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.