Original Article

Rechallenge Treatment with a Platinum-based Regimen in Patients with Sensitive Relapsed Small-Cell Lung Cancer

Yoshiko Naito, Kazuhiko Yamada, Yohei Imamura, Hidenobu Ishii, Norikazu Matsuo, Takaaki Tokito, Takashi Kinoshita, Koichi Azuma, Tomoaki Hoshino

Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan

Correspondence to: Kazuhiko Yamada, M.D., Ph.D., Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan. Tel.: +81-942-31-7560. Fax: +81-942-31-7703. E-mail: kayamada@med.kurume-u.ac.jp

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ABSTRACT

Among patients with relapsed small-cell lung cancer (SCLC), those who relapse >90 days after first-line chemotherapy are classified sensitive relapse. Rechallenge with a first-line platinum-based regimen has been used in sensitive relapsed SCLC patients, but its importance is not known. We evaluated the outcome of rechallenge with platinum-based chemotherapy for sensitive relapse patients. We reviewed consecutive patients with sensitive relapsed SCLC who received second-line chemotherapy between January 1999 and December 2016. We evaluated the treatment outcomes of platinum-based rechallenge and non-rechallenge regimens for second-line chemotherapy in sensitive relapse patients. Of 245 patients, 81 sensitive relapse patients received second-line chemotherapy. Sixty-seven patients (82.7%) were treated with rechallenging platinum-based regimens ("rechallenge group") and 14 patients (17.3%) were treated with other regimens ("non-rechallenge group") as second-line chemotherapy. Median progression-free survival (PFS) was 5.1 months in the rechallenge group and 3.5 months in the non-rechallenge group, and median survival time was 10.8 months and 8.2 months, respectively. There were no significant differences in PFS or overall survival (OS) between the two groups. Sub-analyses of patients who received chemotherapy alone as first-line treatment showed that the rechallenge group had longer PFS than that of the non-rechallenge group (median,

5.4 months *versus* 3.6 months, p=0.0038), and the rechallenge group had a tendency to have longer OS than non-rechallenge group. These data suggest that rechallenge treatment with a platinum-based regimen could be second-line chemotherapy in patients with sensitive relapsed SCLC, especially those treated with chemotherapy alone as first-line therapy.

Key words: small-cell lung cancer, sensitive relapse, rechallenge chemotherapy, second-line chemotherapy

INTRODUCTION

Small-cell lung cancer (SCLC) accounts for ≈15% of all cases of lung cancer [1, 2]. SCLC is very aggressive and is characterized by rapid progression, early metastatic spread, and initial responsiveness to therapy [3]. SCLC shows high sensitivity to chemotherapy and radiotherapy, but most patients experience relapse within 1 year of treatment [4]. Several phase-II trials for patients with relapsed SCLC have demonstrated that patients with a longer treatment-free interval (TFI) following first-line chemotherapy show a high response to second-line chemotherapy [5,6]. Given the difference in efficacy of second-line treatment, patients with relapsed SCLC can be classified into two groups on the basis of the TFI after first-line chemotherapy: sensitive relapse and refractory relapse [5]. Sensitive relapse patients respond to first-line chemotherapy and relapse after a TFI of >60–90 days. Refractory relapse patients are those whose disease progressed during first-line chemotherapy or progressed within 60–90 days. Sensitive relapse patients are more likely to respond to second-line chemotherapy than refractory relapse patients [7–10]. Consequently, second-line chemotherapy is recommended for sensitive relapse patients with good Eastern Cooperative Oncology Group (ECOG) performance status.

Several studies have reported on the efficacy of rechallenge with the same drugs used in

first-line chemotherapy for sensitive relapse patients, but the regimens used in those studies were not standard regimens in previous decades [11, 12]. Whether rechallenge treatment with currently standard platinum-based regimens is effective is not known. It is also unclear which type of patients with sensitive relapsed SCLC may benefit from rechallenge platinum-based treatment. The objective of this retrospective study was to analyze the treatment outcome of rechallenge with platinum-based chemotherapy for sensitive relapsed SCLC patients.

METHODS

Patients

We retrospectively reviewed the medical records of consecutive patients with SCLC treated with first-line platinum-based chemotherapy and who received second-line chemotherapy subsequently at Kurume University Hospital (Fukuoka, Japan) between January 1999 and December 2016. The diagnosis of SCLC was confirmed by histology or cytology.

Definitions

We defined patients who responded to first-line chemotherapy and relapsed >90 days

after the completion of first-line chemotherapy as sensitive relapse, and those who relapsed ≤90 days after the completion of first-line chemotherapy as refractory relapse. We excluded refractory relapse patients and evaluated all the sensitive relapse patients. Disease extent was divided into “limited disease” (LD) and “extensive disease” (ED). LD was defined as disease confined to only one hemithorax, with or without involvement of regional lymph nodes (hilar or mediastinal), with or without involvement of ipsilateral supraclavicular lymph nodes, and without ipsilateral pleural effusions. ED was defined as disease that had spread beyond the boundaries mentioned above [13].

Data collection

The following data were collected: clinical data (patient characteristics, sex, age, ECOG performance status at second-line chemotherapy); levels of tumor markers before second-line chemotherapy; levels of neuron-specific enolase and pro-gastrin-releasing peptide; disease extent at the diagnosis; first- and second-line chemotherapy regimens; the start and final dates of chemotherapy; response to treatment; date of relapse; TFI (from the final date of first-line chemotherapy to the date of relapse); date of final follow-up or death.

Evaluation of treatment efficacy

Tumor response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumor v1.1. Progression-free survival (PFS) was calculated from the start date of second-line chemotherapy to the date of disease progression or death. Overall survival (OS) was measured from the administration of second-line chemotherapy until the date of death or final follow-up.

Statistical analyses

Median PFS and OS were evaluated by Kaplan–Meier point-estimate survival analyses, and survival differences between groups were compared using the log-rank test. Comparison between the two variables was analyzed using a chi-square test or Fisher's exact test for categorical variables and Wilcoxon rank-sum test or Pearson's correlation analysis for continuous variables. $p < 0.05$ was considered significant. Statistical analyses were undertaken using JMP v13 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

From January 1999 to December 2016, 245 patients were treated with a platinum-based

regimen for first-line chemotherapy or chemoradiotherapy. Among them, 180 patients relapsed, and 109 patients had sensitive relapse. Of these 109 patients, 81 (74.3%) received second-line chemotherapy and were enrolled in this study. Of these 81 patients, 67 (82.7%) were treated with rechallenging platinum-based regimens ("rechallenge group"), and 14 patients (17.3%) were treated with non-platinum regimens ("non-rechallenge group") as second-line chemotherapy. Patient characteristics are summarized in Table 1. Thirty-four patients received chemoradiotherapy as first-line treatment and 47 patients received chemotherapy alone. The median TFI of all patients was 167 days, and it was significantly longer in the rechallenge group than in the non-rechallenge group (p = 0.03).

Treatment regimens

The most prevalent regimen of rechallenge chemotherapy was cisplatin with irinotecan (n = 28, 41.8%), followed by carboplatin with etoposide (n = 15, 22.4%) and cisplatin with etoposide (n = 12, 17.9%). In the non-rechallenge group, the most prevalent regimen was amrubicin monotherapy (n = 8, 57.1%), followed by irinotecan monotherapy (n = 3, 21.4%). The median number of treatment cycles was four and three cycles for rechallenge and non-rechallenge groups, respectively (Table 2).

Efficacy of second-line chemotherapy

The objective response rate (ORR) was 52.2% and 64.3% in the rechallenge group and non-rechallenge group, respectively. The disease control rate (DCR) was 82.1% in the rechallenge group and 71.4% in the non-rechallenge group (Table 3). The median PFS was 5.1 months (95% confidence interval [CI] : 4.3−5.4) in the rechallenge group and 3.5 months (95% CI : 2.3−5.9) in the non-rechallenge group (p = 0.95) (Figure 1A), and the median OS was 10.8 months (95% CI : 8.7−14.5) and 8.2 months (95% CI : 5.6−not estimable [NE]), respectively (p = 0.93) (Figure 1B). There were no significant differences in OS or PFS between the two groups.

Sub-analyses of the patients who had received chemotherapy alone as first-line treatment showed that the rechallenge group had longer PFS than the non-rechallenge group (median, 5.4 months *versus* 3.6 months, hazard ratio [HR] ; 0.31, 95% CI ; 0.14−0.76, p = 0.0038) (Figure 2A), and the rechallenge group had a tendency to have longer OS than non-rechallenge group (median, 11.3 months in the rechallenge group *versus* 8.2 months in the non-rechallenge group, HR; 0.53, 95% CI ; 0.21−1.63, p = 0.21) (Figure 2B).

DISCUSSION

Several studies have evaluated the efficacy of second-line chemotherapy for relapsed SCLC. Topotecan is considered to be the standard regimen for second-line chemotherapy worldwide. In a phase-II trial of topotecan as second-line therapy, an ORR of 37.8% was observed in platinum-sensitive patients [5, 14]. Amrubicin, etoposide and irinotecan have been also been reported to be effective in the treatment of relapsed SCLC [15–19]. Phase-II trials have reported the ORR to be 36–52%, 45.5% and 47% for amrubicin, etoposide, and irinotecan, respectively. However, survival advantages have not been demonstrated in phase-III trials, so these drugs are not established as standard second-line chemotherapy for SCLC [20]. Recently, a randomized phase-III trial showed that combination chemotherapy with cisplatin, etoposide, and irinotecan (PEI) improved OS compared with topotecan in sensitive relapsed SCLC patients [21]. Therefore, PEI could be regarded as an option for second-line treatment for sensitive relapse patients. However, the treatment schedule of PEI is less convenient; it requires relatively long-term hospitalization, and a high prevalence of severe myelosuppression (including febrile neutropenia in spite of mandatory use of granulocyte-colony stimulating factor) has been reported, so adaptation is limited.

Rechallenge with first-line platinum-based regimens has been used conventionally in sensitive relapse patients but evidence has been drawn from small trials conducted

primarily in the 1980s [11, 12]. Korkmaz *et al.* reported a retrospective study of the treatment outcome for SCLC patients who received second-line chemotherapy. Subgroup analyses of the platinum-sensitive patients revealed that patients treated with platinum rechallenge had longer PFS, OS and higher ORR than patients not treated with platinum ($p = 0.014$, $p = 0.032$, and $p = 0.002$, respectively) [22]. Similarly, Garassino *et al.* retrospectively reviewed patients who received second-line chemotherapy for SCLC. Their results showed a trend towards higher ORR ($p = 0.06$) and longer OS ($p = 0.08$) for patients with sensitive relapsed SCLC who had rechallenge platinum-based chemotherapy [23]. By contrast, Wakuda *et al.* reported that rechallenge chemotherapy for sensitive relapsed SCLC patients was not superior to other chemotherapies (median survival time, 14.4 months *versus* 13.1 months in rechallenge and other groups, $p = 0.51$) [24].

Similar to the report of Wakuda *et al*. [24], significant differences were not observed for PFS and OS between patients who received rechallenge platinum-based regimens and other regimens in our study. However, sub-analyses of patients who received chemotherapy alone as the first-line regimen revealed that the rechallenge group had significantly favorable PFS compared with the non-rechallenge group. Considering that a combination of chemotherapy and radiotherapy would prolong PFS compared with

chemotherapy alone, not all the patients who relapsed >90 days after first-line chemoradiotherapy might have sensitivity to platinum-based regimens. Most patients who received chemotherapy alone as first-line treatment were ED, elderly, poor-risk or suffering from complications (e.g., interstitial pneumonia). Hence, sensitive relapse patients with these backgrounds might receive benefit from rechallenge treatment with a platinum-based regimen.

The time-to-relapse after first-line chemotherapy is an important factor for predicting the efficacy of second-line treatment for relapsed SCLC patients. Sensitive relapse and refractory relapse are classified according to the duration of the TFI after first-line chemotherapy. Sensitive relapse SCLC patients who had a longer TFI than refractory relapsed SCLC patients showed a favorable response to second-line chemotherapy. Whether the length of the TFI can be used to predict the outcome of second-line chemotherapy among sensitive relapsed SCLC is not known. In our cohort, patients who received rechallenge platinum regimens had a significantly longer TFI than non-rechallenge regimens. However, the length of the TFI after first-line chemotherapy was not related to the ORR ($p = 0.53$) or PFS ($r = 0.15$) of second-line treatment.

The present study had three main limitations. First, it was a retrospective study at a single institution. Second, our study cohort was relatively small. Third, our study was

limited by the heterogeneity of the regimens used for second-line chemotherapy.

CONCLUSIONS

Our results suggest that rechallenge treatment with a platinum-based regimen could be an option of second-line chemotherapy in patients with sensitive relapsed SCLC, especially those who had chemotherapy alone as first-line therapy. Further studies are warranted to establish the optimal regimen for relapsed SCLC.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet. 2005;366:1385–96.
2. Van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011;378:1741–55.
3. Gustafsson BI, Kidd M, Chan A, et al. Bronchopulmonary neuroendocrine tumors. Cancer. 2008;113:5–21.
4. Postmus PE, Smit EF. Treatment of relapsed small cell lung cancer. Semin Oncol. 2001;28:48–52.
5. Ardizzoni A, Hansen H, Dombernowsky P, et al. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol. 1997;15:2090–6.
6. Kim YH, Goto K, Yoh K, et al. Performance status and sensitivity to first-line chemotherapy are significant prognostic factors in patients with recurrent small cell lung cancer receiving second-line chemotherapy. Cancer. 2008;113:2518–23.
7. Giaccone G, Donadio M, Bonardi G, et al. Teniposide in the treatment of small-cell lung cancer: the influence of prior chemotherapy. J Clin Oncol. 1988;6:1264–70.

8. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007;25:2086–92.
9. von Pawel J, Gatzemeier U, Pujol JL, et al. Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. J Clin Oncol. 2001;19:1743–9.
10. Antonio R. Relapsed small-cell lung cancer: platinum re-challenge or not. J Thorac Dis. 2016;8:2360–4.
11. Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. Eur J Cancer Clin Oncol. 1987;23:1409–11.
12. Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. Eur J Cancer Clin Oncol. 1987;23:1697–9.
13. Julie R. Brahmer, David S. Ettinger. The role of topotecan in the treatment of small cell lung cancer. Oncologist. 1998;3:11–14.
14. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006;24:5441–7. 1

15. Johnson DH, Greco FA, Strupp J, et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol. 1990;8:1613–17.

16. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol. 1992;10:1225–9.

17. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol. 2008;20:26: 5401–6.

18. Jotte R, Conkling P, Reynolds C, et al. Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy. J Clin Oncol. 2011; 20: 29:287–93.

19. Inoue A, Sugawara S, Maemondo M, et al. Randomized phase II trial comparing amrubicin with re-challenge of platinum doublet in patients with sensitive-relapsed small-cell lung cancer: North Japan Lung Cancer Study Group trial 0702. Lung Cancer. 2015;89:61–5.

20. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol. 2014;10:32:4012–19.

21. Goto K, Ohe Y, Shibata T, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2016;17:1147–57.

22. Korkmaz T. Seber S, Kefeli U, et al. Comparison of second-line treatment outcomes between sensitive and refractory small cell lung cancer patients: a retrospective analysis. Clin Transl Oncol. 2013;15:535–40.

23. Garassino MC, Torri V, Michetti G, et al. Outcomes of small-cell lung cancer patients treated with second-line chemotherapy: a multi-institutional retrospective analysis. Lung Cancer. 2011;72:378–83.

24. Wakuda K, Kenmotsu H, Naito T, et al. Efficacy of rechallenge chemotherapy in patients with sensitive relapsed small cell lung cancer. Am J Clin Oncol. 2015;38:23–32.

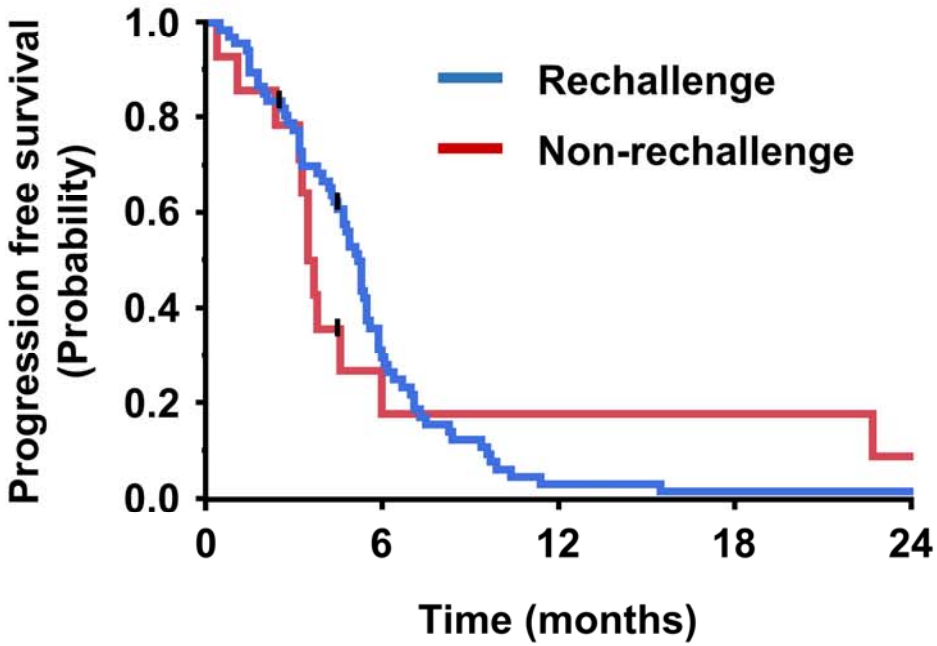
Figure legends

Figure 1. Kaplan–Meier estimates for progression-free survival and overall survival in sensitive-relapsed SCLC patients.

A) Progression-free survival. B) Overall survival.

Figure 2. Kaplan–Meier estimates for progression-free survival and overall survival in sensitive-relapsed SCLC patients who had received chemotherapy alone as first-line treatment.

A) Progression-free survival. B) Overall survival.


Progression free survival
(Probability)
1.0
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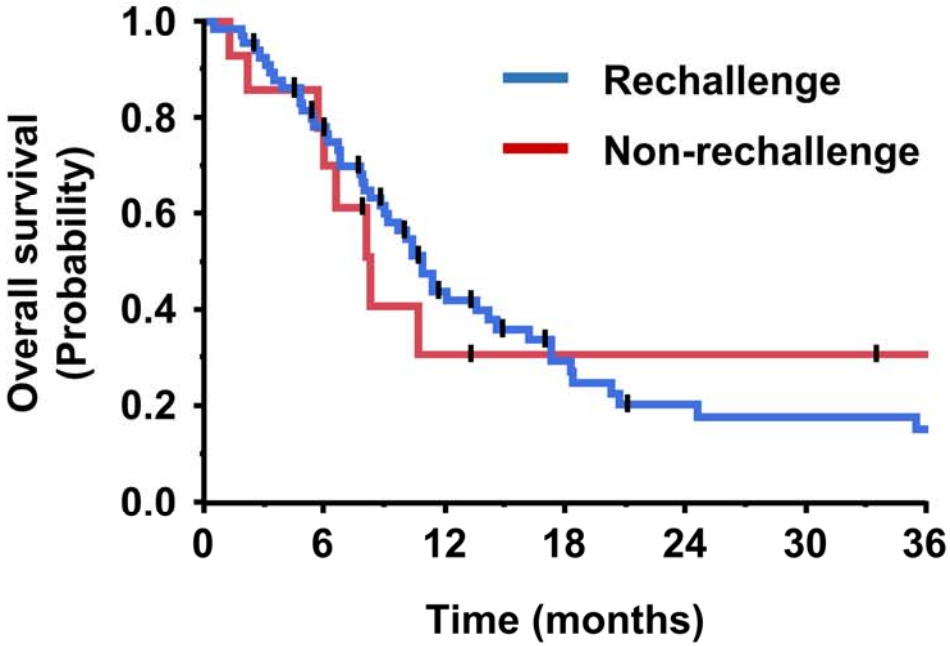
18
24
Time (months)
Rechallenge
Non-rechallenge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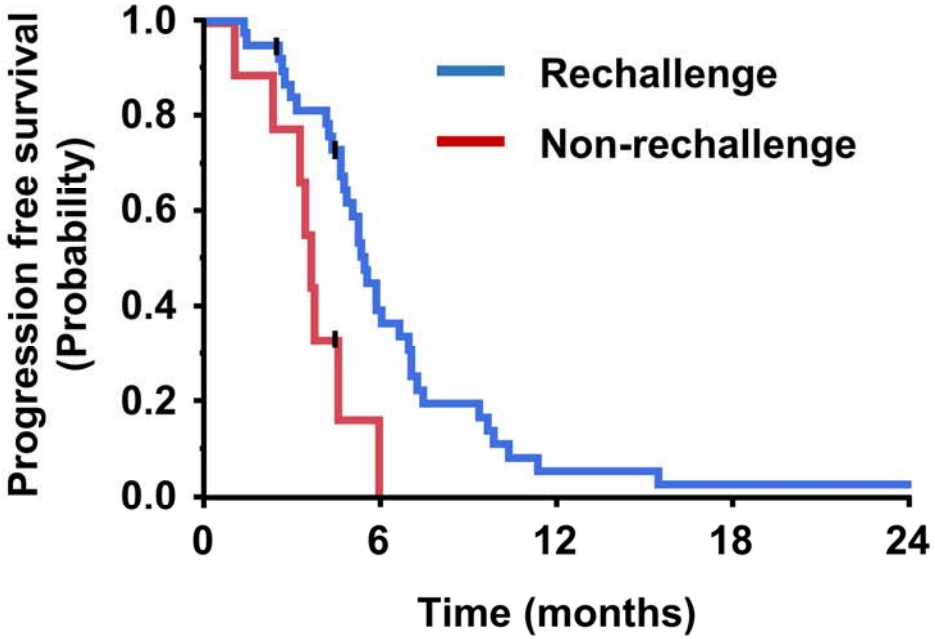
Non-rechallenge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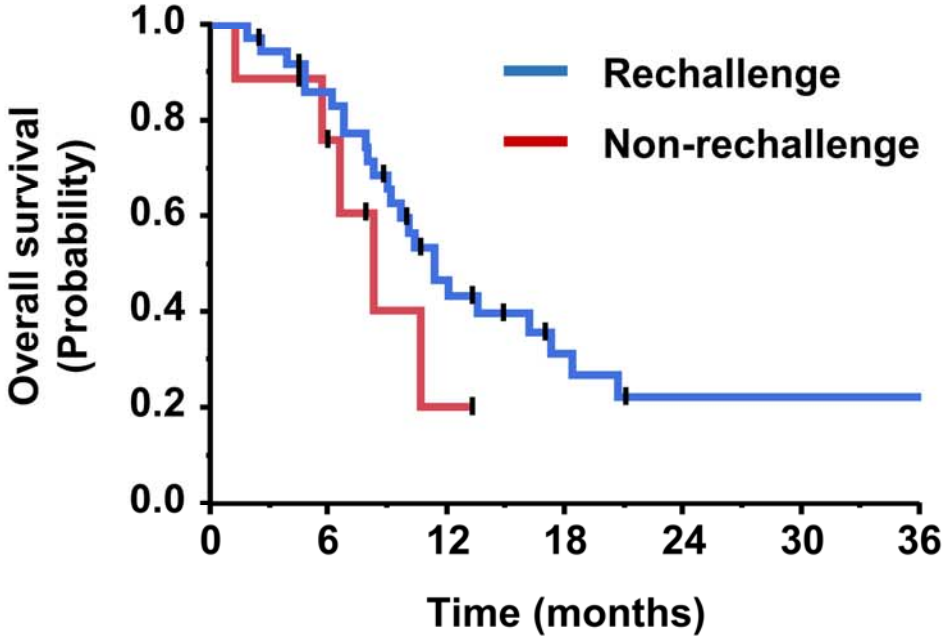
Overall survival
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Time (months)
Rechallenge
Non-rechallenge

Table 1. Patient characteristics

	Rechallenge group n = 67	Non-rechallenge group n = 14	p
Sex			0.29
Male (%)	54 (80.6)	9 (64.3)	
Female (%)	13 (19.4)	5 (35.7)	
Age (years)			0.56
<70 (%)	31 (46.3)	8 (57.1)	
≥70 (%)	36 (53.7)	6 (42.9)	
Performance status			1.00
0–1 (%)	57 (85.1)	12 (85.7)	
≥2 (%)	10 (14.9)	2 (14.3)	
Disease extent			0.77
Limited disease (%)	33 (49.3)	6 (42.9)	
Extensive disease (%)	34 (50.7)	8 (57.1)	
Previous therapy			0.77
Chemotherapy alone (%)	38 (56.7)	9 (64.3)	
Chemoradiotherapy (%)	29 (43.3)	5 (35.7)	
NSE level, median (range)	20.5 (5.3–293)	18.0 (7.4–44.9)	0.43
Pro-GRP level, median (range)	346.5 (9.9–8010)	207.0 (22.1–2460)	0.29
Median TFI (Day, range)	182 (94–1521)	197 (91–424)	0.03

NSE, neuron-specific enolase; Pro-GRP, pro-gastrin-releasing peptide; TFI, treatment-free interval.

Table 2. Second-line chemotherapy regimens

Regimen	Rechallenge group (n = 67)	Non-rechallenge group (n = 14)
cisplatin with irinotecan	28	–
carboplatin with etoposide	15	–
cisplatin with etoposide	12	–
carboplatin with paclitaxel	6	–
cisplatin with amrubicin	3	–
carboplatin with irinotecan	3	–
amrubicin	–	8
irinotecan	–	3
amrubicin with irinotecan	–	1
nab-paclitaxel	–	1
irinotecan with ifosfamide	–	1
Median treatment cycles (range)	4 (1–4)	3 (1–19)

Table 3. Tumor response to second-line chemotherapy

	Rechallenge group n = 67	Non-rechallenge group n =14	Total n =81	p
Response				
CR	2	0	2	
PR	33	9	42	
SD	20	1	21	
PD	9	4	13	
NE	3	0	3	
Objective response rate (%)	52.2	64.3	54.3	0.56
Disease control rate (%)	82.1	71.4	80.2	0.25

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease;

NE, not evaluated