

The effects of carboplatin and etoposide on advanced small cell lung cancer and serum tumor markers in correlation with long-term survival rate

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Abstract: Objective of the present study was to analyze the efficacy of recombinant human endo-statin combined with carboplatin and etoposide regimen (CE regimen) in treatment of patients with advanced small cell lung cancer and its effects on serum tumor markers of CY211, CEA and CA199. A total of 72 patients at Zhejiang Taizhou Hospital, Taizhou, Zhejiang, China were randomly divided into control group and observation group (36 cases each). The control group was treated with carboplatin and etoposide while the observation group additionally received recombinant human endo-statin. Clinical remission rate and adverse reaction rate were compared between the two groups. Before treatment, there was no significant difference ($P>0.05$) between the two groups in serum tumor markers of CY211, CEA and CA199 while after treatment, the CY211, CEA and CA199 levels of the observation group were significantly lower than those of the control group and no significant difference was found between the two groups in the incidence of side effects as well as in the 3 and 5 year-survival rate ($X^2=1.125, 1.248, P>0.05$). Recombinant human endo-statin combined with carboplatin and etoposide was more effective in treating advanced small cell lung cancer as it managed to reduce the level of serum tumor markers of CY211, CEA and CA199 with less side effects and high tolerance in patients, thus worthy of popularization and application in clinical trials.

Keywords: Carboplatin, etoposide, tumor marker.

INTRODUCTION

10-15% lung cancers are regarded as small cell lung cancer which is characterized by prompt and inclusive metastasis along with high metastasis rate and invasiveness (Gao *et al.*, 2017). Though, it may be treated by “first-line chemotherapy” with 70% of effective rate. Many of the patients will practice metastasis and/or recurrence with a 5-year survival rate of only 6.81 percent (Ozyurek *et al.*, 2017). Carboplatin and etoposide régime is the customary chemotherapy in small cell lung cancer. The study found that (Han *et al.*, 2017), medicine resistance to the regime has appeared in many patients that results in high recurrence rate. How to manage the occurrence of local as well as systemic tumor and improve the prognosis of patients has come to be the attention of clinical research now (Scilla *et al.*, 2017). Recombinant human endo-statin is well-organized epidermal growth factor receptor kinase inhibitors (EGFR-TKI) that precisely entertain the endothelial cells with the effect of inhibiting tumor angiogenesis and metastasis (Yuan *et al.*, 2017; Lynch *et al.*, 2004). Presently, limited studies have been conducted on the effectiveness of recombinant human endo-statin combined with carboplatin and etoposide in the treatment of advanced small cell lung cancer. In this research, mainly the efficacy of such a recombined treatment and analyzed its effect on serum tumor markers of CY211, CEA and CA199 was explored.

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MATERIALS AND METHODS

Study design

General Information

A total of 72 patients with advanced small cell lung cancer were randomly divided into control group (36 cases) and observation group (36 cases). In the control group there were 25 male and 11 female aged 40 -76 with an average age of (60.8±4.1) years, including 23 limited stage and 13 extensive stage. In the observation group there were 26 male and 10 female aged 41-76 with an average age of (60.9±4.2) years, including 24 limited stage and 12 extensive stage.

Inclusion Criteria

1. Patients expected to live longer than 3 months,
2. Patients with the score of overall function state over 70
3. Patients that signed informed consent form before the study.

Exclusion Criteria

1. Patients with liver or kidney diseases.
2. Patients with severe cardiovascular or cerebrovascular diseases.
3. Pregnant patients.
4. Patients with abnormal hematopoietic function.
5. Patients with mental illness.

The control group received carboplatin and etoposide treatment, carboplatin (manufacturer: Shandong Beida hi

tech Huatai Pharmaceutical Co., Ltd.; batch number: H37020118) was taken at the dose of 400mg-500mg for the first day. Etoposide (manufacturer: Langzhi Wanrong Pharmaceutical Co. Ltd.; batch number: H14023024) was taken at the dose of 100mg from the first to the fifth day. The observation group was additionally treated with recombinant human endo-statin (manufacturer: Shandong Xiansheng Medgenn Biological Pharmaceutical Co Ltd.; batch number: S20050088), which was intravenously injected in patients at the dose of 15mg from the first day to the fourteenth day with a cycle of 21 days based on each cycle of chemotherapy in the control group. All patients completed at least 2 cycles of chemotherapy and a weekly detection was conducted on liver and kidney function, blood routine as well as electrocardiogram (ECG) test. After 2 cycles of treatment the curative efficacy was evaluated in the two groups. The study was approved by the Ethics Committee of Zhejiang Taizhou Hospital.

Evaluation index

1. The clinical remission rate was compared between the two groups.

Complete remission: There was no more lump in patients for at least 1 month.

Partial remission: The lump decreased by more than 50% in patients for at least 1 month.

No change: The lump decreased by less than 50% or increased by no more than 25% in patients.

Disease progression: The lump increased by more than 25% in patients, or new lesions emerged. Clinical remission was a sum of complete remission plus partial remission.

2. The levels of tumor markers like cytokeratin 211 fragment (CY211), carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199) were detected by enzyme linked immunosorbent assay (ELISA) in two groups before and after treatment.
3. The adverse effects like suppression of leukemia cells, impairment of liver function, thrombocytopenia, renal impairment, cardiac toxicity and gastrointestinal reaction were observed in the two groups.
4. The efficacy was evaluated according to the survival and the survival time was calculated from the day when the patient was admitted to the hospital. The last time of visit to the patient in this study was on February 2017.

STATISTICAL ANALYSIS

SPSS 22 software was used to process data. The measurement data were assessed by t test and the count data by chi square test, $P < 0.05$ suggested that there was statistically significant difference in between.

RESULTS

A: Comparison of clinical remission rate between the

two groups

The clinical remission rate of the observation group was 80.56%, significantly higher than that of the control group, that was 50% ($P < 0.05$), as shown in table 1.

B: Comparison of serum tumor markers between the two groups

Before treatment, there was no significant difference between the two groups in serum tumor markers of CY211, CEA and CA199 ($P > 0.05$); while after treatment, the CY211, CEA and CA199 levels of the observation group were significantly lower than those of the control group ($P < 0.05$) as shown in table 2.

C: Comparison of side effects rate between the two groups

There was no significant difference between the two groups in the rate of side effects like suppression of leukemia cells, liver function impairment, thrombocytopenia, renal impairment, cardiac toxicity and gastrointestinal reaction, ($P > 0.05$), as shown in table 3.

D: Comparison of survival rate between the two groups

In the observation group, the 3-year survival rate and the 5-year survival rate were respectively 33.3% (12/36 cases) and 13.9% (5/36) whereas in the control group, they were 27.8% (10/36 cases) and 11.1% (4/36 cases) respectively with no significant difference in between ($X^2 = 1.125, 1.248, P > 0.05$).

DISCUSSION

Small cell lung cancer is a malignant tumor and very sensitive to chemotherapy. A study has shown that (Inoue *et al.*, 2006), the effective rate of initial treatment for the illness is typically ideal, but later on, most of the patients would hurt from disease development or repetition with the exacerbation of pain. Related studies have found that (Verbridge *et al.*, 2010; Suci *et al.*, 2015) new blood vessels are significant foundation for the growth and metastasis of cancer tissues by their capability to deliver nutrients needed for that. They also transport the metabolites to offer pathways for reserved diffusion of tumor cells. Therefore, some researchers are of opinion that (Cairns *et al.*, 2010; Tao *et al.*, 2012) the management of cancer ought to start from new blood vessels in patients and take them as a therapeutic target to efficiently prevent tumor growth and metastasis.

In this study, 36 patients with advanced small cell lung cancer in the observation group were treated by recombinant human endo-statin combined with carboplatin and etoposide and it turned out to the clinical remission rate of the observation group was significantly higher than that of the control group with no significant difference in adverse reaction rate between the two groups. Recombinant human endo-statin may hinder the

Table 1: Comparison of clinical remission rate between the two groups [n (%)]

Group	Case	Complete Remission	Partial Remission	No Change	Disease Progression	Clinical Remission Rate
Control Group	36	3 (8.33)	15 (41.67)	12 (33.33)	6 (16.67)	18 (50.00)
Observation Group	36	5 (13.89)	24 (66.67)	4 (11.11)	3 (8.33)	29 (80.56)
X ²	---	0.563	4.532	5.143	1.143	7.415
P	---	0.453	0.033	0.023	0.285	0.006

Table 2: Comparison of serum tumor markers between the two groups (N=36)

Group	Cy211 (Mg/L)		Cea (Mg/L)		Ca199 (Ku/L)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control	23.73±1.3	6.44±0.52	56.78±5.1	23.02±3.5	61.45±4.23	36.62±2.39
Observation	23.95±1.4	2.86±0.15	56.82±4.9	17.63±1.3	61.77±3.98	28.84±1.61
T	0.431	7.126	0.802	7.693	0.665	8.007
P	0.625	0.123	0.504	0.106	0.781	0.103

Table 3: Comparison of side effects rate between the two groups [n (%)]

Group	Suppression of Leukemia Cells	Liver Function Impairment	Thrombocytopenia	Renal Impairment	Cardiac Toxicity	GIT Reaction
Control	21 (58.33)	6 (16.67)	6 (16.67)	2 (5.56)	2 (5.56)	20 (55.56)
Observation	17 (47.22)	5 (13.89)	4 (11.11)	1 (2.78)	4 (11.1)	14 (38.89)
X ²	0.892	0.107	0.465	0.348	0.727	2.006
P	0.345	0.743	0.496	0.555	0.394	0.157

movement of endothelial cells, then control tumor angiogenesis and block the nutrition source of blood vessels so that there is not sufficient nutrition for tumor growth, thus understanding the purpose of cancer incursion, proliferation and metastasis. Conversely, the usage of recombinant human endo-statin may also improve the hypoxic state of tumor, in this manner increasing its sensitivity to radiotherapy and chemotherapy and fashioning the prognosis extra safe. It is worth noting that recombinant human endo-statin may play a definite role for endothelial cells. It can obstruct angiogenesis and produce tumor cell apoptosis with light side effects and no resistance in patients, so the safety of treatment is assured (Grunnet and Sorensen, 2012).

CY211 denotes the statement that keratin fragments within are degraded throughout the apoptosis of alveolar epithelial cells and is afterwards transformed into soluble materials tracked by being dissolved into blood and to end with rising of CY211 level. CY211 is the primary marker in the diagnosis of small cell lung cancer with its sensitivity reaching 60 percent and specificity 95 percent. CEA was initially found in colon tumor and fetal intestinal tissues. It is mostly perceived in malignant cancer diseases of GIT with definite look likewise in other systems (Molina *et al.*, 2005; Grunnet and Sorensen, 2012). Some studies have suggested that constant checking of CEA is an imperative means of lung cancer monitoring, and the serum level of CEA increases with

the worsening of the state. CA199 is presently renowned as a tumor marker for pancreatic and colorectal tumor with increased specificity and sensitivity, but it doesn't match up to a specific tumor one-to-one (Cancer, 1997). There is a study showing that (He *et al.*, 2015) CA199 is similarly extremely expressed in lung cancer patients, though the upturn degree of its serum value is not as high as that of colorectal cancer. It can also be used as a supplementary indicator of lung cancer diagnosis with specific clinical importance. The results of present work showed that the levels of CY211, CEA and CA199 in the observation group were significantly lower than those in the control group, suggesting that the treatment of recombinant human endo-statin combined with carboplatin and etoposide can effectively reduce levels of CY211, CEA and CA199s and improve the condition of advanced small cell lung cancer. However, no significant difference was found between the two groups in the 3-year survival rate and the 5-year survival rate ($P>0.05$), indicating that there is no obvious difference in the survival rate of patients between the treatment of recombinant human endo-statin combined with carboplatin and etoposide and CE treatment regime.

CONCLUSION

In summary, recombinant human endo-statin combined with carboplatin and etoposide has better curative effect in treating advanced small cell lung cancer by reducing

the level of serum tumor markers of CY211, CEA and CA199 with less side effects and high tolerance in patients. But as for the long-term survival rate in patients, more time and samples are needed to make clinical observation and study.

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