RESEARCH ARTICLE

Human Recombinant Endostatin Combined with Cisplatin Based Doublets in Treating Patients with Advanced NSCLC and Evaluation by CT Perfusion Imaging

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Abstract

Aims: To study the effectiveness of human recombinant endostatin injection (Endostar®) combined with cisplatin doublets in treating advanced non-small cell lung cancer (NSCLC), and to evaluate outcome by CT perfusion imaging. Methods: From April 2011 to September 2014, 76 patients with advanced NSCLC who were treated with platinum-based doublets were divided into group A (36 patients) and group B (40 patients). Endostar® 15mg/day was administered 4 days before chemotherapy and combined with chemotherapy from day 5 in group A, and combined with chemotherapy from the first day in Group B. Endostar® in the two groups was injected intravenously for 14 days. Results: Treatment effectiveness in the two groups differed with statistical significance ($p<0.05$). Effectiveness evaluated by CT perfusion imaging, BF, BV, MTT and PS also demonstrated significant differences (all $p<0.05$). Adverse reactions in the two groups did not significantly vary ($p> 0.05$). Conclusions: The response rate with Endostar® administered 4 days before chemotherapy and combined with chemotherapy from day 5 in group A was better than Endostar® combined with chemotherapy from the first day, and CT perfusion imaging could be a reasonable method for evaluation of patient outcomes.

Keywords: Advanced NSCLC - platinum containing chemotherapy - CT perfusion imaging

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Introduction

According to WHO statistics, the incidence and motality rate of lung cancer increases year by year. And in China, more than 75% of patients with non-small cell lung cancer (NSCLC) present with locally advanced (stageIIIB) or metastatic (stage IV) disease at diagnosis (Herbst et al., 2008). For patients in this setting, platinum-based chemotherapy is recommended as first-line treatment according to current guideline (Welsh et al., 2013). However, the treatment efficacy is not satisfactory. How to improve the treatment result is a focus of clinical efforts.

In this study, we compared the curative effect of cisplatin double regimens combined with human recombinant endostatin (Endostar®) with different time dose schedules for treating patients with advanced NSCLC; and evaluation of curative effect by CT perfusion imaging.

Materials and Methods

Patients

From April 2011 to September 2014, 76 patients with advanced NSCLC were recruited (42 male, 34 female; 18 to 75 years of age). Diagnosis of all patients with NSCLC were confirmed pathologically and histologically with postoperative recurrence and locally advanced or metastatic diseases.

All patients were with ECOG PS score of 0 to 2, and were expected to survive a period for 3 months or more. Routine blood, liver and kidney function, electrocardiogram (ecg), myocardial enzyme were within normal range. Brain metastasis and symptoms of central nervous system were not found.

Re-examination of these items after . chemotherapy was repeated and compared. All patients were divided into group A (36 patients) and B (40 patients).

Methods

PP Regimen: Pemetrexed 500 mg/m^2, was intravenously (iv) infused on day 1; cisplatin 25 mg/m^2 iv on day 1 to day 3.

DP Regimen: Docetaxel 65 mg/m^2, was iv infused on day 1; cisplatin 25 mg/m^2 iv on day 1 to day 3.

GP Regimen: Gemcitabine 1000 mg/m^2 was iv infused on day 1 and day 8; cisplatin 25 mg/m^2 iv on day 1 to day 3.

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PL Regimen

Pemetrexed 500 mg/m^2 was iv infused; Lobaplatin 20 mg/m^2 was also iv infused on day 1.

In group A (experimental group), there were 12 patients treated with PP, 10 with DP, 10 with GP and 4 with PL regimen. In group B (control group), there were 14 patients treated with PP, 12 with DP, 4 with GP, 10 with PL regimen. Every chemotherapeutic cycle was repeated for every 21 days.

Human recombinant endostatin injection (Endostar®, produced by ShanDong YanTai biological engineering Co., LTD., Registration number of China: S20050088) 7.5 mg/m^2, is iv. Infused within 3-4 hours, from day 1 to day 14 for 1 cycle.

Treatment efficacy

With reference to WHO criteria of response for solid tumor, responsiveness is divided into: (1) complete remission (CR); (2) Partial remission (PR); (3) Stable disease (SD); (4) Progression of diseases (PD). Response rate (RR) = CR + PR; Clinical benefit rate (CBR) = CR + PR + SD.

CT perfusion imaging

In this study, GE Light Speed 64 CT scanner was used. Iodine contrast 40 ml was injecte with a velocity of 4 ml/s throuth elbow vein before scanning. Scanning layer thickness was 5 mm, exposure time 0.5 s, exposure intervel 2 s, getting four images every time. With a reference of thoracic aortic artery, reconstructed tumor blood flow diagram (blood flow, BF), blood volume (blood volume, BV), mean transit time (MTT), capillary permeability surface (PS) diagram. Before chemotherapy, background scanning was taken, and perfusion values of lung cancer, including BF, BV, MTT and PS values were estimated. After 2 cycles of chemotherapy, re-evaluation with chest CT scans, including lung tumor arterial perfusion scanning, with perfusion parameters was performed. Curative effect was evaluated by RECISIT criteria.

Adverse reaction of treatment

With reference to WHO criteria , adverse reaction was divided into 0 - IV degrees, according to clinical reviews after chemotherapy, eg., routine tests for blood cell, liver and kidney function, electrocardiogram (ecg), myocardial enzymes etc.

Statistical method

We used SPSS (version17.0 Inc. Chicago, IL, USA) for statistical analyses. P value less than 0.05 was considered as significant. We have enough experience in conducting clinical and research work and published some results elsewhere (Huang et al., 2014; Ji et al., 2014; Qiu et al., 2014; Liu et al., 2014; Qian et al., 2014; Xiao et al., 2014; Xu et al., 2014).

Results

Characteristics of all patients

All patients completed at least two cycles of tratement. No no significant differences were found between two groups of patients regarding age, surface area, ECOG score, clinical stage, pathological type and viscera metastasis (Table 1).

There were statistically significant differences between

Table 1. Characteristics of All Patients

	Group A(N=36)	Group B(N=40)
Age(year)		
Median	57	60
Range	39-73	36-75
Gender(number)		
Male	20	22
Female	16	18
Area of body surface(m2)		
Median	1.75	1.73
Range	1.40-1.95	1.47-1.87
ECOG score(number)		
0	10	10
1	14	20
2	12	10
Clinical stage(number)		
III	20	18
IV	16	22
Pathological type(number)		
Adenocarcinoma	20	22
Squamous cancer	14	18
Others	2	0
Metastatic disease(number)	18	26

Table 2. A Comparison between two Groups Regarding Response and Clinical Benificial Rates (number,%)

	Number	CR	PR	SD	PD	RR	CBR
Group A	36	0 (0.00)	16(44.44)	16(44.44)	4(11.11)	16(44.44)	32(88.89)
Group B	40	0(0.00)	10(25.0)	18(45.0)	12(30.00)	10(25.00)	28(70.00)
X2 value			1.22	0.056	2.078	2.745	2.116
P			0.061	0.179	0.039*	0.032*	0.0045*

Table 3. A Comparison between two Group Regarding CT Perfusion Imaging($\bar{x}\pm s$)

	N	Timing of test (day)	BF (ml·100mg-1·min-1)	BV (ml·100mg-1)	MTT (s)	PS (ml·100mg-1·min-1)
Group A	36	1	340.4±87.5	11.4±6.8	3.3±1.5	28.3±17.1
		2 after 2 cycles of treatment(45-50)	233.54±71.42	7.8±4.1	5.5±2.0	9.6±3.7
Group B	40	1	331.5±121.0	12.5±5.6	4.0±1.2	27.4±10.5
		2 after 2 cycles of treatment(45-50)	279.6±79.32	8.2±5.8	5.47±2.5	15.5±5.2
T value		Group A with B (after 2 cycles of treatment)	2.821	2.986	1.618	3.143
P value		Group A with B (after 2 cycles of treatment)	0.034	0.019	0.0124	0.006

Table 4. A Comparison between two Group Regarding Side Effects

	Group A (N=36)					Group B (N=40)						
	I	II	III	IV	All	I	II	III	IV	All	X^2 Value	P
Leukocytopenia	14	6	4	0	24	14	6	6	0	26	0.161	0.518
	16	8	8	0	32	18	12	8	0	38	0.154	0.52
Thrombocytopenia	6	4	2	0	12	4	6	0	0	10	0.167	0.511
Anemia	10	8	2	0	20	12	8	4	0	24	0.188	0.457
Nausea/vomiting	8	6	2	0	16	10	2	2	0	14	0.075	0.64
Diarrhea	4	2	2	0	8	2	4	0	0	9	0.064	0.806
Liver dysfunction	6	6	4	0	16	8	4	6	0	0	0.554	0.325
Renal dysfunction	0	0	0	0	0	0	0	0	0	20	/	/
Fatigue	12	4	0	0	16	14	6	0	0	6	0.275	0.34
Fever	2	2	0	0	4	4	2	0	0	8	0.378	0.276
ECG ST-T abnormality	8	0	0	0	8	6	2	0	0	0	0.077	0.781

two groups regarding response rate and CBR (Table 2).

A Comparision between two groups regarding values of BF, BV, MTT and PS that indicating CT perfusion imaging is suggested with statistically significant difference (all $p<0.05$) (Table 3).

Discussion

Lung cancer is a main disease with high mortality worldwide (Herbst et al., 2008). And this is especially significant based on an annual report from China ,which demonstrated that more than 3 million new cases of lung cancer could be diagnosed every year (Fei et al., 2013; Cui et al., 2014; Huang et al., 2014; Ji et al., 2014). Among patients with lung cancer, approximately 85-90% are confirmed with non-small cell lung cancer (NSCLC),which is the most common cancer worldwide. The incidence of NSCLC is still gradually increasing (Herbst et al., 2008). And patients with NSCLC are generally diagnosed with stage IIIB or stage IV disease. For these patients, the median overall survival (OS) with platinum-based chemotherapy is 7.4-9.9 months, and the median OS with combined chemotherapy and bevacizumab is 12.5 months. Median progression-free survival (PFS) with second-line chemotherapy, such as pemetrexed and docetaxel, is approximately 2.2-2.9 months. Although associated with a higher response rate, OS with gefitinib is similar to that of standard carboplatin plus paclitaxel chemotherapy (Fukuoka et al., 2011). The 5-year survival rate of NSCLC is lower than 20% (Klastersky et al., 2001; American Cancer Society, 2011). However, despite the relatively poor prognosis for NSCLC patients, the development of treatments for NSCLC is a focus of research (Bowles et al., 2012). Previous studies suggested that human recombinant endostatin combined NP and GP regimens is associated with improved response rate in treating patients with advanced NSCLC, and good safety frofile (Zhang et al., 2013). It was also suggested that human recombinant endostatin combined with platinum-based chemotherapy could significantly improve time of tumor progression (TTP) and rate of disease control (DCR) in patients with advanced NSCLC (Dai et al., 2012). But, different ways of drug delivery, and different dosing schedule for human recombinant endostatin could lead to different therapeutic effect. Pre-clinical experiment using lung adenocarcinoma SPC A1 was conducted to determine the influence of recombinant human endostatin administrated at different time on the growth of tumor tissue (Wen et al., 2013). The results showed that recombinant human endostatin is associated with anti-tumor angiogenesis, and best delivery time is the day that the tumor was inoculated (Wen et al., 2013). Our current study is designed to compare the curative effect of human recombinant endostatin combined with platinum-based chemotherapy for treating patients with advanced NSCLC. Our results suggested that treatment effectiveness in two groups is different with statistical significance ($p<0.05$), and in favour of the group that human recombinant endostatin was added. And this result is supported by previous report [Tian et al., 2012]. Our current study also revealed that adverse reaction of two groups did not show statistical significance. Thus in conclusion, our study suggested that the response rate of Endostar® administered 4 days before chemotherapy and combined with chemotherapy from day 5 in group A, is better than Endostar® combined with chemotherapy from the first day, and CT perfusion imaging could be a reasonable method for evaluation for patients after treatments.

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