

Treatment of etoposide capsule combined with cisplatin or carboplatin in elderly patients with small cell lung cancer*

Guanzhong Zhang¹, Zhaozhe Liu (Co-first author)¹, Tao Han¹, Fang Guo¹, Qingqing Sun¹, Yanan Ge¹, Yaling Han², Xiaodong Xie (✉)¹

¹ Oncology Department, General Hospital of Shenyang Military Region, Shenyang 110016, China

² Cardiovascular Disease Institute, General Hospital of Shenyang Military Region, Shenyang 110016, China

Received: 11 September 2014 / Revised: 2 October 2014 / Accepted: 25 October 2014

© Huazhong University of Science and Technology 2014

Abstract *Objective:* We aimed to explore the efficacy and safety of etoposide capsule combined with cisplatin or carboplatin in the treatment of elderly patients with small cell lung cancer (SCLC). *Methods:* From October 2011 to November 2013, 32 elderly patients (71–79 years old) with histopathologically confirmed SCLC in general hospital of Shenyang Military Region were enrolled in the research. The patients were administrated with lastet capsule 150–175 mg, d1–5, combined with cisplatin 20 mg/m² d1–3 or carboplatin AUC = 5, applied over 2 days. Twenty-one days were 1 treatment cycle. *Results:* After treatments, 2 cases acquired complete response (CR), 19 cases acquired partial response (PR), 8 cases acquired stable disease (SD), and 3 cases had progression of disease (PD). The objective response rate was 65.6% (21/32), disease control rate was 90.6% (29/32). The median time of progression-free survival (PFS) was 6.9 months, the median survival time was 14.0 months, and 1 year survival rate was 62.4%. The main adverse reactions of I/II leukopenia and gastrointestinal reaction were observed. *Conclusion:* Etoposide capsule combined with cisplatin or carboplatin therapy have curative effect and good tolerance in elderly patients with SCLC.

Key words small cell lung cancer; etoposide capsule; cisplatin; carboplatin; elderly

Lung cancer is one of the worldwide malignant tumors with the highest morbidity and mortality rates. About 1.60 million new patients are diagnosed with lung cancer, and 1.38 million patients die of lung cancer each year [1]. Small cell lung cancer (SCLC) accounts for 10%–15% of all lung cancer, with the characteristics of rapid progression and early metastasis [2]. SCLC is a kind of malignant tumor with extremely poor prognosis, and chemotherapy is the main treatment option [3]. In clinic, etoposide combined with cisplatin or carboplatin is the optimal chemotherapy regimen. However, elderly patients have poor tolerance with standard intravenous chemotherapy. This retrospective study analyzed the effect and adverse reactions of cisplatin or carboplatin treatment combined with oral etoposide capsule, instead of venous etoposide injection in elderly patients with SCLC.

Materials and methods

Clinical data

From October 2011 to November 2013, 32 cases of elderly patients with SCLC in General Hospital of Shenyang Military Region were enrolled in the research. All cases were confirmed by pathology, and had measurable or evaluable lesions. The expected survival time of the cases was more than 3 months, and ECOG score was 0–1. All patients were initially treated and had no contraindication to chemotherapy. The patients aged from 71 to 79 years old, with the median age of 76 years. Among them, 20 cases were female, and 12 cases were male; 21 cases were in limited stage, and 11 cases were in extensive stage. Eighteen cases accepted lastet capsule plus carboplatin, and 14 cases accepted lastet capsule plus cisplatin. All of the patients finished at least 1 cycle of combination therapy. The therapeutic evaluations of all the cases were conducted after treatments. Patients' data were listed in Table 1.

Correspondence to: Xiaodong Xie. Email: doctor_xxd@163.com

* Supported by grants from the Sub-Topics of Major Drug Discovery Platform in the Twelfth-Five Year Research Program of China (No. 2012ZX09303016-002) and China Postdoctoral Science Foundation (No. 2012M512119).

Table 1 Characteristics of patients ($n = 32$)

Characteristics	<i>n</i>	%
Age (years, range)	76 (71–79)	
Sex		
Male	12	37.5
Female	20	62.5
Weight (kg, mean \pm s)	63 \pm 8.9	
Stage		
Limited	21	65.6
Extensive	11	34.4
ECOG Performance status		
0	7	21.9
1	25	78.1

Therapeutic methods

The therapeutic regimen was lastet capsule 150–175 mg, d1–5, cisplatin 20 mg/m² d1–3 or carboplatin AUC = 5, divided into 2 days of application, 21 days were set at 1 therapeutic cycle. Blood sample, liver and kidney function, and electrocardiogram (ECG) were tested before chemotherapy. The treatment was administrated if no obvious abnormal results were found. If the patients couldn't tolerate the adverse reactions, 20% of the dosage was reduced in the next cycle treatment. If the patients were still intolerant to the adverse reactions, the treatment was then stopped. After 2 cycles of chemotherapy, therapeutic effects were evaluated. The treatments were ended if disease progression or intolerant adverse reactions occurred.

Therapeutic effect evaluation and adverse reactions

Baseline examinations were preceded within 1 week before the start of treatment, and the same imaging examination was conducted for therapeutic effect evaluation after the treatment. The short-term therapeutic effect was evaluated by response evaluation criteria in solid tumors (RECIST). It included complete remission (CR), partial response (PR), stable disease (SD) and progression of disease (PD). Objective response rate (ORR) was the percentage of CR + PR in all cases, and disease control rates (DCR) was the percentage of CR + PR + SD in all cases. The long-term therapeutic effect was evaluated by progression-free survival time (PFS) and Overall survival time (OS). PFS was defined as time from randomization until first evidence of tumor progression. OS was defined as the time from randomization to death from any cause. American National Cancer Institute's NCI-CTC 3.0 was used to evaluate the adverse reactions. Responses of all the cases were evaluated every two cycles, and adverse reactions were recorded in each cycle.

Statistical analysis

SPSS 17.0 software was used for the statistical analysis. Chi-square test or Fisher's exact test was used to analyze the short-term therapeutic effect and adverse reactions. Kaplan-Meier and the Log-rank test were used for PFS and OS analysis. $P < 0.05$ was considered to have statistical significance.

Results

Follow-up

The median time from diagnosis to the treatment was 3 months. Thirty-two cases elderly patients with SCLC completed at least 1 cycle of chemotherapy. The total number of chemotherapy cycles was 96, with the median number of 3 (1–6). Because of adverse reactions, the chemotherapy dosage was adjusted in 6 cases (18.8%), and the chemotherapy time was delayed in 7 cases (21.9%). Local radiotherapy was preceded after the chemotherapy was stopped in 20 cases (62.5%). The median follow-up time was 13 months (5–30 months), with the average of 9.8 months. The follow-up was ended on April 30, 2014. None of the patients was lost to follow-up. Therapeutic effect and adverse reactions were evaluated for all patients. Up to now, 11 cases were still alive.

Therapeutic effect evaluation

Two cases acquired CR, 19 cases acquired PR, 8 cases maintained SD, and 3 cases acquired PD. The ORR was 65.6%, DCR was 65.6%, PFS was 6.9 months (95% CI: 5.8–7.9 months), OS was 14.0 months (95% CI: 8.6–17.4 months), and 1-year survival rate was 62.4%. The detail was listed in Table 2 and Fig. 1.

Adverse reactions

The main adverse reactions of I/II leukopenia and digestive tract reaction were found in the patients. III-degree and IV-degree leukopenia was found in 3 cases and 1 case respectively. III-degree of nausea and vomiting occurred in 1 case, and III-degree of renal function change occurred in 1 case. The adverse reactions were mitigated after symptomatic treatment, and no chemotherapy related deaths occurred. The detail was listed in Table 3.

Discussion

SCLC is a subtype of lung cancer, with the features of short doubling-time, early recurrence and metastasis, and poor prognosis. SCLC patients without any treatment often quickly die in 2–4 months [4]. After concurrent chemoradiation, the median survival time of local and extensive SCLC patients are 15–20 months and 8–13 months respectively. The two-year survival rate of local SCLC patients is 20%–40%, while that of extensive SCLC

Table 2 Response for elderly patients with SCLC treated with etoposide capsules plus platinum ($n = 32$)

Response	<i>n</i>	%
CR	2	6.3
PR	19	59.4
SD	8	25.0
PD	3	9.4
ORR	21	65.6
DCR	29	90.6

CR, complete remission; PR, partial response; SD, stable disease; PD, progression of disease; ORR, objective response rate; DCR, disease control rates

Table 3 Toxicity for patients

Toxicity	II/II		III/IV	
	<i>n</i>	%	<i>n</i>	%
Leucopenia	18	56.3	4	12.5
Thrombocytopenia	3	9.4	0	0
Anemia	2	6.3	0	0
Nausea / Vomiting	14	43.8	1	3.1
ALT / AST	5	15.6	0	0
Creatinine	0	0	1	3.1
Pyrexia	2	6.3	0	0
Fatigue	9	28.1	0	0

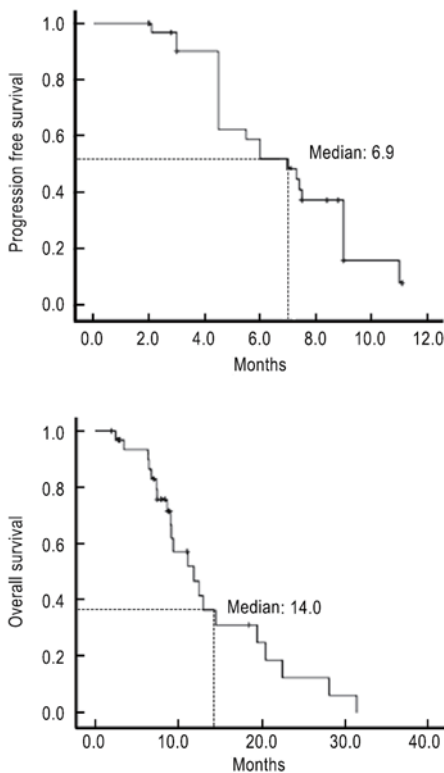


Fig. 1 PFS and OS for elderly patients with SCLC treated with etoposide capsules plus platinum ($n = 32$)

patients is less than 5% [5]. SCLC has the highest sensitivity to chemotherapy in the lung cancer [6]. Early research found that the regimen of cyclophosphamide combined with doxorubicin/epirubicin and vincristine (CAV or CEV) had a better therapeutic effect for SCLC patients [7]. Evans *et al* reported that the ORR of etoposide combined with cisplatin reached 89%, and the ORR could reach 55% even in the relapse cases after anthracycline-based chemotherapy. The median survival time in the local and extensive SCLC patients was 17.5 and 11.8 months respectively [8]. In Fukuoka's study, the ORR of EP and CAV regimen was 78% and 55% respectively, with the

median survival time of 9.9 months [9]. Compared with CAV regimen, EP had a better ORR and the similar OS. The heart and liver toxicity of EP regimen was lower and the tolerance was better. At present, EP becomes the most common regimen for SCLC chemotherapy [10].

SCLC is reported to be closely related to smoking. Typical SCLC patients are often excessively smoking elderly persons. An analysis of the national cancer database showed that the proportion of elderly patients (> 70 years old) was in a significant increasing trend. Ludbrook *et al* [11] analyzed the data of community population and indicated that physical status of patients declined, the complications increased with the increasing of their age. Elderly patients were not suitable for extensive chemotherapy and concurrent chemoradiation. It was difficulty for elderly patients to achieve CR and the prognosis was poor after treatment. Compared with the young patients, side effects of chemotherapy, especially hematologic toxicity was more likely to occur in elderly patients. INT0096 research showed that treatment-related mortality was much higher in elderly patients (< 70 years old, 1% vs. 10%, ≥ 70 years old, $P = 0.01$). Until Now, there are no definite guidelines for the treatment of elderly patients with SCLC. The phase III trial of elderly SCLC patients has not been reported.

In our study, oral etoposide capsule was administrated instead of etoposide intravenous drip in EP regimen for elderly SCLC patients. The therapeutic effect and adverse reactions were retrospectively analyzed. The ORR was 65.6% in 32 cases of elderly SCLC patients after the formulated treatment. Although it was much lower than that of etoposide injection with platinum regimen in Evans's report, more than 50% of the elderly patients achieved good therapeutic effect. It was notable that median PFS of the patients was 6.9 months, which was significantly improved compared to patients without any treatment. In our study, OS of the patients reached 14.0 months and obvious survival benefit was acquired, which was similar to Evans's report and was better than Fukuoka's findings. We found that adverse reaction of etoposide capsule was lower and the tolerance was better even if the combined treatment regimen was administrated in the elderly SCLC

patients.

In this study, etoposide capsules combined platinum acquires ideal therapeutic effect with good tolerance. Therefore, etoposide capsule combined platinum drugs maybe a better treatment option for elderly patients with SCLC.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Ferlay J, Shin HR, Bray F, *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, 2010, 127: 2893–2917.
2. Van Meerbeeck JP, Fennell DA, De Ruyscher DK. Small-cell lung cancer. *Lancet*, 2011, 378: 1741–1755.
3. Wu YL, Gu LJ, Yang XN. Clinical research of lung cancer in China. *Chinese-German J Clin Oncol*, 2002, 1: 132–134.
4. Pelayo Alvarez M, Gallego Rubio O, Bonfill Cosp X, *et al*. Chemotherapy versus best supportive care for extensive small cell lung cancer. *Cochrane Database Syst Rev*, 2009, 4: CD001990.
5. Zhang HN, Liu YP. Advances in study on the therapy for limited-stage small cell lung cancer. *J Cent South Univ*, 2013, 38: 857–862.
6. Kallianos A, Rapti A, Zarogoulidis P, *et al*. Therapeutic procedure in small cell lung cancer. *J Thorac Dis*, 2013, 5 Suppl 4: S420–424.
7. Feld R, Pringle JF, Evans WK, *et al*. Combined modality treatment of small cell carcinoma of the lung. *Arch Intern Med*, 1981, 141: 469–473.
8. Evans WK, Shepherd FA, Feld R, *et al*. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol*, 1985, 3: 1471–1477.
9. Fukuoka M, Furuse K, Saijo N, *et al*. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst*, 1991, 83: 855–861.
10. Chan BA, Coward JI. Chemotherapy advances in small-cell lung cancer. *J Thorac Dis*, 2013, 5: S565–578.
11. Ludbrook JJ, Truong PT, MacNeil MV. Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? a community-based population analysis. *Int J Radiat Oncol Biol Phys*, 2003, 55: 1321–1330.

DOI 10.1007/s10330-314-0003-9

Cite this article as: Zhang GZ, Liu ZZ, Han T, *et al*. Treatment of etoposide capsule combined with cisplatin or carboplatin in elderly patients with small cell lung cancer. *Chinese-German J Clin Oncol*, 2014, 13: –.