Oncology and Translational Medicine
DOI 10.1007/s10330-014-0049-5
February 2015, Vol. 1, No. 1, P26–P31

ORIGINAL ARTICLE

Efficacy analysis and multi-factor retrospective study of third-line chemotherapy in 82 Chinese patients with small cell lung cancer*

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Abstract

Objective As there is currently no clear recommendation for third-line chemotherapy for small cell lung cancer (SCLC), its efficacy is unknown. To date, there have rarely been reports of Chinese patients with SCLC who received third-line chemotherapy. Therefore, we investigated the efficacy, safety, and prognostic factors of Chinese patients with SCLC treated with third-line chemotherapy.

Methods A retrospective analysis of patients with SCLC who received third-line chemotherapy was performed.

Results Between 2007 and 2013, 82 patients [62 men (75.6%), 20 women (24.4%); median age at the time of diagnosis, 55 years] received third-line chemotherapy at our center. Of these patients, 44 had limited-stage disease and 38 had extensive-stage disease. On third-line chemotherapy, 55 (67.1%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, objective response rate of 15.9%, and median overall survival after third-line chemotherapy (OS-3) and median progression-free survival after third-line chemotherapy (PFS-3) of 5.6 months and 3.0 months, respectively. On univariate analysis, PFS-3 was significantly related with ECOG PS ($P = 0.005$), response to second-line chemotherapy ($P = 0.002$), response to third-line chemotherapy ($P < 0.001$), and PFS after second-line chemotherapy ($P = 0.026$). OS-3 was significantly related with ECOG PS ($P < 0.001$), response to third-line chemotherapy ($P = 0.033$), PFS after first-line therapy (P = 0.044), and PFS after second-line therapy (PFS-2) ($P = 0.007$). On multivariate analysis, ECOG PS (P = 0.008) and response to third-line chemotherapy (P = 0.046) were independent prognostic factors for PFS-3, while ECOG PS ($P = 0.007$) and PFS-2 ($P < 0.001$) were independent prognostic factors for OS-3.

Conclusion Few patients with SCLC receive third-line chemotherapy. Our findings suggest that patients with an ECOG PS 0–1 and PFS-2 for >3 months will be benefit from third-line chemotherapy, which should be actively offered to them.

Received: 31 December 2014
Revised: 5 January 2015
Accepted: 12 January 2015

Key words: small cell lung cancer; third-line chemotherapy; prognostic factors

Chemotherapy is one of the main treatment methods for small cell lung cancer (SCLC). Although SCLC is very sensitive to initial chemotherapy, recurrence and metastasis occur in most patients soon after treatment. The median survival time of these patients after further chemotherapy is only 4–5 months [1–2]. After first-line chemotherapy, most patients' symptoms can be significantly relieved by second-line chemotherapy. Second-line treatments differ according to recurrence type. However, among the patients who experience progression or metastasis after second-line treatment, only 20% receive third-line treatments [3]. As there is currently no clear recommendation for third-line chemotherapy for SCLC in the treatment guidelines, its efficacy is uncertain. Very few studies have retrospectively reviewed the curative effects and safety of third-line chemotherapy [4–6], and no study in China has reported on its curative effect in patients with SCLC. Accordingly, this study retrospectively analyzed the curative effect and factors influencing the prognosis of third-line chemotherapy to provide some guidance for

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* Supported by grants from the Jilin Health and Family Planning Commission Scientific Research Project (No. 2014Z014) and the "12th Five" Project of National Key Subject of New Drug Innovation (No. 2013ZX09104001).

third-line treatments and prognostic judgment of patients with SCLC.

Materials and methods

Patient selection

Individual patient data from January 2007 to December 2013 were pooled from our department (Department of Thoracic Oncology, Jilin Provincial Cancer Hospital, Changchun, China). Patients were considered eligible if they met the following criteria: histopathologically or cytologically confirmed SCLC, ≥ 18 years of age, and received third-line chemotherapy and regular follow-up.

Study methods

We retrospectively analyzed the clinical data including age, sex, smoking status, and Eastern Cooperative Oncology Group performance status (ECOG PS); Veterans Administration Lung Study Group (VALSG) stage; metastasis organs; chemotherapy regimens; number of treatment cycles; best response; disease progression time; last follow-up time; and death time. All study patients who were classified by the VALSG stage were restaged according to the Union for International Cancer Control 7th TNM staging. Patients were followed-up until June 6, 2014 or death, whichever occurred first.

Evaluation standard

Tumor response and disease progression were assessed according to RECIST version 1.1. All adverse events (AEs) were recorded and classified by grade according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. We evaluated the overall survival (OS), progression-free survival (PFS) from the initiation of third-line chemotherapy, and the objective response rate (ORR). Patients who relapsed more than 90 days after first-line chemotherapy were classified as sensitive relapse, while those who relapsed within 90 days were classified as refractory/resistance relapse.

Statistical analysis

The data were statistically analyzed using SPSS 22.0. OS and PFS were modeled using Kaplan-Meier estimates. The Cox model was used to test the significance of selected variables in a model in which all of these select variables were controlled. Values of $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

A total of 387 patients with SCLC were treated with cytotoxic drugs at our institution. Of them, 82 (21.2%) received third-line chemotherapy. The median age at diagnosis was 55 years (range, 31–75 years); 62 (75.6%) were men and 20 (24.4%) were women. Of these patients, 44 (53.7%) had limited-stage disease (LS-SCLC) and 38 (46.3%) had extensive-stage disease (ES-SCLC). During third-line treatment, 55 (67.1%) patients had an ECOG PS of 0–1. Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Characteristic	No. of patients	%
Age (years)		
≥ 65	10	12.2
< 65	72	87.8
Sex		
Male	62	75.6
Female	20	24.4
ECOG PS at third-line treatment		
0–1	55	67.1
2–3	27	32.9
Smoking history		
Yes	45	54.9
No	37	45.1
VALSG stage		
LS-SCLC	44	53.7
ES-SCLC	38	46.3
TNM stage		
IIA	3	3.7
IIB	6	7.3
IIIA	28	34.1
IIIB	7	8.5
IV	38	46.3
Liver metastasis		
No	71	86.6
Yes	11	13.4
Brain metastasis		
No	70	85.4
Yes	12	14.6
Bone metastasis		
No	69	84.1
Yes	13	15.9
Adrenal gland metastasis		
No	77	93.9
Yes	5	6.1
Pleural effusion		
No	61	74.4
Yes	21	25.6
Classification of relapse after first-line treatment		
Sensitive	31	37.8
Refractory / resistant	51	62.2

Treatment and curative effect

Treatment regimens and curative effects are shown in Table 2. A median of 6 first-line chemotherapy cycles was administered (range, 1–6), and the ORR was 70.7%. A median of 2 second-line chemotherapy cycles was administered (range, 1–6), and the ORR was 29.5%. In the

Table 2 Chemotherapy regimen efficacy

Item	First-line		Second-line		Third-line	
	No. of patients	%	No. of patients	%	No. of patients	%
Chemotherapy regimens						
Etoposide / platinum	78	95	8	9.7	12	14.6
Irinotecan / platinum	2	2.5	34	14.5	26	31.8
Amrubicin / platinum	2	2.5	0	0	0	0
Topotecan	0	0	11	13.4	9	11.0
Ifosfamide / etoposide / platinum	0	0	14	17.1	8	9.7
Others*	0	0	15	18.3	27	32.9
Median cycles (range)	6 (1–6)		2 (1–6)		2 (1–6)	
Best Response						
CR	16	19.5	1	1.1	0	0
PR	42	51.2	25	28.4	9	10.2
SD	14	17.1	18	20.5	32	36.4
PD	10	12.2	38	43.2	47	53.4
ORR	70.7%		29.5%		15.9%	

* Other regimens included paclitaxel, docetaxel, emcitabine, and vinorelbine

third-line setting, 18 (22%) patients were re-challenged with a chemotherapy regimen similar to that received in the first or second line (11 received etoposide/platinum, 2 received irinotecan/platinum, 5 received other regimens). A median of 2 third-line chemotherapy cycles was administered (range, 1–6 cycles), and the ORR was 15.9%.

PFS of Third-Line Chemotherapy (PFS-3) and Prognostic Factor Analysis

The median PFS of first-, second-, and third-line chemotherapy was 7.4, 3.5, and 3.0 months, respectively. Patients with an ECOG PS of 0–1 on third-line chemotherapy ($P = 0.005$), for whom the best response was complete response (CR) or partial response (PR) in the second- ($P = 0.002$) and third-line ($P < 0.001$) chemotherapy, and with a PFS after second-line chemotherapy (PFS-2) for > 3 months ($P = 0.026$), had a significantly longer PFS-3 duration (Table 3). On multivariate analysis, only ECOG PS ($P = 0.008$) and response to third-line chemotherapy ($P = 0.046$) were independent prognostic factors for third-line chemotherapy. The patients with an ECOG PS of 0–1 and the best response of CR or PR had a better PFS-3 (Table 4).

OS of third-Line chemotherapy and prognostic factor analysis

The median OS of all patients was 17.4 months, while that after third-line chemotherapy (OS-3) was 5.6 months. Univariate analysis identified ECOG PS after third-line chemotherapy ($P < 0.001$), response to third-line chemotherapy ($P = 0.033$), and PFS after first-line chemotherapy (PFS-1) ($P = 0.044$) and PFS-2 ($P = 0.007$) as predictive factors of OS-3. On multivariate analysis, however, only ECOG PS ($P = 0.007$) and PFS-2 retained their statistical significance (Table 5). The median OS-3 of 55 patients with an ECOG PS of 0–1 and 27 patients with an ECOG of 2–3 were 7.8 months [95% confidence interval (CI), 5.0–13.0) and 3.2 months (95% CI, 1.9–5.3), respectively (Fig. 1a). The median OS-3 for patients ($n = 44$) with a PFS-2 for >3 months was 6.7 months (95% CI, 4.5–8.8) and better than 4.5 months (95% CI, 2.6–8.1) for patients ($n = 38$) with a PFS-2 for ≤ 3 months (Fig. 1b).

Toxicity of third-line chemotherapy

All patients can assess toxicity, 73 (89.0%) patients experienced at least one AE during third-line chemotherapy. The most common AEs were fatigue in 72 (87.8%), nausea in 70 (85.4%), neutropenia in 65 (79.3%), vomiting in 59 (72.0%), anorexia in 46 (56.1%), thrombocytopenia in 19 (23.2%), and diarrhea in 10 (12.2%). Grade 3 or 4 AEs were observed in 16 (19.5%) patients (13 with neutropenia, 3 with thrombocytopenia). Two patients had to discontinue treatment because of drug-related serious AEs (neutropenia). No fatal AEs occurred.

Subsequent lines of chemotherapy

Of all patients, 16 (19.5%) went on to receive fourth-line chemotherapy. Only 7 (8.5%) received fifth-line chemotherapy, while none received sixth-line therapy. The ORR and median PFS of those who went on to receive subsequent lines of therapy were 12.5% and 2.9 months, respectively.

Discussion

Because there is no clear driver gene or targeted drug for SCLC, the identification of an effective chemotherapy regimen is very important. Although SCLC is sensitive to chemotherapy and has a high response rate, recurrence or progression occurs in 80% of patients with LS-SCLC and

Table 3 Univariate analysis of progression-free survival (PFS) and overall survival (OS) from the initiation of third-line chemotherapy for 82 patients with small cell lung cancer

Variable	OS-3	95% CI	X^2	*P*	PFS-3	95% CI	X^2	*P*
Sex								
Male	6.85	5.40–8.30	0.007	0.934	3.73	2.89–4.58	1.452	0.228
Female	8.09	5.52–10.65			3.52	2.30–4.73		
Age (years)								
< 65	6.99	5.82–8.15	0.235	0.628	3.70	2.98–4.42	0.160	0.689
≥ 65	8.36	1.49–15.23			3.51	0.81–6.22		
ECOG PS								
0–1	9.10	7.52–10.68	0.209	< 0.0001	4.48	3.62–5.33	7.783	0.005
2–3	3.19	2.41–3.96			2.05	1.08–3.02		
Smoking history								
Yes	6.58	5.29–7.87	0.512	0.474	3.88	2.98–4.78	1.289	0.256
No	7.85	5.53–10.17			3.43	2.32–4.55		
VALSG Stage								
LS-SCLC	7.12	5.25–8.98	0.001	0.977	3.52	2.83–4.22	0.128	0.720
ES-SCLC	7.19	5.52–8.87			3.86	2.56–5.15		
TNM stage								
IIA	10.22	4.23–16.21			5.47	3.21–7.73		
IIIB	10.06	16.97–7.08			5.24	4.33–14.82		
IIIA	7.19	5.52–8.87	0.358	0.209	3.86	2.56–5.15	0.690	0.406
IIIB	6.34	3.11–9.57			3.60	1.71–5.49		
IV	6.20	3.88–8.51			2.84	2.11–3.57		
Liver metastasis								
Yes	7.85	4.72–10.99	0.116	0.734	3.21	0.92–5.49	0.469	0.494
No	7.04	5.67–8.42			3.75	3.01–4.49		
Brain metastasis								
Yes	9.21	4.77–13.65	2.328	0.127	5.10	1.59–8.61	2.966	0.085
No	6.80	5.52–8.08			3.44	2.84–4.04		
Bone metastasis								
Yes	5.29	2.69–7.90	0.752	0.386	2.31	1.42–3.19	2.085	0.149
No	7.50	6.10–8.90			3.94	3.14–4.74		
Adrenal metastasis								
Yes	5.29	4.42–11.01	0.095	0.758	1.77	0.59–2.96	2.220	0.136
No	7.27	5.98–8.57			3.80	3.08–4.53		
Malignant pleural fluid								
Yes	8.36	5.09–11.63	0.510	0.475	3.85	2.52–5.19	0.037	0.848
No	6.74	5.45–8.02			3.62	2.79–4.45		
Response in second-line treatment								
CR + PR	10.66	8.32–13.00	1.772	0.183	5.63	3.99–7.28	9.169	0.002
SD + PD	5.52	4.24–6.81			2.77	2.21–3.34		
Response in third-line treatment								
CR + PR	12.38	7.87–16.88	1.772	0.033	7.10	2.72–11.48	2.468	< 0.001
SD + PD	6.59	5.33–7.84			3.31	2.70–3.92		
PFS after first-line treatment								
≤ 3 months	5.68	4.00–7.36	4.063	0.044	3.70	1.90–5.49	0.272	0.602
> 3 months	7.46	6.00–8.91			3.68	2.91–4.45		
PFS after second-line treatment								
≤ 3 months	5.82	4.48–7.16	4.179	0.007	2.85	2.06–3.64	4.940	0.026
> 3 months	8.15	6.23–10.06			4.30	3.26–5.34		

in almost all patients with ES-SCLC within 1 year after treatment [7–8]. Owing to rapid disease progression, high drug resistance rates, and poor prognosis, only a small number of patients have the opportunity to receive third-line chemotherapy [11]. However, as no unified standard of present third-line chemotherapy for patients with SCLC has been established, its efficacy remains unclear. Therefore, it is of great importance to discuss the curative effect

Table 4 Multivariate analysis of progression-free survival from the initiation of third-line chemotherapy for 82 patients with small cell lung cancer

Variable		HR	95% CI	*P*	Wald
ECOG PS	0–1	3.410	2.641–5.586	0.008	7.134
Response in third-line treatment	CR + PR	0.180	0.033–0.973	0.046	1.967

Table 5 Multivariate analysis of overall survival from the initiation of third-line chemotherapy for 82 patients with small cell lung cancer

Variable		HR	95% CI	*P*	Wald
ECOG PS	0–1	3.149	1.360–7.291	0.007	6.169
PFS-2	> 3 months	2.707	1.228–5.967	0.001	4.101

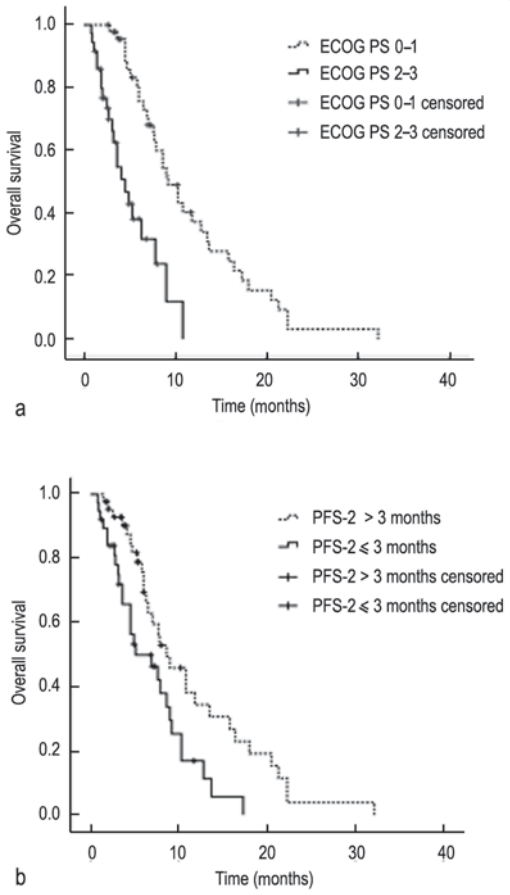

Fig. 1 Kaplan-Meier curves showing overall survival from the initiation of third-line chemotherapy in all patients. (a) Survival curve of patients with an ECOG PS 0–1 or 2–3; (b) Survival curve of patients with a PFS-2 for >3 months and PFS-2 for ≤ 3 months. ECOG PS, Eastern Cooperative Oncology Group performance status; PFS-2, progression-free survival after second-line chemotherapy

of third-line chemotherapy and clearly identify the factors that affect the survival of patients with SCLC.

This study included 82 (21.2%) patients with SCLC who received third-line chemotherapy, similar with previous reports [5–6]. Among them, 18 (22%) patients received the original chemotherapy again as the third-line treatment. Because there was no clear recommendation in the guidelines for the selection of third-line chemotherapy and drug resistance in most patients after first or second-line chemotherapy, clinicians were more likely to select third-generation chemotherapeutic drugs or the topoisomerase I inhibitor irinotecan, which accounted for 32.9% and 31.8% of patients, respectively. Although the effect of the drugs was stronger, no patient achieved CR on third-line chemotherapy and the ORR was only 15.9%. A previous retrospective analysis reported that the ORR of patients who received third-line chemotherapy was 18%–26%. One clinical study of 36 patients with SCLC who received amrubicin on third-line treatment reported that the ORR reached 44.4% [9]. Another study reported that the ORR of SCLC after third-line treatment with lomustine-etoposide-cyclophosphamide was 31.4% [10]. In our study, the ORR was slightly lower than those of the above-mentioned studies, which might be related to the higher proportion of refractory/drug-resistant patients. After first-line chemotherapy, refractory/drug-resistant recurrence occurred in 62.2% of patients. In addition, amrubicin or the combination scheme of three drugs was used more often in previous studies on third-line treatments. However, no patient received amrubicin in this study and only a few patients received the three-drug combination scheme.

To date, only a few studies have discussed the effect of third-line chemotherapy for SCLC. In the single-center retrospective analysis conducted by De Jong *et al*, 35 patients were included and the median OS-3 was 5.0 months [4]. Simos *et al* analyzed the effect of third-line chemotherapy in five centers that included a total of 120 patients with SCLC and found that the median OS-3 was 4.7 months and the median PFS-3 was 2 months [5]. The results of third-line chemotherapy of amrubicin on SCLC showed that the median OS-3 was 5.1 months and the median PFS-3 was 3 months. In the Lebeau B study, the median OS-3 of 35 patients who received lomustine-etoposide-cyclophosphamide was 4.4 months [10]. Our study showed that the median OS of patients with SCLC who received third-line chemotherapy was 5.6 months, while the median PFS was 3.0 months, findings that are similar to the results of the above studies.

This study also analyzed the related factors affecting the prognosis of patients with SCLC after third-line chemotherapy and found that the PFS-3 of patients with SCLC was related to the ECOG PS score after third-line chemotherapy, curative effects of second-line chemotherapy, curative effects of third-line chemotherapy, and PFS-2 classification. In addition, OS-3 was significantly related to the ECOG PS score after third-line chemotherapy, curative effects of third-line chemotherapy, PFS-1 classification, and PFS-2 classification. However, multivariate analysis showed that ECOG-PS was an independent prognostic factor for both PFS-3 and OS-3. In addition, the study found that the curative effect of third-line chemotherapy was an independent prognostic factor for PFS-3. Patients who achieved CR or PR after third-line chemotherapy could have a better PFS-3. PFS-2 was an independent prognostic factor for OS-3. Patients with a PFS-3 for > 3 months had a longer OS-3 on third-line chemotherapy. This finding was consistent with the results reported in the literature [4–5, 12–13]. The result of the study suggests that, during third-line chemotherapy, except for the full consideration of patients' physical state, the curative effects of second-line chemotherapy should also be considered, and that third-line chemotherapy should be actively offered to patients who benefit from second-line chemotherapy.

In this study, of the AEs of the 82 patients who received third-line chemotherapy, fatigue had the highest incidence (87.8%), followed by gastrointestinal reaction and bone marrow suppression, which were mostly grades 1 or 2. The incidence of grade 3 or 4 AEs was 19.5%, and all were bone marrow suppression (mostly neutropenia, some thrombocytopenia). This result also suggests that patients with SCLC have good tolerance to third-line chemotherapy. However, because it is multi-line treatment, the marrow function of patients should be monitored and AEs should be timely treated.

In summary, the results of this study suggests that in clinical work, clinicians can consider whether a patient with SCLC needs third-line chemotherapy according to their clinical features such as ECOG PS and the curative effect of previous treatments. Patients with an ECOG PS of 0–1 and PFS-2 for > 3 months can benefit from third-line chemotherapy. However, because few patients were willing to receive third-line chemotherapy, the sample size of this study was relatively small. In addition, because this study is a retrospective analysis, the results need to be further confirmed by prospective studies. In addition, regarding which plan and administration method is the best, no consensus has been reached here. Future prospective studies are needed to provide more evidence-based data regarding this issue.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-014-0049-5
Cite this article as: Liu JJ, Zhang S, Ma LX, *et al*. Efficacy analysis and multi-factor retrospective study of third-line chemotherapy in 82 Chinese patients with small cell lung cancer. Oncol Transl Med, 2015, 1: 26–31.