Clinical research on therapeutic effect of combined application of lobaplatin and irinotecan in treating recurrant small cell lung cancer

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Abstract: To observe and analyze the therapeutic effect of combinated application of lobaplatin and irinotecan in treating recurrant small cell lung cancer. The 140 patients who were treated in our hospital for recurrant small cell lung cancer were selected as research objects. All selected patients were subjected to combined application of obaplatin and irinotecan, the total therapeutic effect was observed, and the adverse reactions occurring during treatment were recorded. Through observing the total treatment effective ratio of 140 patients recurrant small cell lung cancer, the number of complete remission cases, number of partial remission cases, number of stable disease cases, and number of disease progression cases were 40(28.57%), 28(20.00%), 30(21.43%), 42(30.00%), respectively, with total effective ratio of 48.57%. The average time to progression (TTP) was (4.5±0.8) months, average overall survival (OS) was (7.6±1.2) months. The toxic and adverse effects mainly included hematological toxicity and gastrointestinal adverse reaction, such as leukocyte reduction, neutrophil reduction, thrombocytopenia, decreased hemoglobin, nausea and vomiting, diarrhea. No toxicity-related death occurred. In treatment of patients with recurrant small cell lung cancer, the combined application of lobaplatin and irinotecan can achieve great results, which is a safe and reliable way of treatment.

Keywords: Lobaplatin, irinotecan, recurrant small cell lung cancer, clinical effects.

INTRODUCTION

With the improvement of living standard, people's living habit and dietary structure have changed a lot. In addition, factors such as environmental pollution, decreased air quality, accelerated working pace lead to increased rate of small cell lung cancer. Small cell lung cancer is normally in high malignant degree, which severely affect patient's the daily life and work. For patients with recurrant small cell lung cancer, the patient's life will be endangered if an effective treatment is not given in time (Wang, *et al*., 2014; Xiao, Chen, 2013; Wroblewska, 2015).

Small cell lung cancer (fig. 1) is featured by high malignant degree, fast growth and early metastasis, and most patients with small cell lung cancer are expected to survive less than 1 year. According to relevant statistics, small cell lung cancer account for 20-25% of toal lung cancers (Abdel, 2016). For small cell lung cancer, surgical resection is not a good treatment approach, instead it is extremely sensitive to radiotherapy. For patients with extensive small-cell lung cancer, radiotherapy is a main approach, first-line chemotherapy regimen is EP scheme based on combined application of etoposide and cisplatin. However, for patients with recurrant small cell lung cancer, especially for patients with disease reappearing within 3-6 months, an effective and low toxicity treatment is the key (Hazra, 2015). In this study, the herapeutic effect of combinated application of lobaplatin and irinotecan in treating recurrant small cell lung cancer was investigated.

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MATERIALS AND METHODS

General data

The 140 patients who had been confirmed with small cell lung cancer in Nanjing Chest Hospital from January 2014 to December 2017 were selected as research objects. The selected patients and relatives signed the informed consent before treatment. The inclusion criteria include: extensive small cell lung cancer (fig. 2), KPS score over 60 points, the survival time is expected to be more than 2 months. Before being selected into this study, all patients had been applied with radiotherapy or chemotherapy (combined application of etoposide and cisplatin, or EP scheme of carboplatin), and the disease were completely relieved or partially relieved. Patients with objective and evaluable lesion who have progression of disease within 3-6 months after radiotherapy or chemotherapy. Patients who have stopped chemotherapy and radiation for more than a month. The exclusion criteria: patients with abnormal liver and kidney function or blood disorder, patients with severe posterior ischic optico-neuropthy, mental disturbance or patients who did not accept this study.

All selected patients have signed informed consent form before this study, showing good attitude to treatment. This study obtained approval from Ethical Committee of hospital. 140 patients, there were 95 males and 45 females, with age ranged from 42 to 76 years old (averaging at 56.9±3.2). The number of brain metastasis cases, the number of osseous metastasis cases and the number of intrapulmonary metastasis cases were 43, 66,

31, respectively. The KPS score varied within 60-90 points, averaging at 70.2±10.5 points.

Method

All selected patients were subjected to combined application of lobaplatin and irinotecan. 5mg/m2 lobaplatin was fully diluted with 500mL of 5% glucose, and then intravenously injected into human body for 2 h. Such treatment method was given for the first day of treatment. On the other hand, 80mg/m2 irinotecan was fully diluted with 250mL of normal saline, and then intravenously injected into human body for 1.5 h. Such treatment method was given for the first and the eighth day of treatment. A complete treatment cycle contained 21 days. CT reexamination was performed prior to treatment and 2 weeks after treatment. Prior to chemotherapy, antiemetic therapy was given with receptor antagonist 5-HT3. Blood routine and biochemical indicators were examined once every 7 days, to check if there was liver and kidney dysfunction or myelosuppression. If needed, G-CSF (granulocyte colony-stimulating factor) treatment should be given in time (Chen, *et al*., 2016).

Observation indexes

The total therapeutic effect was observed and recorded. According to criterion of RECIST 1.0, the objective tumor remission rate can be divided into 4 level: Complete remission, partial remission, stable disease, and disease progression. The effective ratio (i.e., objective remission rate) equals to the sum of complete remission rate and partial remission rate. The control rate equals to the sum of complete remission rate and partial remission rate and stable disease rate. Progression-free survival (PFS) is a time period from the date when treatment is accepted to the date when disease progression occurs. Overall survival is a time period from the date when chemotherapy is given to the date when patient is dead or follow-up is finished. Adverse reaction was evaluated according to the CTCAE (toxicity evaluation criteria) prescribed by The American National Cancer Institute (NCI) (Meng, *et al*., 2015).

STATISTIC ANALYSIS

SPSS21.0 software was used for statistical analysis. The measurement data was expressed in the form of mean ± average ($\bar{x}$ ±s), and intergroup difference was compared by t test. The enumeration data was expressed by natural number (n) and percentage (%) and the intergroup difference was tested by chi-square. The intergroup difference was of statistical significance when $p<0.05$.

RESULTS

Therapeutic effect

As shown in table 1, after combined application of lobaplatin and irinotecan, there was no one withdrawal case during 12 months of follow-up. Among 140 selected patients, the number of complete remission cases, number of partial remission cases, number of stable disease cases, and number of disease progression cases were 40 (28.57%), 28 (20.00%), 30 (21.43%), 42 (30.00%), respectively and the final total effective rate was 48.57%.

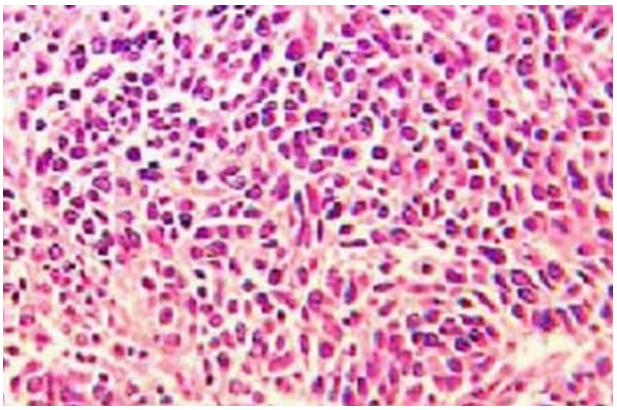

Fig. 1: Small cell lung cancer

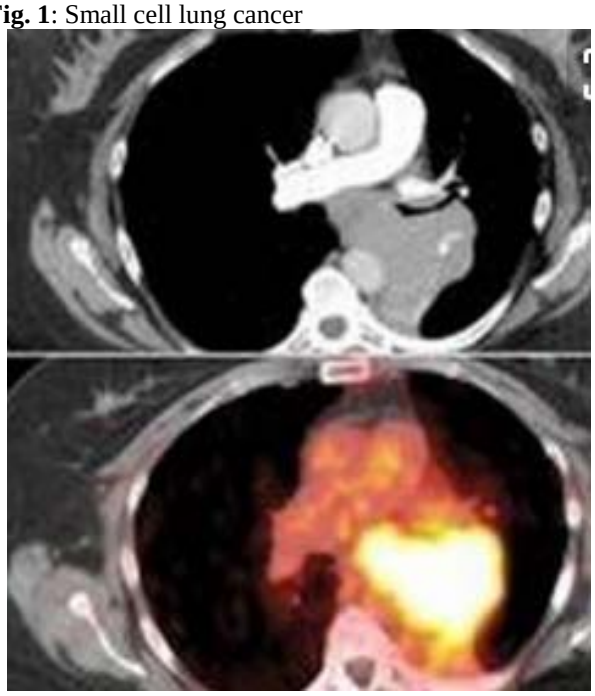

Fig. 2: Extensive small cell lung cancer

Chemotherapy cycle, time to progression and overall survival

As shown in table 2, there are total 92 chemotherapy cycles, including 7 longest chemotherapy cycles, 2 chemotherapy cycles, averaging at (3.9±0.6) cycles; the averaged time to progression was (4.5±0.8) months, and the averaged overall survival was (7.6±1.2) months.

Toxic and adverse reactions

As shown in table 3. The toxic and adverse reactions mainly include hematological toxicity and gastrointestinal adverse reaction, such as leukocyte reduction, neutrophil reduction, thrombocytopenia, decreased hemoglobin,

Table 1: Total effective rate of 140 selected patients [n (%)]

Case number	Complete remission	Partial remission	Stable disease	Disease progression	Total effective rate
140	40	28	30	42	68(48.57)

Table 2: Chemotherapy cycle, time to progression, and overall survival ($\bar{x} \pm s$)

Case number	Chemotherapy cycle	Time to progression	Overall survival
140	3.9±0.6	4.5±0.8	7.6±1.2

Table 3: Toxic and adverse effects of 140 patients

Toxic and adverse reactions	Toxicity level			
	Level 1	Level 2	Level 3	Level 4
Leukocyte reduction	18(12.86)	35(25.00)	32(22.86)	28(20.00)
Neutrophil reduction	29(20.71)	38(27.14)	35(25.00)	21(15.00)
Thrombocytopenia	42(30.00)	22(15.71)	16(11.43)	10(7.14)
Decreased hemoglobin	49(35.00)	8(5.71)	10(7.14)	0(0.00)
Diarrhea	45(32.14)	26(18.57)	26(18.57)	25(17.86)
Abnormal liver function	9(6.43)	0(0.00)	0(0.00)	0(0.00)
Mucositis	6(4.29)	12(8.57)	0(0.00)	0(0.00)
Alopecia	12(8.57)	0(0.00)	0(0.00)	0(0.00)
Nausea and vomiting	30(21.43)	12(8.57)	9(0.00)	0(0.00)

nausea and vomiting, diarrhoea, etc. No toxicity-related death occurred.

DISCUSSION

Many researches have been conducted on the molecular occurrence mechanism of small ceel lung cancer, indicating that various genes are involved in the occurrence of this disease. Some research pointed out the cancer suppressor gene p53 (fig. 3), RB gene (retinoblastoma gene), oncogene Bcl-2, Myc gene, PI3K/AKT/mTOR signal transduction pathway were associated with the occurrence of small cancer lung cell (Xiao, *et al*., 2017; Ofori-Kwakye, 2016. Currently, the recommended first-line chemotherapy regimens are mainly combined chemotherapy protocols, including EP regimen, i.e. combined application of toposide and cisplatin; CAV regimen, i.e. CTX + ADM+ VCR 1; combined application of irinotecan and cisplatin. After first-line chemotherapy regimen, topotecan, taxus and amrubjcin can be considered (Attari, 2016).

In recent years, combined application of lobaplatin and irinotecan has been extensively used in treatment of recurrant small cell lung cancer, with good results being achieved. Lobaplatin, as generalized alkylation agent, is a typical 1, 2-diamine methyl-cyclobutane- lactic acid platinum, which has cytotoxic effect to tumor cell line of human and various kinds of animals. In addition, it has similar tumor inhibitory effect as cis-platinum, but also exerts cytotoxic effect to the cisplatin-resistant cell line. The mainly toxic adverse reaction of lobaplatin is marrow toxicity, especially leading to thrombocytopenia. However, a proper dosage will not lead to significant toxic adverse reaction, so it is safe. Irinotecan of which the main ingredient is irinotecan hydrochloride, is a semisynthetic derivative of camptothecin.

Camptothecin can specifically bond with topoisomerase I, leads to reversible single-strand breaks, and thus unwinding the double-chain structure of DNA. Moreover, irinotecan and its active metabolite SN-38 can bond with topoisomerase I-DNA compound, so as to inhibit the re-connection of broken single chains. The results of this study showed the total effective rate after combined application of lobaplatin and irinotecan in treatment recurrant small cell lung cancer was 48.57%, which is a good result.

Through observing the overall therapeutic efficiency of 140 patients with recurrent small cell lung cancer, it can be known that the number of complete remission cases, number of partial remission cases, number of stable disease cases, and number of disease progression cases were 40(28.57%), 28(20.00%), 30(21.43%), 42(30.00%), respectively and the final total effective rate was 48.57%. the averaged time to progression was (4.5±0.8) months, and the averaged overall survival was (7.6±1.2) months. The toxic and adverse reactions mainly included hematological toxicity and gastrointestinal adverse reaction, such as leukocyte reduction, neutrophil reduction, thrombocytopenia, decreased hemoglobin, nausea and vomiting, diarrhoea, etc. No toxicity-related death occurred. This fully demonstrates that combined

application of lobaplatin and irinotecan can achieve a good result in treating recurrant small cell lung cancer.

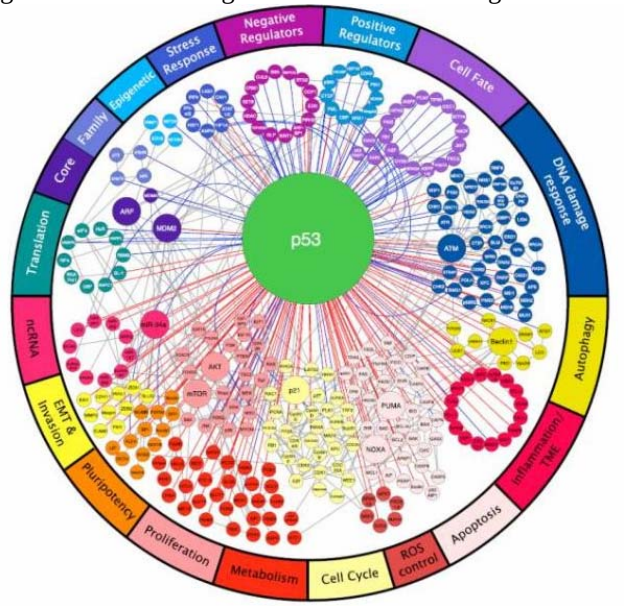

Fig. 3: Cancer suppressor gene p53

CONCLUSION

In conclusion, Lobaplatin is a typical 1, 2-diamine methyl-cyclobutane-lactic acid (cisplatin), which can exert cytotoxic effects on cisplatin resistant cell lines. The main toxic side effect of Lobaplatin is bone marrow toxicity. Especially for reducing platelets, it has a dose-limiting toxicity, which will not present significant toxic side effect. The results of this study show that combined application of lobaplatin and irinotecan can achieve a good result in treatment of patients with recurrent small cell lung cancer, which is safe and reliable and does not produce significant adverse reactions. So this combined therapy is worth of being promoted in clinics.

REFERENCES

Abdel MS (2016). Design and synthesis of some substituted thiazolo [3,2-a] pyrimidine derivatives of potential biological activities. *Saudi Pharm. J.*, **24**(2): 119-132.

Attari Z (2016). Enhanced *ex vivo* intestinal absorption of olmesartan medoxomil nanosuspension: Preparation by combinative technology. *Saudi Pharm. J.*, **24**(1): 57-63.

Chen L, Huang P, Zhang XJ, Liang D, Hou BX, Feng J and Li RC (2016). Evaluation of therapeutic effect and safety for combined application of lobaplatin and irinotecan in treatment of patients with liver metastasis of small cell lung cancer who have failed in etoposide chemotherapy. *Hebei Medical Journal*, **38**(20): 3098-3100.

Hazra M (2015). Designing polymeric micro particulate drug delivery system for hydrophobic drug quercetin. *Saudi Pharm. J.*, **23**(4): 429-36.

Meng W (2015). Observation of clinical effect of combined application of lobaplatin and irinotecan in treating 40 patients with recurrant small cell lung cancer. *Chinese Journal of Modern Drug Application*, **9**(17): 138-139.

Ofori-Kwakye K (2016). Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. *Saudi Pharm. J.*, **24**(1): 82-91.

Wang XJ, Shou T, Li LH, Miao K and Chen XD (2014). Clinical research of second-line treatment for small cell lung cancer using combined application of lobaplatin and irinotecan. *Chongqing Medicine*, **43**(18): 2294-2296.

Wroblewska K (2015). Characterization of new eye drops with choline salicylate and assessment of their irritancy by in vitro short time exposure tests. *Saudi Pharm J.*, **23**(4): 407-412.

Xiao XG and Chen Y (2013). Clinical observation of combined application of lobaplatin and irinotecan in treating extensive small cell lung cancer. *Chinese Journal of Clinical Pharmacology and Therapeutics*, **18**(09): 1049-1052.

Xiao Y, Liu MR, Xu ZL, Zheng G and Wang Y (2017). Observation of clinical effect of combined application of lobaplatin, irinotecan and recombinant human endostatin in treating recurrant small cell lung cancer. *China Pharmacy*, **28**(20): 2843-2846.