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ORIGINAL ARTICLE

Influence of tumor response on the survival of patients with extensive-stage small-cell lung cancer treated with the etoposide plus cisplatin chemotherapy regimen*

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Abstract

Objective In this study, we evaluated the difference of progression-free survival (PFS) and overall survival (OS) between extensive-stage small-cell lung cancer (ES-SCLC) patients who acquired partial response (PR) or complete remission (CR) after two cycles of first-line chemotherapy with the etoposide plus cisplatin (EP) regimen and those who acquired PR or CR after four or six cycles.

Methods A total of 106 eligible patients treated with the EP chemotherapy regimen for two to six cycles, at The General Hospital of Shenyang Military Region (China) between November 2004 and May 2011, were enrolled in this study. RECIST version 1.1 was used for the evaluation of chemotherapy efficiency. We followed up all eligible patients every 4 weeks. All statistical data were analyzed by using SPSS 21.0 statistical package for Windows.

Results After a median follow-up of 293 days (range, 62–1531 days), all patients had died by the cutoff date. Fifty-one patients acquired PR or CR after two cycles of chemotherapy; the median PFS reached 6.0 months (95% CI, 5.1–6.9), and the median OS was 10.5 months (95% CI, 8.6–12.4). Twenty-eight patients acquired PR or CR after four or six cycles; the median PFS was 4.8 months (95% CI, 4.4–5.2), and the median OS was 7.5 months (95% CI, 6.8–8.2). Both PFS and OS showed a statistical difference between the two groups.

Conclusion ES-SCLC patients who acquired PR or CR after two cycles of the EP regimen as first-line therapy had longer PFS and OS than those who acquired PR or CR after four or six cycles.

Key words: extensive-stage small-cell lung cancer (ES-SCLC); tumor response; progression-free survival (PFS); overall survival (OS)

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Approximately 70% of all small-cell lung cancer (SCLC) cases in Asian patients were extensive-stage SCLC (ES-SCLC); its median survival can be as low as 6 months, which indicates a very poor prognosis compared with other malignancies [1]. The disease progresses easily and has a very high mortality. Clinical trials, both published and ongoing, have failed to show new chemotherapeutics or targeted drugs with better efficiency than the standard chemotherapy of platinum combined with etoposide. Nevertheless, studies on many promising targeted

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Table 1 General clinical information of the enrolled patients (*n*)

Subgroups	Enrolled amounts	PR/CR after 2 cycles	PR/CR after 4/6 cycles
Cases	106	51	28
Mean age (years)	62.1	60.9	63.6
Age (years)			
≥ 60	62	26	16
< 60	44	25	12
Metastatic sites			
Bone	24	11	3
Lung	19	10	6
Liver	34	16	14
Brain	13	4	3
Kidney/adrenal	27	17	5
Others	39	21	6

therapies and other chemotherapeutic agents are under way [2]. The initial response rate to chemotherapy in EC-SCLC patients could reach as high as 80%. Additionally, a longer survival may be possible with chemotherapeutics than with best supportive care. Therefore, further research is needed on whether chemotherapy sensitivity is related to survival, so that clinicians can help ES-SCLC patients benefit more from chemotherapy and thus survive longer.

Progression-free survival (PFS) is a factor used in evaluating the treatment efficiency. Because SCLC shows a very poor prognosis, it seems that the endpoint of overall survival (OS) is initially determined by whether the patient's disease has progressed. PFS involves acquiring stable disease (SD) for a long time, so that it could provide a more direct evaluation of whether the treatment method was potentially beneficial to the patient. The typical definition of PFS is the moment from randomization or study registration to the time of either first disease progression or death from any cause. However, the accuracy and effectiveness of PFS as an endpoint also need to be carefully considered. OS is the most important endpoint for most diseases; however, it can be influenced by many factors. We studied the difference of both PFS and OS between ES-SCLC patients who acquired partial response (PR) or complete remission (CR) after two cycles of first-line chemotherapy with the etoposide plus cisplatin (EP) regimen and those who acquired PR or CR after four or six cycles.

Materials and methods

Patient selection

A total of 106 eligible patients at The General Hospital of Shenyang Military Region (China) treated between November 2004 and May 2011 were enrolled in our retrospective study. All of them had a diagnosis of ES-SCLC. Recurrent or metastatic disease was diagnosed pathologically, or according to the presence of a measurable lesion on computed tomography (CT) scans and bronchoscopy or on CT-guided biopsy. Nonoperative staging was applied according to the classification published by the American Joint Committee on Cancer (version 7).

Treatment and evaluation

All eligible patients were treated with EP-etoposide was administered at a dose of 100 mg/m^2 on days 1–3, and cisplatin was administered at a dose of 75 mg/m^2 on day 1 of each cycle (3 weeks)—which was the standard first-line chemotherapy treatment regimen. Each eligible patient received two to six cycles of the first-line chemotherapy, which was administered every 3 weeks. Adjuvant drugs were administered, such as antanacathartic, colony-stimulating factor, and diphosphonate, to reduce the adverse effects of the chemotherapeutics, when necessary.

The Response Evaluation Criteria in Solid Tumors version 1.1 was used for the evaluation of chemotherapy efficiency, i.e., tumor response. According to the standard, we classified the final response to chemotherapy into four classes: CR, PR, SD, and progression of disease. CR, PR, and SD were taken as the disease control rate. The efficiency of treatment was evaluated after every two courses of standard chemotherapy.

Follow-up

We followed up all the eligible patients every 4 weeks after all of them had completed all cycles of standard chemotherapy or until they died. At the end of the study, the life or death status was recorded for all eligible patients.

Statistical analysis

All statistical data were analyzed by using SPSS 21.0 statistical package for Windows. We expressed continuous data as mean ± standard deviation and categorical data as percentages (%). The statistical differences in PFS and OS between ES-SCLC patients who acquired PR or CR after two cycles of standard chemotherapy and those who acquired PR or CR after four or six cycles were assessed by using the Kaplan–Meier curves. Qualitative data were analyzed by using the χ^2 test. The PFS and OS were taken as the primary and secondary endpoints. A P value of < 0.05 was accepted as statistically significant in all statistical analyses.

Results

After a median follow-up of 293 days (range, 62–1531 days), all patients had died by the cutoff date. The general clinical information of the 106 enrolled patients was shown in Table 1. Seventy-nine patients acquired PR or CR. The response rate of all patients was 74.5%. The

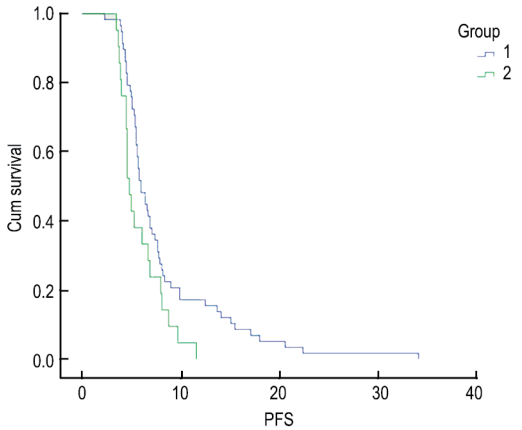

Fig. 1 Kaplan-Meier curves for PFS. Group 1 comprised ES-SCLC patients who acquired partial response or complete remission after two cycles of the EP regimen as first-line therapy. Group 2 comprised ES-SCLC patients who acquired partial response or complete remission after four or six cycles of the EP regimen as first-line therapy

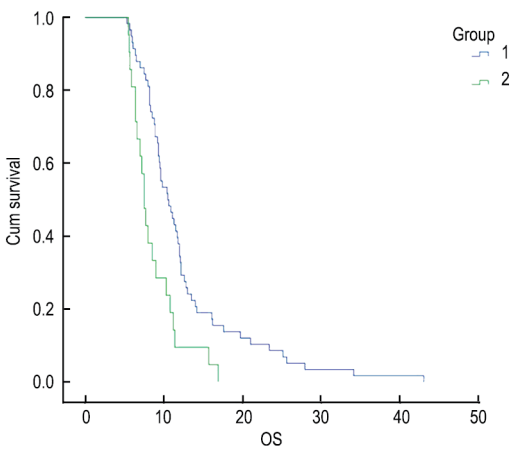

Fig. 2 Kaplan-Meier curves for OS. Group 1 included ES-SCLC patients who acquired partial response or complete remission after two cycles of the EP regimen as first-line therapy. Group 2 included ES-SCLC patients who acquired partial response or complete remission after four or six cycles of the EP regimen as first-line therapy

median PFS and median OS were 5.8 months (95% CI, 5.2–6.4) and 9.6 months (95% CI, 8.4–10.8), respectively. Fifty-one patients acquired PR or CR after two cycles of chemotherapy; the median PFS reached 6.0 months (95% CI, 5.1–6.9). Twenty-eight patients acquired PR or CR after four or six cycles; the median PFS was 4.8 months (95% CI, 4.4–5.2). A statistical difference was found between the two groups ($P = 0.029$; Fig. 1).

The statistical data of OS after the follow-up were as follows: the median OS was 10.5 months (95% CI, 8.6–12.4) in patients who acquired PR or CR after two cycles of chemotherapy compared with 7.5 months (95% CI, 6.8–8.2) in those who acquired PR or CR after four or six cycles, with statistical significance ($P = 0.001$; Fig. 2).

Discussion

SCLC is one of the most common neuroendocrine malignancies, and it is very sensitive to chemotherapeutics. It is now well known that the standard therapy for ES-SCLC patients is platinum-based chemotherapy, which is first administered for four to six cycles, and, if the patient responds, prophylactic cranial irradiation follows thereafter [3–4]. Although the response rate to chemotherapy of ES-SCLC patients can reach as high as 70–85%, and although 10–25% of them can acquire CR, almost all of the patients' malignancies will recur [5]. The efficiency of the first-line chemotherapy regimen is directly related to survival. Both PR and CR are independent prognostic factors for PFS and OS [6]. However, chemosensitivity varies among patients. In our study, ES-SCLC patients who acquired PR or CR after two cycles of the EP regimen as first-line chemotherapy had longer PFS and OS than those who acquired PR or CR after four or six cycles, which means that patients who are more sensitive to chemotherapy could achieve a longer survival.

According to the guidelines, only a subgroup of ES-SCLC patients can potentially receive second-line chemotherapy; in addition, these patients should be carefully selected. The factors that need careful consideration are whether the patient's response to first-line treatment was good, the time duration since the termination of the first-line treatment, the remaining toxicity from the first-line chemotherapy, and the performance status, all of which have been found to affect the survival of patients [7]. In our study, second-line treatments are administered according to the guidelines published by the National Comprehensive Cancer Network (NCCN). The second-line treatments are not unified because the NCCN published updated versions in 2004 and 2011. Although the second-line treatments and other treatments influence survival, we cannot analyze those factors after the first-line chemotherapy because of the limited number of cases.

In previous studies, parameters such as metastatic site, sex, age, and tumor markers have been important topics, and they have been proved to affect patient survival. It has been clarified that being younger, being female, stopping smoking before or after diagnosis, and having no brain metastasis have a certain positive influence on survival; nevertheless, recurrence or metastatic disease during treatment confers a poorer prognosis. In previous studies, some prognostic markers for ES-SCLC patients' survival have been identified; however, previous evidences have been inconsistent. It was reported in some studies that carcinoembryonic antigen (CEA), serum lactate dehy-

drogenase, neuron-specific enolase (NSE), and albumin levels are related to the prognosis of lung malignancies (including non-small-cell lung cancer and SCLC) [8–11]. Some authors report that a patient with a normal serum CEA level before receiving first-line chemotherapy has a better chance to achieve CR [12]. However, there is still no evidence showing that there is a relation between survival and the expression of CEA, NSE, or cancer antigen 125 in ES-SCLC patients [13–14]. Therefore, which is the more vital parameter to predict the response to chemotherapy and the survival of ES-SCLC patients is still under debate. However, prognostic parameters were not evaluated in our study because the sample was too small and not all patients were tested for prognostic factors.

Conclusion

ES-SCLC patients who acquired PR or CR after two cycles of the EP regimen as first-line therapy had longer PFS and OS than those who acquired PR or CR after four or six cycles.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Kuo YH, Lin ZZ, Yang YY, *et al.* Survival of patients with small cell lung carcinoma in Taiwan. Oncology, 2012, 82: 19–24.
2. Neal JW, Gubens MA, Wakelee HA. Current management of small cell lung cancer. Clin Chest Med, 2011, 32: 853–863.
3. 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: 528–531.
4. Fruh M, De Ruysscher D, Popat S, *et al*. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2013, 24: 99–105.
5. Lally BE, Urbanic JJ, Blackstock AW, *et al.* Small cell lung cancer: have we made any progress over the last 25 years? Oncologist, 2007, 12: 1096–1104.
6. Ma M, Wang M, Xu Y, *et al.* First-line chemotherapy and its survival analysis of 394 patients with extensive-stage small cell lung cancer in a single institute. Chin J Lung Cancer (Chinese), 2014, 17: 8–14.
7. Wu C, Li F, Jiao SC. Prognostic factors for survival of patients with extensive stage small cell lung cancer–a retrospective single institution analysis. Asian Pac J Cancer Prev, 2012, 13: 4959–4962.
8. Mall JW, Schwenk W, Philipp AW, *et al*. Serum vascular endothelial growth factor levels correlate better with tumour stage in small cell lung can cer than albumin, neuron-specific enolase or lactate dehydrogenase. Respiralogy, 2002, 7: 99–102.
9. Arrieta O, Saavedra-Perez D, Kuri R, *et al*. Brain metastasis development and poor survival associated with carcinoembryonic antigen (CEA) level in advanced non-small cell lung cancer: a prospective analysis. BMC Cancer, 2009, 9: 119.
10. Tomita M, Shimizu T, Hara M, *et al.* Serum carcinoembryonic antigen level in non-small-cell lung cancer patients with preoperative normal serum level. Gen Thorac Cardiovasc Surg, 2009, 57: 303–306.
11. Yang X, Wang D, Yang Z, *et al.* CEA is an independent prognostic indicator that is associated with reduced survival and liver metastases in SCLC. Cell Biochem Biophys, 2011, 59: 113–119.
12. Sculier JP, Feld R, Evans WK, *et al*. Carcinoembryonic antigen: a useful prognostic marker in small-cell lung cancer. J Clin Oncol, 1985, 3: 1349–1354.
13. Hatzakis KD, Froudarakis ME, Bouros D, *et al*. Prognostic value of serum tumor markers in patients with lung cancer. Respiration, 2002, 69: 25–29.
14. Paesmans M, Sculier JP, Lecomte J, *et al.* Prognostic factors for patients with small cell lung carcinoma: analysis of a series of 763 patients included in 14 consecutive prospective trials with a minimum follow up of 5 years. Cancer, 2000, 89: 523–533.

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