JBUON 2021; 26(2): 306-312
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of EP chemotherapy followed by IP chemotherapy combined with radiotherapy in the treatment of extensive-stage small-cell lung cancer

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Summary

Purpose: *To explore the efficacy and safety of etoposide + cisplatin (EP) and irinotecan + cisplatin (IP) sequential chemotherapy combined with radiotherapy in the treatment of extensive-stage small-cell lung cancer (SCLC).*

Methods: *A total of 108 patients with extensive-stage SCLC were divided into the EP+IP group (n=54, sequential IP chemotherapy), and the EP group (n=54, EP chemotherapy). The changes in the level of serum tumor markers and the number of circulating tumor cells (CTCs) in the peripheral blood were compared between the two groups of patients before and after treatment. The patients were followed up to record the survival status and tumor progression.*

Results: *The overall effective rate for bone metastases in the EP+IP group was significantly higher than that in the EP group. The EP+IP group displayed significantly lower levels of serum VEGF, Ki-67 and peripheral blood CTCs than the EP group. In addition, the follow-up results manifested that the median overall survival (OS) in the EP+IP group and the EP group were 16.2 months and 12.7 months, respectively, and the median progression-free survival (PFS) was 8.4 months and 5.9 months, respectively. The 2-year OS was 13.0% and 7.4%, respectively. Furthermore, the log-rank test illustrated that the OS and PFS in the EP+IP group were significantly superior to those in the EP group.*

Conclusions: *EP and IP sequential chemotherapy combined with radiotherapy is more effective than EP chemotherapy combined with radiotherapy in the treatment of extensive-stage SCLC. The former can markedly reduce the levels of serum tumor markers and peripheral blood CTCs, increase the long-term survival of patients and reduce the occurrence of blood-related adverse reactions.*

Key words: *etoposide, cisplatin, irinotecan, small-cell lung cancer, extensive-stage, efficacy*

Introduction

Small-cell lung cancer (SCLC) takes up 20-25% of all lung cancers, and 60-70% of new SCLC cases are in extensive stage. SCLC has a high malignant behavior, and is prone to early and extensive metastasis. Most SCLC patients suffer from hematogeneous metastasis, and the lesions are confined to thoracic cavity in only one third of them [1,2]. SCLC is highly sensitive to chemotherapy and radiotherapy, with a high remission rate after initial treatment, but SCLC patients are prone to secondary drug resistance and eventually die of tumor recurrence [3]. Surgery, radiotherapy and chemotherapy are the currently main methods for treating SCLC, dominated by concurrent radiotherapy based on chemotherapy [4,5].

Since 1980s, etoposide+cisplatin (EP) chemotherapy has gradually replaced cyclophosphamide+adriamycin+vincristine (CAV) and ultimately

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Received: 05/10/2020; Accepted: 17/11/2020

became the first-line standard treatment for SCLC owing to its survival advantage. The objective response rate (ORR) of EP chemotherapy combined with three-dimensional conformal radiotherapy is 60-70%, the median OS is 9-11 months, and the 2-year survival is <5% [6,7]. SCLC progression occurs in most patients within 6 months after chemotherapy. Hence, the way to improve the treatment efficiency of SCLC, prolong the survival of patients and reduce drug resistance has become a hot spot in clinical research. In addition, irinotecan + cisplatin (IP) chemotherapy is another major chemotherapy regimen for extensive-stage SCLC. It has been confirmed in studies that IP is more effective than EP [8,9].

The aim of this study was to explore the efficacy and safety of EP and IP sequential chemotherapy combined with radiotherapy in the treatment of extensive-stage SCLC.

Methods

General data

A total of 108 patients who were definitely newly diagnosed with extensive-stage SCLC by pathology were collected. Inclusion criteria were as follows: patients aged >18 years, those who met the diagnostic criteria of SCLC formulated by the International Association for Lung Cancer Research and were definitely diagnosed with extensive-stage SCLC by pathological examination or cytology, those with at least one measurable lesion confirmed by computed tomography (CT) examination, those with Eastern Cooperative Oncology Group score of 0-2 points, those receiving no other surgery, chemotherapy, radiotherapy or immunotherapy before, and those with an estimated survival of over 3 months. Exclusion criteria were as follows: patients complicated with severe dysfunction of the heart, liver, kidney or other important organs, those with uncontrollable infectious or autoimmune diseases, those with abnormal hematopoietic function of bone marrow, or those intending to undergo other immunotherapies. The patients were divided into EP and IP sequential chemotherapy combined with radiotherapy group (EP+IP group, n=54) and EP chemotherapy combined with radiotherapy group (EP group, n=54). There were 83 males and 25 females with an average age of 55.26±9.65 years. The baseline data of the two groups of patients before treatment are shown in Table 1, displaying no statistically significant differences (p>0.05). This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center and complied with the Declaration of Helsinki. All the patients enrolled were informed of the study and signed the informed consent.

Treatment regimens

All the patients received first-line EP chemotherapy combined with 6MV-X-ray three-dimensional conformal radiotherapy, and the latter was performed simultaneously with the first cycle of chemotherapy. After radiotherapy, the EP group continuously underwent 4 cycles of EP chemotherapy, while the EP+IP group further received 4 cycles of IP chemotherapy.

EP group: Patients were intravenously infused with 100-125 mg/m^2 etoposide + 25 mg/m^2 cisplatin on days 1-3.

EP+IP group: Patients underwent intravenous infusion of 65 mg/m^2 irinotecan + 30 mg/m^2 cisplatin on days 1 and 8.

Three-dimensional conformal radiotherapy: KMX-8000 64-slice spiral CT (Philips) was used for continuous scanning, with a thickness of 5 mm, from the cricoid cartilage to adrenals. Following scanning, the images were transmitted to the three-dimensional treatment planning system, and two doctors in our hospital sketched the important organs and target areas, and then made a reasonable radiotherapy plan according to the specific

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*EP+IP group (n=54)* *n (%)*	*EP group (n=54)* *n (%)*	*p value*
Age, years	54.36±9.55	55.94±9.73	0.396
Gender (Male/ Female)	39/15	44/10	0.362
Smoking history			0.272
Yes	37 (68.5)	43 (79.6)	
No	17 (31.5)	11 (20.4)	
TNM stage			0.432
≤III	35 (64.8)	30 (55.6)	
IV	19 (35.2)	24 (44.4)	
ECOG score			0.301
0	14 (25.9)	18 (33.3)	
1	30 (55.6)	22 (40.7)	
2	10 (18.5)	14 (25.9)	

EP: etoposide + cisplatin; IP: irinotecan + cisplatin; TNM: tumor, lymph node, metastasis; ECOG: Eastern Cooperative Oncology Group.

conditions of patients and determined the actual radiation dose. It was worth noting that the radiation dose of various tissues and organs, including esophagus and spinal cord, should be strictly controlled during radiotherapy. Finally, a PRECISE linear accelerator was utilized to carry out 6MV-X-ray irradiation, with the irradiation dose of 66-70 Gy (2.0-2.5 Gy/ time, 6 times/w).

Observational indexes

According to the response evaluation criteria in solid tumors (RECIST), the treatment efficacy in the two groups of patients was evaluated, and was classified into complete response (CR, all target lesions disappeared for at least 4 weeks), partial response (PR, the sum of the maximum diameters of baseline lesions was decreased by ≤30% for at least 4 weeks), stable disease (SD, the sum of the maximum diameters of baseline lesions that decreased but did not reach PR standard or increased but did not reach PD standard) and progressive disease (PD, the sum of the maximum diameters of baseline lesions was increased by ≥20% or new lesions appeared). ORR= (CR cases + PR cases)/total cases × 100%.

On the 1st day before chemotherapy and at the end of chemotherapy, 5 mL of fasting peripheral venous blood was taken from the patients in the morning, let stand at room temperature for 30 min and centrifuged at 3000 r/min for 10 min. Next, serum tumor markers including vascular endothelial growth factor (VEGF) and Ki-67 were detected by enzyme-linked immunosorbent assay (ELISA) using the kit provided by Wuhan BOSTER Biological Technology Co., Ltd. (Wuhan, China) in strict accordance with the instructions. Before and after chemotherapy, 7.5 mL of blood samples were collected, and the peripheral blood circulating tumor cells (CTCs) were counted using CellSearch method. Besides, adverse reactions were evaluated and recorded during treatment, which were classified into leukopenia, hemoglobin reduction, thrombocytopenia, nausea and vomiting, delayed diarrhea and liver function damage *as per* the WHO classification standards for acute and subacute side effects of anticancer drugs.

The survival status of patients was recorded during followed up through blood routine tests, serum tumor markers, liver and kidney functions and chest CT, and bone scan or PET-CT. The survival of patients was recorded, and the patients who were lost to the follow-up were regarded as censoring from the date of their loss. Overall survival (OS) is the time from enrollment to death (for any reason), and the progression-free survival (PFS) refers to the time from the first day of treatment to disease progression or recurrence and metastasis. The follow-up ended in May 2020.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and intergroup comparison was conducted via t-test. Clinical data were compared by x^2 test or Fisher's exact test. Later, intragroup matching data of serological indicators were detected via t-test, and

Table 2. Comparison of tumor response of patients in the two studied groups

Parameters	*EP+IP group (n=54)* *n (%)*	*EP group (n=54)* *n (%)*	*p value*
CR	0 (0)	0 (0)	
PR	37 (68.5)	16 (29.6)	
SD	13 (24.1)	27 (50.0)	
PD	4 (7.4)	11 (20.4)	
ORR (CR + PR)	37 (68.5)	16 (29.6)	0.001

EP: etoposide+cisplatin; IP: irinotecan+cisplatin; CR: complete response; PR: partial response; SD: stable disease; PD: Progressive disease; ORR: overall response rate.

Table 3. Comparison of pretreatment and posttreatment serum tumor markers and peripheral blood circulating tumor cells of patients in the two studied groups

	EP+IP group (n=54)	*EP group (n=54)*	*p value*
VEGF (pg/mL)			
Pretreatment	566.58±130.92	560.23±136.86	0.606
Posttreatment	409.39±81.59	442.62±90.46	0.048
Ki-67 (pg/mL)			
Pretreatment	293.31±66.85	295.54±68.46	0.664
Posttreatment	116.75±39.47	156.52±38.74	0.001
Peripheral blood CTCs			
Pretreatment	8.44±0.73	8.51±0.80	0.536
Posttreatment	3.75±0.37	4.94±0.42	0.001

EP: etoposide+cisplatin; IP: irinotecan+cisplatin; VEGF: vascular endothelial growth factor; CTCs: circulating tumor cells.

intergroup group comparison was carried out using two-way analysis of variance (ANOVA). Finally, Kaplan-Meier curve and log-rank test were used for survival analysis, and $p<0.05$ indicated statistically significant difference.

Results

Comparison of efficacy against bone metastases between the two groups of patients

All the patients were evaluated after treatment. In the EP+IP group, there were 0 cases of CR, 37 cases (68.5%) of PR, 13 cases (24.1%) of SD and 4 cases (7.4%) of PD, with an ORR of 68.5% (37/54). In the EP group, there were 0 cases of CR, 16 cases (29.6%) of PR, 27 cases (50.0%) of SD and 11 cases of (20.4%) PD, with an ORR of 29.6% (16/54). The ORR in the EP+IP group was significantly higher than in the EP group ($p<0.001$) (Table 2).

Comparisons of serum tumor markers and peripheral blood CTCs levels between the two groups of patients before and after treatment

There were no statistically significant differences in the levels of serum VEGF, Ki-67 and peripheral blood CTCs between the two groups of patients before treatment ($p>0.05$). Following treatment, the levels of serum VEGF and Ki-67 in both groups were significantly lower than those before treatment ($p<0.05$), and the peripheral blood CTC count in both groups was decreased from 8.44±0.73/7.5 mL and 8.51±0.80/7.5 mL to 3.75±0.37/7.5 mL and 4.94±0.42/7.5 mL, respectively. In addition, following treatment, the EP+IP group displayed significantly lower levels of serum VEGF, Ki-67 and peripheral blood CTCs than the EP group ($p=0.048$, $p<0.001$, $p<0.001$) (Table 3).

Comparisons of adverse reactions

During treatment, the main adverse reactions in the two groups included nausea and vomiting, leukopenia, anemia, thrombocytopenia, fever, fatigue, delayed diarrhea and liver function damage. In the EP+IP group, 33 cases (61.1%) had leukopenia and 29 cases (53.7%) suffered from thrombocytopenia, which were significantly lower than those in the EP group (45 cases;83.3% and 18 cases;33.3%) ($p=0.017$, $p=0.042$). Moreover, the number of patients with delayed diarrhea in the EP+IP group (n=22;40.8%)) was significantly larger than in the EP group (n=5;9.3%) ($p<0.001$). No statistically significant differences were detected in other treatment-related adverse reactions between the two groups of patients ($p>0.05$) (Table 4).

Follow-up results of patient survival

All the 108 patients were followed up for 3-24 months until May 2020. The median OS was 16.2 months in the EP+IP group and 12.7 months in the sEP group. The one-year OS rate was 59.3% (32/54) and 38.9% (21/54), respectively, and the two-year OS was 13.0% (7/54) and 7.4% (4/54), respectively in the two groups. Besides, the median PFS in the EP+IP group and the EP group were 8.4 and 5.9 months, respectively. The one-year PFS rate was 31.5% (17/54) and 16.7% (9/54), respectively, and the two-year PFS rate was 0 in the two groups. Kaplan-Meier method was performed (Figure 1) and log-rank test showed that the OS and PFS in the EP+IP group were significantly superior to those in EP group ($p=0.040$, $p=0.039$).

Discussion

At present, chemotherapy is the main treatment for extensive-stage SCLC, and the sensitivity of first-line chemotherapy can reach 60-70%. Through chemotherapy, the survival of most patients can be prolonged, but the long-term survival can rarely be achieved [10]. Great progress has been made in the multidisciplinary comprehensive treatment and individualized treatment of

Table 4. Comparison of adverse reactions of patients in the two studied groups

Parameters	*EP+IP group (n=54)* *n (%)*	*EP group (n=54)* *n (%)*	*p value*
Leukopenia	33 (61.1)	45 (83.3)	0.017
Anemia	14 (25.9)	11 (20.4)	0.549
Thrombocytopenia	29 (53.7)	18 (33.3)	0.042
Nausea and vomiting	37 (68.5)	42 (77.8)	0.385
Delayed diarrhea	22 (40.8)	5 (9.3)	0.001
Fatigue	33 (61.1)	39 (72.2)	0.308
Fever	15 (27.8)	19 (35.2)	0.535
Liver function damage	8 (14.8)	10 (18.5)	0.697

EP: etoposide + cisplatin; IP: irinotecan + cisplatin

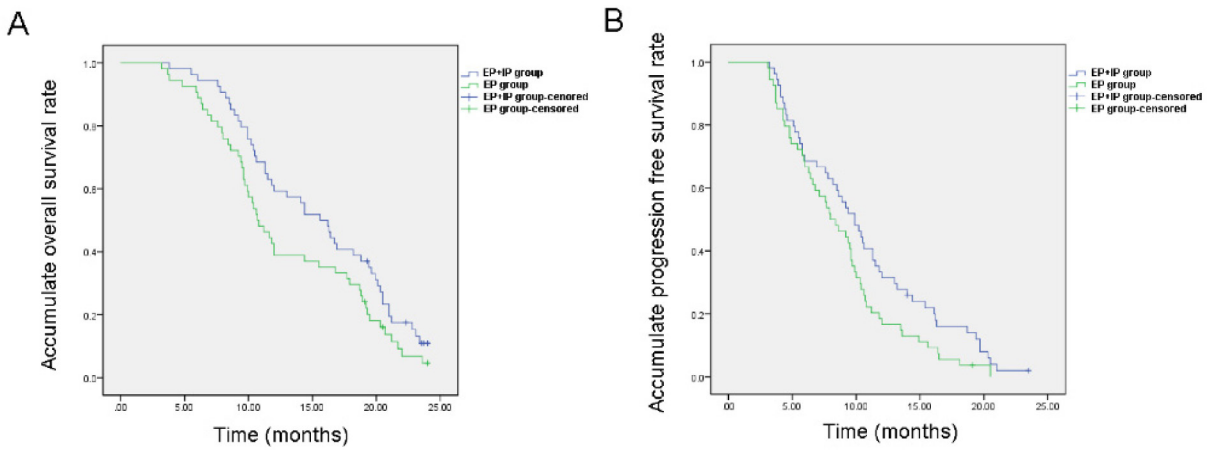

Figure 1. Kaplan-Meier survival curves of patients in the EP+IP group and the EP group. **A:** The overall survival rate of patients in the EP+IP group was significantly higher than that of the EP group (p=0.040). **B:** The progression-free survival rate of patients in the EP+IP group was significantly higher than that of the EP group (p=0.039).

SCLC. The National Comprehensive Cancer Network (NCCN) guidelines suggest that concurrent radiotherapy and chemotherapy is recommended for the treatment of limited-stage SCLC, that is, synchronous chest radiotherapy with 2 cycles before conventional chemotherapy [7]. The benefits of three-dimensional conformal radiotherapy for extensive-stage SCLC have been affirmed and recognized. Radiotherapy is able to eliminate some residual cancer cells resistant to chemotherapy in primary lesions to the greatest extent, and further reduce the risk of recurrence of chest lesions, which is of great significance for prolonging the survival of patients [11].

The clinical study of IP chemotherapy in the treatment of SCLC has started since 1990s. The JCOG9511 study of Japanese Clinical Oncology Organization confirmed for the first time that IP chemotherapy is superior to the classical EP chemotherapy in the first-line treatment of SCLC, and can remarkably prolong the survival of patients. However, the incidence rate of life-threatening bone marrow suppression of IP chemotherapy is lower than that of EP chemotherapy, which indicates the direction for the treatment of SCLC [12]. In 2006, North America, Australia and SWOG0124 studies failed to obtain the desirable results. Researchers believed that it may be because of the different dosages and administration intervals of IP chemotherapy drugs, differences in pharmacogenomics between North American and Japanese populations, and the molecular differences of lung cancer between Asian and North American populations [13], indicating that IP chemotherapy is not worse than EP chemotherapy in the first-line treatment of SCLC. Later, in the phase III clinical study, Schmittel et al [14] from Germany considered that IP and EP chemotherapy have the same efficacy in the first-line treatment of SCLC, which built up the status of IP chemotherapy in the first-line chemotherapy of SCLC. Jagasia et al [15] found that irinotecan has strong anti-tumor activity, no cross-resistance with etoposide and platinum, and a synergistic effect in combined application with cisplatin. As such, in 2009, NCCN recommended IP chemotherapy as the first-line standard treatment regimen for SCLC. In 2010, Zatloukal et al [16] conducted a multi-center, open, randomized and large-sample Phase III clinical trial in 59 centers in 12 European countries. The results revealed that in the western population, the efficacy of IP in the first-line treatment of extensive-stage SCLC is not worse than that of EP. Furthermore, Jiang et al [17] carried out a meta-analysis of 1476 patients in 6 trials of treating SCLC with IP and compared with EP chemotherapy in the past 10 years, and found that IP improves the ORR. Besides, compared with EP, IP exhibits survival advantages and produces tolerable adverse reactions, so it was concluded that IP can replace EP in the first-line treatment of SCLC.

In this study, patients with extensive-stage SCLC were treated with EP followed by IP combined with radiotherapy. It was discovered that the ORR of patients after treatment was 68.5% in the EP+IP, which was significantly higher than that of patients in the EP group (29.6%, p<0.001). Moreover, the incidence rates of leukopenia and thrombocytopenia declined. However, it was worth noting that the incidence of delayed diarrhea in the EP+IP group was higher than that in the EP group, which may be related to the application of cisplatin, but it was of grade 1-2 in most patients. Additionally, oral loperamide and rehydration treatment could

alleviate the disease, and no diarrhea-related death occurred, indicating that in practical application, attention should be paid to gastrointestinal reactions such as delayed diarrhea for good prevention and treatment.

Ki-67 is a reliable marker of cell proliferation, which is associated with the occurrence, development, invasion, metastasis and prognosis of many tumors. Ki-67 is expressed in cells in G/S and M phases, which can accurately and comprehensively evaluate the cell proliferation activity [18]. VEGFs are able to stimulate the migration and proliferation of vascular endothelial cells, speed up the formation of tumor neovascularization, and participate in tumor invasion and metastasis [19,20]. The detection of CTCs is of vital clinical significance in the early diagnosis of SCLC, stabilization of chemotherapy efficacy, monitoring of recurrence and metastasis, and prognosis judgment [21]. A study manifested that the larger the number of CTCs, the larger the number of metastatic foci, the higher the pathological stages, and the lower the sensitivity to chemotherapy [22]. The results of this study illustrated that EP followed by IP exerted a more remarkable effect on serum tumor markers and peripheral blood CTCs, achieving a more favorable anti-tumor effect.

The current study was a single-center retrospective study with some limitations such as small sample size, short follow-up period, and not comprehensive follow-up content. In the future, there is a necessity to design more rigorous and scientific prospective multi-center randomized controlled studies with a large sample size to confirm the conclusions of the present study.

Conclusions

Compared with EP chemotherapy combined with radiotherapy, EP and IP sequential chemotherapy combined with radiotherapy is more effective in the treatment of extensive-stage SCLC, which can notably reduce the levels of serum tumor markers and peripheral blood CTC, improve the long-term survival rate of patients and reduce the occurrence of blood-related adverse reactions.

Conflict of interests

The authors declare no conflict of interests.

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