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ORIGINAL ARTICLE

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Which chemotherapy regimen might be the best for the second-line treatment of patients with small-cell lung cancer?

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ABSTRACT

Introduction. Small-cell lung cancer (SCLC) is an aggressive disease. Despite the first-line (1L) chemotherapy, almost all patients need the second-line (2L) treatment within a year. However, there is no general agreement on standard 2L treatment.

This study aimed to determine outcomes obtained with different treatment regimens, factors affecting the results, and standard approach in the 2L treatment of SCLC.

Material and methods. This was a singlecenter, retrospective, cross-sectional, cohort study. The inclusion criteria were age ≥ 18, histologically or cytologically proven SCLC, progressive disease after 1L treatment, and receiving 2L chemotherapy.

Results. A total of 89 patients were assessed in this study. The patients were classified into three groups: 35 patients received the combination of doxorubicin, cyclophosphamide, and vincristine (CAV), 24 patients received single-agent topotecan (TPT), and 30 patients received numerous different treatment schemes. The overall response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), and median overall survival (OS) were 19.1%, 46.1%, 3.5 months, and 6.4 months, respectively. Although no statistically significant difference was found between the three groups in PFS ($p = 0.195$) and OS ($p = 0.286$), there were numerically better outcomes with CAV. In univariate analyses, the comorbidity was related to decreased PFS ($p = 0.044$). However, this relationship could not maintain its statistical significance in multivariate analysis ($p = 0.224$).

Conclusions. It is still impossible to make a standard recommendation for the 2L treatment of patients with SCLC. However, the numerical difference in favor of CAV may be clinically meaningful.

Key words: small-cell lung cancer, second-line, chemotherapy, CAV, topotecan

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Introduction

Lung cancer, divided into two main subtypes based on tumor histology, as non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), is the most common and lethal cancer worldwide [1]. The SCLC, which accounts for approximately 1/7 of lung cancer cases, exhibits a more aggressive course associated with shorter survival [2]. SCLC is generally classified as a limited-stage disease and an extensive-stage disease. The limited disease was characterized by tumors confined to one hemithorax, although local extension and ipsilateral or supraclavicular nodes could also be present, provided they could be encompassed in the same radiation portal as the primary lesion. All other cases were classified as an extensive disease. Approximately two-thirds of patients with SCLC have an extensive-stage disease at initial diagnosis. Although immunotherapy drugs have been added to the current treatment algorithms, conventional chemotherapy still constitutes the

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basis of the treatment of extensive-stage SCLC [3, 4]. Patients with SCLC usually respond to platinum-based treatment in the first-line (1L) setting, with a response rate of 60–70%. However, disease progression is inevitable within one year after the initial treatment in almost all cases, and a second-line (2L) therapy is needed in surviving patients [3, 5].

There are some studies on the efficacy and toxicity of 2L chemotherapy, including many cytotoxic drugs, particularly amrubicin, topotecan (TPT), and irinotecan single-agent regimens, and the combination of cyclophosphamide, doxorubicin, and vincristine (CAV) in patients with SCLC. Among them, TPT is the most often recommended therapy for the 2L treatment in Europe and the United States, however not worldwide [6–11]. As there is no substantial proven superiority between the different treatment regimens, there are no definitive and standard 2L treatment recommendations for patients with SCLC [12–14].

Besides using different chemotherapy regimens, especially the CAV regimen was widely used for many years in our cancer center as a standard 2L treatment in patients with SCLC. Recently, we have started to introduce the single-agent TPT regimen as almost standard in 2L treatment, which is reported to be less toxic than the CAV regimen and stands out in the European and American guidelines. However, in our retrospective observation, we determined that the treatment outcomes of patients who received single-agent TPT were not better than those who received CAV and even had a relatively poorer result. Thereupon, we conducted a study based on this observation.

This study aimed to determine the response rates and survival outcomes obtained with different treatment regimens, the factors affecting the results, and the standard approach in the 2L treatment of patients with extensive-stage SCLC.

Material and methods

This singlecenter, retrospective, cross-sectional, and cohort study was an internal medicine specialty thesis. The inclusion criteria were age ≥ 18, having histologically or cytologically proven SCLC, having progressive disease after 1L treatment of extensive-stage disease, and receiving at least one course of 2L chemotherapy. In this study, medical records of all eligible patients who were treated and followed up in our cancer center between July 2009 and July 2019 were evaluated without any exception. All of the data were meticulously collected and recorded by the thesis assistant, and the data entries were checked and verified one by one by the medical oncologist, the thesis supervisor.

The staging of all patients in this study was determined according to the 7th edition of the American Joint Committee on Cancer staging system. The response evaluation of the patients was done according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The patients who achieved a complete response (CR), partial response (PR), and stable disease (SD) in accordance with RECIST were defined as 'responders'. In contrast, the patients with progressive disease (PD) were identified as 'non-responders'. The disease control rate (DCR) was defined, taking into account all responders, including CR, PR, and SD. However, the overall response rate (ORR) is defined by considering responders, including only CR or PR. The Eastern Cooperative Oncology Group-Performance Score (ECOG-PS) was used to determine the patients' performance status. ECOG-PS ≤ 2 was named 'good performance', whereas ECOG-PS ≥ 3 was called 'poor performance'.

Survival definitions consisted of progression-free survival (PFS) and overall survival (OS). PFS was calculated as (1) the time from the beginning of the 2L treatment to the date of first disease progression despite the 2L treatment (2) the time from the beginning of the 2L treatment to death from any cause in the period of 2L treatment or, (3) the time from the beginning of the 2L treatment to the final visit. Furthermore, OS was calculated as the time from the beginning of the 2L treatment to the date of death or final visit. All patients underwent PFS and OS analysis.

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was required for statistical significance. Primary statistical analysis has included descriptive statistics of the patients including age, gender, smoking history, other comorbid diseases ('positive' means having one or more of the diseases including diabetes mellitus, hypertension, ischemic heart disease, heart failure, arrhythmia, chronic obstructive pulmonary disease, tuberculosis, chronic asthma, chronic renal failure, chronic liver disease, acquired immune deficiency syndrome/AIDS, and secondary malignancy), performance status, the initial stage of the disease, a history of surgery for the primary tumor, a history of the concurrent chemoradiotherapy for the primary tumor, sites of metastasis, and chemotherapy regimens performed in the 1L treatment of extensive-stage SCLC. Descriptive statistics were calculated as proportions and medians. The Kaplan-Meier method was used for survival analysis. Log-Rank analysis was performed to compare the different subgroups. Univariate and multivariate Cox regression analyses were used to identify independent variables.

Results

A total of 89 patients were assessed in this study. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. The baseline demographic and clinical characteristics of the patients

		n, 89	%, 100.0
Age	**years**		
minimum	30.00		
maximum	79.00		
mean	58.03		
Gender			
female		4	4.5
male		85	95.5
Smoking cigarettes			
never		4	4.5
ex-smoker		8	9.0
active-smoker		77	86.5
Comorbidity			
positive		32	36
negative		57	64
Performance status			
ECOG-PS:1–2		76	85.4
ECOG-PS:3–4		13	14.6
Initial stage			
stage I		0	0
stage II		0	0
stage III		11	12.4
stage IV		78	87.6
Surgery for the primary tumour			
yes*		1	1.1
no		88	98.9
Concurrent chemoradiotherapy for the limited-stage disease			
yes		11	12.4
no		78	87.6
Sites of metastasis			
multiple		60	67.4
bone		6	6.7
liver		2	2.2
brain		11	12.4
adrenal		2	2.2
Final status			
died		87	97.8
alive		2	2.2

ECOG-PS — Eastern Cooperative Oncology Group-Performance Score; *Surgery was mainly done for diagnostic purposes

All our patients received 1L chemotherapy for extensive-stage SCLC. It was determined that 71 of the patients (79.8%) received the cisplatin+etoposide (EP) combination, 17 patients (19.1%) received the carboplatin+etoposide combination, and only one patient (1.1%) received the CAV regimen in the 1L treatment. When the responses obtained with 1L treatment were examined, no CR was detected; 60 patients (67.4%) had PR, 18 patients (20.2%) had SD, and 11 patients (12.4%) had PD. With 1L chemotherapy, the DCR was 87.6% and the ORR was 67.4%. Disease progression was detected in all patients despite 1L treatment, and therefore they received 2L chemotherapy.

In the 2L treatment, it was determined that 35 patients (39.3%) received the CAV regimen (doxorubicin, 50 mg/m^2 on day 1, cyclophosphamide, 750 mg/m^2 on day 1, and vincristine, 1.4 mg/m^2 with maximum 2 mg on day 1 every 3 weeks) and 24 patients (27%) received single-agent TPT (4 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle). Moreover, many different treatment schemes were used in the remaining patients (1/3 of all analyzed patients). The study population was classified into three main groups as CAV-treated, TPT-treated, and others. The details of the chemotherapy regimens used in the 2L treatment are shown in Table 2.

An average of 4.2 cycles of chemotherapy was applied in the 2L treatment (range: 1–16 cycles). With the 2L treatment, the ORR was 19.1% for the whole study population, 22.9% for the patients receiving CAV, 16.7% for the patients receiving TPT, and 16.7% for the patients receiving the other chemotherapy regimens. The DCR was 46.1% for the whole study population, 57.1% for the patients receiving CAV, 33.3% for the patients receiving TPT, and 43.3% for the patients receiving the other chemotherapy regimens.

Moreover, with the 2L treatment, the median PFS (mPFS) was 3.5 months for the whole study population (95% Confidence Interval (CI): 2.847 — 4.052), 4.3 months for the patients receiving CAV (95% CI: 3.314–5.294), 2.3 months for the patients receiving TPT (95% CI: 1.347–3.318), and 3.1 for the patients receiving the other chemotherapy regimens (95% CI: 1.995–4.182). Furthermore, the median OS (mOS) was 6.4 months for the whole study population (95% CI: 5.596–7.283), 9.5 months for the patients receiving CAV (95% CI: 6.905–12.084), 5.9 months for the patients receiving TPT (95% CI: 2.904–9.055), and 4.7 months for the patients receiving the other chemotherapy regimens (95% CI: 1.909–7.553). Figure 1 shows the Kaplan-Meier curves for PFS and OS. The details of the outcomes obtained by the 2L treatment are shown in Table 2.

Since the patients who received treatments other than CAV and TPT showed a very heterogeneous distribution, analyses for ORR, DCR, mPFS, and mOS were not performed one by one for each regimen standing in this group.

Table 2. The details of the preferred chemotherapy regimens and the outcomes in the 2L treatment

	n, 89 %, 100.0	
The chemotherapy regimens used in 2L treatment		
group 1: CAV	35	39.3
group 2: TPT	24	27.0
group 3: Others (the following drugs)	30	33.7
cisplatin + etoposide	5	5.6
cisplatin + irinotecan	5	5.6
etoposide + cyclophosphamide	5	5.6
irinotecan	5	5.6
carboplatin + paclitaxel	3	3.4
carboplatin + etoposide	2	2.2
etoposide	2	2.2
capecitabine + temozolomide	1	1.1
gemcitabine	1	1.1
paclitaxel	1	1.1

Responses to 2L treatment

	group 1: CAV, n: 35	group 2: TPT, n: 24	group 3: Others, n: 30
CR	0	0	0
PR	8	4	5
SD	12	4	8
PD	15	16	17
ORR (%)	22.9	16.7	16.7
DCR (%)	57.1	33.3	43.3
mFPS(mo)	4.3	2.3	3.1
mOS (mo)	9.5	5.9	4.7

2L — second-line; CAV — combination of cyclophosphamide; doxorubicin; and vincristine; TPT — topotecan; CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease; ORR — objective response rate; DCR — disease control rate; mPFS — median progression-free survival; mOS — median overall survival; n — number of patients; mo — months

Although the results presented here were numerically different, no statistically significant difference was found in mPFS (p: 0.195) and OS (p: 0.286). Moreover, to clarify the effects of 2L treatment on PFS and OS, analyses were made by dividing the patients into many different groups according to the treatments they received. For example, Group 1 — Arm A: CAV, Arm B: TPT, and Arm C: the others; Group — 2: Arm A: CAV, Arm B: TPT, Arm C: platinum-based and Arm D: the others; Group 3 — Arm A: CAV and Arm B: TPT + irinotecan; Group 4 — Arm A: CAV, Arm-B: topoisomerase inhibitors-based; Group 5 — ArmA: CAV and Arm B: TPT. However, no statistically significant difference was found in all these analyses.

In addition, when we grouped our patients as persons aged over or under 65 years to evaluate the effects of age at the time of diagnosis on survival, there was no statistically significant difference between the two groups. The mPFS was 2.4 months and mOS was 4.7 months in the patients older than 65 years (95% CI for PFS: 0.000—5.219 and 95% CI for OS: 1.538–7.924, respectively, and p = 0.578) whereas mPFS was 3.5 months and mOS was 6.4 months in patients' age equal to or under 65 years (95% CI for PFS: 2.870–4.029 and 95% CI for OS: 4.951–7.928, respectively, and p = 0.696).

A univariate analysis was performed to determine factors affecting survival outcomes — only the presence of other comorbid diseases was associated with decreased PFS (p = 0.044). However, this relationship did not maintain its statistical significance in multivariate analysis (p = 0.224). In addition, no statistically significant difference was found for OS between the groups. The mPFS was 2.9 months and mOS 5.9 months in the patients with the comorbid disease (95% CI for PFS: 1.948–3.769 and 95% CI for OS: 2.883–9.076, respectively) whereas mPFS was 3.8 months and mOS was 6.6 months in

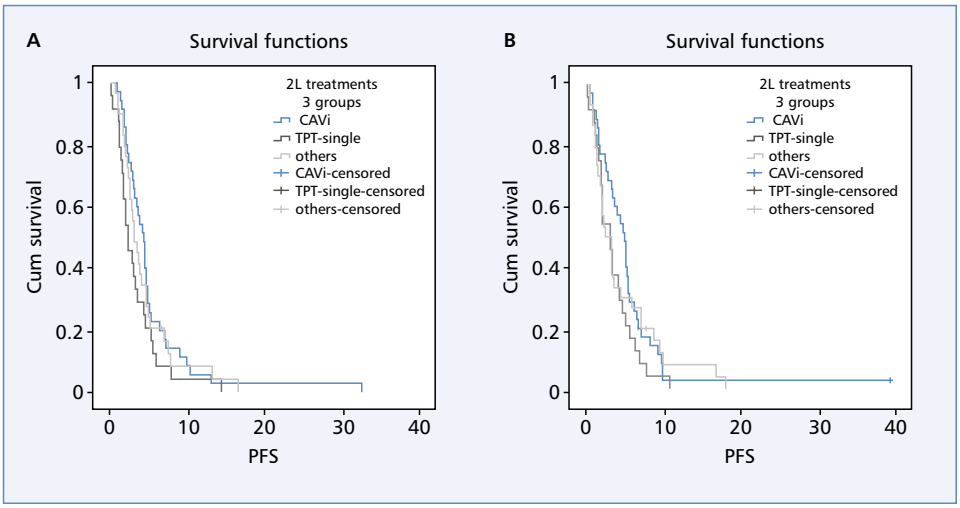

Figure 1. The Kaplan-Meier curves according to 2L chemotherapy regimens; A. For PFS; B. For OS; PFS — progression-free survival; OS — overall survival

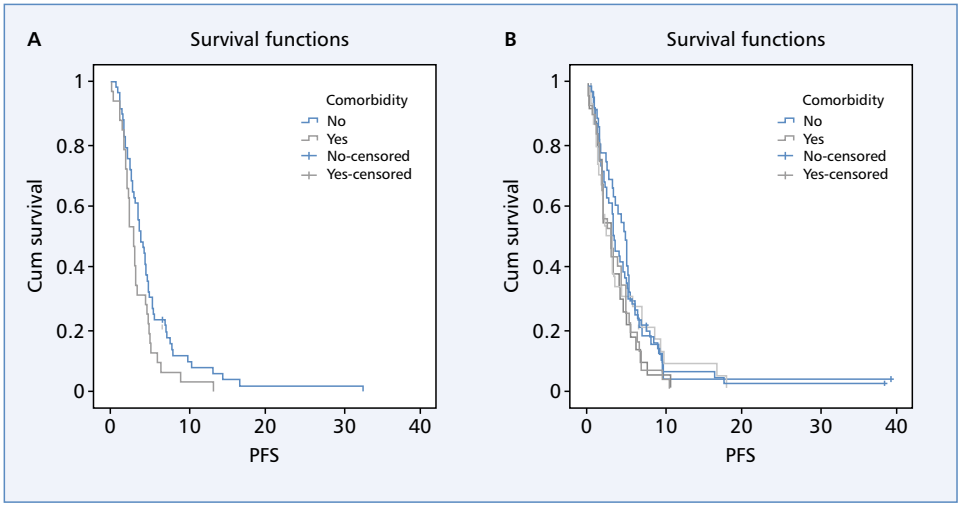

Figure 2. The Kaplan-Meier curves according to comorbidity; **A**. For PFS; **B**. For OS; PFS — progression-free survival; OS — overall survival

the patients without comorbid diseases (95% CI for PFS: 2.964–4.724 and 95% CI for OS: 5.087–8.186, respectively). Figure 2 shows the Kaplan-Meier curves for PFS and OS according to comorbidity.

Although it was determined that 87 of 89 patients (97.8%) had PD despite the 2L treatment, only two patients (2.2%) still did not have PD at the end of the study.

Discussion

SCLC still represents an extremely aggressive disease. Although high response rates are obtained with 1L chemotherapy, almost all extensive-stage SCLC patients would need the 2L treatment within a year [3]. However, there is no 2L treatment recommendation based on sufficiently strong evidence and accepted by all current treatment guidelines [4]. This retrospective study aimed to address the uncertainty on this issue and illuminate the way for clinicians. This study is one of the few studies conducted in the last decade on patients with SCLC who received 2L chemotherapy including CAV regimen. Moreover, this is a critical study because it reveals current real-life data. Furthermore, although this is a singlecenter study, it is valuable as it contains a significant amount of patient data.

This study determined that CAV and TPT regimens were predominantly preferred for 2L therapy in our cohort. It was found that there was a very heterogeneous distribution of treatment preferences in the remaining 1/3 of our patients. The study population was classified into three main groups as CAV-treated, TPT-treated, and others. Since there were very different treatment regimen selections in the last group, as combination regimens including cisplatin + etoposide (EP), carboplatin + etoposide, cyclophosphamide + etoposide, cisplatin + irinotecan, carboplatin + paclitaxel, capecitabine + temozolomide, and as single-agent regimens including irinotecan, etoposide, gemcitabine, and paclitaxel, this group was not heavily addressed in the discussion part of this study. Our discussion was mainly focused on the comparison of CAV and TPT regimens to avoid any bias. There was no statistically significant difference in PFS and OS among the three groups. However, a numerical difference was found, giving the impression that the CAV regimen could produce a survival advantage. Moreover, we determined in our cohort that the presence of other comorbid diseases was associated with shorter PFS. Also, we revealed that age has no prognostic significance.

The standard treatment for patients with extensive-stage SCLC is still chemotherapy, and the treatment is given for palliative purposes. Treatment with cytotoxic drugs has shown developments and changes over the years. In the 1970s, it was demonstrated that the CAV regimen was effective and well-tolerated and was commonly used as a standard 1L treatment [15]. Then, in the 1980s, with the EP regimen, which showed a synergistic effect in preclinical models, it was observed that excellent responses were obtained in limited-stage patients who did not respond to induction chemotherapy with CAV or relapsed after treatment with anthracycline-containing regimens. Thereupon, the EP regimen was increasingly used in the treatment of SCLC [16]. In addition, many previously untreated patients achieved complete responses with the EP regimen, and increased survival was obtained in that way [17]. Studies comparing the EP regimen versus CAV regimen in the 1L treatment reported improved survival and less hematologic toxicity with the EP regimen, making the EP regimen

the most commonly used 1L chemotherapy regimen for extensive-stage SCLC and virtually eliminating the CAV regimen from the 1L treatment [17, 18]. This is still the current situation. When reviewing the treatments our cohort received in the 1L, we detected that almost all patients had received the EP regimen. This result was in agreement with the literature.

Unfortunately, most patients experience disease progression within one year after 1L treatment, and success rates are meager despite 2L treatment [3, 19]. However, unlike the 1L treatment with EP, which has been accepted for almost 40 years, there is still no more standardized 2L treatment protocol. In these patients with relapsed SCLC, in addition to rechallenge therapy with the EP regimen, which has been applied for a long time, CAV regimen or single-agent TPT treatments have also been used frequently, especially in the last two decades. Moreover, apart from these, many different drugs were investigated in the 2L treatment of SCLC [4, 6–11, 16, 20–22]. The most preferred treatment regimens in our cohort were CAV and TPT. Other treatment options, gathered together as a heterogeneous third group, included the treatment options described in the literature. Preferred drug practices in 2L therapy in our cohort were consistent with the current literature.

In the late 1980s, Sculier et al. [22] conducted a phase II study and evaluated the CAV regimen in 2L therapy with a response rate of 13% and median response duration of 26 weeks. Subsequently, two separate comparative studies showed significantly superior results with the CAV regimen compared to oral etoposide, and therefore the studies were interrupted before the planned schedule [23, 24]. About one decade after the article of Sculier et al., von Pawel et al. evaluated the effectiveness of CAV compared to infusional TPT in the 2L treatment of SCLC in a 1:1 randomized, multicenter study including a total of 211 patients. They reported that ORRs were 18.3% and 24.3%, mPFS were 12.3 weeks and 13.3 weeks, and mOS was 24.7 weeks and 25 weeks in patients receiving CAV and TPT, respectively. Moreover, they concluded no statistically significant difference in efficacy between the treatment arms [10]. After that, in the first years of the 21st century, O'Brien et al. conducted a Phase III, multicenter trial comparing supportive care alone with supportive care + oral TPT in the 2L treatment of patients with relapsed SCLC. In this 1:1 randomized study, a total of 141 patients were enrolled, and with oral TPT, the ORR was 7%, and the DCR was 44%, and an mOS with supportive care was 13.9 weeks, and TPT was 25.9 weeks. As a result, they reported a statistically significant prolonged OS with the addition of oral TPT compared to supportive care alone [11]. Later, Eckardt et al. compared the efficacy of oral TPT and infusional TPT in the 2L treatment in a randomized, phase III trial involving a total of 309 patients with SCLC. The rates of ORR were 18.3% with oral TPT and 21.9% with infusional TPT; mOS was 33.0 weeks for oral TPT and 35.0 weeks for infusional TPT. Moreover, the 1- and 2-year survival rates were 32.6% and 12.4% for oral TPT and 29.2% and 7.1% for infusional TPT. Since there was no statistically significant difference between the two groups, they concluded that oral and infusional TPT could be used in the 2L treatment of recurrent SCLC [25]. Although, after these studies, TPT was recommended as the dominant treatment option in the 2L treatment of relapsed SCLC, particularly in Europe and the United States, this suggestion was not adopted worldwide.

Researches continued in many parts of the world due to the lack of strongly recommended 2L standard therapy. In Italy, Garassino et al. conducted a retrospective study in 161 patients with SCLC to evaluate the clinical outcomes of 2L chemotherapy after the initial treatment with EP regimen. In this study, the researchers divided patients into four subgroups by type of 2L treatment: (1) platinum-based rechallenge; (2) anthracycline-based regimens; (3) topotecan; (4) other single agents. They reported that ORR, mPFS, and mOS were 22.9%, 4.3 months, and 5.8 months, respectively. Also, they concluded that there was a statistically significant trend toward higher ORR (34.5% *vs.* 17.5%) and mOS (9.2 months *vs.* 5.8 months) for patients who were rechallenged with platinum-based chemotherapy due to the sensitivity in 1L treatment. Moreover, they offered the platinum-based rechallenge as a standard comparator in future randomized controlled trials of 2L chemotherapy [26]. In a 2:1 randomized, multicenter, phase III trial of amrubicin, a third-generation anthracycline and potent topoisomerase II inhibitor, versus TPT as 2L treatment in a total of 637 patients with SCLC, von Pawel et al. reported that ORR was 31.1% *vs.* 16.9%, mPFS was 4.1 months *vs.* 3.5 months, and mOS was 7.5 months *vs.* 7.8 months, with amrubicin and with TPT, respectively. Moreover, they concluded that amrubicin did not improve survival when compared with TPT [27]. Li et al. conducted a retrospective study in China to compare the effectiveness of 2L treatment versus supportive care and compare the efficacy and safety of different 2L treatment regimens, including etoposide, TPT, irinotecan, and taxanes. A total of 309 patients were evaluated, and 157 received the best supportive care, and the rest of the patients (n = 152) received 2L chemotherapy. The researchers demonstrated that the patients administered 2L chemotherapy lived significantly longer, with a total OS from 1L therapy of 11.5 months compared to 6.0 months in the patients with the best supportive care alone. Also, they reported that the ORR, DCR, mPFS, and mOS were 39.5%, 59.2%, 3.3 months, and 5.3 months, respectively. Moreover, they divided the patients into subgroups by types of 2L

chemotherapy regimens and concluded that there was no statistical difference in ORR, DCR, and mPFS among all of the subgroups, and only treatment with TPT revealed a mild significant mOS advantage [28]. In Japan, Goto et al. compared the combined chemotherapy with cisplatin, etoposide, and irinotecan versus TPT alone as 2L treatment in a multicentre, open-label, randomized phase 3 trial, including 180 patients with relapsed SCLC. The researchers demonstrated a survival advantage of approximately six months favoring the combined chemotherapy arm (18.2 months *vs.* 12.5 months). As a result, they concluded that combination chemotherapy with cisplatin + etoposide + irinotecan could be considered the standard 2L chemotherapy for selected patients with SCLC [14]. Also, the efficiency of different 2L chemotherapy regimens, including irinotecan, TPT, paclitaxel, and docetaxel, was compared in a retrospective analysis of 116 patients with SCLC. The researchers reported that the ORR was 19.05%, DCR was 61.90%, mPFS was 75 days, and mOS was 180 days. Moreover, they showed that paclitaxel achieved the best DCR of 78.57%, while irinotecan achieved the best ORR of 22.22%. Besides, they revealed that patients treated with irinotecan also achieved the best mPFS and mOS of 91 and 595 days, while the mPFS of TPT, paclitaxel, and docetaxel were 74.5, 81, and 50 days respectively, and the mOS of them were 154, 168.5, and 184 days, respectively [29]. In another study, Xing et al. examined 107 SCLC patients to evaluate the efficacy and safety of single-agent irinotecan in the 2L treatment of refractory and relapsed SCLC. They showed that ORR was 16.82%, DCR was 55.14%, mPFS was 3.8 months, and mOS was 8.1 months. Moreover, they concluded that for patients with SCLC, the single-agent irinotecan in the 2L chemotherapy has a certain effect [30].

The results of our study are consistent with the data in the literature we tried to summarize above. Although in the statistical analysis we performed by applying various grouping formations a statistically significant difference was not detected among the groups in terms of survival, this may be due to the small number of our cohort. On the other hand, when viewed numerically, a survival trend in favor of CAV stands out. It can be assumed that the superiority of the CAVi combination regimen over single-agent TPT might be significant once the number of patients was greater. However, considering all these results and current data in the literature, it is still impossible to make a standard recommendation for the 2L treatment of patients with SCLC.

It was suggested that there are some tricks in selecting a 2L treatment to be applied in case of disease progression after 1L treatment. The most important are advanced age, performance status, other comorbid diseases, and side effects due to initial chemotherapy [31]. Although advanced age was suggested as a handicapped situation, Siu et al. evaluated 608 patients with SCLC and demonstrated that age did not matter as a prognostic factor [32]. We found in our study that age has no prognostic significance. Besides, we determined that the presence of other comorbid diseases in our cohort was associated with shorter PFS. Although progression occurred later in the patients without other comorbid diseases, the presence of comorbidity did not have a statistically negative effect on OS in our cohort. Based on these results, it is worth emphasizing that it will not be suitable to decide whether or not to offer a treatment option based on age or comorbidities only.

In addition, when our study was initially designed, we also planned to analyze the adverse events that occurred with 2L treatment regimens. However, while recording the data, it was determined that most of the side effect data were not noted in the patients' files. Furthermore, we were not sure about the adequacy and reliability of the limited number of adverse events recorded. When real-life data are based on the retrospective review of patient records, such deficiencies may be unavoidable. In our opinion, the most important reasons for this undesirable situation are a lack of sufficient time to record treatment-related side effects in complicated outpatient settings. Therefore, side effect data were not analyzed in order to avoid any bias.

The strengths of this study are that it was based on real-life data, data of all eligible patients having the inclusion criteria were recorded without exception, a single person did all data entries with the same care and consistency, and the entries were checked and verified by a second researcher one by one. On the other hand, the weaknesses of this study are that it was a retrospective and single-center study with no randomization including a relatively small number of patients. Moreover, the existence of a heterogeneous third group other than the homogeneous CAV-treated and TPT-treated groups, and the absence of the data including adverse events of the treatments may cause difficulty in formulating final conclusions.

Conclusions

In this study, no statistically significant difference was found in survival outcomes between 2L treatment regimens applied in patients with SCLC. Therefore, it is still impossible to make a standard recommendation for the 2L treatment of patients with SCLC. However, we think that the difference determined numerically in favor of CAV regimen may be significant, and it will be essential to verify these results with prospective, randomized, multicenter studies with larger patient numbers.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical statement

The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee of the university (Local Ethics Committee approval number: 10.05.2019-2019/1849). Since this was a retrospective file screening study, informed consent was not required.

Authors' contributions

All authors contributed significantly to the study from beginning to the end by making essential additives to conception, design, the collection of data, or analysis and interpretation of data, drafting the manuscript, or revising it critically. All authors read and approved the final status of the manuscript.

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