Research Article

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Effectiveness of treatment with endostatin in combination with emcitabine, carboplatin, and gemcitabine in patients with advanced non-small cell lung cancer: a retrospective study

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Abstract: This study investigated the clinical efficacy, safety and tolerance of endostatin combined with gemcitabine and carboplatin for patients with advanced non-small cell lung cancer (NSCLC).

From January 2010 to January 2014, 49 patients with advanced NSCLC were retrospectively evaluated; we defined 2 subgroups: a combination group (chemotherapy + anti-angiogenic therapy) and a chemotherapy group (chemotherapy only). The cases in the chemotherapy group received treatment with gemcitabine and carboplatin only, whereas the cases in the combination group received endostatin in combination with gemcitabine and carboplatin. The patients received 2 cycles of treatment (21 days/cycle). The clinical efficacy and adverse events were observed and compared.

The disease control rate in the combination group was significantly higher compared with the chemotherapy group ($P < 0.05$). When comparing the cases of squamous carcinoma, the disease control rate in the combination group was significantly higher than the chemotherapy group ($P < 0.05$). Moreover, the progression free survival in the combination group was higher than that for the chemotherapy group, with a statistically significant difference ($P < 0.05$).

The combination of endostatin with chemotherapeutic agents is improve to the survival of patients with advanced NSCLC favorably; the adverse events of this regimen are well tolerated.

Keywords: Gemcitabine; Carboplatin; Angiogenesis Inhibitors; NSCLC

1 Introduction

Lung cancer is a leading cause of cancer death worldwide [1]. About 1.8 million lung cancer cases were newly diagnosed in 2012, accounting for about 13% of total cancer cases [2]. The 5-year survival rate for all stages of non-small cell lung cancer (NSCLC) is quite poor, only 18.2% [3]. Due to the lack of a convenient and effective strategy, most patients with advanced NSCLC lose the opportunity for surgery; therefore, palliative treatment is mainly the only choice to prolong life and to improve the quality of life for those patients [4, 5]. The chemotherapy regimen relieves symptoms and improves quality of life of advanced NSCLC patients to a certain extent; however, the overall survival (OS) is still low [6]. It has been reported that chemotherapy combined with other strategies significantly prolongs the survival of NSCLC patients [7-10]. Thus, a chemotherapy-based combination regimen has become an attractive strategy for treatment of advanced NSCLC.

Endostatin, a 20-KDa C-terminal fragment of collagen XVIII, is a broad-spectrum angiogenesis inhibitor that can interfere with the pro-angiogenic action of growth factors such as VEGFs and FGFs, resulting in inhibition of endothelial proliferation, angiogenesis, and tumor growth [11, 12]. Several studies have tested and clinically proven that endostatin in combination with chemother-

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apy achieves a good response rate and significantly prolongs median time of tumor progression, based on different types of cancer, without increasing the risk of serious adverse events, [13-16]. However, the effect remains poorly understood for endostatin treatment in combination with chemotherapy in advanced NSCLC patients with poor performance status (defined as grade 2-4 according to the scale of Eastern Cooperative Oncology Group). Here, we aimed to retrospectively investigate the therapeutic efficacy of endostatin in combination with gemcitabine and carboplatin for patients with advanced NSCLC.

2 Materials and methods

2.1 Patients

This retrospective study (project number: Z-2014-06-16344) was performed according to the Helsinki declaration and approved by the institutional review board of Central South University, Changsha, China. From January 2010 to January 2014, 49 patients with complete clinical and pathological data were diagnosed in the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University. They were divided into a combination group and a chemotherapy group. There were 24 patients in the combination group that included 17 males and 7 females, aged 56.33 ± 9.55 years; 12 cases of adenocarcinoma and 12 cases of squamous cell carcinoma; 9 cases at stage III and 15 cases at stage IV. Among the 25 patients in the chemotherapy group, there were 19 males and 6 females, aged 56.56 ± 7.62; 11 cases of adenocarcinoma and 14 cases of squamous cell carcinoma; 10 cases at stage III and 15 cases at stage IV. There were no significant differences in age, gender, histological type and stage (Table 1). The patients had not been treated previously, and their Karnofsky (KPS) scores were above 70. A computed tomography (CT) scan was used to monitor tumor size every two cycles of therapy. Blood, liver, kidney and lung functions, as well as an electrocardiogram (ECG) were examined before and after the treatment.

Informed consent: Informed consent has been obtained from all individuals included in this study.

2.2 Treatment

All the patients received at least 2 cycles of chemotherapy (21 days for each cycle). The patients in the chemotherapy group only received a treatment with gemcitabine (Hansoh pharmaceutical Group Co., Ltd, China) and carboplatin (Qilu Pharmaceutical Co., Ltd, China); the cases in the combination group received an endostatin (Simcere Pharmaceutical Co., Ltd, China) treatment combined with gemcitabine and carboplatin. Gemcitabine (1000 mg/m^2) was administered intravenously on days 1 and 8, carboplatin (area under the curve [AUC) = 5]) was administered intravenously on day 1, and endostatin (7.5 mg/m^2) was administered intravenously on days 1 and 14. Treatment was not initiated until the disease progressed.

Table 1: Clinical characteristics of patients

	Chemotherapy group (n = 25)	Combination group (n = 24)	P
Age (years)	56.56 ± 7.62	56.33 ± 9.55	0.875
Sex (n)			0.682
Male	19	17	
Female	6	7	
Tumor type (n)			0.674
Adenocarcinoma	11	12	
Squamous cell carcinoma	14	12	
TNM stage (n)			0.858
Stage III	10	9	
Stage IV	15	15	

2.3 Assessments

Patients were subjected to safety evaluation weekly, as well as to tumor response assessments by CT scan before treatment and after every two cycle-chemotherapy. The response evaluation was based on the criteria for solid tumors defined and revised by the RECIST guideline (version 1.1) [17]. Accordingly, it was recorded as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the sum of the CR and PR rate; the disease control rate (DCR) was defined as the combination of CR, PR, and SD. The progression free survival (PFS), defined as the time from enrollment to disease progression or death, and overall survival (OS), calculated from the time from diagnosis to death, were observed. The adverse events were evaluated based on the National Cancer Institute Common Terminology Criteria (Version 3.0) [18].

2.4 Statistical analysis

SPSS software 20.0 (SPSS Inc., Chicago) was used for statistical analyses. The chi square or Fisher exact probabilities methods were used to evaluate the differences in clinical baseline. The Kaplan-Meier and log-rank test was conducted to estimate the association between clinical characteristics and either PFS or OS.

3 Results

3.1 Baseline characteristics of patients

49 patients were enrolled in this retrospective study. The clinical characteristics of the patients are shown in Table 1. The average age of patients in the chemotherapy group was 56.56 ± 7.62 years, in the combination group 56.33 ± 9.55 years; the difference was not significant (P= 0.875). Histopathological analysis indicated that there were 11 cases of adenocarcinoma and 14 cases of squamous cell carcinoma in the chemotherapy group, in the combination group 12 cases of adenocarcinoma and 12 cases of squamous cell carcinoma; the difference was not significant (P = 0.674). Moreover, based on the TNM (tumor, node and metastasis) stage, there were 10 stage III cases and 15 stage IV cases among patients in the chemotherapy group; in the chemotherapy group, 9 stage III cases of and 15 stage IV cases; the difference was not significant (P = 0.858).

3.2 Efficacy

There was 1 case of CR, 10 cases of PR, 11 cases of SD and 2 cases of PD in the combination group PD. whereas in the chemotherapy group there was no case of CR, 6 cases of PR, 11 cases of SD and 8 cases of. Although the ORR in the combination group was higher compared with that of the chemotherapy group (45.8% vs 24.0%), with no significant difference (P = 0.108). Furthermore, we also evaluated DCR, showing that the DCR in the combination group (91.7%) was much higher than that in the chemotherapy group (68.0%), with a significant difference (P = 0.040) (Table 2). Taken together, the results suggest that the combination strategy mediated by chemotherapy and anti-angiogenic therapy offers a much better anti-cancer effect in treatment for advanced NSCLC patients.

To further identify the response of different subtype of advanced NSCLC to the treatments, we analyzed the subgroups. 66.7% of ORR and 28.6% of ORR were obtained in the squamous cell carcinoma patients of the combination group and the chemotherapy group (Table 3), respectively; while 25.0% of ORR and 18.2% of ORR were observed in the adenocarcinoma patients of the combination group and the chemotherapy group (Table 3), respectively. Like previous analysis, no significant differences were found (*P*= 0.052 and *P*= 0.692, respectively) (Table 3). For the DCR analysis, the rate of the squamous cell carcinoma patients in the combination group and the chemotherapy group was 100% and 71.4% respectively, with significant difference (P = 0.048) (Table 3); however, in case of adenocarcinoma subtype, there was no significant difference (83.3% VS 63.6%, P = 0.641) (Table 3). Our results suggest that endostatin- and chemotherapeutic agent-based com-

Table 2: Treatment response in the two groups

Groups	CR(n)	PR(n)	SD(n)	PD(n)	ORR(%)	DCR(%)
Combination group (n = 24)	1	10	11	2	45.8	91.7
Chemotherapy group (n= 25)	0	6	11	8	24.0	68.0
P					0.108	0.040

Table 3: Subgroup analysis in two groups

	Chemotherapy group (n = 25)		Combination group (n = 24)		P
	Squamous cell carcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma	
ORR (%)	28.6	/	66.7	/	0.052
	/	18.2	/	25.0	0.692
DCR (%)	71.4	/	100	/	0.048
	/	63.6	/	83.3	0.283

bination strategy is likely much more responsive to the squamous cell carcinoma subtype of advanced NSCLC.

Finally, the survival of patients was examined. All patients were followed up to February 2016. The PFS of the combination group was significantly different from that of the chemotherapy group (8.2 VS 5.1 months, P = 0.046) (Table 4 and Figure 1). Although the 1-year survival rate of combination group was like that of the chemotherapy group (66.7% VS 60.0%, P = 0.641) (Table 4), the quality of life for the patients in the combination group was much better than the patients in the chemotherapy group. Thus, it is beneficial for advanced NSCLC patients treated with the combination strategy.

3.3 Adverse events

The major adverse events for the patients were gastrointestinal side effects, such as nausea, vomiting, and marrow depression mainly including leucopenia and thrombocytopenia. Nausea/vomiting and leucopenia were most commonly found in both groups. There were no significant differences in two groups with adverse events (Table 5).

4 Discussion

The major therapeutic goals for patients with advanced NSCLC should be to improve symptoms of disease and attempt to prolong survival while minimizing the toxicity of the treatment strategy. Based on the theory that tumor cells rapidly proliferate and rely on the abundant neovascularization for nutrition, blocking nutrition supply for malignant tumor cells could eliminate tumor cells or suppress their growth. Endostatin has achieved the goal of anti-tumor angiogenesis by inhibiting vascular endothelial cell proliferation and VEGF/VEGFR signal transduction. Animal experiments have confirmed that the blood vessels density of lung cancer in mice were significantly lower after subjecting to endothelial inhibition, and the blood vessel growth was also restrained [19]. The anti-angiogenesis drugs can normalize the tumor blood vessels

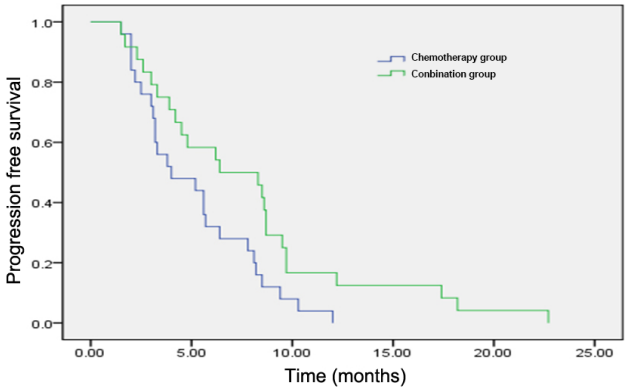

Figure 1: Progression free survival rates in advanced NSCLC patients received chemotherapy alone (chemotherapy group) and endostatin combined with chemotherapy (combination group). The median PFS of the combination group (8.2 ± 1.3) was longer than that of the chemotherapy group (5.1 ± 0.6) but with statistical significance (P = 0.046).

Table 4: The PFS and 1-year survival rate of the two groups

Groups	PFS (months)	P	1-year survival rate (%)	P
Combination group (n = 24)	8.2 ± 1.3	0.046	66.7	0.641
Chemotherapy group (n = 25)	5.1 ± 0.6		60.0	

Table 5: Differences of adverse events between two groups

	Chemotherapy group (n = 25)		Combination group (n = 24)		P
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Nausea/vomiting	9	1	14	1	0.115
Leucopenia	7	1	11	0	0.325
Thrombocytopenia	2	0	1	0	0.580
Anemia	5	0	3	0	0.482
Hepatic dysfunction	4	0	2	0	0.418
Rash	1	0	2	0	0.531
Arrhythmia	0	/	1	/	0.307

and microenvironment [20, 21] and increase the amount of perivascular support cells and the ability of vascular supply nutrients and resist erosion, leading to easily affect tumor.

In this study, DCR of the combination group was obviously higher than the chemotherapy group, and the difference was statistically significant. The result was in line with the previous report [22]. ORR of the combination group was higher than the chemotherapy group, but there was no statistically significant difference, being consistent with one study [23]. It was reported that endostatin combine with chemotherapy could improve the PFS and 1-year survival rate of lung cancer patients [24]. In this study, the PFS of combination group was higher than that of chemotherapy group, with significant difference; 1-year survival rate of combination group was also higher than that of chemotherapy group, without significant difference. The result was not completely consistent with previous report, which may be due to the different subsequent treatment. Endostatin associated with the chemotherapy drug did not increase the side effects of the drugs. This study also confirmed that there was no significant difference in the two groups regarding adverse reactions, which was consistent with the report of other studies [25, 26].

Angiogenesis is a tightly regulated process that occurs only during certain conditions in normal status, but the balance between positive and negative control is disturbed in pathological conditions, such as tumor growth. Moreover, it has been elucidated that the proliferation of tumor cells led the unbalance to malignant angiogenesis, highlighting several pivotal factors, like hypoxia, growth factors, and cell adhesion molecules [27]. Thus, anti-angiogenic therapy is an ideal strategy to impede tumor growth and metastasis, and normalize tumor vascular, which makes nutrition supply and drug delivery balance with a proposed rationale [28]. Endostatin is a broad anti-angiogenesis spectrum and inhibits angiogenesis by modifying 12% of the human genome without side-effects [12]. Due do the limitations of chemotherapy for patients with advanced NSCLC, it is likely that a therapeutic strategy for long-term survival can be achieved by chemotherapy in combination with endostatin that can inhibit angiogenesis involved in lung cancer progression.

5 Conclusion

This study showed a treatment with endostatin combined with gemcitabine and carboplatin for advanced NSCLC patients, achieving a better DCR compared to chemotherapy group. Our results suggest that endostatin combined with gemcitabine and carboplatin for advanced NSCLC treatment, especially patients with squamous cell carcinoma, worthy of further promotion in clinic.

Conflicts of interest: The authors have no conflicts of interest to declare.

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