Outcomes of Platinum-Sensitive Small-Cell Lung Cancer Patients Treated With Platinum/Etoposide Rechallenge: A Multi-Institutional Retrospective Analysis

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Abstract

Small-cell lung cancer has a high chemotherapeutic sensitivity but with disappointing outcome results. Patients with "sensitive disease" are those who respond to treatment with a long relapse-free interval (RFI): in these cases rechallenge with first-line chemotherapy might represent a therapeutic opportunity. Our largest retrospective experience confirmed that rechallenge is feasible with interesting outcome results; there are no statistical differences between RFI and outcome.

Introduction: Patients with small-cell lung cancer (SCLC) that progresses after first-line (FL) chemotherapy have a poor prognosis and second-line (SL) chemotherapy has limited efficacy. Patients whose disease relapses/progresses > 90 days after FL platinum-based treatment are considered platinum-sensitive and could be rechallenged with a similar regimen. We conducted a multicenter retrospective analysis to evaluate outcomes of SCLC patients rechallenged with platinum/etoposide. **Patients and Methods:** Records of all SCLC patients treated in 7 institutions between January 2007 and December 2011 were reviewed. The primary end point was overall survival from the time of rechallenge (OS-R); secondary end points were progression-free survival (PFS) and overall survival from the time of diagnosis (OS-D). Survival curves were calculated using the Kaplan–Meier method. **Results:** Of the 2000 SCLC patients identified, 112 (5.6%) had sensitive disease treated with rechallenge platinum/etoposide; 65% were men with a median age of 64 years. At the time of diagnosis, 44% of patients had limited disease, 82% had an Eastern Cooperative Oncology Group performance status of 0 to 1. A median of 4 cycles of rechallenge was administered. Tumor response was 3% for complete response and 42% for partial response, 19% of patients maintained stable disease, 27% progressive disease, and 9% were not evaluable. Median PFS from the time of rechallenge was 5.5 months (95% confidence interval [CI], 4.4-6.3). Median OS-R and OS-D were 7.9 months (95% CI, 6.9-9.7) and 21.4 months (95% CI, 19.8-24.1), respectively. Subgroup analysis according to relapse-free interval (90-119 vs. 120-149 vs. > 150 days) did not show any statistically significant difference in PFS or OS-R. **Conclusion:** The outcome for SL chemotherapy for SCLC is poor. Rechallenge platinum/etoposide is a reasonable option with potentially better outcomes than standard chemotherapy.

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Introduction

Small-cell lung cancer (SCLC) accounts approximately for 13% to 15% of all lung cancer cases[1,2] and approximately 70% of patients have extensive disease at presentation.[3] Platinum-based chemotherapy is the cornerstone of treatment for SCLC but unfortunately most patients will develop disease relapse or progression, with an overall survival of 2 to 4 months for patients who receive only best supportive care (BSC).[3]

Patients who receive a platinum-based treatment can be empirically divided into refractory, resistant, and sensitive on the basis of response to first-line (FL) chemotherapy and relapse/progression-free interval (RFI). Patients who progress through FL chemotherapy are considered to have refractory disease, and those who show initial response to treatment but have disease progression within 3 months of completing chemotherapy are considered to have resistant disease. The sensitive subgroup includes patients who have an RFI of at least 3 months from completion of treatment.

These criteria were based on small old studies and were inconsistent among different studies.[4] Recently, a meta-analysis designed with a strict methodology validated these criteria, and established the separation of relapsed SCLC into sensitive and resistant based on an RFI cutoff of 60 days.[5]

Platinum-sensitive patients are commonly rechallenged with platinum with etoposide chemotherapy because it seems to produce a tumor response and this is based on a retrospective analysis of 50 patients.[4] Refractory and resistant patients have a worse prognosis and are usually treated with topotecan or an anthracycline-based regimen. At present, topotecan is the only drug approved as second-line treatment for recurrent SCLC[6] on the basis of an improvement in survival and quality of life against BSC[7,8] and similar activity to cyclophosphamide, doxorubicin, and vincristine (CAV).[9]

Platinum with etoposide rechallenge represents a potential effective strategy for the management of relapsed or progressed platinum-sensitive SCLC, but there is no worldwide agreement on the use of this strategy because of the lack of prospective large randomized trials in which standard second-line chemotherapy such as topotecan or CAV was compared with a platinum with etoposide rechallenge.

Therefore, to evaluate the clinical effect of a platinum with etoposide rechallenge, we performed a large retrospective multicenter analysis of platinum-sensitive relapsed SCLC patients.

Patients and Methods

We reviewed records of all of the consecutive SCLC patients treated in 7 Institutions (4 in Italy, 1 in the United Kingdom, 1 in Turkey, 1 in Japan) between January 2007 and December 2011. Platinum-sensitive patients who were rechallenged with platinum (carboplatin or cisplatin) and etoposide chemotherapy were included in the analysis. Patients were identified from the pharmacy database at each different institution and case notes were manually reviewed for quality assurance.

Data collected included demographic characteristics, performance status (PS), disease stage at diagnosis, FL regimen received, response to FL treatment, RFI, type of platinum given at rechallenge, response to rechallenge, type of further-line chemotherapy, progression-free survival (PFS), and overall survival from the time of rechallenge (OS-R) and from the time of diagnosis (OS-D). Objective response was defined according to the Response Evaluation Criteria in Solid Tumors version 1.0.[10] All patients were restaged every 2 cycles or earlier if clinically indicated. Patients without a radiological reassessment were considered not evaluable. The protocol of this retrospective study was approved at each institution.

Statistical Analysis

The primary end point was OS-R; secondary end points were OS-D, PFS, and rate of response to rechallenge therapy.

Overall survival from rechallenge and OS-D were defined as the interval between the date of starting rechallenge chemotherapy or date of diagnosis, and the date of death from any cause, or date of last follow-up for patients still alive. PFS was defined as the interval between the date of starting rechallenge therapy and disease progression or the date of death in the absence of progression, or the date of last follow-up.

Progression-free survival and overall survival (OS) were estimated using the Kaplan–Meier method and survival curves were compared using the log-rank test. Hazard ratios and their 95% confidence intervals (CIs) were estimated using a Cox proportional hazard model that was used to investigate factors that influenced survival or responsiveness to rechallenge chemotherapy.

Relapse-free interval was defined as the interval between completion of FL chemotherapy and documentation of disease progression. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC).

Results

Of the 2000 consecutive SCLC patients reviewed, 112 (5.6%) had sensitive disease treated with platinum with etoposide

Table 1 Patient Characteristics (n = 2000)

Characteristic	Value
Patients Analyzed	112 (5.6)
Smoking History	
Current smoker	47 (42)
Former smoker	59 (53)
Never smoker	6 (5)
Sex	
Female	39 (35)
Male	73 (65)
Median Age (Range), Years	64 (40-83)
Stage at Time of Diagnosis	
Limited disease	49 (44)
Extensive disease	63 (56)
Performance Score at Time of Diagnosis	
0-1	97 (87)
2	15 (13)
First-Line Chemotherapy Regimen	
Carboplatin and etoposide	51 (46)
Cisplatin and etoposide	61 (54)
Median Courses of First-Line Chemotherapy (Range)	5 (1-6)

Data are presented as n (%) except where otherwise noted, and values are calculated according to the 112 analyzed patients.

Table 2 Additional Line of Treatment

	n	(%)
Chemotherapy		
Yes	40	36
No	72	64
Regimen		
Cyclophosphamide with adriamycin and vincristine	10	25
Topotecan	10	25
Other	8	20
Carboplatin/etoposide	6	15
Cyclophosphamide with epirubicin and vincristine	3	7.5
Cisplatin/etoposide	1	2.5
Carboplatin/irinotecan	1	2.5
Gemcitabine/paclitaxel	1	2.5

rechallenge (carboplatin or cisplatin). Seventy-three (65%) patients were male with a median age of 64 years (range, 40-83 years). At diagnosis, 49 (44%) patients had limited disease. Eastern Cooperative Oncology Group PS was 0 and 1 for 97 (87%) patients and PS was 2 for the remaining 15 (13%) patients. Patient characteristics are summarized in Table 1.

The most common FL regimen was cisplatin/etoposide (54%) and median number of cycles administered was 5 (range, 1-6). Response to FL chemotherapy was complete response (CR) for 16 patients (14%), partial response (PR) for 94 patients (84%), and stable disease (SD) for 2 (2%) patients. Median RFI was 240 days (range, 90-1200 days).

Rechallenge chemotherapy with carboplatin with etoposide and cisplatin with etoposide was administered in 96 (86%) and 16 (14%) patients, respectively. The median number of cycles was 4 (range, 1-7). The response to rechallenge chemotherapy was CR in 3%, PR in 42%, and SD in 19%. Twenty-seven percent of patients had progressive disease and 9% were not evaluable for response. Further-line chemotherapy was administered to 40 (36%) patients. The most commonly given regimens were CAV and topotecan (25% for both), followed by carboplatin with etoposide (15%) and cyclophosphamide with epirubicin and vincristine (7.5%). Approximately 20% of patients received other monotherapy regimens. The types of further lines of chemotherapy are shown in Table 2.

Median PFS from the time of rechallenge chemotherapy was 5.5 months (95% CI, 4.4-6.3); median OS-R and OS-D were 7.9 months (95% CI, 6.9-9.7) and 21.4 months (95% CI, 19.8-24.1) respectively, likely driven by the fact that 44% of the patients had limited-stage disease at presentation. PFS and OS curves are shown in Figures 1, 2, and 3.

We also conducted an exploratory subgroup analysis that evaluated the effect of RFI on PFS and OS from rechallenge. Based on the length of RFI, we arbitrarily divided the whole analyzed population in 3 subgroups: RFI, 90-119 days (n = 13), 120-149 days (n = 8), and > 150 days (n = 91). Despite that there was a numerically longer PFS for the longer RFI subgroup, this did not reach statistical significance, as shown in Table 3. Similarly, we did not find any difference in OS-R, according to the different RFI

Figure 2 Overall Survival (OS) From the Time of Starting Rechallenge Therapy

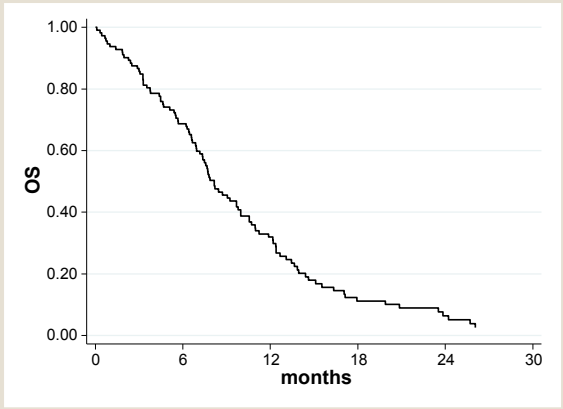

Figure 1 Progression-Free Survival (PFS) From the Time of Starting Rechallenge Therapy

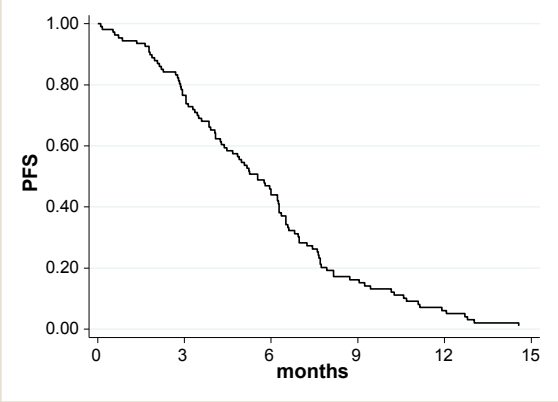

Figure 3 Overall Survival (OS) From the Time of Diagnosis

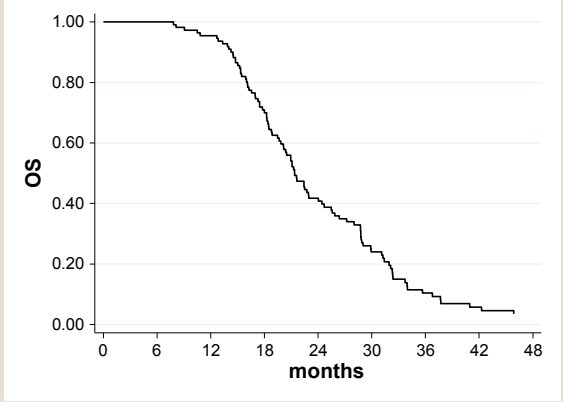

Table 3 Progression-Free Survival and OS According to RFI

RFI, Days	n	Median PFS, Months (95% CI)	HR (95% CI)	*P*	Median OS, Months (95% CI)	HR (95% CI)	*P*
90-119	13	3.1 (1.8-6.2)	1.41 (0.77-2.55)	.26	8.2 (3.3-10.0)	1.35 (0.73-2.48)	.341
120-149	8	4.8 (1.6-7.9)	1.30 (0.60-2.83)	.50	11.9 (3.0-13.8)	0.76 (0.33-1.75)	.527
≥150	91	6.0 (4.9-6.5)	1.00	—	7.9 (6.9-10.0)	1.00	—

Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival; RFI = relapse-free interval.

subgroups (Table 3). A univariate analysis was performed to evaluate the effect of the most commonly given third-line regimens (anthracycline-based, platinum with etoposide, and topotecan) on PFS after third-line and OS-R. We did not find a statistically significant difference in PFS or OS-R according to the different third-line regimens given but there was a trend for numerically longer OS-R for patients who received platinum with etoposide, as reported in Table 4.

Discussion

Prognosis of patients with relapsed SCLC is poor and the evidence of clinical benefit for second-line chemotherapy is limited. In this setting, topotecan is the only agent approved by the US Food and Drug Administration, despite modest efficacy.[7-9]

Recently the separation of relapsed SCLC patients into sensitive and resistant categories based on an RFI cutoff of 60 days was validated, confirming RFI as a relevant prognostic factor and as an important predictor of the probability of a response to second-line chemotherapy.[5]

It is common in clinical practice to rechallenge patients with platinum and etoposide chemotherapy if they had a response that lasted at least 90 days since completion of FL chemotherapy. However, this evidence is drawn from small clinical trials mostly conducted in the 1980s,[11-14] which are summarized in Table 5.[11-19] Notably, American College of Chest Physicians and National Comprehensive Cancer Network guidelines suggest rechallenge to be used for patient with an RFI > 6 months.[20,21]

Considering the limitations of the current available evidence, we performed a multicenter international analysis to evaluate the effect of platinum-based rechallenge on OS in an era in which better supportive medicines are available.

Our results are similar to those reported in phase III randomized trials that evaluated second-line CAV or topotecan,[7-9] although in our retrospective study we analyzed only sensitive SCLC patients, whereas in the prospective trials there were patients with sensitive and resistant disease. Our exploratory subgroup analysis on the effect of different ranges of RFI on PFS and OS-R did not demonstrate any significant difference but this could be related to the small sample in the 90 to 119 days and 120 to 149 days subgroups. Potential reasons for these results might be the retrospective design of our study and the differences of analyzed patients and their clinical characteristics and management.

Similarly, in a meta-analysis from Ardizzoni et al,[5] who increased the RFI cut beyond 90 days, it is not possible to identify a group of patients with a higher probability of response to topotecan.

Furthermore, it is very difficult to draw conclusions from our analysis on the effect of the 3 most common third-line chemotherapy regimens because of the very small sample size and number of events; it seems that no regimen performs better than another. Intriguingly, the OS is numerically longer for patients re-treated with platinum with etoposide and this might suggest that some neoplastic clones maintain platinum sensitivity also at the time of disease progression.

Garassino et al reported on the clinical outcomes of 161 SCLC patients of whom 30 (19%) had sensitive SCLC treated with rechallenge of FL platinum with etoposide.[15] Compared with other rescue regimens, the platinum-based regimen yielded better results of OS and PFS, although it did not reach statistical significance (log rank test; $P = .08$).

Similarly Korkmaz and colleagues[16] analyzed the outcome of patients with relapsed SCLC treated with rechallenge or other regimens. Sensitive SCLC patients treated with platinum rechallenge had a better response rate, PFS, and OS. Multivariate analysis identified PS, extent of disease at the time of diagnosis, and platinum sensitivity as independent prognostic factors for survival.

Contrarily, Wakuda et al,[17] in their series of sensitive SCLC patients did not find any differences in activity and efficacy between rechallenge and other schedules including amrubicin.

Compared with the experience of Garassino et al[15] and Wakuda et al,[17] we recorded a slightly greater response rate for rechallenge,

Table 4 Further-Line Chemotherapy and Effect on PFS and OS From Time of Rechallenge

Further-Line Therapy	Patient n	PFS From Time of Rechallenge			PFS From Time of Third-Line Therapy		OS From Time of Rechallenge			OS From Time of Third-Line Therapy	
		Events, n	Median PFS (95% CI)	*P*	Median PFS (95% CI)	*P*	Events, n	Median OS (95% CI)	*P*	Median OS (95% CI)	*P*
Anthracycline-Based Regimen	13	13	6.3 (5.0-6.9)	—	3.4 (0.5-7.7)	—	11	10.6 (7.3-12.4)	—	5.4 (2.1-7.7)	—
Platinum-Etoposide	7	7	7.4 (2.1-10.6)	—	5.0 (0.7-14.0)	—	5	19.9 (3.8-23.8)	—	9.7 (0.7-15.1)	—
Topotecan	10	10	6.3 (1.6-7.6)	.190	1.7 (0.0-2.7)	.009	9	11.5 (3.5-15.1)	.049	5.2 (1.7-7.9)	.454

Abbreviations: OS = overall survival; PFS = progression-free survival.

Table 5 Studies That Evaluated Rechallenge of First-Line Chemotherapy

Reference	Patient n	Regimen	Complete Response, %	Partial Response, %	Median PFS, Months[a]	Median OS, Months[a]
Batist et al[11]	5	CMC VAP Ifo./VP-16	40	40	10	NR
Giaccone et al[12]	13	VAP CDDP/VP-16 CDE	17	33	NR	6.5
Postmus et al[13]	37	CDE	26	46	6.5	NR
Vincent et al[14]	15	CBCDA/VP-16 A/VP-16/V → C	0	67	3	5
Garassino et al[15]	30[b]	Platinum-based	NR	35	NR	9.2
Korkmaz et al[16]	11[b]	Platinum-based	NR	NR	6.2	11.4
Wakuda et al[17]	13[b]	Platinum/etoposide	NR	37	5.6	14.4
Goto et al[18]	90	Platinum/etoposide/ irinotecan	NR	NR	5.7	18.2
Nakamura et al[19]	30	Platinum-based	NR	43	5.0	NR

Abbreviations: A/VP-16/V → C = adriamicyn, etoposide, vincristine, and cyclophosphamide; CBCDA/VP-16 = carboplatin and etoposide; CDDP/VP-16 = cisplatin and etoposide; CDE = cyclophosphamide, doxorubicin, and etoposide; CMC = cyclophosphamide, methotraxete, and nitrous urea; Ifo./VP-16 = etoposide and iphosphamide; VAP = vincristine, adriamicyn, and procarbazine.
[a]From starting rechallenge.
[b]Patients treated with first-line platinum/etoposide rechallenge.

probably because of the higher number of patients analyzed and timing of response assessment. At the American Society of Clinical Oncology 2014, Goto et al presented preliminary results of a randomized phase III prospective trial in which 180 platinum-sensitive SCLC patients were treated with topotecan or platinum, etoposide and irinotecan supported with granulocyte colony-stimulating factor.[18] Patients treated with platinum-based chemotherapy had better outcomes compared with those treated with single-agent chemotherapy, with results similar to our retrospective analysis.

Nakamura et al[19] treated sensitive SCLC patients with rechallenge of platinum doublet chemotherapy or amrubicin: monochemotherapy yielded a greater response rate compared with rechallenge but disease control rate and PFS were similar.

This is, to our knowledge, the largest series to evaluate rechallenge with platinum with etoposide as second-line treatment for SCLC patients. We acknowledge the limitations of the retrospective analysis and the heterogeneity of the different institutional protocols for patient management. Unfortunately, we were not able to collect data on the site and number of metastases, data on radical radiotherapy to the chest, or prophylactic cranial irradiation and toxicity. Nonetheless, we believe our study provides considerable insight on clinical outcomes for this strategy in the recent era. According to our results, platinum with etoposide rechallenge is a reasonable option with potentially better outcomes than standard approved second-line chemotherapy. A definitive answer about the potential superiority of platinum with etoposide rechallenge over the other regimens will require other prospective randomized studies.

Conclusion

Small-cell lung cancer is an aggressive tumor characterized by a high chemotherapeutic sensitivity, nevertheless the outcome results are disappointing. Based on the response registered with FL chemotherapy and the interval between progression of disease and the end of therapy, we can recognize patients with "sensitive disease," who might benefit from a rechallenge of FL therapy. Although this strategy is not supported by robust scientific evidence, it represents an opportunity in daily clinical practice. Herein we report on a large series of "sensitive" SCLC patients treated with a FL rechallenge; despite the limit of its retrospective design with no control arm treated with other regimens, our series confirms the interesting outcome results in patients with sensitive disease treated with rechallenge of FL chemotherapy. Prospective trials with sensitive SCLC patients randomized between FL rechallenge and other rescue regimens are warranted to verify the superiority of platinum-based chemotherapy compared with standard second-line treatment.

Clinical Practice Points

- Rechallenge of FL chemotherapy in the treatment of sensitive patients with relapsed SCLC represents a treatment option, although based on results of a small single institution retrospective series.
- Our multicenter series, the largest reported in the literature to our knowledge, of sensitive SCLC patients treated with rechallenge of FL chemotherapy, confirms that rechallenge is a viable therapeutic option in daily clinical practice, especially for patients who have a very delayed relapsed disease.
- Further prospective studies are needed to validate the effectiveness of rechallenge of FL chemotherapy compared with a not cross-reagent second-line chemotherapy and to verify the correct threshold to define a 'sensitive' patient with relapsed SCLC.

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Disclosure

The authors have stated that they have no conflicts of interest.

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