

Chemotherapy plus atezolizumab for a patient with small cell lung cancer undergoing hemodialysis: A short report

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Research Article

Keywords: extensive-stage small cell lung cancer, carboplatin, etoposide, atezolizumab, hemodialysis

Posted Date: February 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-240530/v1>

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Abstract

Background

The addition of the programmed death-ligand 1 inhibitor atezolizumab to the carboplatin and etoposide combination is the standard first-line treatment for patients with previously untreated extensive-stage small cell lung cancer (ES-SCLC). However, there is little information about its safety in an increasing number of cancer patients undergoing hemodialysis (HD).

Case presentation

An 80-year-old male received carboplatin (AUC = 5 125 mg/body on day 1), etoposide (40 mg/m² on days 1, 2, and 3), and atezolizumab (1200 mg/body on day 1) as the first-line therapy for ES-SCLC. He was undergoing HD thrice a week for 7 years owing to chronic renal failure. HD was provided 16 hours after carboplatin administration. During the first cycle, grade 4 neutropenia (neutrophil count: 74 / μ L) and leukopenia (white blood cell count: 680 / μ L) occurred. Therefore, the chemotherapy was performed with a reduced dose of carboplatin (AUC = 4 100 mg/body) and etoposide (30 mg/m²) from the second to fourth cycles. After 4 cycles, the patient did not develop any severe non-hematologic adverse events, showing a remarkable response.

Conclusion

We conclude that the carboplatin, etoposide, and atezolizumab combination can be safely administered to cancer patients undergoing HD.

1 Introduction

Lung cancer remains a major cause of cancer incidence and mortality worldwide [1]. Small cell lung cancer (SCLC) accounts for 13–17% of all diagnosed lung cancer cases and is characterized by a rapid proliferation of widespread metastases, high growth fragments, and early development [2]. The prognosis of extensive-stage SCLC (ES-SCLC) is very poor, with a 5-year survival rate of only 6–7% [3].

Platinum-based chemotherapy has long been the first-line treatment of choice for ES-SCLC patients [4]. However, the development of immune checkpoint inhibitors such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors has revolutionized the ES-SCLC treatment strategy. More recently, the addition of the PD-L1 inhibitor atezolizumab to the carboplatin and etoposide combination significantly improved overall survival and progression-free survival [4]. Therefore, this treatment has become the standard first-line treatment for patients with previously untreated ES-SCLC [4].

Today, > 1 million people benefit from long-term dialysis worldwide [5]. With the increasing number of hemodialysis (HD) patients, physicians are likely to encounter lung cancer patients with chronic renal failure who are undergoing HD [6]. Since patients undergoing HD have limited renal function, they may require dose reduction to avoid overdose and drug toxicity [5]. Additionally, drug clearance on dialysis must be

considered for proper chemotherapy timing, because HD may also remove the drugs [5]. Nevertheless, the safety of atezolizumab in chemotherapy for ES-SCLC patients undergoing HD has barely been reported.

Herein, we report an ES-SCLC patient undergoing HD who received chemotherapy plus atezolizumab.

2. Case Presentation

An 80-year-old male was diagnosed with relapsed stage IV ES-SCLC (cT4N3M1c; T4 showed a tumor size of > 7 cm, N3 showed enlarged lymph nodes in the contralateral mediastinum, and M1c showed multiple distant metastases to the liver, bone, kidney, and retroperitoneum). The patient's performance status was 1. He had been undergoing HD thrice a week for 7 years due to chronic renal failure. HD was performed using APS-21SA (Asahikasei, Tokyo, Japan) for 4 hours at a time.

We initiated carboplatin (125 mg/body on day 1), etoposide (40 mg/m² on days 1, 2, and 3), and atezolizumab (1200 mg/body on day 1) as the first-line therapy. On day 1 of each cycle, the patient received carboplatin 16 hours before the start of dialysis and received HD thrice a week as usual. During the first cycle, thrombocytopenia (grade 1), neutropenia (grade 4, neutrophil count: 74/μL), and leukopenia (grade 4, white blood cell count: 680/μL) were observed. He did not develop any severe non-hematologic adverse events.

The second, third, and fourth chemotherapy cycles were performed with a reduced dose of carboplatin (100 mg/body) and etoposide (30 mg/m²), since grade 4 neutropenia occurred during the first cycle. After the initiation of the second cycle, the patient developed grade 3 neutropenia but did not develop any severe non-hematologic adverse events.

After four cycles of therapy, contrast-enhanced chest-abdominal computed tomography and brain magnetic resonance imaging showed marked tumor shrinkage (Fig. 1). At present, the patient has received atezolizumab maintenance therapy for 4 months.

3 Discussion

The patient presented in this case exhibited a remarkable response to carboplatin, etoposide, and atezolizumab despite the dose and schedule adjustment due to HD. Additionally, he did not develop any severe adverse events.

The metabolic and excretion routes of each drug in patients with normal organ function are reported as follows: carboplatin is not the first drug to bind into proteins, but the majority of the drugs bind to proteins by 24 hours, whereas 55–70% of the drugs become excreted by the kidneys during the first 24 hours [7]. Etoposide is excreted by the kidneys in 56% of the doses found in urine (45% as an invariant drug), and the remaining 44% is excreted through the bile and stool [8]. Atezolizumab is thought to be metabolized and excreted in the same way as other monoclonal antibodies (mAbs). Because of their molecular size, mAbs are not excreted in the urine, but are metabolized to peptides and amino acids that can be reused by the body for de novo synthesis of proteins, or are excreted by the kidneys [9].

In this case, we administered carboplatin (AUC = 5 125 mg/body on day 1) 16 hours before the start of dialysis. The culvert formula has been extensively used to determine carboplatin dosing for fixed AUC and glomerular filtration rate (GFR). This formula can be used in patients with end-stage renal disease undergoing HD by assuming a zero GFR [5, 7]. If HD is provided in the first 12–18 hours after infusion, approximately 70% of the carboplatin is removed, and the drug remainder lasts until the next dialysis session. Additionally, the results of dialysis 16 hours after administration showed that the AUC was similar to that of patients with normal renal function, according to a previous report [7]. As for the etoposide, a dose reduction should be recommended in HD patients based on the studies conducted in this cohort [5]. It recommended that the etoposide dose should be reduced by 50% and administered at a dose of 25–75 mg/m²/day to avoid hematological toxicity in patients with renal insufficiency. Furthermore, HD does not primarily remove etoposide; hence, it can be administered before or after an HD session [8]. Finally, given the significant molecular weight of atezolizumab (145 kDa) and its physicochemical characteristics, drug removal through dialysis is unlikely, with the blood concentration staying the same irrespective of HD [10]. The results of previous reports [11–14] on PD-1/PD-L1 inhibitor for lung cancer patients on HD are summarized in Table 1. Therefore, from these results, we initiated carboplatin (AUC = 5 125 mg/body on day 1), etoposide (40 mg/m² on days 1, 2, and 3), and atezolizumab (1200 mg/body on day 1).

Table 1
Published cases who received PD-1/PD-L1 inhibitor for lung cancer during hemodialysis

Reference	N	Disease	Regimen	Dose (schedule)	HD schedule	Adverse events (grade ≥ 3)	Response
Our case	1	SCLC	CBDCA Etoposide Atezolizumab	125 mg/body (day 1) 40 mg/m ² (days 1, 2, 3) 1200 mg/body (day 1)	16 h after the initiation of CBDCA	Neutropenia, leukopenia	PR
Ishizuka et al. [11]	1	NSCLC	Pembrolizumab	200 mg/body	Detail unknown	None	PR
Rubens et al. [12]	1	Melanoma	Pembrolizumab	2 mg/kg	Detail unknown	None	CR
Jawaher et al. [13]	1	Renal cell carcinoma	Nivolumab	3 mg/kg	Detail unknown	None	PR
Osa et al. [14]	1	NSCLC	Pembrolizumab	200 mg/body	Detail unknown	None	No data
Abbreviations: SCLC: small cell lung cancer, CBDCA: carboplatin, NSCLC: non-small cell lung cancer, PR: partial response, CR: complete response							

It is not clear how dialysis affects the blood levels of each drug in our case, since we did not investigate each drug's blood concentration. However, the patient exhibited a remarkable response and did not develop severe adverse events. From Japanese data of the impower 133 trial, severe non-hematologic adverse events (grade ≥ 3) occurred in approximately 6% of patients, and the response rate was about 75% [15]. Considering these data and the treatment course of our patient, the combination therapy in our case may be feasible and effective even for SCLC patients undergoing HD.

In conclusion, we can safely administer a combination of carboplatin, etoposide, and atezolizumab for a patient undergoing HD, which in our case demonstrated a remarkable response. This combination may be feasible and effective even for patients with SCLC undergoing HD.

Declarations

Funding: Not applicable

Conflicts of interest:

Dr. Fujimoto reports personal fees from AstraZeneca KK, Ono Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, Chugai Pharmaceutical, MSD KK, Boehringer Ingelheim Japan, Eli Lilly Japan KK, and Novartis Pharma KK, all outside the submitted work.

Dr. Yamamoto reports grants and personal fees from MSD KK, AstraZeneca, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Takeda Pharmaceutical, Chugai Pharmaceutical, Eli Lilly Japan KK, Boehringer-Ingelheim, Novartis, and Pfizer; personal fees from Thermo Fisher Scientific, Bristol-Myers Squibb, Life Technologies Japan, Nippon Kayaku, and Merck Biopharma; and grants from Astellas Pharma, Tsumura & Co., Shionogi, AbbVie GK, Amgen, Kyorin Pharmaceutical, Eisai, Terumo, Toppan Printing, and TOSOH, all outside the submitted work.

The remaining authors have no conflict of interest.

Availability of data and material: Not applicable.

Code availability: Not applicable.

Authors' contributions: All authors contributed to the study conception. The literature search was performed and the first draft of the manuscript was written by Mihoko Imaji. The manuscript was corrected by Daichi Fujimoto. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from the individual participant included in the study.

Consent for publication: The patient signed informed consent regarding the publication of his data and images.

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Figures

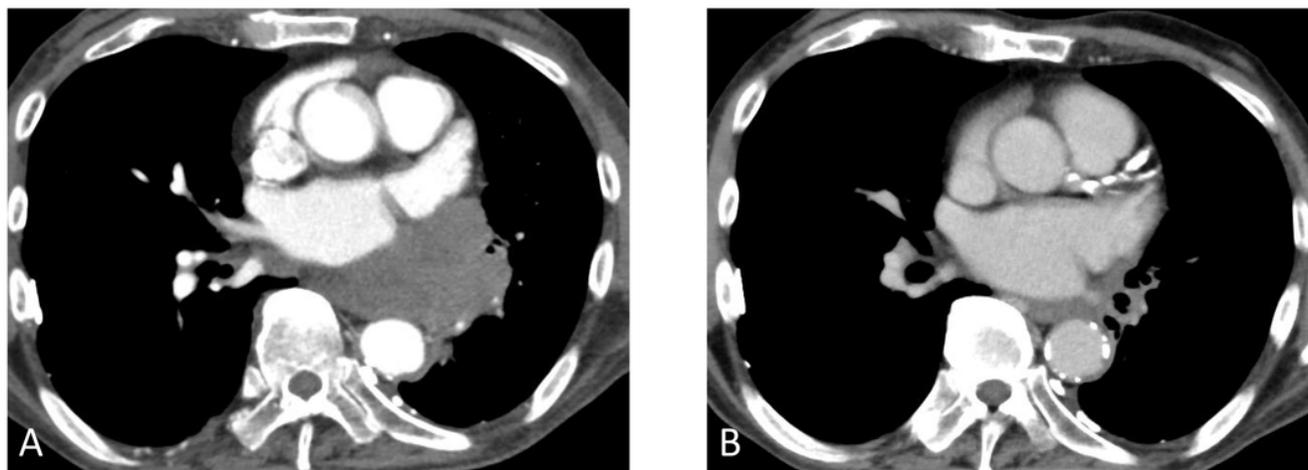


Figure 1.

Figure 1

The CT image before (A) 4 cycles and after (B) the initiation of this combination therapy. The primary lesion reduced in size