Case Reports in Oncology

Case Rep Oncol 2018;11:622–632

DOI: 10.1159/000492780
Published online: September 7, 2018

Case Report

Rechallenge with First-Line Platinum Chemotherapy for Sensitive-Relapsed Small-Cell Lung Cancer

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Keywords

Small-cell lung cancer · Sensitive relapse · Rechallenge chemotherapy · Progression-free survival · Overall survival

Abstract

Background: Sensitive-relapsed small-cell lung cancer (SCLC) is thought to be sensitive to chemotherapy; therefore, second-line chemotherapy is recommended. Although platinum re-challenge is performed in the second-line chemotherapy for sensitive-relapsed SCLC, it remains unclear whether such a strategy is effective. ***Methods:*** We retrospectively analyzed the outcome of rechallenge chemotherapy for sensitive-relapsed SCLC. The endpoints of this study were progression-free survival from the time of relapse (PFS-Re) and overall survival from the time of relapse (OS-Re). We also compared the toxicity profile of rechallenge chemotherapy to that of first-line chemotherapy. ***Results:*** Of the 133 SCLC patients who received first-line treatment, 20 patients satisfied the definition of sensitive relapse and received rechallenge

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chemotherapy. Combined carboplatin and etoposide was the most commonly used rechallenge regimen, and 17 (85%) received it at a reduced dose due to hematological toxicity during the first-line treatment. Median PFS-Re and OS-Re were 4.5 months (95% CI: 3.5–5.4) and 10.5 months (95% CI: 7.9–13.0), respectively. There was no association between dose adjustment and survival. The frequency of hematologic toxicity tended to be lower with rechallenge than first-line treatment. The incidence of grade 3 febrile neutropenia decreased from 40% in first-line treatment to 15% in rechallenge. ***Conclusion:*** Platinum rechallenge could be a useful second-line option for sensitive-relapsed SCLC, having favorable efficacy and safety. Dose adjustment at rechallenge based on the toxicity profile during the first-line chemotherapy could reduce toxicity without weakening efficacy.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Small-cell lung cancer (SCLC) accounts for approximately 13% of all lung cancer cases [1]. Although SCLC shows high sensitivity to first-line chemotherapy and radiotherapy, most patients develop disease relapse or progression [2]. The prognosis of relapsed SCLC patients is only 2–4 months without second-line chemotherapy.

Two major factors for predicting the efficacy of second-line chemotherapy in relapsed SCLC patients have been reported: (1) the response to first-line chemotherapy and (2) the relapse/progression-free interval [3–5]. According to these factors, relapsed SCLC can be divided into two main groups: sensitive and refractory relapse. Patients who achieve a complete or partial response to the initial chemotherapy and relapsed more than 90 days after the last exposure to first-line chemotherapy are categorized as sensitive relapse, whereas those who failed to respond to the first-line chemotherapy or developed recurrence within 90 days after the last exposure to first-line chemotherapy are categorized as refractory relapse. While sensitive relapse is thought to be responsive to further chemotherapy, second-line chemotherapy is recommended if the patient remains in good physical condition.

The second-line treatment options for SCLC are limited. Topotecan is the only approved drug for second-line treatment for relapsed SCLC in the USA and EU. Single-agent oral topotecan has shown to prolong overall survival (OS) and improve the quality of life, as compared with the best supportive care (median OS: 25.9 vs. 13.9 weeks; hazard ratio [HR] = 0.69; 95% confidence interval [CI]: 0.45–0.90; $p = 0.01$) [6]. In addition, the results of a past randomized study demonstrated that topotecan had similar efficacy to that of combined chemotherapy with cyclophosphamide plus doxorubicin plus vincristine, and improved control of several symptoms [7]. Therefore, topotecan is regarded as the standard second-line regimen for patients with sensitive-relapsed SCLC.

Second-line chemotherapy using the same regimen as the first-line chemotherapy, so-called "rechallenge chemotherapy," is occasionally performed in clinical practice for patients with sensitive-relapsed SCLC. However, there are only a few studies about the efficacy of platinum rechallenge chemotherapy. A retrospective analysis ($n = 112$) showed that the median OS from the initial diagnosis and that from rechallenge chemotherapy were 21.4 and 7.9 months, respectively [8]. They described that rechallenge chemotherapy with platinum and

etoposide is a reasonable option that can potentially achieve better outcomes than standard monotherapy. Another report of second-line chemotherapy of SCLC showed that rechallenge chemotherapy (n = 30) was associated with better results for tumor response and OS, as compared with other single agents, including topotecan (response rate: 35 vs. 18%, p = 0.06; median OS: 9.2 vs. 5.8 months, p = 0.08) [9]. In contrast, Wakuda et al. [10] found no significant difference in OS between rechallenge chemotherapy (n = 19) and monotherapy including amrubicin (n = 46) (14.4 vs. 13.3 months, HR = 0.89, 95% CI: 0.63–1.22; p = 0.51). Thus, whether rechallenge chemotherapy using the first-line regimen is effective remains unclear due to a lack of evidence. Moreover, the safety profile of rechallenge chemotherapy was not well documented in either report.

In the current study, we retrospectively evaluated the clinical efficacy and safety of second-line rechallenge chemotherapy for sensitive-relapsed SCLC.

Patients and Methods

We defined sensitive relapse according to previous reports: (1) an objective response to first-line chemotherapy or chemoradiotherapy and (2) relapse or progression more than 90 days after the last exposure to first-line chemotherapy [3–5].

We screened clinical data from the medical records of patients with SCLC treated at the University of Tsukuba Hospital (Tsukuba, Japan) between January 2000 and December 2016. The collected clinical data included demographic characteristics, performance status at the time of relapse, disease stage at diagnosis (limited disease and extended disease), first-line regimen, response to first-line and rechallenge chemotherapies, type and dose of platinum regimen at rechallenge chemotherapy, and toxicity of both first-line and rechallenge chemotherapies.

Computed tomography scans of the chest and abdomen and magnetic resonance imaging of the head were used to evaluate tumors according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0.10). Patients without a radiological assessment were considered unevaluable and were excluded from this study. The objective response rate (ORR) was defined as the proportion of patients achieving either a complete response (CR) or a partial response (PR). The disease control rate (DCR) was defined as the proportion of patients achieving CR, PR, and stable disease.

Platinum regimen toxicities of both first-line and rechallenge chemotherapy were evaluated by reviewing the medical records. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). The study protocol was approved by the Institutional Review Board of the University of Tsukuba Hospital.

The endpoints of this study were survival and the incidence of toxicity. Progression-free survival from relapse (PFS-Re) was defined as the interval from the initiation of rechallenge chemotherapy to disease progression or death from any cause. Similarly, overall survival from relapse (OS-Re) was defined as the interval from the initiation of rechallenge chemotherapy to death from any cause. Clinical evaluations of PFS-Re and OS-Re were conducted using the Kaplan-Meier method. Statistical analyses were performed using IBM SPSS statistics (version 24.0) for Windows (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

Figure 1 shows the flow diagram of the current study. Clinical data were collected from 133 SCLC patients who received first-line chemotherapy or chemoradiotherapy. Ninety-one patients were confirmed to have disease progression or relapse after first-line treatment in our institute. Thirty-nine and 52 patients were categorized as having sensitive relapse and refractory relapse, respectively. In the sensitive-relapsed group, 28 patients received second-line chemotherapy. Among the sensitive-relapsed SCLC patients who received second-line chemotherapy, 20 received platinum rechallenge and the remainder received amrubicin monotherapy.

The characteristics of patients who received rechallenge chemotherapy are summarized in Table 1. The median age was 65 years (range 52–84), and 85% were males. Eleven patients presented at diagnosis with limited disease, and the other 9 presented with extended disease. The most common first-line regimen was combined carboplatin and etoposide (CBDCA/ETP; 14/20, 70%). The median relapse/progression-free interval was 115 days (range 91–404).

Rechallenge Dose

Among the patients who received rechallenge chemotherapy, 17 (85%) patients started a reduced-dose second-line chemotherapy because of severe adverse events during first-line treatment. In all, 13 patients received an 80% dose, one received a 75% dose, and the other 3 received a 70% dose. Only 3 patients could start the second-line rechallenge chemotherapy at full dose.

Toxicity

Table 2 shows treatment-related adverse events associated with the first-line and rechallenge chemotherapy. Grade 3 or worse hematological toxicity was noted in both groups. However, it appeared to be less frequent in rechallenge chemotherapy. The incidence of febrile neutropenia tended to be higher in the first-line than in the rechallenge chemotherapy (grade 3: 8 [40%] first-line vs. 3 [15%] rechallenge). Nonhematologic toxicity was relatively mild in both groups. No treatment-related death occurred in either group.

Efficacy

The median number of cycles with rechallenge chemotherapy was 3 (range 1–4). The response to rechallenge chemotherapy was CR of 0%, PR of 50% (10/20), stable disease of 30% (6/20), and progressive disease of 20% (4/20), with ORR of 50% and DCR of 80%. In amrubicin-treated patients, the ORR was 25% and DCR was 88%.

In the patients treated with rechallenge chemotherapy, the median PFS-Re and OS-Re were 4.5 months (95% CI: 3.5–5.4; Fig. 2a) and 10.5 months (95% CI: 7.9–13.0; Fig. 2b), respectively. We further evaluated whether dose adjustment at rechallenge chemotherapy affected the PSF-Re and OS-Re. Figure 3 presents the correlation between PFS-Re and rechallenge chemotherapy dose; dose reduction of rechallenge chemotherapy did not affect PFS-Re. Similarly, dose reduction did not affect OS-Re (data not shown).

Subsequent Therapy

Among the patients who received rechallenge chemotherapy, 12 (60%) received third-line chemotherapy. The remaining 8 patients did not receive third-line chemotherapy because they were transferred to the palliative care unit, refused further chemotherapy, or died. Among the patients who received third-line chemotherapy, 11 received amrubicin, and the other patient received topotecan.

Discussion

Rechallenge with a first-line platinum regimen has been performed in clinical practice for patients with sensitive-relapsed SCLC without clear evidence that rechallenge chemotherapy is useful for them. The results of this study showed that rechallenge chemotherapy had a favorable efficacy and safety profile.

We showed that most patients received rechallenge chemotherapy safely by optimal dose adjustment. A combination of CBDCA and ETP was the most commonly used platinum regimen as the first-line treatment, and 17 of 20 (85%) patients experienced hematologic toxicity of grade 3 or higher. We then selected the patients who needed dose adjustment of rechallenge chemotherapy based on the toxicity profiles during the first-line treatment. As a result, the incidence of hematologic toxicity decreased compared to that in first-line therapy, especially, the frequency of grade 3 febrile neutropenia from 40 to 15%. Neither treatment failure due to toxicity nor treatment-related death was observed. Thus, we could reduce the toxicity at rechallenge chemotherapy adequately because we referred to a toxicity profile of the first-line chemotherapy. We consider that the optimal dose adjustment for reasonable toxicity profile is an important advantage of rechallenge chemotherapy, because candidates for the second-line chemotherapy are heavily treated previously, and therefore severe hematological toxicity is anticipated.

In the current study, rechallenge chemotherapy showed a favorable efficacy; median PFS-Re and OS-Re were 4.5 and 10.5 months, respectively. Moreover, PFS-Re and OS-Re were not associated with dose adjustment of rechallenge chemotherapy. Previous studies showed that median PFS and OS from relapse were 5.5 and 7.9–14.4 months, respectively [8–11]. Although these outcomes were comparable to those of the current study, the association between survival and dose intensity has not been documented in either report. A recent randomized phase 3 trial compared the efficacy of combined therapy with cisplatin, etoposide, and irinotecan (PEI) to topotecan monotherapy in patients with sensitive-relapsed SCLC [12]. In this study, PEI consisted of alternating weeks of the two platinum combinations, cisplatin plus etoposide (PE) and cisplatin plus irinotecan (PI). PEI can be regarded as combined therapy with two platinum rechallenges because both PI and PE were used as first-line regimen. Although many patients who received PEI required a dose reduction due to severe hematological toxicity, PEI showed better OS than the topotecan group (18.2 vs. 12.5 months; HR = 0.67, 95% CI: 0.51–0.88; $p = 0.0079$). Since sensitive-relapsed SCLC remained sensitive to first-line platinum regimen, rechallenge chemotherapy showed favorable efficacy even though the patients received it at a reduced dose.

There were several limitations in this study. First, the current study was a single-institution, retrospective study with a relatively small sample size. Therefore, we consider that this

study is a hypothesis-generating study for future investigations. Second, an optimal comparator for the rechallenge chemotherapy group was lacking because there were only a few patients who received monotherapy. All patients received amrubicin as the second-line monotherapy. Amrubicin, a fully synthetic 9-aminoanthracycline, is widely used for the second-line treatment of SCLC in Japan. Several studies reported that the efficacy of amrubicin as a second-line treatment for SCLC was promising, with an ORR of 31–52% and median PFS of 3.5–4.2 months [13–15]. Amrubicin could be a reasonable comparator if the randomized phase III trial to evaluate the efficacy of rechallenge chemotherapy is performed in the future.

In conclusion, the results of the current study showed that rechallenge chemotherapy could be a useful second-line option for sensitive-relapsed SCLC, with favorable efficacy and safety. Optimal dose adjustment of rechallenge chemotherapy is an important treatment strategy to reduce toxicity without adversely affecting survival.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University of Tsukuba Hospital.

Disclosure Statement

The authors declare no conflict of interest associated with this paper.

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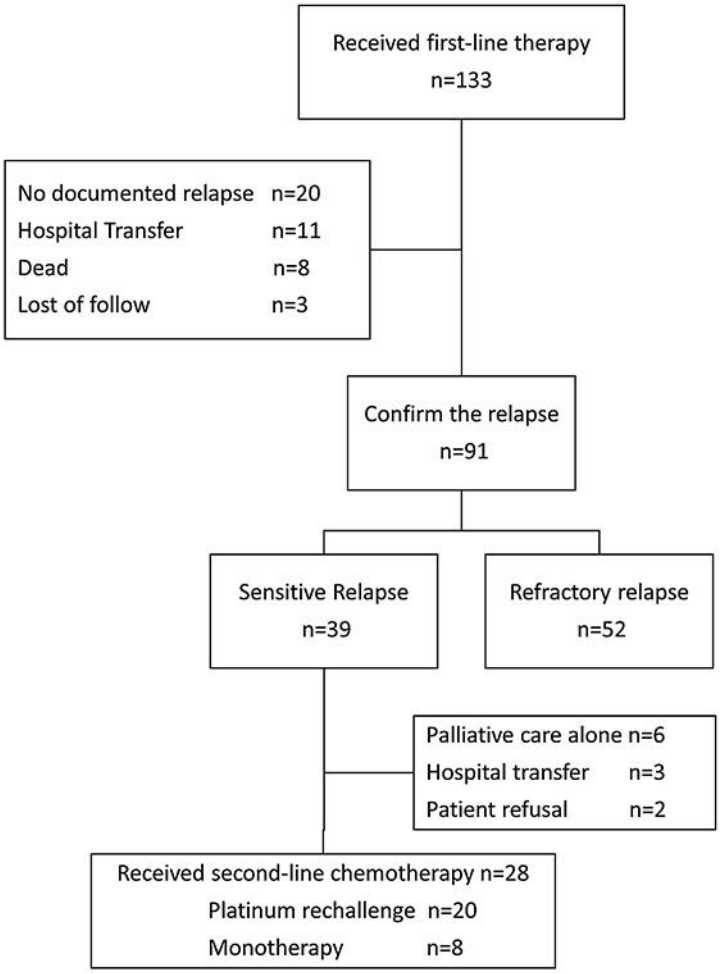
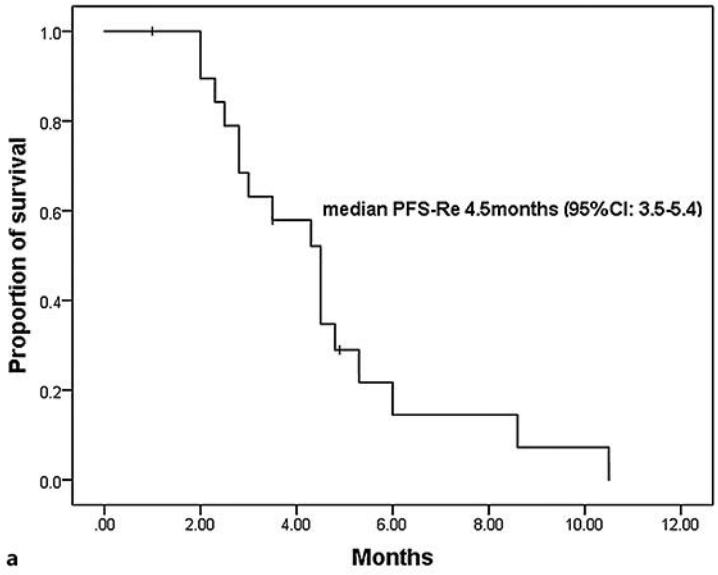


Fig. 1. CONSORT flow diagram of the current study.



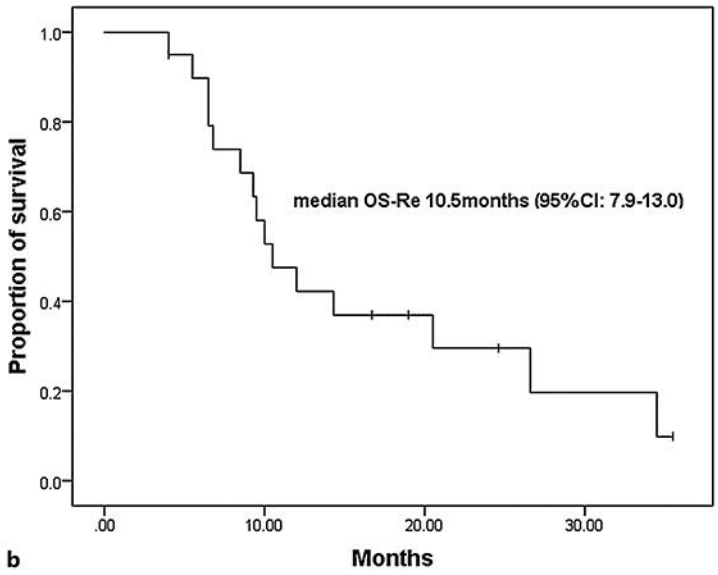


Fig. 2. Kaplan-Meier curves of PFS-Re (**a**) and OS-Re (**b**) for patients receiving second-line platinum rechallenge (n = 20).

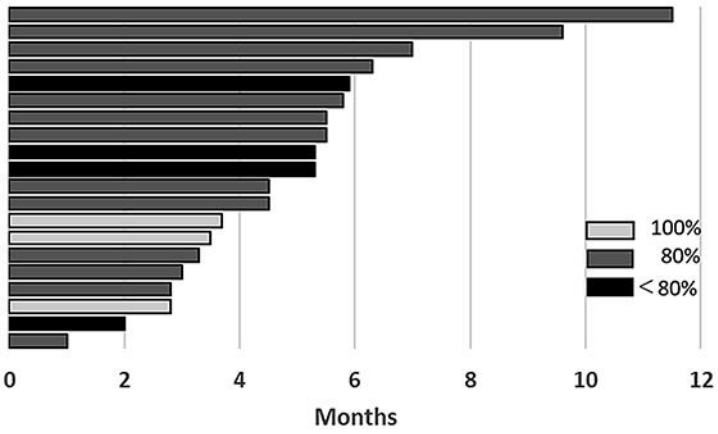


Fig. 3. Swimmer plots for patients receiving rechallenge chemotherapy. Bar length indicates PFS-Re for each patient. Patients receiving rechallenge chemotherapy at full dose are presented in gray, whereas those receiving rechallenge chemotherapy at an 80% and less than 80% are presented in dark gray and black, respectively.

Table 1. Patient characteristics in the platinum rechallenge group (n = 20)

Age, years	65 (52–84)
Gender	
Male/Female	17/3
Performance status at the relapse	
0	7
1	11
2	0
3	2
Disease extent at the initial diagnosis	
Limited disease	11
Extended disease	9
First-line therapy	
Chemoradiotherapy	9
Chemotherapy	11
First-line regimen	
Carboplatin and etoposide	14
Cisplatin and etoposide	5
Cisplatin and irinotecan	1
Recurrence-free intervals, (days	115 (91–404)

Table 2. Adverse event at first-line and rechallenge treatment

Grade	First-line, %				Rechallenge, %			
	2	3	4	3+4	2	3	4	3+4
Hematological								
Leukopenia	2	8	8	80	4	8	7	75
Neutropenia	1	6	11	85	1	9	4	65
Anemia	2	1	0	5	1	0	0	0
Thrombocytopenia	2	3	2	25	3	2	0	10
Febrile neutropenia	0	8	0	40	0	3	0	15
Nonhematological								
Anorexia	3	3	0	15	4	0	0	0
Nausea/vomit	3	1	0	5	2	0	0	0
Diarrhea	1	0	0	0	0	0	0	0
Fatigue	3	0	0	0	2	0	0	0
Edema	1	0	0	0	1	0	0	0
Increased AST/ALT	1	0	0	0	0	0	0	0
Increased creatinine	2	1	0	5	1	0	0	0