


## Research Article

# Real-World Outcomes of Second-Line Treatment in Sensitive Relapsed Small-Cell Lung Cancer: A Multicenter Retrospective Cohort Study

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### Abstract

**Objectives:** To compare the efficacy and safety of platinum-etoposide rechallenge, topotecan and CAV in sensitive relapsed (SR)-SCLC.

**Methods:** It was a retrospective observational study. Patients with SR-SCLC from three oncology centers were included in the study. Clinical outcomes were compared.

**Results:** Of 102 patients, 39.8% (n=41) were treated with topotecan, 43.7% (n=45) with platinum-etoposide, and 16.5% (n=17) with CAV. The mPFS was 2.5 months (95% CI 1.9-3.1) in the topotecan, 5.5 months (95% CI 4.8-6.2) in the platinum-etoposide, and 5.1 months (95% CI 3.1-7.1) in the CAV groups. The difference between the topotecan and platinum-etoposide groups was significant ( $p < 0.001$ ). The mOS was 3.2 months (95% CI 0.2-6.2) in the topotecan, 11.2 months (95% CI 6.9-15.3) in the platinum-etoposide, and 7.9 months (95% CI 6.3-9.4) in the CAV groups. The difference between topotecan and platinum-etoposide groups was significant ( $p=0.011$ ). The ORR was 9.8% in the topotecan, 37.8% in the platinum-etoposide, and 41.2% in the CAV groups ( $p=0.005$ ). Although a trend towards increased toxicity with platinum-etoposide was observed, all three regimens showed similar safety profiles.

**Conclusion:** It was suggested that platinum-etoposide rechallenge improved PFS, OS and ORR with a similar safety profile over topotecan in SR-SCLC.

**Keywords:** Sensitive relapse, SCLC, rechallenge, platinum-etoposide

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Small-cell lung cancer (SCLC) constituted nearly 10%–15% of all lung cancers. It has an aggressive nature and a poor prognosis. Approximately 60%-70% of patients

have extensive stage disease (ES-SCLC) at the time of diagnosis.<sup>[1]</sup> The platinum-etoposide regimen in non-Asian patients with ES-SCLC and chemoradiotherapy (with the

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platinum-etoposide regimen) in limited stage disease (LS-SCLC) are the backbone of treatments.<sup>[2]</sup> Recently, it was shown that the addition of atezolizumab or durvalumab to carboplatin plus etoposide improved overall survival in ES-SCLC.<sup>[3, 4]</sup> In spite of the initial responses in most of the patients, eventually progression or relapse occurs during or after first-line treatment in almost all of the patients with ES-SCLC and approximately three-fourths of the patients with LS-SCLC.<sup>[5]</sup>

The treatment-free interval (TFI) determines the prognosis of patients who progress or relapse during or after first-line treatment.<sup>[6]</sup> Patients who had a response with first-line treatment and relapsed with a TFI  $\geq 90$  days defined as "sensitive relapsed SCLC (SR-SCLC)". On the other hand, patients who relapsed with a TFI  $< 90$  days defined as "refractory or resistant relapsed SCLC (RR-SCLC)". Based on early re-induction trials, cyclophosphamide plus doxorubicin plus vincristine (CAV) is administered to relapsed SCLC.<sup>[7]</sup> On the other hand, oral topotecan improved overall survival (OS) over best supportive care (BSC) in relapsed SCLC.<sup>[8]</sup> Furthermore, intravenous topotecan was found to be as effective as CAV with an improved symptom control in relapsed SCLC ( $\geq 60$  days).<sup>[9]</sup> Likewise, clinicians administered platinum-etoposide as a rechallenge at second-line treatment in SR-SCLC. The efficacy of platinum-etoposide rechallenge was demonstrated in retrospective studies and meta-analysis.<sup>[10, 11]</sup> Recently, in a phase III French trial, it was revealed that carboplatin plus etoposide rechallenge improved progression-free survival (PFS) and overall response rate (ORR) compared to topotecan in SR-SCLC. Of note, patients with late relapse ( $\geq 180$  days) benefited more from rechallenge. Unfortunately, these PFS and ORR differences did not turn into an OS advantage.<sup>[12]</sup> Nonetheless, topotecan is the only approved treatment option in relapsed SCLC at second-line treatment in Europe and the USA. Despite all these contradictory data, platinum-etoposide rechallenge still remains as a reasonable treatment option in clinical practice. Therefore, we aimed to compare the efficacy and safety of platinum-etoposide rechallenge, topotecan, and CAV as second-line treatment in SR-SCLC retrospectively.

## Methods

### Patient Eligibility

The study is a retrospective multicentric observational study. Patients with relapsed sensitive SCLC who were admitted to the medical Oncology Clinics of Gazi University School of Medicine, University of Health Sciences, Dr Abdurrahman Yurtaslan Ankara Oncology Teaching and Research Hospital, and Hacettepe University School of Medi-

cine between January 2009 and April 2021 were screened. Inclusion criteria were defined as being 18 years of age or older, having SCLC histopathology, having relapsed with a TFI of 90 days or longer, and having received at least one cycle of topotecan, platinum-etoposide, or CAV at second-line treatment. Exclusion criteria were defined as secondary malignancy or mixed histopathology. The data were retrieved from the medical records of patients.

The TFI was the time between the end of first-line treatment and the first relapse (in days). A TFI of 90 days or longer was accepted as a sensitive disease. The PFS was the time between the initiation of second-line treatment and disease progression or death (in months). The Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) criteria were used to define progression. The OS was the time between the initiation of second-line treatment and death (in months). The patients who lose follow-up were censored. The National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0, were used to grade adverse events.

### Chemotherapeutic Agents

All three chemotherapeutic regimens were used as a standard treatment protocol in our clinics. Topotecan was administered 1.5 mg/m<sup>2</sup>/day intravenously (iv) on days 1–5 and repeated every 28 days. Platinum-etoposide was administered as cisplatin 80 mg/m<sup>2</sup> iv on day 1 or carboplatin (AUC5) iv on day 1, etoposide 100 mg/m<sup>2</sup>/day iv on days 1-3, and repeated every 21 days. CAV was administered as doxorubicin 50 mg/m<sup>2</sup> iv on day 1, cyclophosphamide 1000 mg/m<sup>2</sup> iv on day 1, and vincristine 1.4 mg/m<sup>2</sup> (maximum dose: 2 mg) iv on day 1 and repeated every 21 days. Each of the three regimens received up to six cycles.

### Statistical Analysis

Statistical analysis was performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical analyses were conducted to illustrate the distribution and homogeneity of the variables. Continuous variables were reported using the median (min-max); categorical variables were reported using Pearson's chi-squared test or Fisher's Exact test. Survival curves were created by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses were conducted to show the effects of variables on PFS and OS. All tests were bidirectional, and the  $p < 0.05$  was accepted as significant.

## Results

One hundred and two patients who met the eligibility criteria were included in the study. At all, 39.8% (n=41) of the patients were treated with topotecan, 43.7% (n=45) of the patients

were treated with platinum-etoposide, and 16.5% (n=17) of the patients were treated with CAV at second-line treatment. Patient characteristics were similar between groups except for stage at diagnosis, lung metastasis, treatment-free interval, and history of thorax radiotherapy (p=0.011, p=0.040, p<0.001 and p=0.011, respectively) (Table 1).

The median duration of follow-up was 3.2 months (0.2-52.3) in the topotecan, 9.5 months (0.2-33.8) in the platinum-etoposide, and 7.6 months (0.2-23.9) in the CAV groups (p=0.059). The overall response rate (ORR) was 9.8% in the topotecan, 37.8% in the platinum-etoposide, and 41.2% in the CAV groups, and the difference was significant (p=0.005) (Table 2).

The mPFS was 2.5 months (95% CI 1.9-3.1) in the topote-

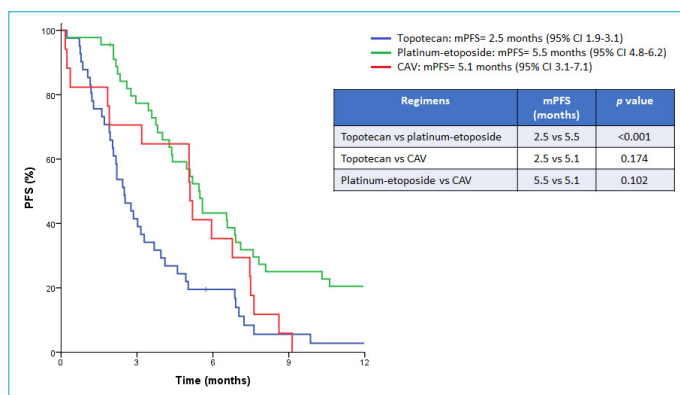
can, 5.5 months (95% CI 4.8-6.2) in the platinum-etoposide, and 5.1 months (95% CI 3.1-7.1) in the CAV groups. The difference between the topotecan and platinum-etoposide groups was significant (p<0.001) (Fig. 1). In the univariate analyses to estimate PFS, while extensive stage at diagnosis (HR 2.07; 95% CI 1.36-3.14; p<0.001), and bone metastasis (HR 1.63; 95% CI 1.08-2.47; p=0.023) were associated with shorter PFS, TFI of 180 days or longer (HR 0.54; 95% CI 0.36-0.81; p=0.003), history of thorax radiotherapy (HR 0.55; 95% CI 0.37-0.82; p=0.004), and platinum-etoposide chemotherapy (HR 0.40; 95% CI 0.25-0.60; p<0.001) were associated with longer PFS. In the multivariate analysis to estimate PFS with these factors, it was observed that platinum-etoposide chemotherapy increased PFS (HR 0.50; 95% CI 0.27-0.90; p=0.021) (Table 3).

**Table 1.** Patient characteristics

Variable	Topotecan	Platinum-etoposide	CAV	p
Number of patients, n (%)	41 (39.8)	45 (43.7)	17 (16.5)	-
Median age, years (min-max)	60.1 (47.7-81.7)	59.4 (45.0-85.6)	60.2 (49.3-68.9)	0.394
Elderly, n (%)				
<65 years old	29 (70.7)	37 (82.2)	14 (82.4)	0.389
≥65 years old	12 (29.3)	8 (17.8)	3 (17.6)	
Sex, n (%)				
Female	5 (12.2)	7 (15.6)	4 (23.5)	0.555
Male	36 (87.8)	38 (84.4)	13 (76.5)	
ECOG PS at second-line treatment, n (%)				
0-1	35 (85.4)	42 (93.3)	12 (70.6)	0.064
2	6 (14.6)	3 (6.7)	5 (29.4)	
Stage at diagnosis, n (%)				
Limited stage	<b>9 (22.0)</b>	<b>24 (53.3)</b>	<b>7 (41.2)</b>	<b>0.011</b>
Extensive stage	<b>32 (78.0)</b>	<b>21 (46.7)</b>	<b>10 (58.8)</b>	
Metastatic site, n (%)				
Lung	<b>17 (41.5)</b>	<b>20 (44.4)</b>	<b>13 (76.5)</b>	<b>0.040</b>
Distant Lymph Nodes	12 (29.3)	14 (29.1)	4 (23.5)	0.842
Bone	20 (48.8)	12 (26.7)	9 (52.9)	0.054
Liver	18 (43.9)	12 (26.7)	7 (41.2)	0.222
Brain	9 (22.0)	9 (20.0)	3 (17.6)	0.930
Others	22 (53.7)	18 (40.0)	5 (29.4)	0.191
Treatment-free interval, n (%)				
90-180 days	<b>31 (75.6)</b>	<b>9 (20.0)</b>	<b>10 (58.8)</b>	<b>&lt;0.001</b>
≥180 days	<b>10 (24.4)</b>	<b>36 (80.0)</b>	<b>7 (41.2)</b>	
Response to first-line chemotherapy, n (%)				
Complete/partial response	36 (87.7)	44 (97.8)	14 (82.4)	0.094
Stable disease	5 (12.2)	1 (2.2)	3 (17.6)	
Prophylactic cranial irradiation, n (%)				
No	34 (82.9)	27 (60.0)	11 (64.7)	0.060
Yes	7 (17.1)	18 (40.0)	6 (35.3)	
History of thorax radiotherapy, n (%)				
No	<b>26 (63.4)</b>	<b>14 (31.1)</b>	<b>8 (47.1)</b>	<b>0.011</b>
Yes	<b>15 (36.6)</b>	<b>31 (68.9)</b>	<b>9 (52.9)</b>	

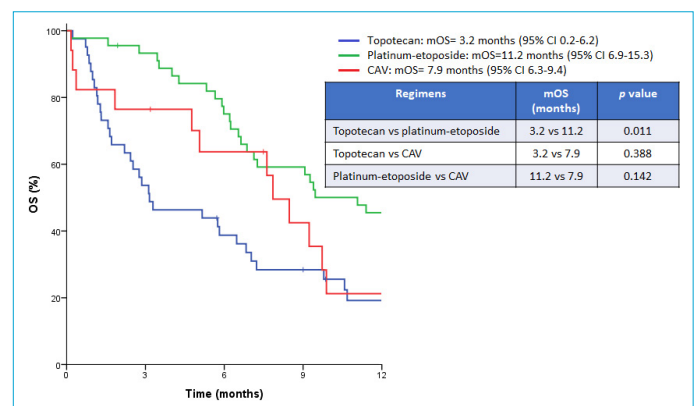
**Table 2.** Treatment exposure and response rates with second-line treatment

Variable	Topotecan	Platinum-etoposide	CAV	p
Median duration of follow up, months (min-max)	3.2 (0.2-52.3)	9.5 (0.2-33.8)	7.6 (0.2-23.9)	0.059
Median duration treatment, months (min-max)	<b>2.5 (0.2-15.9)</b>	<b>5.5 (0.2-30.0)</b>	<b>5.1 (0.2-9.1)</b>	<b>0.001</b>
Median time to best response, months (min-max)	2.2 (0.2-7.0)	3.0 (2.2-9.9)	2.4 (0.2-5.8)	0.167
Disease control rate, n (%)	<b>7 (17.1)</b>	<b>28 (62.2)</b>	<b>10 (58.8)</b>	<b>&lt;0.001</b>
Objective response rate, n (%)	<b>4 (9.8)</b>	<b>17 (37.8)</b>	<b>7 (41.2)</b>	<b>0.005</b>
Complete response, n (%)	1 (2.4)	3 (6.7)	0 (0.0)	0.397
Partial response, n (%)	<b>3 (7.3)</b>	<b>14 (31.1)</b>	<b>7 (41.2)</b>	<b>0.005</b>
Stable Disease, n (%)	3 (7.3)	11 (24.4)	3 (17.6)	0.101
Progressive Disease, n (%)	<b>34 (82.9)</b>	<b>17 (37.8)</b>	<b>7 (41.2)</b>	<b>&lt;0.001</b>

**Figure 1.** Kaplan-Meier curves of progression-free survival (PFS) with second-line treatment in patients with sensitive relapsed SCLC.

The mOS was 3.2 months (95% CI 0.2-6.2) in the topotecan, 11.2 months (95% CI 6.9-15.3) in the platinum-etoposide, and 7.9 months (95% CI 6.3-9.4) in the CAV groups. The difference between the topotecan and platinum-etoposide groups was significant ( $p=0.011$ ) (Fig. 2). In the univariate analyses to estimate OS while ECOG PS of 2 (HR 1.97; 95% CI 1.05-3.70;  $p=0.035$ ) and extensive stage at diagnosis (HR 2.25; 95% CI 1.46-3.46;  $p<0.001$ ) were associated with shorter OS, TFI of 180 days or longer (HR 0.50, 95% CI 0.33-0.76;  $p=0.001$ ), history of thorax radiotherapy (HR 0.51; 95% CI 0.34-0.78;  $p=0.002$ ) and platinum-etoposide chemotherapy (HR 0.56; 95% CI 0.36-0.89;  $p=0.014$ ) were associated with longer OS. In the multivariate analysis to estimate OS with these factors, it was seen that the extensive stage at diagnosis decreased OS (HR 2.41; 95% CI 1.78-4.78;  $p=0.012$ ) (Table 4).

Patients' toxicity profiles are given in Table 5. Neutropenia was the most common adverse event among grade 3 or higher adverse events in all groups. At least one dose delay was 26.8% in the topotecan, 51.1% in platinum-etoposide, and 29.4% in the CAV groups, and the difference was not significant ( $p=0.050$ ). Primary GCSF prophylaxis application rate was 39.0% in the topotecan, 80.0% in the platinum-etoposide, and 75.0% in the CAV groups ( $p<0.001$ ).

**Figure 2.** Kaplan-Meier curves of overall survival (OS) with second-line treatment in patients with sensitive relapsed SCLC.

## Discussion

In the current study, we compared the efficacy and the safety of platinum-etoposide rechallenge, topotecan, and CAV at second-line treatment in patients with SR-SCLC. It was obtained that platinum-etoposide rechallenge improved PFS, OS, and ORR with a similar safety profile over topotecan at second-line treatment in SR-SCLC.

In the real-life, most of the patients with SCLC could not receive second-line treatment. In The German Tumor Registry Lung Cancer Cohort, it was reported that 50% of the patients with ES-SCLC could receive second-line treatment.<sup>[13]</sup> Likewise, in a retrospective Swedish study, it was reported that 26% of the patients with ES-SCLC and 58.1% of the patients with LS-SCLC could receive second-line treatment after relapse or progression with first-line treatment.<sup>[14]</sup> Response to first-line treatment and TFI are two of the most important prognostic factors. Although topotecan is the only approved treatment for relapsed SCLC, in early trials reinduction chemotherapy approach was also applied. Since topotecan was shown as effective as CAV with a favorable safety profile, CAV was no longer used. Instead, in clinical practice, platinum-etoposide rechallenge is widely used by clinicians.

**Table 3.** Univariate and multivariate analyses for PFS

Variable	Univariate Analysis			Multivariate Analysis		
	HR	CI (95%)	p	HR	CI (95%)	p
Elderly						
<65 years old	Ref			-	-	-
≥65 years old	1.21	0.74-1.97	0.454			
Sex						
Female	Ref			-	-	-
Male	0.72	0.41-1.26	0.273			
ECOG PS at second-line treatment						
0-1	Ref			-	-	-
2	1.17	0.64-2.11	0.607			
Stage at diagnosis						
Limited stage	Ref					
Extensive stage	2.07	1.36-3.14	<0.001	1.79	0.91-3.52	0.091
Metastatic site						
Lung	0.97	0.65-1.44	0.868	-	-	-
Distant Lymph Nodes	0.72	0.60-1.13	0.144	-	-	-
Bone	1.63	1.08-2.47	0.023	1.26	0.80-1.98	0.313
Liver	1.13	0.74-1.71	0.580	-	-	-
Brain	1.11	0.68-1.80	6.760	-	-	-
Others	1.04	0.70-1.55	0.854	-	-	-
Treatment-free interval						
90-180 days	Ref					
≥180 days	0.54	0.36-0.81	0.003	0.98	0.56-1.73	0.947
Response to first-line chemotherapy						
Complete/partial response	Ref					
Stable disease	1.77	0.89-3.53	0.133	-	-	-
Prophylactic cranial irradiation						
No	Ref			-	-	-
Yes	0.70	0.46-1.08	0.096			
History of thorax radiotherapy						
No	Ref					
Yes	0.55	0.37-0.82	0.004	1.02	0.52-2.01	0.948
Second-line chemotherapy						
Topotecan	Ref					
Platinum-etoposide	0.40	0.25-0.63	<0.001	0.50	0.27-0.90	0.021
CAV	0.64	0.36-1.15	0.134	0.72	0.40-1.30	0.275

Platinum-etoposide rechallenge was recruited in a few retrospective studies, and limited randomized phase III trials. In the multicenter multinational retrospective study by Genestreti et al. it was reported that the mPFS was 5.5 months (95% CI 4.4-6.3), the mOS was 7.9 months (95% CI 6.9-9.7), and the ORR was 45% with platinum-etoposide rechallenge.<sup>[10]</sup> In a retrospective study by Wakuda et al it was observed that the platinum-etoposide rechallenge showed similar OS and ORR compared to the other regimen group.<sup>[15]</sup> On the other hand, in a phase III Japanese trial, irinotecan was added to carboplatin-etoposide to inhibit both topoisomerase I and II to promote rechallenge responses,

and it was compared with topotecan at second-line treatment in SR-SCLC. Indeed, it was shown that the triple combination prolonged OS (18.2 vs. 12.5 months,  $p=0.0079$ ), PFS (5.7 vs. 3.6 months,  $p<0.0001$ ), and increased ORR (84% vs. 27%,  $p<0.001$ ).<sup>[16]</sup> Furthermore, based on the aforementioned Japanese trial, in a three-arm retrospective study by Wakuda et al, although platinum-etoposide rechallenge was not superior to amburicin, the platinum-etoposide-irinotecan group had longer OS compared with the platinum-etoposide and amburicin groups.<sup>[17]</sup> On the other hand, in the phase III French trial, it was demonstrated that the mPFS was 4.7 months and 2.7 months ( $p=0.041$ ), and

**Table 4.** Univariate and multivariate analyses for OS

Variable	Univariate Analysis			Multivariate Analysis		
	HR	CI (95%)	p	HR	CI (95%)	p
Elderly						
<65 years old	Ref			-	-	-
≥65 years old	1.17	0.69-2.00	0.548			
Sex						
Female	Ref			-	-	-
Male	0.84	0.47-1.50	0.557			
ECOG PS at second-line treatment						
0-1	Ref					
2	1.97	1.05-3.70	0.035	1.51	0.76-2.99	0.242
Stage at diagnosis						
Limited stage	Ref					
Extensive stage	2.25	1.46-3.46	<0.001	2.41	1.78-4.78	0.012
Metastatic site						
Lung	1.12	0.74-1.69	0.594	-	-	-
Distant Lymph Nodes	0.98	0.62-1.55	0.935	-	-	-
Bone	1.48	0.96-2.28	0.076	-	-	-
Liver	0.85	0.55-1.33	0.478	-	-	-
Brain	1.27	0.77-2.09	0.357	-	-	-
Others	1.10	0.73-1.67	0.645	-	-	-
Treatment-free interval						
90-180 days	Ref					
≥180 days	0.50	0.33-0.76	0.001	0.70	0.40-1.22	0.206
Response to first-line chemotherapy						
Complete/partial response	Ref			-	-	-
Stable disease	1.76	0.88-3.52	0.109			
Prophylactic cranial irradiation						
No	Ref			-	-	-
Yes	0.68	0.44-1.06	0.089			
History of thorax radiotherapy						
No	Ref					
Yes	0.51	0.34-0.78	0.002	1.22	0.62-2.41	0.560
Second-line chemotherapy						
Topotecan	Ref					
Platinum-etoposide	0.56	0.36-0.89	0.014	0.71	0.41-1.24	0.230
CAV	0.82	0.44-1.50	0.515	0.78	0.41-1.46	0.431

the ORR was 39% and 19% ( $p=0.0024$ ) in the carboplatin-etoposide rechallenge and topotecan groups, respectively. Unfortunately, in this phase III trial, carboplatin-etoposide did not show any OS advantage.<sup>[12]</sup>

Our study showed an ORR of 37.8%, a mPFS of 2.5 months, and a mOS of 11.2 months with platinum-etoposide rechallenge. The ORR and PFS results in our study were consistent with the previous phase III French trial. But the mOS (11.2 months) was numerically higher in our study than that of the French trial (7.5 months). There might be some potential reasons for this OS difference. The patient characteris-

tics of the studies were different. First of all, more than half of the patients (53.3%) in the platinum-etoposide rechallenge group in our study had LS-SCLC, but in the French trial one third of the patients (36.0%) had LS-SCLC. Secondly, there were more patients with late relapses (TFI  $\geq 180$  days) in platinum-etoposide rechallenge group in our cohort than in the French trial (80.0% vs. 30.0%). As expected, late relapses are deemed to be benefited more from platinum-etoposide rechallenge. Lastly, there were more patients with history of thorax radiotherapy (68.9% vs. 48.0%), and less liver (26.7% vs. 44.0%) and brain (20.0% vs. 33.0%) metastases in our cohort than in the French trial.<sup>[16]</sup>

**Table 5.** Adverse events and GCSF prophylaxis at second-line treatment

Variable, n (%)	Topotecan		Platinum-etoposide		CAV		p	
	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade
Neutropenia	8 (19.5)	14 (34.1)	12 (26.7)	25 (55.6)	4 (23.5)	6 (35.3)	0.735	0.101
Anemia	4 (9.8)	24 (58.5)	4 (8.9)	32 (71.1)	3 (17.6)	15 (88.2)	0.591	0.077
Thrombocytopenia	5 (12.2)	14 (34.1)	5 (11.1)	20 (44.4)	3 (17.6)	5 (29.4)	0.783	0.453
Liver toxicity	1 (2.4)	5 (12.2)	1 (2.4)	3 (6.7)	0 (0.0)	1 (5.9)	0.815	0.597
Renal toxicity	2 (4.9)	5 (12.2)	1 (2.2)	11 (24.4)	0 (0.0)	2 (11.8)	0.564	0.260
Febrile neutropenia	4 (9.8)		9 (20.0)		2 (11.8)		0.380	
≥1 dose reduction	5 (12.2)		13 (28.9)		2 (11.8)		0.101	
≥1 dose delay	11 (26.8)		23 (51.1)		5 (29.4)		0.050	
Treatment cessation	2 (4.9)		3 (6.7)		3 (17.6)		0.238	
Primary GCSF prophylaxis	<b>16 (39.0)</b>		<b>36 (80.0)</b>		<b>12 (75.0)</b>		<b>&lt;0.001</b>	
Secondary GCSF prophylaxis	8 (19.5)		18 (40.0)		4 (26.7)		0.111	

In our study, the topotecan group had more patients with poor prognostic factors than the platinum-etoposide rechallenge group. However, in the multivariate analysis to estimate PFS, it was observed that platinum-etoposide rechallenge was the only factor associated with a longer PFS. On the other hand, in the multivariate analysis to estimate OS, ES-SCLC at the initial diagnosis was the only variable associated with poor OS. In the topotecan group, there were more patients with ES-SCLC at initial diagnosis. Furthermore, it was known that prophylactic cranial irradiation (PCI) was associated with a better prognosis previously.<sup>[18]</sup> There was a non-significantly higher rate of PCI in the platinum-etoposide rechallenge group than in the topotecan group.

In our study, we also analyzed the toxicity profiles at second-line treatment. Although the rate of primary GCSF prophylaxis was significantly higher in the platinum-etoposide group than that of the topotecan group, the rate of febrile neutropenia was numerically higher in the platinum-etoposide rechallenge than that of the topotecan group. As a result, a trend towards an increased rate of secondary prophylaxis, dose delays, and dose reductions were also more common in the platinum-etoposide rechallenge group.

Our study has several limitations. It was a retrospective observational study. However, the multicenter nature added some value. The patient number was small. Of note, there was no retrospective study with a large number of patients with SR-SCLC. The efficacy and safety comparisons between cisplatin and carboplatin in the platinum-etoposide group could not be conducted because of the lack of the data. In addition, treatment exposure and compliance data are not available beyond progression in the topotecan arm. Lastly, the evaluation of progression was conducted every three cycles by different radiologists, so potential interobserver variations might be a limitation.

In the current study, it was suggested that platinum-etoposide rechallenge improved PFS, OS, and ORR over topotecan, which is the standard treatment at this point, in SR-SCLC. A trend towards an increased but tolerable toxicity profile was observed in the platinum-etoposide rechallenge group. Given the scarcity of the third-line treatment, sparing topotecan to third-line treatment and rechallenge with platinum-etoposide at second-line treatment should be a reasonable option in fitted patients.

#### Disclosures

**Ethics Committee Approval:** Ethical approval was waived by the local Ethics Committee of Gazi University School of Medicine (04.05.2021, 2021-531).

**Peer-review:** Externally peer-reviewed.

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