EFFICACY AND ADVERSE REACTIONS OF ETOPOSIDE COMBINED WITH CISPLATIN AND IRINOTECAN COMBINED WITH CISPLATIN IN STABLE PATIENTS WITH SMALL CELL LUNG CANCER

Tingting Shao, Wanzhen Zheng, Jiyuan Ding, Liujie Gao*
Department of Traditional Chinese Comprehensive Medical Oncology, Hangzhou Cancer Hospital, Hangzhou, PR China

ABSTRACT

Objective: *To explore the efficacy and adverse reactions when etoposide is combined with cisplatin and irinotecan is combined with cisplatin in treating stable patients with small cell lung cancer.*

Methods: *A total of 78 patients with small cell lung cancer who were admitted to our hospital from October 2016 to December 2017 were analysed retrospectively. According to their different treatment methods, the patients were divided into a group that received etoposide combined with cisplatin (EP) and a group that received irinotecan combined with cisplatin (IP). The EP group comprised 41 patients, and 37 patients were in the IP group. The short-term efficacy and PFS as well as incidence, reduction and delay of side effects were analysed.*

Results: *The objective remission rate was 82.93% in the EP group and 83.78% in the IP group, meaning no significant difference in remission was evident between the two groups (P>0.05). The median PFS was 5.6 months in the EP group and 6.1 months in the IP group, implying no significant difference between the two groups (P>0.05). The leucopoenia rate of grade III-IV in the EP group was 36.59%, and that of grade III-IV in the IP group was 10.81%, showing a significant difference between the two groups (P<0.05). No significant difference between the two groups was noted in terms of degree I-II leucopoenia, degree I-II anaemia, degree III-IV anaemia, degree I-II thrombocytopenia or degree III-IV thrombocytopenia (P>0.05). The percentages of reduction and delay of side effects in the EP group were 19.51% and 21.95%, respectively, while in the IP group the figures were 2.70% and 5.41%, respectively (P<0.05).*

Conclusion: *Etoposide combined with cisplatin and irinotecan combined with cisplatin can be used as the first-line chemotherapy for small cell lung cancer patients. However, the occurrence of side effects when irinotecan is combined with cisplatin in the treatment of small cell lung cancer is slightly lower, and the reduction and delay caused by the side effects are less.*

Keywords: *Etoposide, cisplatin, irinotecan, small cell lung cancer.*

DOI: 10.19193/0393-6384_2021_2_163

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Introduction

Small cell lung cancer can be divided into a limited stage and an extensive stage according to the scope of focus. About 70% of patients are in the extensive stage upon disease diagnosis. After treatment, the median survival time of patients is 9-13 months, and the 2-year survival rate is only 5%[1-2]. Compared with other types of lung cancer, radiotherapy and chemotherapy are more effective in treating small lung cancer. However, when small cell lung cancer patients are diagnosed, cancer cells may have already spread widely, making a cure problematic[3]. Most small cell lung cancer is closely related to smoking. In addition, environmental and genetic factors can also serve as inducing factors for small cell lung cancer[4]. To some extent, while the clinical symptoms of this malady resemble those of non-small cell lung cancer, its tumour growth rate is rapid, its degree of malignancy is high and time to extensive metastasis is early; moreover, endocrine syndrome may appear[5].

Although small cell lung cancer is highly sensitive to radiotherapy and chemotherapy, most patients

will eventually experience diffusion and metastasis. Therefore, combined radiotherapy and chemotherapy remains the most effective means for treating small cell lung cancer[6]. Although the prognosis of small cell lung cancer is very poor, systemic chemotherapy can significantly prolong survival time and relieve patients' pain.

However, the problem of drug resistance remains; thus, comprehensive treatment is key. Etoposide combined with cisplatin or irinotecan combined with cisplatin are two choices for first-line chemotherapy for small cell lung cancer in a wide range of stages as recommended by NCCN guidelines. Previous studies have confirmed that the progression-free survival for the two schemes is similar, but the total survival in cases where irinotecan has been combined with cisplatin is relatively longer[7-8]. However, no independent data were available for the patients in previous studies, making it unclear whether the two schemes are superior or inferior in comparison to one another.

Therefore, this study examined cases where etoposide was used in combination with cisplatin and, alternatively, irinotecan was combined with cisplatin in treating patients with small cell lung cancer, aiming to explore the efficacy and adverse reactions for the two schemes in such treatment.

Materials and methods

General information

In this study, 78 patients with small cell lung cancer admitted to our hospital from October 2016 to December 2017 were analysed retrospectively.

The criteria for inclusion were:

• Extensive stage of small cell lung cancer was clearly diagnosed by pathology or cytology;

• Measurable lesions existed;

• Expected survival time ≥3 months;

• This would be their initial treatment;

• Informed consent was signed by all patients;

• Ethical review by the hospital was approved by batch.

Patients were divided into an etoposide plus cisplatin (EP) group and an irinotecan plus cisplatin (IP) group. The EP group consisted of 41 patients, 21 males and 20 females, with an average age of (45.96±9.89) years. The IP group comprised 37 patients, 20 males and 17 females, with an average age of (46.01±9.56) years. No significant difference was noted in terms of general information between the two groups (P>0.05).

Method

Patients in the EP group were treated with etoposide (GJZ: h20561145, produced by Sichuan Baojiantang Pharmaceutical Co., Ltd) and cisplatin (GJZ: h24561185, produced by Yunnan Bio-Valley Pharmaceutical Co., Ltd), intravenous drip of etoposide 100mg/m^2 for the first to the third day, intravenous drip of cisplatin 75mg/m^2 for the first day, repeated once every 3 weeks for 12 weeks.

Patients in the IP group were treated with irinotecan (GJZ: h25880573 produced by Qilu Pharmaceutical Co., Ltd) and cisplatin. On the 1st, 8th and 15th day, irinotecan 60mg/m^2 was infused intravenously; on the 1st day, cisplatin (75mg/m^2) was given intravenously once every 3 weeks. Treatment continued for 12 weeks.

Observation index

• According to the evaluation standard of new solid tumour curative effect, the curative effect of the two groups was evaluated.

Complete remission

All target lesions disappeared, lasting for more than 4w.

Partial remission

The maximum diameter of lesions decreased by more than 30%, lasting for more than 4w.

Stability

The total maximum diameter of lesions decreased by less than 30%.

Progress

The total maximum diameter of lesions increased by more than 20%, or new lesions were observed. Objective remission rate = (number of complete remission cases + number of partial remission cases)/total cases × 100%.

• Progression-free survival (PFS) was used to evaluate the long-term efficacy of the two groups, that is, the time from the date of chemotherapy to the discovery of small cell carcinoma progression or death.

• According to the general toxicity standard of the National Cancer Institute of the United States, the side effects of chemotherapy in the two groups were evaluated.

• The reduction and delay were compared for the two groups.

Statistical methods

SPSS 24.0 software was used to analyse the data. The clinical efficacy and side effects for the two groups were expressed in [n%], and χ^2 was used to test. P<0.05 means the difference was significant.

Results

Comparison of the short-term efficacy between the two groups

The objective remission rate was 82.93% in the EP group and 83.78% in the IP group, meaning that no significant difference was seen between the two groups (P>0.05). See Table 1.

Group	n	Complete remission	Partial remission	Stable	Progress	Objective response rate
EP	41	3 (7.32)	31 (75.61)	3 (7.32)	3 (7.32)	34 (82.93)
IP	37	3 (8.11)	28 (75.68)	4 (10.81)	2 (5.41)	31 (83.78)
χ^2						0.010
P						0.919

Table 1: Comparison of short-term efficacy between the two groups [n (%)].

Comparison of long-term effect between two groups

The median PFS was 5.6 months in the EP group and 6.1 months in the IP group. No significant difference was noted between the two groups (P>0.05). See Figure 1.

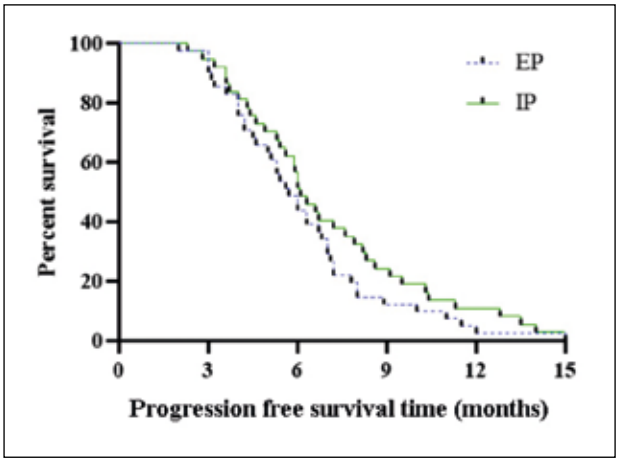

Figure 1: Comparison of long-term effects between the two groups.

Comparison of side effects between the two groups

The leucopoenia rate of grade III-IV in the EP group was 36.59% compared to 10.81% in the IP group. Thus, evidence showed a significant difference between the two groups (P<0.05). No significant difference existed between the two groups in terms of degree I-II leucopoenia, degree I-II anaemia, degree III-IV anaemia, degree I-II thrombocytopenia or degree III-IV thrombocytopenia (P>0.05). See Table 2.

Toxic side effects	EP	IP	χ^2	*P*
I-II degree leukopenia	14 (34.15)	12 (32.43)	0.026	0.873
Degree III-IV degree leukopenia	15 (36.59)	4 (10.81)	7.012	0.008
I~II degree anaemia	8 (19.51)	7 (17.07)	0.004	0.907
III~IV degree anaemia	1 (2.44)	2 (5.41)	0.463	0.496
I~II degree thrombocytopenia	4 (9.76)	2 (5.41)	0.519	0.472
III~IV degree thrombocytopenia	3 (7.32)	1(2.70)	0.851	0.356

Table 2: Comparison of side effects between the two groups [n (%)].

Comparison between two groups of patients due to reduction of toxic and side effects and delay of toxic and side effects

The percentages of reduction and delay of side effects in the EP group were 19.51% and 21.95%, respectively, while the figures for the IP group were 2.70% and 5.41%, respectively (P<0.05). See Table 3.

Group	n	Reduction due to toxic and side effects	Reduction period due to toxic and side effects
EP	41	8 (19.51)	9 (21.95)
IP	37	1 (2.70)	2 (5.41)
χ^2		5.384	4.394
P		0.020	0.035

Table 3: Comparison between the two groups due to the reduction of side effects and the delay of side effects in chemotherapy [n (%)].

Discussion

Small cell lung cancer is characterized by high malignancy and rapid disease progression. Because most patients are at the stage where the cancer is widely dispersed when they are diagnosed, the prognosis for small cell lung cancer is relatively poor, making the treatment of this malady extremely challenging. While chemotherapy has remained the cornerstone of the treatment of small cell lung cancer, in the past 20 years, its developmental level has remained relatively stable. Thus, the current relevant research has not shown significant progress[9-10]. Furthermore, the side effects caused by chemotherapy play an important role in the treatment of small cell

lung cancer, critically affecting the choice of treatment plan. Clinical studies have confirmed that the objective effective rate of etoposide combined with cisplatin or carboplatin is as high as 90%. Although many scholars have tried to discover more efficient and reliable treatment schemes, studies have not achieved significant survival benefits[11-12].

Irinotecan, which was used in clinical practice to treat small cell lung cancer in the 1970s, is now mostly used in treating gastrointestinal cancer[13]. In 2002, irinotecan established a position in the field of first-line treatment of extensive small cell lung cancer. Relevant research shows that when irinotecan is combined with cisplatin in the treatment of small cell lung cancer patients, the median survival time, PFS and 2-year survival rate are significantly higher than the results shown in combining etoposide with cisplatin; moreover, the myelosuppression rate is significantly reduced[14-15]. However, the results of this study showed an objective remission rate for the EP group of 82.93% in comparison to 83.78% for the IP group. No significant difference in remission was therefore noted between the two groups ($P>0.05$). The median PFS was 5.6 months in the EP group and 6.1 months in the IP group, again not significantly different ($P>0.05$). This study did not confirm the results of previous studies in terms of improving the survival of patients but was consistent with the results of two related studies in North America. The findings show that while the short-term and long-term effects in the two groups implies effective treatment of small cell lung cancer, the survival benefit of irinotecan combined with cisplatin is slightly higher.

Relevant domestic studies also reveal that irinotecan combined with cisplatin demonstrates higher efficiency and survival benefit[16]. Munker et al.[17] found that the survival time of patients with small cell lung cancer treated with irinotecan and carboplatin was slightly higher than for those treated with etoposide and carboplatin, findings that are consistent with the results of this study. The leucopoenia rate of grade III-IV in the EP group was 36.59%, and that of grade III-IV in the IP group was 10.81%, showing a significant difference between the two groups ($P<0.05$). The percentages of reduction and delay of side effects in the EP group were 19.51% and 21.95%, respectively, while those in the IP group were 2.70% and 5.41%, respectively ($P<0.05$). This study also found that the risk of myelosuppression for irinotecan combined with cisplatin was low, and the reduction and delay caused by side effects were less than with treatment involving etoposide.

However, the current survival benefit from small cell lung cancer treatment is not considerable, and some genes have been shown to have mutated[18]. Most molecular targets have been identified; however, targeted treatment has not achieved satisfactory results in clinical practice, and no accurate and efficient targeted drug treatment is currently available in the clinical treatment of small cell lung cancer. Thus, a long journey remains in the endeavour to further explore effective treatment in such cases.

In all, etoposide in combination with cisplatin and irinotecan combined with cisplatin have an obvious therapeutic effect, promoting their use as the first-line chemotherapy for small cell lung cancer patients. However, slightly fewer side effects have been observed in combining irinotecan with cisplatin in the treatment of small cell lung cancer than with the use of etoposide, and the reduction and delay caused by side effects are lower.

References

1) Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017; 33: 832-837.
2) Sivignon M, Monnier R, Tehard B, Roze S. Cost-effectiveness of alectinib compared to crizotinib for the treatment of first-line ALK+ advanced non-small-cell lung cancer in France. PLoS One 2020; 15: 226196.
3) Yang XB, Chai XS, Wu WY, Long SQ, Deng H, et al. Gefitinib plus Fuzheng Kang'ai Formula in Patients with Advanced Non-Small Cell Lung Cancer with Epidermal Growth Factor Receptor Mutation: A Randomized Controlled Trial. Chin J Integr Med 2018; 24: 734-740.
4) Martinez-Marti A, Felip E, Matito J, Mereu E, Navarro A, et al. Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). Ann Oncol 2017; 28: 2451-2457.
5) Yao Y, Zhou Y, Yang Z, Huang H, Shen H. Adjuvant Chemotherapy Following Surgical Resection Improves Survival in Patients with Early Stage Small Cell Lung Cancer. Oncol Res 2019; 27: 203-210.
6) Luo LX, Li Y, Niu YZ, Wang YW, Wang QQ, et al. Identification of a potent kinase inhibitor targeting EML4-ALK fusion protein in non-small cell lung cancer. Medchemcomm 2017; 8: 1914-1918.
7) de Man FM, Goey AKL, van Schaik RHN, Mathijssen RHJ, Bins S. Individualization of Irinotecan Treatment: A Review of Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics. Clin Pharmacokinet 2018; 57: 1-26.

8) Chaudhari U, Nemade H, Gaspar JA, Hescheler J, Hengstler JG, et al. MicroRNAs as early toxicity signatures of doxorubicin in human-induced pluripotent stem cell-derived cardiomyocytes. Arch Toxicol 2016; 90: 3087-3098.
9) Matsumura Y, Hishida T, Shimada Y, Ishii G, Aokage K, et al. Impact of extratumoral lymphatic permeation on postoperative survival of non-small-cell lung cancer patients. J Thorac Oncol 2014; 9: 337-344.
10) Fan G, Zhang K, Ding J. Prognostic value of EGFR and KRAS in circulating tumor DNA in patients with advanced non-small cell lung cancer a systematic review and meta-analysis. Oncotarget 2017; 8: 33922-33932.
11) Yang C, Liu Y, Xi WQ, Zhou CF, Jiang JL, et al. Relationship between UGT1A1*6/*28 polymorphisms and severe toxicities in Chinese patients with pancreatic or biliary tract cancer treated with irinotecan-containing regimens. Drug Des Devel Ther 2015; 9: 3677-3683.
12) Igarashi K, Kawaguchi K, Kiyuna T, Murakami T, Miwa S, et al. Temozolomide combined with irinotecan caused regression in an adult pleomorphic rhabdomyosarcoma patient-derived orthotopic xenograft (PDOX) nude-mouse model. Oncotarget 2017; 8: 75874-75880.
13) Huang YF, Zhu DJ, Chen XW, Chen QK, Luo ZT, et al. Curcumin enhances the effects of irinotecan on colorectal cancer cells through the generation of reactive oxygen species and activation of the endoplasmic reticulum stress pathway. Oncotarget 2017; 8: 40264-40275.
14) Edelman MJ, Juan O, Navarro A, Golden G, Saunders A. 88P Feasibility of outpatient dinutuximab (D) and irinotecan (I) for second-line treatment of relapsed or refractory small cell lung cancer (RR SCLC): Part 1 of an open-label, randomized, phase 2/3 study. J Thorac Oncol 2018; 13: 48-49.
15) Ahmad N, Alam MA, Ahmad R, Umar S, Jalees Ahmad F. Improvement of Oral Efficacy of Irinotecan through Biodegradable Polymeric Nanoparticles through Invitro and Invivo Investigations. J Microencapsul 2018; 35: 1-35.
16) Misumi Y, Okamoto H, Sasaki J, Masuda N, Ishii M, et al. Phase I/II study of induction chemotherapy using carboplatin plus irinotecan and sequential thoracic radiotherapy (TRT) for elderly patients with limited-disease small-cell lung cancer (LD-SCLC): TORG 0604. BMC Cancer 2017; 17: 377-385.
17) Munker S, Vogelhuber M, Bornschein J, Stroszczynski C, Evert M, et al. EpiCO (epirubicin, cyclophosphamide and vincristine) as treatment for extrapulmonary high-grade neuroendocrine neoplasms. Z Gastroenterol 2020; 2: 1.
18) Agulló-Ortuño MT, Gómez-Martín Ó, Ponce S, Iglesias L, Ojeda L, et al. Blood Predictive Biomarkers for Patients with Non-small-cell Lung Cancer Associated With Clinical Response to Nivolumab. Clin Lung Cancer 2020; 21: 75-85.

Corresponding Author:
Liujie Gao
Email: kneic7@163.com
(China)