A retrospective analysis of cisplatin, pemetrexed, and bevacizumab in previously treated non-small-cell lung cancer

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ABSTRACT

Patients with non-small-cell lung cancer (NSCLC) often have an advanced disease when firstly diagnosed. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR). In this study, we retrospectively analyzed the efficacy of cisplatin, pemetrexed, and bevacizumab in previously treated advanced NSCLC. Results showed that the objective response rate(ORR) of this novel regimen is 43%, median progression-free survival (PFS) was 5.2 months (95% CI, 3.7 to 6.7 months) and median overall survival (OS) was 11.4 months (95% CI, 8.8 to 13.9 months). Adverse events were generally mild, ranging from grade 1 to grade 3. In conclusion, the combination of cisplatin, pemetrexed, and bevacizumab obtained promising results in selected patients with NSCLC. Randomized clinical trials are needed to further investigate the efficacy of this regimen.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is one of the most common carcinoma worldwide [1]. The prognosis of patients with advanced NSCLC is poor, with a median progression-free survival (PFS) of 4–6 months and median overall survival (OS) of 8–10 months [2–7]. Patients harbor epidermal growth factor receptor (EGFR) mutations may benefit from treatment with tyrosine kinase inhibitors (TKIs) such as erlotinib [8] and gefitinib [9]. However, for patients with EGFR wild-type NSCLC, platinum-based chemotherapy is still used for front line treatment.

Angiogenesis is necessary for cancer cells to proliferate and metastasize. The vascular endothelial growth factor (VEGF) could promote tumor angiogenesis [10–12]. Previous studies indicate that VEGF is over expressed in several malignant tumors [13, 14]. Bevacizumab is a monoclonal antibody against VEGF receptor, hence exerts antitumor effect by inhibiting abnormal vascular growth in malignant tumors [15–18]. When adding bevacizumab to platinum-based chemotherapy in the E4599 study, the median OS of nonsquamous NSCLC patients was prolonged to one year (12.3 months), with relatively tolerable toxicities [19]. Based on results from the above study, the U.S. Food and Drug Administration (FDA) approved the use of bevacizumab as first-line therapy for advanced NSCLC [20].

Till date, only single antitumor agents such as erlotinib [21], docetaxel [22, 23] and pemetrexed [24], are recommended in second line therapy. Platinum-based chemotherapy combined with bevacizumab may be effective if patients failed in previously first-line therapy of erlotinib or crizotinib. However, several studies investigated the efficacy of bevacizumab combined with chemotherapeutical drugs for previously treated NSCLC [25–29]. These studies showed increased objective response rate (ORR) and enhanced PFS when compared with the standard second-line therapy.

The regimen of cisplatin plus pemetrexed is extensively used for advanced nonsquamous NSCLC in the clinic [30–36]. This combination produced superior effect than that of cisplatin plus gemcitabine. In addition, results from a phase III study showed improved efficacy when adding bevacizumab to this regimen in front line treatment [37]. Currently, there are no reports concerning the combination of cisplatin, pemetrexed, and bevacizumab for advanced NSCLC beyond first-line settings. Hence, we retrospectively analyzed this regimen for NSCLC patients in our Cancer Center.

RESULTS

Patient characteristics and treatment

The number of eligible patients in our study was 7. The clinical characteristics of these patients are listed in Table 1. Among all the patients, 5 patients (71%) were < 60 years of age (median 50 years; range 28–63 years) and 6 patients (86%) were male. Most patients had a performance status of 1 score and adenocarcinoma subtype (both 86%). Two patients (29%) were EGFR gene mutated, three patients (42%) were wild-type and the remaining two patients (29%) were not taken gene sequencing. Patients had received at least one line of therapy before the initial treatment. In our study, all patients received bevacizumab (7.5 mg/kg), cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) administered every 3 weeks. Dexamethasone, folic acid and vitamin B12 were administered routinely and treatment continued until patients having a progressed disease. Treatment sustained for at least 2 cycles or until disease progression or unacceptable toxicity or economic factors. A median of 4 cycles were administered in this study.

Efficacy

As is illustrated in Table 2, disease control of this novel combination was observed in 6 of 7 NSCLC patients in the study (43% for PR and 43% for SD). Objective

Table 1: Patient characteristics

Patient characteristics	*n*	(%)
Age		
Median	50	
Range	28–63	
Years		
18–60	5	(71%)
60–70	2	(29%)
Sex		
Male	6	(86%)
Female	1	(14%)
ECOG PS		
0	1	(14%)
1	6	(86%)
Smoking history		
Yes	4	(57%)
No	3	(43%)
Pathological type		
Adenocarcinoma	6	(86%)
Large cell	1	(14%)
No. prior regimens		
1	1	(14%)
2	3	(43%)
3	2	(29%)
4	1	(14%)
EGFR status		
Mutation	2	(29%)
Wild-type	3	(42%)
NOS	2	(29%)

Table 2: Efficacy results

Variable	No	%
Response		
PR (%)	3	43
SD (%)	3	43
PD (%)	1	14
Median PFS (months)	5.2	
95% CI	3.7 to 6.7	
Median survival (months)	11.4	
95% CI	8.8 to 13.9	

response rate was 43%. Only one patient obtained PD after 2 cycle of therapy. Median PFS was 5.2 months (95% CI, 3.7 to 6.7 months, Figure 1) and median OS was 11.4 months (95% CI, 8.8 to 13.9 months, Figure 2).

Adverse events

Main toxicities possibly related to therapy are listed in Table 3. Adverse events of this chemotherapeutical regimen were generally mild, ranging from grade 1 to grade 3. Hematologic toxicities observed in the study were mainly grade 1. The most common grade 2 adverse events were non-hematologic toxicities, including 4 episodes of nausea and 3 episodes of anorexia and fatigue. Grade 3 toxicities were anorexia (42.9%), fatigue (28.6%) and nausea (14.3%). No patients in the study had severe adverse events.

DISCUSSION

Standard second-line treatments for patients with advanced NSCLC are mainly single agents. For third-line or beyond therapy, possible choices are erlotinib (regardless of EGFR gene status), crizotinib (if ALK fusing gene existed), clinical trial or best support therapy. Bevacizumab showed encouraging efficacy as first-line therapy for nonsquamous NSCLC patients. In the AVAPEAL study, the treatment results were increased when adding bevacizumab to the combination of cisplatin plus pemetrexed.

Bevacizumab showed increased efficacy in previously treated advanced NSCLC when combined with erlotinib [38, 39]. In one study, the response rates of bevacizumab plus erlotinib was 51.3%, median PFS and OS was 4.4 and 13.7 months, respectively [39]. The combination of bevacizumab, oxaliplatin and pemetrexed for previously treated NSCLC was also investigated [26]. Clinical beneficial rate was 71% and median PFS and OS was 5.8 and 12.5 months, respectively. These studies suggested that bevacizumab may benefit patients with advanced nonsquamous NSCLC in second-line or beyond settings.

In our former study, we investigated the chemotherapeutic regimen of pemetrexed plus bevacizumab in previously treated NSCLC [29]. Results showed that disease control rate was 54.84%, median PFS was 4.37 months and median OS was 15.83 months. Toxicities of this combination treatment are generally tolerable. According to the results of above studies, we conducted this study analyzing the effect of cisplatin, pemetrexed, and bevacizumab for advanced nonsquamous NSCLC beyond first-line settings. This study showed encouraging findings, with ORR 43%, median PFS 5.2 months and median OS 11.4months. Toxicities were also manageable, which rarely produced grade 3 or higher adverse events. These results may possibly due to the young population and good performance status of patients in our study (all are $\leq$ 65 years and PS $\leq$ 1). As the number of patients in this study was relatively small, additional studies are needed to further evaluate the efficacy of this combination beyond first-line setting.

In the study, all patients received EGFR TKIs treatment before the combination therapy. The period ranged from 1 to 14 months, the median therapeutic time was 7 months. After failed from oral EGFR TKIs treatment, patients received salvage therapy of cisplatin, pemetrexed, and bevacizumab for a median time of 4 cycles. The median number of therapeutic time is third-line. Four patients took another EGFR TKIs after failed from this treatment, a strategy according to previous reports. One of the four patients was later found to be ALK fusing gene mutated and received crizotinib for about 1 year. Therefore, the combination regimen of cisplatin, pemetrexed, and bevacizumab enhanced overall survival of patients with advanced NSCLC.

In previous studies, the dose of bevacizumab as second-line or beyond was 15 mg/kg, such as that administered in the E4599 study. The AVAiL study compared the effect of bevacizumab in different doses (7.5 and 15 mg/kg) in combination with chemotherapy [40]. Results showed that both low and high dose level of bevacizumab enhanced median PFS compared to

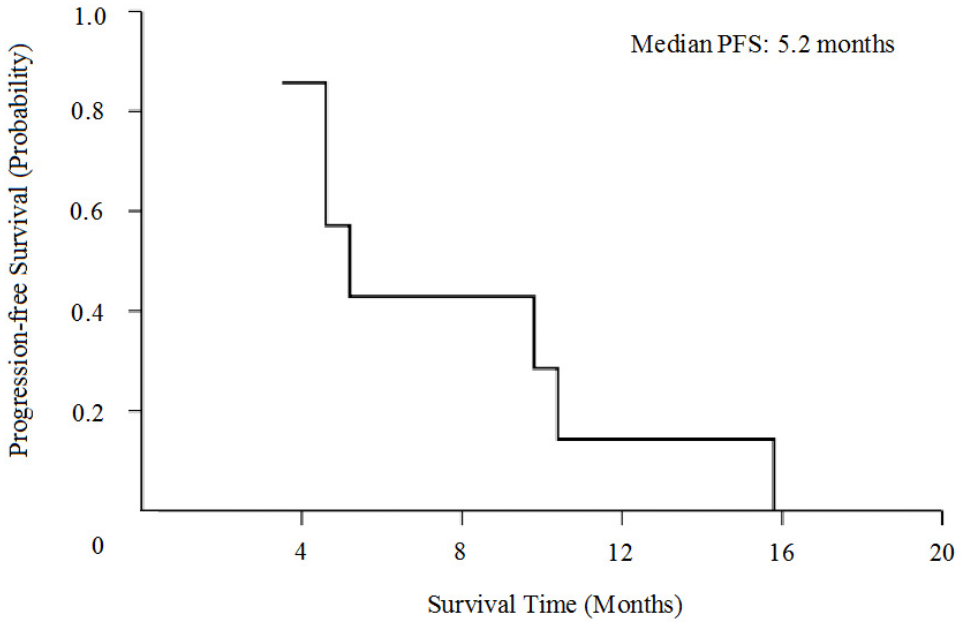

Figure 1: Kaplan-Meier curves for progression-free survival (PFS).

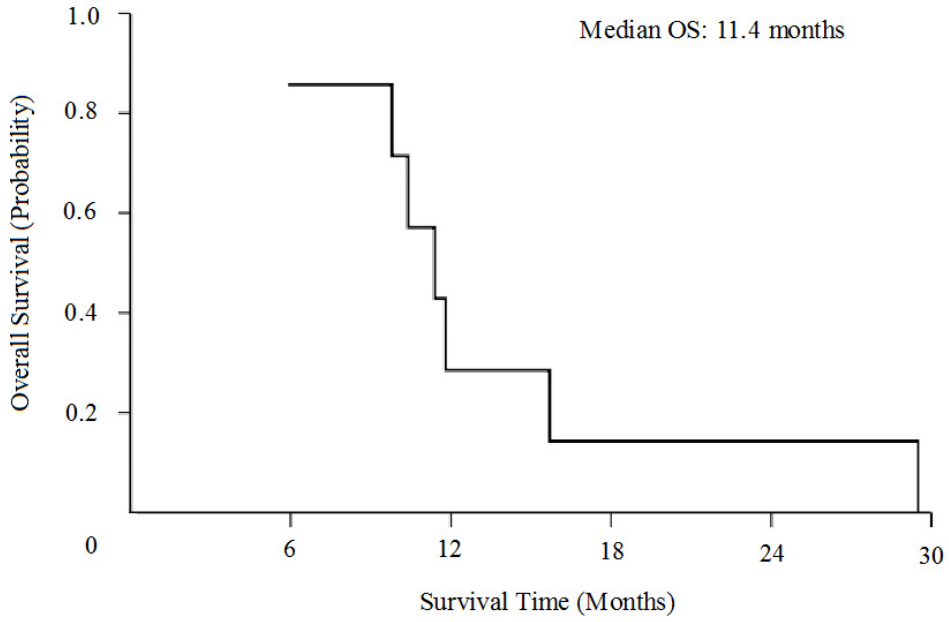

Figure 2: Kaplan-Meier curves for overall survival (OS).

chemotherapy alone arm. In the later AVAPEAL study, researchers used the low dose level (7.5 mg/kg) and also produced favorable results [37]. Nowadays, there are no reports concerning 7.5 mg/kg bevacizumab plus chemotherapy for previously treated advanced NSCLC. In addition, the prescription of bevacizumab seems expensive for patients living in developing countries. Our study showed that the dose of 7.5 mg/kg bevacizumab also works when combined to cisplatin and pemetrexed in the second-line and beyond settings.

In conclusion, the combination of cisplatin, pemetrexed, and bevacizumab obtained promising efficacy in selected patients with previously treated NSCLC. More clinical trials are needed to further elaborate the relationship between this novel regimen and advanced NSCLC in sencon-line or beyond setting.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of patients with previously treated nonsquamous NSCLC at Sun Yat-Sen University Cancer Center from December 2011

Table 3: Treatment-related adverse events

Toxicity	Grade 1	Grade 2	Grade 3
Neutropenia	1	0	0
Thrombocytopenia	1	0	0
Anemia	4	1	0
Dizziness	3	1	0
Fever	1	0	0
Infection	1	2	0
Bleeding	3	0	0
Fatigue	0	3	2
Nausea	0	4	1
Vomiting	0	2	0
Alopecia	1	1	0
Anorexia	1	3	3
Dyspnea	3	1	0
Constipation	1	2	0
Cough aggravation	3	1	0
Abdominal pain	1	1	0
Diarrhea	1	0	0
Rash	1	0	0
Pruritus	0	1	0
ALT ↑	2	0	0
Thirst	4	1	0
Insomnia	0	0	0

to September 2012. The eligible patients were ≥ 18 years old, with cytological or histological confirmation of stage IIIB (with pleural effusion) and stage IV nonsquamous NSCLC (The International Association for the Study of Lung Cancer 7th edition of Tumor Node Metastasis Staging classification) and had already failed at least one platinum-based chemotherapy regimen. Patients whose clinical information could not be completely obtained were excluded from our analysis.

Data collection

The clinical data of patients in our studies were collected carefully. All the patients had an ECOG PS of 0 to 1. Patient history, physical examination and complete blood work were recorded at baseline and before each cycle of treatment. Tumor response was evaluated by computed tomography scans according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Disease control was defined as complete remission (CR), partial remission (PR) or stable disease (SD). Patients who had a progression disease after two cycles of treatment were defined as progression disease (PD). PFS was defined as time between the start of the treatment and disease progression or death. OS was defined as time between the start of the treatment and last contact or death. Toxicities were recorded and classified in the light of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Statistical analysis

Statistical analysis was performed by Statistical Product and Service Solutions (SPSS) 18.0 software. Estimates of PFS and OS were calculated using the Kaplan-Meier method and two-sided 95% confidence interval were obtained.

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None.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

Abbreviations

NSCLC; non-small-cell lung cancer, PFS; progression-free survival, OS; overall survival, EGFR; epidermal growth factor receptor, TKIs; tyrosine kinase inhibitors, VEGF; Vascular epidermal growth factor, FDA; the U.S. Food and Drug Administration, ORR; objective response rate, RECIST Response Evaluation Criteria in Solid Tumors, CR; complete remission, PR; partial remission, SD; stable disease, PD; progression disease, NCI-CTCAE; National Cancer Institute Common Terminology Criteria for Adverse Events, SPSS; Statistical Product and Service Solutions.

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