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RESEARCH ARTICLE

Comparison of second-line treatment outcomes between sensitive and refractory small cell lung cancer patients: a retrospective analysis

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Abstract
Purpose Small cell lung cancer (SCLC) has a high relapse rate despite being very chemosensitive. The efficacy of second-line treatment is dismal. Our aim was to evaluate the outcome of second-line treatment.
Methods We retrospectively assessed data of 120 SCLC patients who failed first-line treatment and received second-line treatment at three medical oncology centers.
Results Median age of group was 58. 82 % had an ECOG PS of 0–1 at the time of relapse. 39 % were at limited stage (LS) at the time of diagnosis. Patients who progressed more than 3 months after first-line therapy were categorized as having platinum-sensitive disease (PSD) (64 %). The number of patients who received platin-based combination treatment was 33 (27 %). The median OS time starting from the initiation of second-line treatment was 7 months. Multivariate analysis identified PS ($p = 0.006$), extent of disease at diagnosis (0.014) and PSD (0.001) as the independent prognostic factors for survival. Subgroup analyses of the patients with PSD indicated platin rechallenge yields higher progression-free survival, overall survival and overall response rate.
Conclusion Patients with good ECOG PS,who have PSD or initially presenting with LS, have a good prognosis and in patients with PSD, platinum-based therapy would be more appropriate.

Keywords Platinum sensitive disease · Platinum refracter disease · Second-line chemotherapy · Small cell lung cancer

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Introduction

Lung cancer is the most common cancer worldwide, with an estimated 1,600,000 new cases and 1,380,000 deaths in 2008 [1]. Proportionally, small cell lung cancer (SCLC) consists of about 14 % of all lung cancers. Approximately 70 % of SCLC patients are staged as extensive stage (ES) and the rest are staged as limited stage (LS) at the time of diagnosis [2].

Despite the fact that SCLC is highly sensitive to chemotherapy and to radiotherapy at initial diagnosis, SCLC usually relapses and becomes refractory to treatment within 1–2 years because of the emergence of drug-resistant cancer cells during the first-line chemotherapy or the existence of such cells before chemotherapy [3]. Prognosis for patients with SCLC is poor, even in those with early stage SCLC. From the time of diagnosis, the median ranges of survival for those with limited stage disease (LS-SCLC) and extensive stage disease (ES-SCLC) are 15–20 and 8–13 months, respectively. Approximately 20–40 % of patients with LS-SCLC and 5 % of patients with ES-SCLC survive beyond 2 years [4].

In SCLC, rapid tumor growth and impairment of patient performance status limit the ability to use second-line therapy and contribute to the overall poor outcome and lack of progress. Therefore, expected survival in untreated patients in this group is 2–3 months [5].

Second-line chemotherapy response is influenced by the time to progression after completion of first-line therapy. Patients who relapse less than 3 months after first-line therapy are commonly termed "platinum-refractory" and have overall response rate (ORR) that is lower than those of patients who relapse more than 3 months after therapy, who are usually termed "platinum-sensitive" [6].

The number of studies assessing prognostic factors affecting survival and treatment outcomes in the setting of relapsed SCLC is limited. The purpose of this retrospective study was to evaluate the treatment outcome of relapsed SCLC in a Turkish population and to identify certain subgroups which benefit from different treatment approaches.

Materials and methods

This retrospective study consisted of relapsed SCLC patients who received second-line chemotherapy. We retrospectively gathered data from 120 SCLC patients treated in three institutions between January 2003 and February 2011. Demographic characteristics at the time of the second-line therapy, disease stage at relapse, Eastern Cooperative Oncology Group (ECOG) performance status (PS), first-line regimen received, response to second-line treatment, choice of second-line regimen, progression-free survival (PFS) and overall survival (OS) were included in the analysis.

Tumor response was evaluated by radiologists located in the treating medical centers at the time of treatment using CT scans according to World Health Organization (WHO) criteria. There was no central imaging review.

The study was approved by the Ethical Committee for Research Projects of Dr. Lutfi Kirdar Research and Training Hospital, Istanbul, Turkey.

Statistical analysis

A p value less than 0.05 was considered to be statistically significant. Median and minimum–maximum levels were used when data were not normally distributed. The variables considered were gender, age, ECOG PS, stage of disease at initial diagnosis, chemotherapy regimens, platinum sensitivity, and weight loss. Kaplan–Meier method was used for survival analysis. The univariate analysis of potential prognostic factors was assessed using the log-rank test. The Cox regression model was used for multivariate analysis. The PFS time was measured from the date of disease recurrence to progression or death from any reason. Overall survival time was measured from the date of disease recurrence to death. Patients who had a treatment-free interval of more than 3 months were included in the platinum-sensitive group (PS). Patients who did not respond to first-line treatment or who had a disease recurrence within 3 months were identified as platinum-refractory (PR). Weight loss was defined as loss of more than 5 % of total body weight at the start of second-line treatment in comparison to body weight at first diagnosis. All statistical analyses were performed using SPSS v16.0 (SPSS Inc., Chicago, IL, USA).

Results

Our study group consisted of 120 patients with a median age of 58 (range 33–78); 20 % of patients were more than 65 years of age, 84 % of patients were male, and 39 % of patients had LS disease at the time of initial diagnosis. Our study groups' clinical characteristics are summarized in Table 1. Chemotherapy regimens received by the patients are shown in Table 2. The median number of chemotherapy cycles that were delivered during the treatment period was 4 (2–8). The patient group was categorized according to platinum sensitivity; 64 % (77) of the patients had platinum-sensitive disease and 42.8 % of this group was treated with platinum-based treatment. The median treatment ORR of the study group was 40.8 %, the median PFS was 4 months (the 95 % confidence interval was 2.9–5.02) and the median OS was 7 months (the 95 % confidence interval was 4.7–9.2). When the study group was evaluated in terms of survival times, patients who were platinum sensitive, who had a good PS, and who had limited stage disease at the time of diagnosis had significantly longer survival time in univariate analysis (Table 3).

Survival curves according to the ECOG PS is depicted in Fig. 1 (median OS 9 months (95 % CI, 6.1–11.2) for ECOG PS 0–1 compared to 5.8 months (95 % CI, 2.6–7.4) for ECOG PS 2; HR = 0.63; 95 % CI, 0.526–0.78; $p = 0.002$), sensitivity to first-line chemotherapy shown in Fig. 2 (median OS 10 months (95 % CI 7.8–12.2) for platinum-sensitive patients compared to 6.1 months (95 % CI, 4.1–9.3) for platinum-refractory patients; HR = 0.69; 95 % CI, 0.52–0.81; $p = 0.016$), and stage at the initial diagnosis are shown in Fig. 3 (median OS 8.9 months (95 % CI, 5.9–10.1) for patients with LS at diagnosis compared to 5.4 months (95 % CI, 3.8–7.6) for patients with ES; HR = 0.78, 95 % CI, 0.62–0.86; $p = 0.014$).

In the multivariate analysis performance score (HR 2.2; 95 % CI (1.14–3.41); $p = 0.014$), platinum sensitivity (HR 4.1; 95 % CI (2.1–5.27); $p > 0.000$), and disease stage

Table 1 Main patient characteristics

Patient characteristic	*n*	%
Median age at relapse (ranges)	58 (33–78)	
≥65 years	24	20
<65 years	96	80
Gender		
Male	101	84
Female	19	16
ECOG PS at relapse		
0–1	99	82
2	21	18
Stage at diagnosis		
LS	47	39
ES	73	61
Stage at relapse		
LS	5	4
ES	115	96
Response to 2 line therapy		
CR + PR	6 + 43	40.8
SD + PD	11 + 60	59.2
Platinum sensitivity		
Sensitive	77	64
Refractory	43	34

Table 2 Second-line chemotherapy regimens given to patients

Regimen	$n = 120$	Platinum-sensitive group ($n = 77$)	Platinum-refractory group ($n = 43$)
EP	11	11	–
IP	22	22	–
CAV	6	2	4
Topotecan	34	16	18
Irinotecan	45	25	20
Oral etoposid	2	1	1

EP etopois plus cis/carboplatin, *IP* irinotecan and cis/carboplatin, *CAV* cyclophosphamide plus doxorubycinplus vincristine

(HR 1.7; 95 % CI (1.18–2.78); $p = 0.04$) at initial diagnosis were found to be significant prognostic factors for median OS.

Subgroup analysis of the platinum-sensitive patients revealed that patients treated with platinum rechallenge ($n = 33$) had higher PFS, OS and ORR than patients treated without platinum ($n = 44$) ($p = 0.014$, $p = 0.032$, and $p = 0.002$, respectively; Table 4). No difference was observed between platinum-sensitive and refractory groups receiving monotherapy with either irinotecan or topotecan in terms of ORR, PFS and OS (Table 4).

Table 3 Univariate analysis for response rate and survival

	ORR (%)	*p*	PFS (months)	*p*	OS (months)	*p*
Age						
>65	34	0.2	3.6	0.159	6.9	0.172
<65	40		4.1		8	
Gender						
Male	36.6	0.5	3.7	0.02	7	0.051
Female	42		5.1		11	
ECOG PS						
0–1	41.4	0.04	4.8	0.005	9	0.002
2	14.2		2.7		5.8	
Weight loss						
>5 %	31.6	0.79	3.2	0.7	7	0.111
<5 %	37.9		4		8.1	
Initial stage of disease						
LS	39.7	0.7	4.2	0.1	8.9	0.014
ES	37.3		3.1		5.4	
Platinum sensitivity						
Sensitive	46.3	0.002	5.6	0.0041	10	0.016
Refractory	18.6		3		6.1	

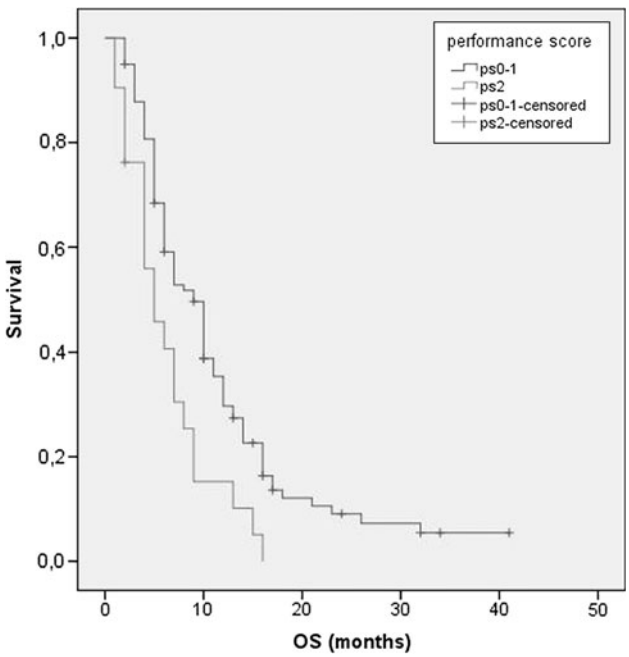

Fig. 1 Overall survival according to ECOG PS at the time of relapse

Discussion

At the time of diagnosis, SCLC is extremely sensitive to chemotherapy; second-line chemotherapy is generally less effective than the initial treatment but it can provide

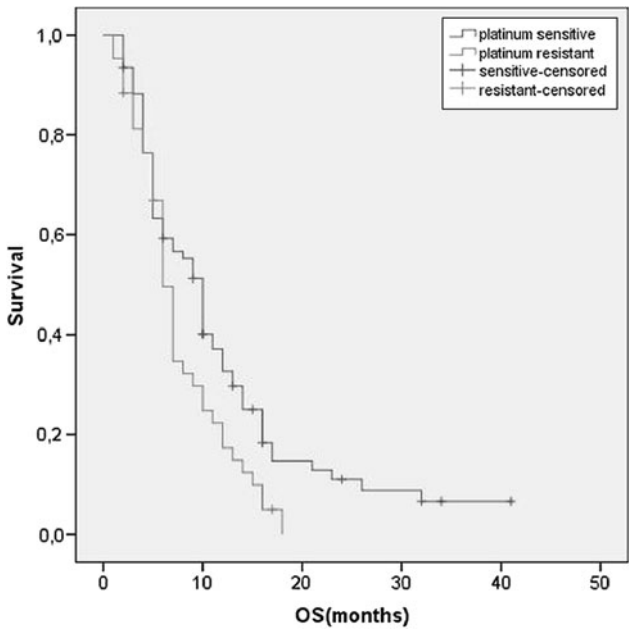

Fig. 2 Overall survival according to platinum sensitivity

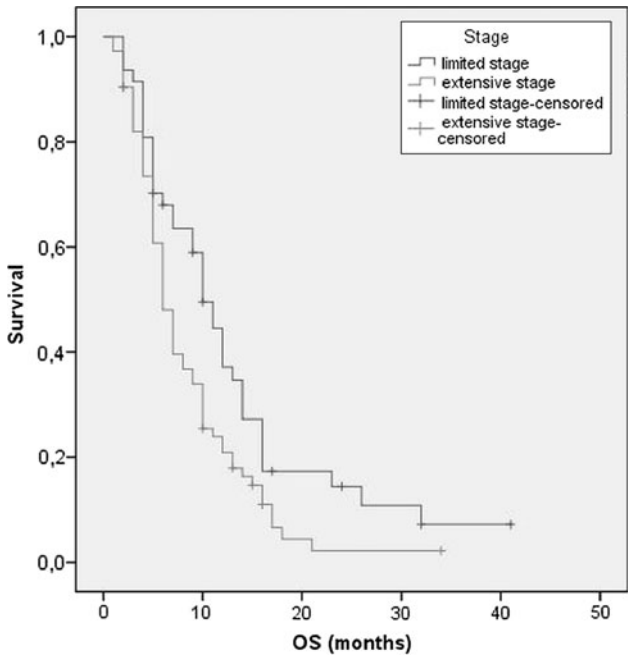

Fig. 3 Overall survival according to disease stage at the time of diagnosis

significant palliation for many patients. The available data make it difficult to draw robust conclusions on the optimal second-line regimen. This uncertainty is reflected in clinical practice and in our series.

A poor understanding of the biology of SCLC, difficulty in early diagnosis, the lack of dependable biomarkers, and the presence of few clinical trials and poor accrual in these trials could have contributed to the lack of improvement in survival in SCLC.

Factors to consider in deciding whether to attempt salvage therapy include the patient's current performance status, the length of the interval between recurrence and the end of the last cycle, and the original treatment regimen.

Although it is generally considered that patients who have a progression-free interval of more than 3 months after the first-line therapy are platinum-sensitive [7], the benefit of giving platinum-based chemotherapy in the second-line setting has not been shown in any randomized trial so far.

In the literature, Sundstrom et al. [8], who analyzed 19 clinical factors, suggested that the PS at the time of disease recurrence was the only significant prognostic indicator for survival after second-line chemotherapy and they did not find any correlation between the sensitivity status to first-line chemotherapy and survival. However, Kim et al. [9], in a retrospective trial, reported that PS and sensitivity to first-line chemotherapy were important prognostic factors with recurrent patients. Garassino et al. [10] reported that, in a multivariate analysis, PS at second-line therapy ($p = 0.004$) and the achievement of a response to first-line therapy ($p = 0.022$) were prognostic factors for survival.

The probability of an objective response to second-line therapy depends upon several factors. One of them is the duration of the response to first-line therapy. In general, refractory SCLC is associated with a lower ORR to salvage therapy compared to platinum-sensitive disease [6]. Evans et al. [11] reported a ORR of 50 % when the time off chemotherapy exceeded 3 months while Johnson et al. [12] reported that the ORR was 12.5 % when the time off chemotherapy was less than 90 days. The other factor is PS. In one report, PS was the second most important predictor of response to second-line therapy, following initial response to first-line chemotherapy [13]. In our study, we found that platinum-sensitive disease and good PS were associated with a higher ORR.

In the literature, stage at the time of diagnosis and recurrence is reported to be prognostically significant [9, 14]. Because the majority of our study group had ES disease at recurrence, we did not evaluate the prognostic significance of stage of the relapsed patients. Hence, we assessed the prognostic significance of initial stage of disease. Our findings showed that patients having LS disease had higher OS than patients having ES disease. In the group of 47 patients who had LS at the time of diagnosis, 29 (61 %) had platinum-sensitive disease and 40 (85 %) had an ECOG PS of 0–1. In our study group patients with LS at initial presentation were observed to have similar RR and had an unsignificant 1-month PFS advantage when compared to the group of patients who were diagnosed to have ES. However the LS group of patients had a

Table 4 Subgroup analysis of treatment outcomes in different second-line chemotherapy regimens according to platinum sensitivity

Chemotherapy regimens	ORR *n* (%)	*p*	PFS (months)	*p*	OS (months)	*p*
Platinum-sensitive patients						
Treated with platinum based	33 (55)	0.002	6.2	0.014	11.4	0.032
Treated without platinum	44 (39)		4.3		8.1	
Platinum-sensitive patients						
Treated with only irinotecan	25 (34)	0.71	4	0.46	7.1	0.6
Treated with only topotecan	16 (37)		4.1		7	
Platinum-refractory patients						
Treated with only irinotecan	20 (17)	0.52	3.1	0.63	6.1	0.27
Treated with only topotecan	18 (19)		2.9		5.8	

remarkably longer period OS when compared to the group of patients who had ES at initial diagnosis. One plausible explanation to this phenomenon could be that the majority of the patients in the LS group with a longer PFS of 1 month, still had a good PS at the time of progression after second-line treatment and these patient groups were eligible for receiving third-line chemotherapy.

The findings reported on the effect of gender on treatment outcomes in the second-line setting are conflicting. Von Pawel et al. [15] reported that women had higher ORR than men. Response rates were 30.4 % for women compared with 19.7 % for men in a group of patients who received topotecan for second-line disease. Ardizzoni et al. [6] reported that in the EORTC trial, the male patients had a response rate of 25 versus 13.8 % in females. Bishnoi et al. [14] reported poorer outcomes for male patients. In our study group, female patients had a slightly better ORR although this difference was not statistically significant.

Most trials excluded patients above the ages of 65–70 years, whereas this group would account for a large portion of patients presenting with SCLC. The patient group regarded as elderly should be considered for treatment based on other clinical prognostic factors, chiefly PS and presence of other co-morbidities rather than purely chronological age. Those with good PS and minimal co-morbid illness should be treated in a similar manner to younger patients. Our trial results indicated that there were similar treatment outcomes for these two different age groups of patients.

Oral and intravenous formulations of topotecan have been extensively evaluated for the second-line treatment of relapsed or refractory SCLC [16–19]. The antitumor efficacy and tolerability of oral topotecan appear to be similar to the intravenous formulation [18]. A randomized trial showed similar efficacy of intravenous topotecan when compared to anthracycline containing chemotherapy, with an improvement of cancer-related symptoms in the topotecan arm [17]. In a phase III study conducted by Eckardt et al. [18] a response rate for platinum sensitive patients receiving intravenous topotecan was reported as 22 %. Another study done by EORTC (6) was reported ORR of 38 % in platinum-sensitive population which is similar to the rates reported in our study.

Irinotecan has been evaluated much less extensively than topotecan but it appears to have some activity in the second-line setting. As a single agent, irinotecan is associated with a 16–47 % ORR in patients with sensitive or refractory SCLC [20, 21]. The ORR appears to be higher in patients with sensitive, rather than refractory, disease [19]. Response rates up to 50 % and complete response (CR) of 13 % have been observed with a median OS of 10 months when carboplatin was added to irinotecan [22].

In our study group analysis, platinum-sensitive patients had higher ORR than platinum-refractory patients. Platinum is the backbone of treatment and platinum and etoposide/irinotecan combination therapy has emerged as a standard treatment in the first-line setting. Although solid evidence does not exist as in platinum-sensitive patients of relapsed ovarian cancer, for the additional advantage of platinum rechallenge in patients with platinum-sensitive relapsed SCLC, adding platinum to monotherapy in this set of patients is generally considered to be equally beneficial. However, prospective data are lacking for superiority of platinum-based second-line regimens compared to single-agent regimens in patients who have relapsed more than 3 months after completion of first-line chemotherapy. In the literature, Garassino et al. [10] reported that there was a trend toward higher ORR (34.5 vs. 17.5 %, p for trend: 0.06) and OS (9.2 vs. 5.8 months, $p = 0.08$) for patients with sensitive disease who were rechallenged with platinum-based chemotherapy in their retrospective study. The non-statistical significance could be related to having small number of patients in this subgroup (only 18 platinum-sensitive patients and 12 platinum-refractory patients were included in the study group). Consistently we explored the benefit of platinum-based therapy in platinum-sensitive patients.

When irinotecan and topotecan treatment arms were compared in terms of treatment response, we were unable to detect any differences, either with respect to survival or ORR, in neither platinum-sensitive nor platinum-refractory patients. In platinum-sensitive and platinum-refractory patients, this data showing irinotecan would be at least as effective as topotecan in patients with relapsed SCLC.

The retrospective nature of the study is our main limitation. Our analysis is limited by the heterogeneity of the characteristics and management of the patients evaluated, possible sampling error discrimination in terms of platinum sensitivity, the limited number of cases that received platinum-based therapy, as well as different potential treatment paradigms. In addition, evaluation of response to treatment was made by the patients' own treating physicians with different institutional protocols. A higher ORR is observed in our whole study group than previously reported in literature. In our view, the high ORR could be related to the fact that the majority of our patients were platinum-sensitive (64 %), had good PS (82 %). Another reason for this observation could be the non-standardized assessment of response performed by radiologists from different study centers.This observation could also be providing a relevant insight into the efficacy of second-line treatment of SCLC in a well defined population. As a result the subgroup of patients with a good PS, long platinum-free interval, and diagnosis of LS disease at initial presentation having the good prognosis. There is insufficient evidence to recommend one second-line treatment over another but a platinum-based regimen is feasible for platinum-sensitive patients.

Conflict of interest The authors declare that they have no conflict of interests.

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