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Comparison of carboplatin and paclitaxel with or without bevacizumab in chemotherapeutic regimens for unresectable stage III non-small cell lung cancer

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Abstract. – OBJECTIVE: Our study aimed to compare the chemoradiotherapeutic regimens of carboplatin and paclitaxel with or without bevacizumab for stage III non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS: From July 2010 to December 2016, 102 patients with inoperable stage III NSCLC were finally included and divided randomly into two groups. Patients in the CP group received the treatment of carboplatin (area under the curve of 6) on day 1 and paclitaxel (80 mg/m^2) on days 1, 8, and 15. Patients in the CPB group received the treatment of carboplatin (area under the curve of 6) on day 1, paclitaxel (80 mg/m^2) on days 1, 8, and 15 plus bevacizumab (15 mg/kg) on day 1. The two chemotherapy regimens were repeated every 4 weeks. Patients were treated for about 4-6 cycles until the occurrence of toxicity or patient refusal, or progressive disease.

RESULTS: The median overall survival (OS) and progression-free survival (PFS) in the CPB treated group were significantly higher than that in the CP treated group (OS: $p<0.01$; PFS: $p<0.01$; respectively). The rates of response and disease control were higher in the CPB treated group (77%, 98%, respectively) compared to the CP treated group (59%, 94%, respectively), although there was no statistical significance. Regarding the toxicities of chemotherapy, we found higher rates of leukopenia and neutropenia in the CPB group, while frequent occurrence of esophagitis, eruption and thrombocytopenia in the CP group.

CONCLUSIONS: The carboplatin plus paclitaxel plus bevacizumab regimen was more effective and well tolerated in patients with unresectable stage III NSCLC compared with the carboplatin plus paclitaxel regimen. The CPB regimen may be a better alternative to the current standard regimen.

Key Words
Human non-small-cell lung cancer, Carboplatin, Paclitaxel, Bevacizumab, Chemotherapy.

Introduction

Lung cancer is one of the critical cancer death causes and it has apoptosis resistance against various anticancer agents[1,2]. Lung cancer can be divided into the small cell lung cancer (SCLC) and the non-small cell lung cancer (NSCLC). Almost 80% of lung cancer cases are NSCLC, and it mainly consists of the squamous cell, the large cell carcinoma, and the adenocarcinoma[3,4]. Lung cancer normally progresses asymptomatically at early stages and it is usually diagnosed at advanced stages. The rate of 5-year survival in patients at advanced stage is merely 3.6% in spite of the development in surgical techniques and chemoradiation[5]. Besides, more and more lung cancer survivors suffer from the lung dysfunction, especially those after the lung surgery[6]. Thus, further studies concerning the development of efficient novel anticancer agents against lung cancer are in urgent need. Some randomized stage III trials have recently suggested that the sequential chemoradiotherapy is less effective than the concurrent chemoradiotherapy concerning the survival and response in NSCLC patients[7]. Nevertheless, concurrent chemoradiotherapy usually results in much more acute toxicities, including esophagitis and bone marrow suppression, than chemotherapy followed by the radiotherapy[8]. For patients diagnosed of advanced NSCLC, the platinum based two-drug chemotherapy regimens have been accepted as standard treatment due to their survival benefit[9,10]. The regimen of carboplatin and paclitaxel is becoming a kind of the commonly used therapies for NSCLC patients. A phase III trial demonstrated that the occurrence of grade 2/3 neuropathy was lower after the weekly paclitaxel regimen through comparing

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carboplatin plus standard paclitaxel with carboplatin plus weekly paclitaxel[11]. Thus, we choose carboplatin plus weekly paclitaxel (CP) as our basic chemotherapy regimen. Bevacizumab has been shown to benefit patients with different kinds of cancers, such as NSCLC and breast cancer[12, 13]. As a kind of monoclonal antibodies against the vascular endothelial growth factor (EGF), bevacizumab can inhibit tumor growth by blocking the angiogenesis[13]. Therefore, carboplatin plus paclitaxel with bevacizumab is becoming one of the standard regimens for the treatment of advanced stage III NSCLC. However, it is still uncertain whether carboplatin plus weekly paclitaxel in combination with bevacizumab (CPB) shows clinical benefits regarding efficacy and the reduction of adverse events, including peripheral neuropathy, compared to carboplatin plus weekly paclitaxel. In our work we conducted a randomized controlled pilot study to investigate the efficacy and feasibility of carboplatin plus weekly paclitaxel with bevacizumab for treating stage III NSCLC patients compared to carboplatin plus weekly paclitaxel. Our aim was to determine if this combination is a beneficial alternative regimen to carboplatin plus weekly paclitaxel.

Patients and Methods

Patient's Selection

We selected 102 patients diagnosed of unresectable stage III NSCLC and divided them randomly into two groups. One group was treated with carboplatin and paclitaxel (CP), while another with carboplatin and paclitaxel plus bevacizumab (CPB) at the Nanjing Cancer Center from July 2010 to December 2016. TNM stages were graded according to the TNM stage version 6[14]. Based on the T factor, 'unresectable' was considered as T4 disease or pulmonary metastasis in the same lobe. Based on the N factor, 'unresectable' was considered as cytologically/histologically proven bulky N2, N3, multiple N2 or both N1 and N2 positive. Generally speaking, lymph nodes ≥ 10 mm were considered as metastatics. Detailed inspections were carried out before chemotherapy for all the included patients, such as abdominal CT, chest CT and brain CT. The inclusion criteria were: age ≤ 75 years, performance status (PS) ≤1, serum creatinine ≤ 1.5 mg/dl, total bilirubin ≤ 1.5 mg/dl, white blood cells ≥ $3.0*10^3/mm^3$, platelet ≥ $1.0*10^5/mm^3$, neutrophil ≥ $1.5*10^3/mm^3$. The exclusion criteria were: malignant pleural, pericardial effusion or interstitial lung disease, and some serious complications, including active infection, severe respiratory failure, severe heart disease, and poorly controlled diabetes mellitus/hypertension. an Informed consent was given by each patient before the study. This study was approved by the Ethics Committee of People's Hospital of Rizhao. Signed written informed consents were obtained from all participants before the study.

Treatment Schedule

All included patients were divided randomly into two groups to receive CP or CBP chemotherapy regimens. Patients in the CP group received the treatment of carboplatin (area under the curve of 6) on day 1 plus paclitaxel (80 mg/m^2) on days 1, 8, and 15. Patients in the CPB group received the treatment of carboplatin (area under the curve of 6) on day 1 plus paclitaxel (80 mg/m^2) on days 1, 8, and 15 plus bevacizumab (15 mg/kg) on day 1. The two chemotherapy regimens were repeated every 4 weeks. Patients were treated for about 4-6 cycles until the occurrence of toxicity or patient refusal, or progressive disease. Dose modification was allowed when the toxicity occurred. When dose reductions were carried out, the dose would not be re-escalated. After the treatment, prophylactic cranial irradiation (PCI) was available for patient who had obtained good partial response or complete response.

Evaluation of Toxicity and Response

The included patients were thought appreciable for the toxicity and response measures. Complete blood counts, blood chemistry measurement, and chest radiography, were carried out every week during the period of treatment. The responses were assessed following the Response Evaluation Criteria in Solid Tumor (RECIST)[14]. The toxicity of any treatment for all the patients was assessed and classified basing on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0[15].

Statistical Analysis

The intentions to the two-treatment analysis were implemented. The progression-free survival (PFS) was defined as a data from the beginning of the chemotherapy until patients' death or the disease progression. The patients had not progressed when the treatment suspended would continue to be evaluated before the progression was confirmed. The overall survival (OS) was defined as

Table I. The baseline characteristics of patients.

	Carboplatin plus paclitaxel (N =49)	Carboplatin plus paclitaxel plus bevacizumabin (N = 53)	*p*-value
Gender, n (%)			
Male	40 (81.6)	41 (77.4)	0.594
Female	9 (18.4)	12 (22.6)	
Age (Years)			
Median	66	66	0.319
Range	44-74	48-77	
Histology, n (%)			
Adeno	24 (49.0)	28 (52.8)	0.880
Sq	18 (36.7)	19 (35.9)	
Other	7 (14.3)*	6 (11.3)**	
PS, n (%)			
0	29 (59.2)	23 (43.4)	0.273
1	19 (38.8)	28 (52.8)	
2	1 (2.0)	2 (3.8)	
Smoking history, n (%)			
Never	9 (18.4)	11 (20.8)	0.762
Smoker	40 (81.6)	42 (79.2)	
EGFR status, n (%)			
Mutant	4 (8.2)	6 (11.3)	0.766
Wild-type	15 (30.6)	18 (34.0)	
Unknown	30 (61.2)	2 9 (54.7)	
Stage, n (%)			
IIIA	26 (53.1)	28 (52.8)	0.981
IIIB	23 (46.9)	25 (47.2)	

Adeno, adenocarcinoma; Sq, squamous cell carcinoma; AS, adenosquamous cell carcinoma; Large, large cell carcinoma; PS, performance status; EGFR, epidermal growth factor receptor. *Three adenosquamous cell carcinomas, one basaloid carcinoma and three not otherwise specified (NOS) patients, **two large cell carcinoma and four NOS.

a data from the beginning of the chemotherapy until patients' death and was computed from the trial starting to the death day. The day for the surviving patient was carefully censored on the day they were found alive at the last time. PFS was calculated from the trial starting to the death day, follow-up completion, or disease relapse, whichever firstly occurred. Results of our patients that were progression free or alive were carefully censored when the last follow-up completed. Rates of PFS and OS were computed with Kaplan-Meier test and $p \leq 0.05$ was thought to be statistically significant.

Results

Characteristics of Patients

Baseline characteristics of our selected patients were shown in Table I. Results suggested that no statistical difference was found between the two treated groups concerning their age, gender, histology, smoking history, performance status (PS), stage and the mutations of EGF receptor (EGFR). Thus, the two treated groups were comparable concerning the baseline characteristics.

Toxicity

The adverse events observed in all 102 patients were listed in Table II. Regarding the grade 3 or higher toxicities of chemotherapy, we found higher rates of leukopenia and neutropenia in the CPB group (leukopenia, $p<0.01$; neutropenia, $p<0.01$). Meanwhile, we found frequent occurrence of grade 3 or more severe esophagitis, eruption and thrombocytopenia in the CP group than that in the CPB group (esophagitis, $p=0.023$; eruption, $p=0.053$; thrombocytopenia, $p=0.065$). No treatment-associated death was found in both two groups. Median cycles of the chemotherapy were respectively 4 (rang 1-6) in the CP treated group and the same 4 (range 1-6) in the CPB treated group. There were no significant differences in the cycle numbers of chemotherapy between the two treated groups ($p=0.887$).

Table II. Toxicities experienced using the two combination therapies.

	Carboplatin plus paclitaxel (N =49)						Carboplatin plus paclitaxel plus bevacizumabin (N = 53)					
	Gr1	Gr2	Gr3	Gr4	≥Gr3	All	Gr1	Gr2	Gr3	Gr4	≥Gr3	All
Leukopenia	10	19	12	4	33%	92%	1	11	28	8	68%	43%
Neutropenia	5	14	9	5	29%	67%	3	10	23	12	66%	91%
Anemia	18	13	9	2	22%	86%	10	20	12	3	28%	85%
Thrombocytopenia	22	6	4	5	18%	76%	16	1	2	1	6%	38%
Fatigue	19	12	4	0	8%	71%	26	9	0	0	0%	66%
Anorexia	14	15	6	0	12%	71%	26	13	4	0	8%	81%
Constipation	18	14	0	0	0%	65%	25	10	0	0	0%	66%
Diarrhea	11	6	0	0	0%	35%	7	6	0	0	0%	25%
Nausea	22	13	3	0	6%	78%	25	15	5	0	9%	85%
Vomiting	11	5	0	0	0%	33%	3	7	2	0	4%	23%
Infection	0	6	9	0	18%	31%	3	3	5	0	9%	21%
Febrile neutropenia	0	0	7	0	14%	14%	0	0	6	0	11%	11%
Bilirubin	13	9	0	0	0%	45%	11	4	0	0	0%	28%
AST	9	5	0	0	0%	29%	6	2	0	0	0%	15%
ALT	12	0	5	0	10%	35%	10	0	1	0	2%	21%
Hyponatremia	27	10	5	0	10%	86%	22	0	5	0	9%	51%
Creatinine elevation	15	0	0	0	0%	31%	13	0	0	0	0%	25%
Pneumonitis	26	13	2	0	4%	84%	33	10	3	0	6%	94%
Esophagitis	23	13	5	0	10%	84%	30	13	0	0	0%	88%
Dermatitis	38	8	0	0	0%	94%	44	4	1	0	2%	93%
Eruption	4	4	6	0	12%	29%	12	2	1	0	2%	26%

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

Comparison of Treatment Response

Among the 49 patients in the CP group, 17, 2, 29 and 1 appeared stable disease (SD), progressive disease (PD), complete response (CR)/partial response (PR) and were not evaluated (NE), respectively. As shown in Table III, the response rate of the CP treatment was 59%, and the rate of disease control was 94%. Meanwhile, among the 53 patients in the CPB treated group, 1, 11 and 41 patients showed a PD, SD and CR/PR, respectively. The response rate of the CPB treatment was 77% and the disease control rate was up to 98%. The rates of response and disease control were higher in the CPB group compared to CP group, although there was no statistical significance (rate of response, p=0.210; rate of disease control, p=0.146).

Table III. Tumor response to combination therapies.

	Carboplatin plus paclitaxel (N =49)		Carboplatin plus paclitaxel plus bevacizumabin (N = 53)	
	n	%	n	%
CR/PR	29	59%	41	77%
SD	17	35%	11	21%
PD	2	4%	1	2%
NE	1	2%	0	0%
Response rate (%)	59%*		77%*	
Disease control rate (%)	94% **		98% **	

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.
p-value was calculated to be *0.210 by the χ^2 test, **0.146 by Fisher's exact test.

Comparison of Treatment Survival

As shown in Figure 1 and Figure 2, the median OS and PFS were 24 months (2-39 months) and 20 months (2-37 months) in the CP treated group, respectively. On the other hand, the median OS and PFS were 31 months (4-44 months) and 29 months (5-44 months) in the CPB treated group, respectively. Data suggested that the median OS and the median PFS in the CPB treated group were both significantly higher than that in the CP treated group (OS: $p<0.01$; PFS: $p<0.01$).

Discussion

In this study, we made two important clinical observations. Carboplatin plus weekly paclitaxel and carboplatin plus weekly paclitaxel plus bevacizumab were compared concerning the toxicity, treatment response, and survival of these two chemotherapy regimens. This is, to our known, the first randomized controlled trial to explore the effect of bevacizumab as a kind of consolidated drugs in the chemotherapy for the stage III NSCLC. We found reasonable data of survival in the CPB treated group that the median survival time was 30.7 months and rate of three-year survival was up to 41.5%. Data suggested that the median OS and the median PFS in the CPB treated group were both significantly higher than that in CP treated group. Also, rates of the response and disease control were higher in the CPB treated group (77%, 98%, respectively) compared to CP group (59%, 94%, respectively), although there was no statistically significance. Regarding the grade 3 or higher toxicities of chemotherapy, we found higher rates of leukopenia and neutropenia in the CPB group. On the other hand, we found frequent occurrence of grade 3 or more severe esophagitis, eruption and thrombocytopenia in the CP group than that in the CPB treated group. In the past several years, cancer chemoprevention concerning the use of synthetic or natural agents to retard, reverse or inhibit tumorigenesis, has received elevated attention[16]. Demonstrating the underlying mechanisms involved in the anticancer activity will provide valuable evidence for the development of further anticancer drug. In the carboplatin plus paclitaxel regimen, it was reported that the weekly administration of paclitaxel improved the overall response rate compared to the standard triweekly administration of paclitaxel[11]. Additionally, prior studies have suggested that weekly paclitaxel treatment has antiangiogenic properties[17,18]. Weekly paclitaxel may have a synergistic effect with bevacizumab. Our results also suggest that carboplatin plus weekly paclitaxel with bevacizumab may represent an alternative regimen to carboplatin plus weekly paclitaxel in terms of efficacy. Besides, the toxicities of the two chemotherapy regimens, including peripheral neuropathy, were well tolerated. Leukopenia and neutropenia were the most common grade 3/4 hematological toxicity after the CPB treatment in our study. Previous reports have demonstrated that weekly administration of paclitaxel reduces the appearance of neutropenia, peripheral neuropathy, and myalgia/arthralgia[19]. These findings support our results. Regarding adverse events of bevacizumab, we should pay attention to hemorrhage, including hemoptysis,

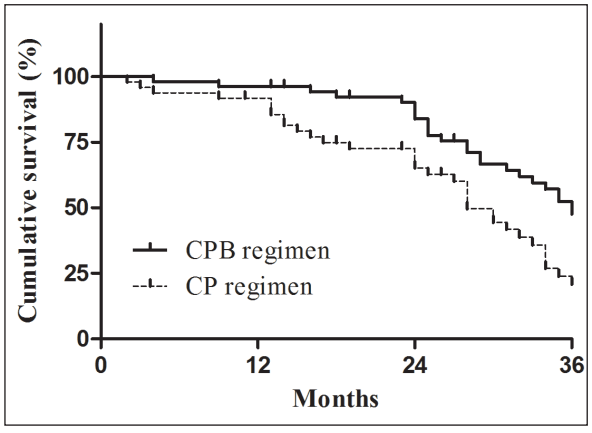

Figure 1. Kaplan-Meier curves for the overall survival (OS) of the patients treated with CP and CPB chemotherapy regimens are shown.

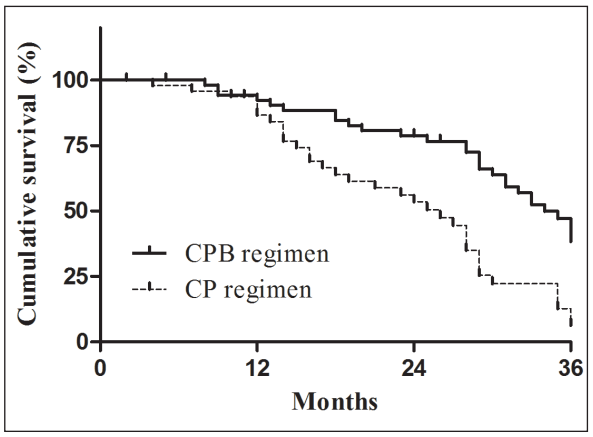

Figure 2. Kaplan-Meier curves for the progression-free survival (PFS) of the patients treated with CP and CPB chemotherapy regimens are shown.

a life-threatening toxicity. Hemoptysis did not occur in this study. The exclusion criteria of this study included patients with a history of hemoptysis, tumor invasion to major blood vessels, and a cavitated tumor as risk factors for pulmonary hemorrhage[20]. The new results in our study were that median OS and median PFS in the CPB treated group were both significantly higher than that in CP treated group. Besides, rates of response and disease control were also higher in the CPB treated group compared with the CP group, although there was no statistically significance. In addition, toxicities of the two chemotherapy regimens were comparable and tolerated by most of the patients. Therefore, the regimen of carboplatin plus paclitaxel plus bevacizumab was more effective and well tolerated in most of the patients with unresectable stage III NSCLC compared with the carboplatin plus weekly paclitaxel regimen. More randomized studies comparing this regimen with carboplatin plus standard paclitaxel with bevacizumab is warranted. This regimen may be a better alternative to the current standard regimen. However, the clear mechanisms underlying the bevacizumab action and its utility for the treatment of lung cancer in human beings still need to be further investigated.

Conclusions

The carboplatin plus paclitaxel plus bevacizumab regimen was more effective and well tolerated in patients with unresectable stage III NSCLC compared with the carboplatin plus paclitaxel regimen. The CPB regimen may be a better alternative to the current standard regimen.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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