR: 3 cases SD: 6 cases PD: 11 cases	G1 fatigue (1/21), G1 rash (1/21), G2 fatigue (2/21), G2 pneumonitis (1/21), hearing loss (grade not reported) (1/21), myositis (Grade not reported) (1/21), hypothyroidism (grade not reported) (2/21), none (13/21)
AVE	Merkel cell carcinoma: 1 case	PD	Hypothyroidism (grade not reported)

Abbreviations: ATE, atezolizumab; AVE, avelumab; CR, complete response; NA, not available; NIVO, nivolumab PD, progressive disease; PEM, pembrolizumab; PR, partial response; SD, stable disease.

1/PD-L1 antibody in non-dialysis patients (20.21%).[7] In line with the antitumor effect, the incidence of immune-related adverse events in dialysis patients was 5.8% for skin disorders, 5.8% for lung disorders, 5.8% for hypothyroidism, and 3.8% for neuromuscular and joint disorders, which were similar to those in non-dialysis patients.[8,9] Additionally, the metabolism of atezolizumab does not differ between patients on dialysis and non-dialysis patients. Atezolizumab binds extensively to target antigens in the plasma or on the cell surface, and then degrades via endocytosis and non-specific proteolytic catabolism. These processes are not influenced by impaired renal function or dialysis.[10] One crucial point is that atezolizumab should be administered before CBDCA/VP-16 in patients on dialysis to keep the interval between administration of cytotoxic drugs and dialysis and avoid volume overload caused by the volume of saline solution (100–375 mL) required to dilute the atezolizumab. Therefore, atezolizumab was intravenously injected before the administration of CBDCA/VP-16 and dialysis in our cases.

In this report, we planned to administer CBDCA (300 mg/m^2) on day 1 and VP-16 (50 mg/m^2) on days 1 and 3, according to the dialysis schedule (Table 1). Previous studies have shown that the pharmacokinetics of CBDCA in patients treated with hemodialysis 1 hour after the end of the CBDCA (300 mg/m^2) infusion is similar to that of patients with normal renal function.[2] Additionally, initiating a 4-hour dialysis 2 hours after completing VP-16 (50 mg/m^2) results in a similar drug metabolism pattern to that of non-dialysis patients treated with VP-16 (100 mg/m^2),[3] allowing the volume of drug diluent to be reduced by the dose reduction of VP-16. Following these findings, we modified the dose and schedule of CBDCA/VP-16.

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.

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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