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ORIGINAL ARTICLE

Comparative assessment of three different second-line regimens in chemotherapy resistant/refractory small-cell lung cancer

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Summary

Purpose: *Small cell lung cancer (SCLC) patients unresponsive or relapsing within 90 days following frontline chemotherapy have poor prognosis and they should be treated with different chemotherapy regimens other than those used in the first-line regimen. Currently there is no globally accepted standard chemotherapeutic regimen for the treatment of these patients. This retrospective study was designed to compare CAV (Cyclophosphamide, Doxorubicin, Vincristine), weekly topotecan and weekly irinotecan regimens and to evaluate the efficacy of the three regimens in patients with chemotherapy resistant/refractory (CRR) SCLC.*

Methods: *A total of 67 CRR-SCLC patients, who were treated with CAV, weekly topotecan and weekly irinotecan were reviewed for weekly irinotecan (27 for 60 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle,24 for CAV (Cyclophosphamide 750 mg/m^2 on day 1, Doxorubicin 50 mg/m^2 on day 1 and Vincristine 1.4mg/m^2 on day 1 every 3 weeks), 16 for weekly topotecan (4 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle).*

Results: *The median follow-up time was 12.45 months, there was no difference about disease control rates (DCR) between three chemotherapy regimens (DCR; 25.9% with irinotecan, 29.2% with CAV and 31.3% with topotecan, p=0.92). Objective response rates (ORR) for irinotecan, CAV and topotecan groups were 3,7%, 8,8%, and 0%, respectively (p=0.63). Median progression free survival (PFS) and overall survival (OS) were similar according to irinotecan, CAV, and topotecan (PFS: 1.93 months, 2.30 months and 3.45 months; OS: 2.89 months, 4.79 months and 5.81 months, respectively). The adverse events were generally mild and manageable for both hematological and nonhematological toxicities in all three arms.*

Conclusions: *Weekly irinotecan, CAV and weekly topotecan are similarly effective and safe chemotherapy protocols for the treatment of CRR-SCLC patients.*

Key words: *small cell lung cancer, platinum resistance, CAV, irinotecan, topotecan*

Introduction

Small cell lung cancer (SCLC) is the most aggressive lung cancer subtype and represents approximately 10% to 15% of all lung cancer cases [1]. Early diagnosis of SCLC is uncommon, and between 60 to 70% of patients have already extensive disease (ED) with metastases at diagnosis [2]. For patients with ED-SCLC, standard front-line treatment includes 4-6 cycles of cisplatin or carboplatin and etoposide [3]. Unfortunately, despite initial response, patients with ED develop drug resistance and die of disease at a median of 10 to 12 months from diagnosis [4].

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According to genereal definition, a progression ≥90 days from last platinum dose is accepted as "platinum sensitive", however, progression <90 days is accepted as "platinum refractory". Refractory patients do not achieve any objective response while resistant disease is characterized by initial response followed by very early disease recurrence usually within 90 days of completing frontline therapy [5]. Patients with chemotherapy-refractory or resistant disease (CRR) have poor prognosis and 10% response to subsequent chemotherapy [6]. CRR-SCLC patients are treated with chemotherapy regimens other than the first-line regimen. In more recent years, although targeted therapy and immunotherapy have also been actively tested with many disappointments but also with some encouraging results, currently chemotherapy has been the mainstay of treatment for CRR-SCLC [7]. After relapse, topotecan is the only second-line drug approved by the US Food and Drug Administration (FDA). Single agent chemotherapy agents and combinations like CAV, amrubicin, gemcitabine, vinca alcaloids, taxanes, temozolomide, irinotecan, topotecan have been widely used in CRR-SCLC patients. However, there is no currently globally accepted standard chemotherapeutic regimen for the treatment of these patients [8-15]. Potential changes in the efficacy and safety of second line therapy for refractory SCLC have not been well studied.

Despite the limited antitumor activity shown by these agents, none of the limited phase II randomized trials comparing different chemotherapy regimens has shown superiority in survival, therefore, currently no standard chemotherapy regimen for CRR-SCLC patients has been identified.

The aim of this study was to compare the efficacy and safety of weekly irinotecan, weekly topotecan and cyclophosphamide regimen in patients with CRR-SCLC. Additionally, this is the first article to compare the vincristine, irinotecan and topotecan all together in a single study for CRR-SCLC.

Methods

This retrospective study was approved by the Institutional Review Board of the Sakarya University (71522473/050.01.04/200-18.06.2018). We retrospectively reviewed our medical records and collected data on SCLC patients who had been treated with first- and second-line chemotherapy at the oncology department from June 2009 to August 2020. Histopathologically confirmed SCLC patients who had received at least one cycle of chemotherapy for platinum refractory disease as second-line chemotherapy, and at least two response assessments over 6-8 weeks after the start of chemotherapy were included in the study. CRR patients were defined as those who relapsed within 3 months of the completion of first-line platinum and etoposide chemotherapy or progressed during this chemotherapy regimen. Patients who had second malignancies or exhibited insufficient hematological, hepatic and renal functions, were excluded from the analysis.

A total of 67 CRR- SCLC patients were treated as follows: Irinotecan, 60mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle; Topotecan, 4 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle; Doxorubicin, 50 mg/m^2 on day 1, cyclophosphamide, 750 mg/m^2 on day 1 and vincristine, 1.4mg/m^2 with maximum 2mg on day 1 every 3 weeks, total 6 cycles. Weekly irinotecan and topotecan were continued until disease progression, unacceptable toxicity, patient refusal or the physician's decision. Response evaluation was performed every 8-12 weeks according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) [16] and the adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 which is usually applied in hematooncology clinical trials [17]. Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Disease control rate (DCR) is defined as the sum of objective response and SD (CR+PR+SD). Progression free survival (PFS) was measured from treatment initiation until the first evidence of disease progression or last follow up date. The overall survival (OS) was measured from treatment initiation until death or last follow up date. If a patient had died to supposed PD in the absence of radiographic evidence of progression, the date of death was used as the date of disease progression.

Statistics

All statistical analyses were performed using PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc. Patient demograhic and clinical characteristics, DCR, response rate and treatment-related toxicities were compared using chi-square test. Survival curves were generated using the Kaplan-Meier method and were compared by log-rank test. Cox regression method was used for survival analyses. Differences between results were considered statistically significant for p values <0.05.

Results

Patient characteristics

The baseline demograhic and clinical characteristics of the study group are shown in Table 1. A total of 67 patients who progressed during chemotherapy or within 3 months of platinum-based chemotherapy were analyzed. Of these, 13 (19.4%) patients progressed during platinum-based chemotherapy and 54 (80.6%) progressed within 3 months of therapy. Baseline clinical characteristics including age, gender, smoking history and pack-year, clinical node positivity, primary tumor location and the first-line chemotherapy regimens and best responses also showed no significant dif-

Table 1. Demographic and clinical characteristics of the study subjects

Variables	*All (n=67)*	*Irinotecan (n=27)*	*CAV (n=24)*	*Topotecan (n=16)*	*p value*
Age, years					0.58
Median	57	58	56	59	
Interquartile range	52-65	51-67	51-64	53-64	
Gender, n (%)					0.52
Female	10 (14.9)	5 (18.5)	2 (8.3)	3 (18.8)	
Male	57 (85.1)	22 (81.5)	22 (91.7)	13 (81.3)	
ECOG-PS,n (%)					0.20
0-1	51 (76.1)	16 (59.3)	21 (87.5)	14 (87.5)	
2	16 (23.9)	11 (40.7)	3 (12.5)	2 (12.5)	
Smoking					
n (%)	62 (95.4)	27 (100)	21 (91.3)	14 (93.3)	0.31
Pack-year, median (IQR)	40 (30-50)	40 (30-50)	50 (40-60)	40 (35-45)	0.21
Stage at diagnosis, n (%)					0.51
Limited stage	17 (25.4)	6 (22.2)	8 (33.3)	3 (18.8)	
Extensive stage	50 (74.6)	21 (77.8)	16 (66.7)	13 (81.2)	
Primary location, n (%)					0.05
Right lung	40 (59.7)	13 (48.1)	19 (79.2)	8 (50.0)	
Left lung	27 (40.3)	14 (51.9)	5 (20.8)	8 (50.0)	
Clinical T stage at the diagnosis, n (%)					0.01
T1-T2	29 (43.3)	6 (22.2)	14 (58.3)	9 (56.3)	
T3-T4	38 (56.7)	21 (77.8)	10 (41.7)	7 (43.8)	
Patients with clinical nodal involvement, n (%)	59 (90.8)	25 (92.6)	22 (91.7)	12 (85.7)	0.75
Patients with cranial metastasis, n (%)	10 (14.9)	4 (14.8)	4 (16.7)	2 (12.5)	0.93
Metastatic site, n (%)					
Bone(s)	28 (53.8)	14 (58.3)	7 (46.7)	7 (53.8)	0.77
Liver	17 (32.7)	12 (50.0)	3 (20.0)	2 (15.4)	0.04
Lung	7 (13.5)	0 (0)	5 (33.3)	2 (15.4)	0.01
Lymph node(s)	26 (50.0)	11 (45.8)	8 (53.3)	7 (53.8)	0.85
Adrenal(s)	3 (5.8)	1 (4.2)	1 (6.7)	1 (7.7)	0.89
First-line treatment setting, n (%)					0.02
Chemoradiotherapy	4 (6.0)	0 (0)	1 (4.2)	3 (18.8)	
Chemotherapy	58 (86.6)	26 (96.3)	19 (79.2)	13 (81.3)	
Sequential chemotherapy and radiotherapy	5 (7.4)	1 (3.7)	4 (16.7)	0 (0)	
First-line chemotherapy, n (%)					0.62
Cisplatin-etoposide	62 (92.5)	24 (88.9)	23 (95.8)	15 (93.8)	
Carboplatin-etoposide	5 (7.5)	3 (11.1)	1 (4.2)	1 (6.3)	
Platinum resistance, n (%)					0.69
During treatment	13 (19.4)	4 (14.8)	5 (20.8)	4 (25.0)	
<3 months	54 (80.6)	23 (85.2)	19 (79.2)	12 (75.0)	
Best response at first-line, n (%)					0.63
Complete	3 (4.5)	0 (0)	1 (4.2)	2 (12.5)	
Partial	31 (46.3)	13 (48.1)	12 (50.0)	6 (37.5)	
Stable	10 (14.9)	5 (18.5)	3 (12.5)	2 (12.5)	
Progressive	23 (34.3)	9 (33.3)	8 (33.3)	6 (37.5)	
Grade 3 or above toxicity at first-line, n (%)	7 (10.8)	3 (11.1)	3 (13.0)	1 (6.7)	0.82

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status

ferences among the groups. Moreover, ECOG-PS, clinical T stage and the first-line treatment setting were significantly different among groups (p=0.02, p=0.02, and p=0.017, respectively). Although cranial metastasis and metastasis to bone, lymph node and adrenals were similar, contralteral lung and liver metastasis were significantly different (p=0.01 and p=0.04, respectively).

Treatment efficacy

Median OS was 4.14 months (95%CI, 2.75-5.52) in all groups. Patients who received irinotecan had a median OS of 2.89 months (95% confidence interval (CI), 2.44-3.33), compared with the 4.79 months (95% CI, 3.26-6.33) observed for patients in the CAV group and 5.81 months (95%CI, 3.56-8.06) in the topotecan group (p=0.18, Figure 1B, Table 4). Up to 88.1% of the patients had died at the end of the study. This rate was 96.3% in the irinotecan group, 91.7% in the CAV group and 68.8% in the topotecan group. In addition, median PFS was 2.49 months (95%CI, 2.24-2.75) in all groups. Patients who received irinotecan had a median PFS of 1.93 months (95%CI, 1.27-2.60), compared with the 2.30 months (95% CI, 1.77-2.82) observed for patients in the CAV group and 3.45 months (95%CI, 2.41-4.48) in the topotecan group (p=0.47, Figure 1A). All patients in the irinotecan group, up to 91.7% in the CAV group and 93.8 % in the topotecan group had PD at the end of the study.

DCR at the first-line setting was 65.7% and for the second-line setting the DCR was 28.4%. Table 2 shows the response rates that were comparable among treatment groups. The DCR rates were 25.9% in the irinotecan group, 29.2% in the CAV and 31.3% in the topotecan group (p=0.92). In addition, discontinued treatment due to treatment-related death or because of intolerable adverse effects was similar among groups (for all, p>0.05).

Median follow-up time (from diagnosis to last control) was 12.45 months (95%CI 10.64-14.25). The median total survival measured from the date of first detected disease to the date of death or loss to follow-up was also analyzed and was 11.69 months for the overall study population. It was 9.82 months (95%CI, 8.10-11.54) in the irinotecan group, 13.14 months (95%CI, 9.70-16.57) in the CAV group and 12.71 months (95%CI, 11.11-14.31) in the topotecan group (p=0.75). In univariate analysis, median PFS and median OS time of the CRR-SCLC patients who received second-line chemotherapy were similar (Table 3).

Toxicity

Grade 3 or above toxicity profiles are shown in Table 3. Although grade 3 or above toxicity was

Table 2. Treatment responses

Variables	*Irinotecan (n=27)*	*CAV (n=24)*	*Topotecan (n=16)*	*p value*
Best response during treatment, n (%)				0.81
Complete response	0	1 (4.2)	0	
Partial response	1 (3.7)	1 (4.2)	0	
Stable disease	6 (22.2)	5 (20.8)	5 (31.3)	
Progressive disease	20 (74.1)	17 (70.8)	11 (68.8)	
Treatment discontinuation, n (%)	3 (11.1)	5 (20.8)	2 (12.5)	0.59
Treatment related death	2 (66.6)	2 (40.0)	1 (50.0)	0.97
Adverse event(s)	1 (33.3)	3 (60.0)	1 (50.0)	0.76

Table 3. Grade ≥3 treatment toxicity at the second-line settings

Variables	*Irinotecan (n=27)*	*CAV (n=24)*	*Topotecan (n=16)*	*p value*
Grade 3 or above toxicity, n (%)	10 (37.0)	12 (50.0)	5 (31.3)	0.45
Emesis	3 (11.1)	7 (29.2)	2 (12.5)	0.19
Stomatitis	1 (3.7)	2 (8.3)	0 (0)	0.44
Diarrhea	1 (3.7)	0 (0)	1 (6.3)	0.24
Neuropathy	1 (3.7)	2 (8.3)	1 (6.3)	0.78
Neutropenia	5 (18.5)	7 (29.2)	4 (25.0)	0.66
Febrile neutropenia	0 (0)	2 (8.3)	1 (6.3)	0.33
Anemia	1 (3.7)	2 (8.3)	3 (18.8)	0.24
Thrombocytopenia	1 (3.7)	1 (4.2)	2 (12.5)	0.45

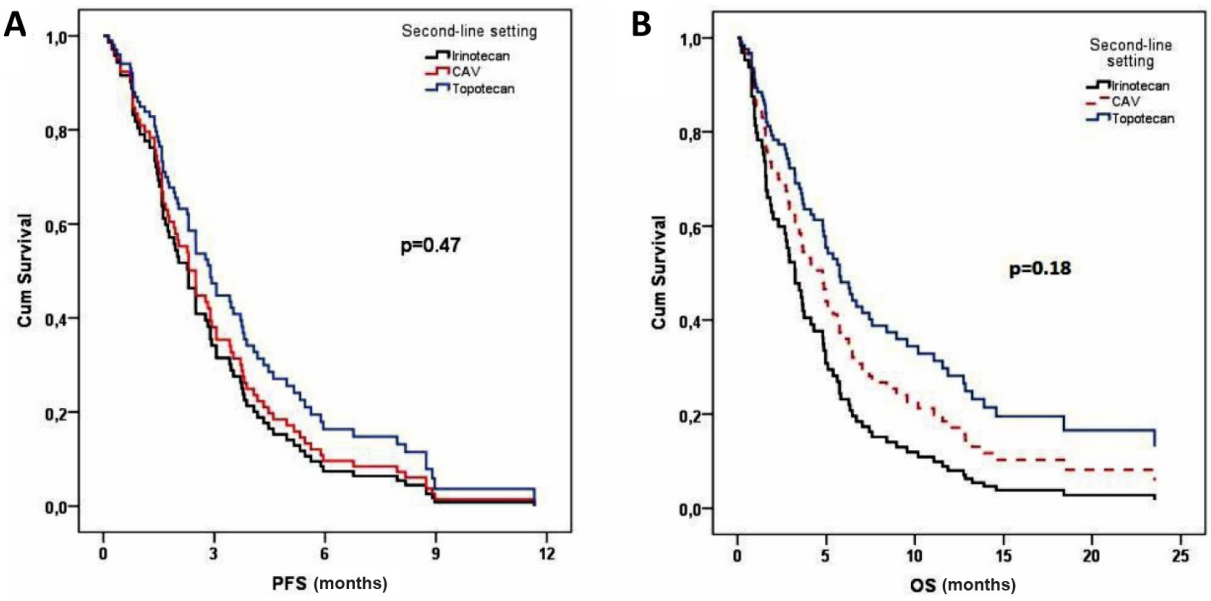

Figure 1. A: Kaplan-Meier estimates of progression free survival (PFS) according to chemotherapeutic regimen. The median PFS was 1.9 months, 2.3 months and 3.45 months in the irinotecan, CAV and topotecan arms, respectively (p>0.05). **B:** The median OS was 2.89 months, 4.79 months, 5.81 in the irinotecan, CAV and topotecan arms, respectively (p>0.05).

Table 4. Univariate analysis of progression free survival and overall survival of the study subjects

Variables	*Progression-free survival*		*Overall survival*	
	Median (95%CI)	*p*	*Median (95%CI)*	*p*
Age, years		0.09		0.38
>57	1.74 (0.97-2.50)	0.68	2.72 (0.98-4.46)	
≤57	2.82 (2.29-3.36)	0.39	4.96 (3.66-6.25)	
Gender		0.12		0.91
Female	1.61 (1.05-2.17)	0.13	3.68 (3.11-4.25)	
Male	2.49 (2.00-2.99)	0.98	4.14 (2.64-5.63)	
ECOG PS				0.30
0-1	2.49 (2.01-2.97)	0.56	4.86 (3.35-6.36)	
2	2.26 (0.91-3.61)	0.58	2.79 (2.27-3.30)	
T stage		0.10		0.76
T1-T2	2.82 (1.41-4.23)	0.90	5.09 (3.69-6.48)	
T3-T4	1.93 (1.18-2.69)		3.48 (2.38-4.57)	
Clinical N				0.48
Present	2.30 (1.87-2.72)		3.68 (2.58-4.77)	
Absent	3.74 (0.91-8.51)		8.41 (4.09-12.7)	
Brain metastasis				0.69
Present	2.30 (1.79-2.80)		4.14 (3.02-5.26)	
Absent	2.49 (1.69-3.29)		3.74 (2.01-5.47)	
Metastatic site				
Liver	2.49 (1.85-3.14)		3.74 (2.08-5.41)	0.74
Lung	1.44 (0.91-3.26)		4.14 (2.95-5.32)	0.38
Platinum resistance				0.16
During treatment	1.77 (0.73-2.81)		2.79 (0.44-5.14)	
<3 months	2.49 (1.91-3.07)		4.86 (3.20-6.51)	
Best response at first-line				0.84
Complete response	2.49 (1.76-3.23)		3.64 (3.01-4.27)	
Partial response	2.49 (1.95-3.03)		4.96 (3.54-6.37)	
Stable disease	2.30 (0.26-4.33)		3.68 (0.78-6.58)	
Progressive disease	1.77 (0.86-2.68)		3.48 (2.31-4.64)	

numerically higher in the CAV group, there was no significant difference among groups (p=0.44). Both hematologic and non-hematologic toxicities were comparable among groups (p>0.05 for all comparisons).

Discussion

The outcomes in current study showed that three chemotherapy regimens were similar in prolonging PFS and OS of second-line chemotherapy for CRR-SCLC patients. Simultaneously, toxicity reactions were increased in CAV group than in other groups. Response rate to second-line therapy in SCLC patients is very low due to wide chemoresistance, and it is highly linked with the response to frontline therapy and with the duration of treatment-free interval. This chemoresistance is far more important in refractory SCLC patients than in sensitive patients. In a systematic analysis that evaluated efficacy of second-line chemotherapy in sensitive and refractory SCLC, the overall RR was 17.9% with a higher RR of 27.7% for sensitive SCLC versus 14.8% for refractory patients. Median OS was 6.7 months with a weighted survival of 7.7 and 5.4 months for sensitive and refractory SCLC, respectively [18]. Second-line chemotherapy for CRR-SCLC remains disappointing with short survival times. In the subgroup analysis of very few studies previous studies, the efficacy and safety of chemotherapy regimens using salvage chemotherapy in refractory SCLC seemed to vary greatly and these regimens were not been established as standard chemotherapy in this setting. Despite using many chemotherapeutic agents as combinations or single-agent as topotecan, irinotecan, VAC, taxane, bendamustine and vinca alkaloids, the optimal dosage and timing of these regimens are still unclear [11,13,19].

Several studies described the effects of CAV regimen in SCLC patients. Two studies involving CAV therapy achieved second-line response rates of 13% and 28% in sensitive and CRR-SCLC patients respectively [20,21]. In a randomized trial, topotecan was shown to be as effective as CAV and topotecan showed significant improvements across several disease-related symptoms over CAV [22]. The only US Food and Drug Administration (FDA)-approved agent in relapsed SCLC patients is topotecan on the basis of this trial. A recent systematic review, Horita et al reported that the ORR of topotecan for patients with refractory-relapsed SCLC is only approximately 5%, pooled 6-month and 1-year OS rates estimated from four cohorts were 37% and 9%, respectively [23].

Topotecan has been the most investigated chemotherapy agent for relapsed SCLC, but optimal topotecan dose and schedule in recractory SCLC are not well descripted in this setting. Intermittent treatment schedules (e.g., weekly dosing) have been associated with comparable clinical efficacy at doses associated with more tolerable toxicity profiles with some cytotoxics like topotecan, irinotecan, paclitaxel and gemcitabine [24-27]. In an effort to prevent toxicity and to improve tolerability, different chemotherapy dosages and schedules such as different infusion durations or different individual peak doses are being used in SCLC. Weekly topotecan regimens have been investigated in patients with a variety of solid tumors. Some investigators have claimed that, based on preclinical and clinical evidence, weekly administration of topotecan may be a feasible alternative to the daily×5 schedules in many solid tumor types [28,29]. Weekly topotecan (4 mg/m^2 for 12 consecutive weeks) was associated with comparable clinical activity and a lower incidence of adverse effects compared with published results of the standard 5-day regimen [30]. Patients with chemosensitive SCLC were approximately twice as likely to respond to this weekly topotecan regimen versus patients with chemorefractory disease (6% versus 3%, respectively); however, the median OS of 4.5 months was comparable between treatment groups (chemosensitive, 5.6 months; chemoresistant, 3.2 months> p=0.05). Similarly, in a phase II trial with small number of patients, weekly topotecan demonstrated low response rates (<10%) and short survival time but tolerable toxicity profile in refractory SCLC [31-33].

With regard to irinotecan as a single agent (100 mg/m^2), recent phase II studies demonstrated survival benefit with tolerable toxicities in relapsed SCLC patients. Among the patients who had sensitive relapse, an ORR of 61% was achieved, whereas of the patients who had refractory disease, only 9% achieved response. The median PFS of chemotherapy-sensitive relapse and chemotherapy-refractory relapse was 5.2 months and 2.1 months, respectively. The median OS of sensitive relapse and refractory relapse were 11.6 months and 7.7 months, (p<0.05) [34]. In a few recent studies, irinotecan had limited clinical activity (ORR <10%) and tolerable toxicity profile like as topotecan [10, 35-37]. The results of the present study were similar to those previously reported by studies investigating topotecan, irinotecan and CAV regimens. In fact, the adverse events encountered in our study were much milder than those reported with irinotecan monotherapy in the literature. As regards toxicity, all three regimens were associated with a manageable toxicity profile. In the current study the adverse events were generally mild and manage-

able for both hematological and nonhematological toxicities.

Recently, many targeted therapies and immunotherapies have also been actively tested in platinum-refractory SCLC patients. In a multicenter phase I/II trial, the aurora kinase-A inhibitor alisertib produced an ORR of 21% in CRR- SCLC patients [38]. Recently, a phase II trial demonstrated the clinical activity of the tyrosine kinase inhibitor pazopanib in the second-line treatment of CRR-SCLC patients (ORR 13.8, median PFS 2.5 months and OS 6.0 months) [39]. In another phase 1/2 trial, checkpoint inhibitors also demonstrated activity in CRR-SCLC patients [40].

In our pooled analysis we observed that patients with disease refractory to frontline therapy were also less likely to respond to second-line chemotherapy in general and consequently had a worse survival outcome. Nonetheless, our data demonstrated that patients with CRR derived clinical benefit with the administration of second-line therapy in contrast to historical experience with untreated CRR- SCLC where the survival is measured in weeks.

This study had certain limitations due to the indirect comparison and retrospective design. Pertinent limitations of our study include the retrospective nature of this analysis and the potential imbalances in important clinical characteristics that may also affect the clinical outcome of SCLC patients such as gender, presence of brain metastasis, overall disease burden and dose intensity. We were unable to compare grade 1-2 toxicities due to insufficient records in the medical charts. However, despite these limitations, the results of our study may be considered as a major reference that retrospective analysis including patients with CRR-SCLC treated with three different regimens reflects the outcome of "real world" patients.

We conclude that the CRR-SCLC patients represent a biologically separate subgroup of SCLC that needs personalised therapeutic approaches. In the absence of a highly effective salvage therapy regimen, we suggest that patients with resistant/ refractory disease should be considered for novel clinical trials, particularly studies that are designed to explain the underlying drug resistance and tumor biology. Future studies are needed to determine the relative benefits of different novel agents and regimens in terms of survival and quality of life in patients with CRR-SCLC. Moreover, weekly dosing regimens may provide a greater convenience to patients receiving topotecan or irinotecan as single agents or combination with other agents.

Conflict of interests

The authors declare no conflict of interests.

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