

# Efficacy of third-line pemetrexed monotherapy versus pemetrexed combination with bevacizumab in patients with advanced EGFR mutation-positive lung adenocarcinoma

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**Objective:** The purposes of this study were to observe the effects of different treatment strategies, including third-line pemetrexed alone versus its combination with bevacizumab, in patients with advanced epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma, and to analyze the effects of the different medication orders of first- and second-line drugs on third-line efficacy.

**Patients and methods:** One hundred and sixteen cases of patients with EGFR-positive lung adenocarcinoma who had received third-line pemetrexed alone or in combination with bevacizumab between March 2010 and March 2014 at Guangzhou Institute of Respiratory Diseases, the First Affiliated Hospital of Guangzhou Medical University were analyzed retrospectively. Additionally, all the patients were treated with first-line gemcitabine and cisplatin (GP) chemotherapy and second-line EGFR tyrosine kinase inhibitor (TKI) or with first-line EGFR-TKI and second-line GP chemotherapy.

**Results:** The median survival of 61 cases with third-line pemetrexed monotherapy was 36.22 months, the median survival time of 55 cases with third-line pemetrexed plus bevacizumab was 38.76 months, and there was a significant difference in survival time between the two groups ( $P=0.04$ ). Subgroup analysis revealed that among the 55 cases with third-line bevacizumab plus pemetrexed treatment, the median survival of 29 patients with first-line GP and second-line EGFR-TKI was 42.80 months, while the median survival of 26 patients with first-line EGFR-TKI and second-line GP was only 34.46 months; additionally, there was a significant difference in the survival time between the two subgroups ( $P=0.001$ ). Among 61 cases with third-line pemetrexed treatment, the median survival of 34 patients with first-line GP and second-line EGFR-TKI was 38.72 months, while the median survival of 27 patients with first-line EGFR-TKI and second-line GP was only 32.94 months; the survival time of the two subgroups was significantly different ( $P=0.001$ ).

**Conclusions:** Regardless of the order of the first- and second-line chemotherapy and TKI therapy, the pemetrexed plus bevacizumab regimen was superior to the pemetrexed monotherapy as the third-line therapy in patients with advanced EGFR-positive lung adenocarcinoma. However, this strategy is worth further investigation in prospective studies.

**Keywords:** Epidermal growth factor receptor (EGFR) mutation; lung adenocarcinoma; pemetrexed; bevacizumab

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## Introduction

Lung adenocarcinoma is the main type of lung cancer (1,2), and several prospective clinical studies have confirmed that epidermal growth factor receptor (EGFR) mutation-sensitive lung adenocarcinoma patients may be the targeted population of EGFR tyrosine kinase inhibitors (TKIs), after EGFR-TKI therapy, the progression-free survival (PFS) and overall survival (OS) of these patients were significantly longer than those with chemotherapy alone (3-5). Different from conventional cancer chemotherapy patterns, EGFR-TKI targeted therapy inhibits tumor cell proliferation by suppressing specific cell signaling transduction related to the occurrence and development of the tumor (6,7). Significant clinical efficacy has been achieved, as a survival benefit was noted for patients with EGFR mutation-sensitive lung cancer in the first-, second- or third-line therapy (6). Compared with conventional cytotoxic chemotherapy, EGFR-TKI targeted therapy has better selectivity and shows relatively minor damage to normal cells (8-11). However, drug resistance appears in almost all patients after a certain period of time. The PFS of most EGFR mutation-positive patients fails to exceed 12 to 14 months (6). How to choose third-line treatment after receiving two lines of treatment, or whether the different medication orders of first- and second-line in the first two lines of therapy affect the efficacy of the third-line treatment, has not yet been reported. Due to various factors, bevacizumab and pemetrexed in particular are currently classified as self-financed drug items in most areas of China. Thus, many patients in China received first-line cisplatin-based chemotherapy and second-line EGFR-TKI therapy or first-line EGFR-TKI and second-line of cisplatin-based chemotherapy, but didn't receive pemetrexed or bevacizumab. Considering this phenomenon, a retrospective analysis was conducted on selected cases of EGFR mutation-sensitive lung cancer patients treated with third-line pemetrexed monotherapy or cisplatin-based chemotherapy in combination with bevacizumab at Guangzhou Institute of Respiratory Diseases, the First Affiliated Hospital of Guangzhou Medical University between March 2010 and March 2014.

## Patients and methods

### Patients

One hundred and sixteen cases of patients with EGFR mutation-positive lung cancer, who had received

**Table 1** Baseline of the two groups of patients

Characteristics	Pemetrexed + bevacizumab, n=55 (%)	Pemetrexed monotherapy, n=61 (%)
Age in years, median [range]	58 [38-78]	59 [38-79]
Gender		
Male	24 (43.64)	29 (47.54)
Female	31 (56.36)	32 (52.46)
Smoking patients	5 (9.09)	8 (13.11)
Clinical stage		
IIIB	7 (12.73)	8 (13.11)
IV	48 (87.27)	53 (86.89)
ECOG PS score		
1	41 (74.55)	45 (73.77)
2	14 (25.45)	16 (26.23)
First-, second-line drugs		
First GP then TKI	29 (52.73)	34 (55.74)
First TKI then GP	26 (47.27)	27 (44.26)
EGFR mutation status		
Exon19del	35 (63.64)	38 (62.30)
Exon21L858R	17 (30.91)	20 (32.79)
Others	3 (5.45)	3 (4.92)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; GP, gemcitabine and cisplatin; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor.

gemcitabine and cisplatin (GP) chemotherapy, one type of EGFR-TKI therapy and a third-line application of pemetrexed alone or in combination with bevacizumab at Guangzhou Institute of Respiratory Diseases, the First Affiliated Hospital of Guangzhou Medical University between March 2010 and March 2014, were retrospectively reviewed. The diagnosis of all the patients was confirmed as EGFR mutation-sensitive positive adenocarcinoma by histopathology and cytology. Among them, there were 73 cases of EXON-19DEL, 37 cases of EXON-21-L858R and 6 cases of other rare mutations. The lesions were computed tomography (CT) measurable, heart, kidney and liver functions were normal, and no bone marrow suppression was found. All the patients received two-line therapy, 63 cases of first-line GP and second-line EGFR-TKI, and 53 cases of first-line EGFR-TKI and second-line GP. The median age of all the patients was 59 years old (range, 38-79 years old) (Table 1).

**Table 2** Efficacy of the third-line pemetrexed monotherapy group, pemetrexed plus bevacizumab group and subgroups

Groups	N	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
Pemetrexed + bevacizumab	55	27.27	80.00	13.64	38.76
First GP then TKI	29	31.03	82.76	17.00	42.80
First TKI then GP	26	23.08	76.92	9.70	34.46
Pemetrexed monotherapy	61	24.59	77.05	9.49	36.22
First GP then TKI	34	29.41	82.35	13.80	38.72
First TKI then GP	27	18.52	70.37	8.80	32.94

ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; GP, gemcitabine and cisplatin; TKI, tyrosine kinase inhibitor.

### Treatment

In pemetrexed monotherapy group, pemetrexed 500 mg/m<sup>2</sup> was added to 100 mL of saline, and the solution was administered over 10 min of intravenous infusion every 21 days for one cycle. Daily oral supplements of 400 µg of folic acid were started 1 week before pemetrexed therapy, and an intramuscular injection of vitamin B12 1,000 µg was repeated every 9 weeks until 3 weeks after the end of the final treatment cycle. Dexamethasone tablets (4 mg) were orally administered 1 day before and on the first and second day of pemetrexed treatment, twice a day. In pemetrexed plus bevacizumab combination group, bevacizumab 7.5 mg/kg, diluted with 100 mL of 0.9% sodium chloride, was administered by intravenous infusion on the first day after chemotherapy (the first infusion time >90 min, no less than 30~60 min afterwards); pemetrexed 500 mg/m<sup>2</sup>, dissolved in 100 mL of 0.9% sodium chloride solution, was administered intravenously by infusion on the second day (intravenous infusion time >10 min), and the pretreatment of pemetrexed was the same as the pemetrexed monotherapy group.

### Efficacy evaluation

Response Evaluation Criteria in Solid Tumors (RECIST) criteria were utilized to assess efficacy, including complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), the objective response rate [ORR; percentage of (CR + PR) patients of the entire group], and the disease control rate [DCR; percentage of (CR + PR + SD) patients of the entire group]. Third-line PFS refers to the time from the first third-line treatment to PD in patients. OS refers to the time from the diagnosis to any cause of death. Subgroup survival curves are plotted with the time of observation on the horizontal axis and

the survival rate on the vertical axis; each time point is connected to its corresponding survival rate.

### Statistical analysis

Using Statistical Product and Service Solutions (SPSS) 16.0 software, efficacy analysis was performed using the *t*-test and self-control *t*-test. The Kaplan-Meier method was used for survival analysis. Two-tailed tests were performed, and P values less than 0.05 were considered to be statistically significant.

## Results

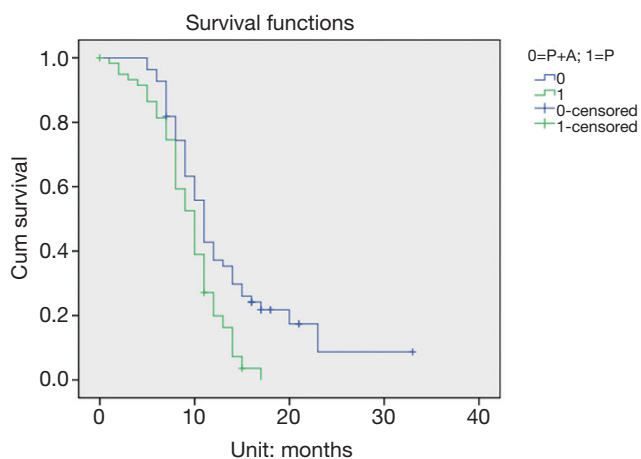
### Efficacy

After third-line treatment, the ORRs of patients in the pemetrexed monotherapy group and pemetrexed plus bevacizumab dual-drug combination group were 24.59% and 27.27%, respectively; and the DCRs were 77.05% and 80.00%, respectively. The difference was not statistically significant (Table 2).

In the pemetrexed plus bevacizumab dual-drug combination group of 55 cases, there were 29 cases of first-line GP and second-line EGFR-TKI and 26 cases of first-line EGFR-TKI and second-line GP. Subgroup analysis showed that the short-term efficacy of first-line GP and second-line EGFR-TKI in 29 patients (ORR and DCR were 31.03% and 82.76%, respectively) was better than that of first-line EGFR-TKI and second-line GP in 26 patients (ORR and DCR were 23.08% and 76.92%, respectively); however, no statistical difference was reached (Table 2).

### Survival

The median PFS values of patients with third-line treatment



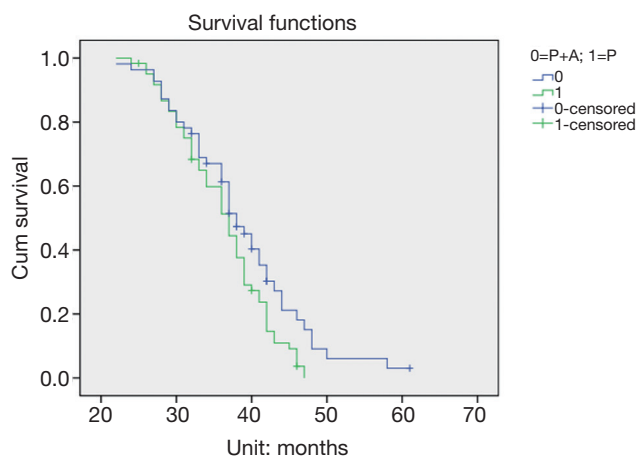
**Figure 1** The progression-free survival (PFS) times of patients in the third-line pemetrexed monotherapy group (P) and pemetrexed plus bevacizumab double-drug combination group (P + A) were 9.49 and 13.64 months, respectively ( $P=0.001$ ).

in the pemetrexed monotherapy group and pemetrexed in combination with bevacizumab group were 9.49 and 13.64 months, respectively ( $P=0.001$ ) (Figure 1). The median OS was 36.22 and 38.76 months, respectively ( $P=0.04$ ) (Figure 2).

Subgroup analysis of the third-line pemetrexed plus bevacizumab dual-drug combination group in 55 cases showed that the long-term efficacy of first-line GP and second-line EGFR-TKI in 29 cases of patients (median PFS and OS were 17.00 and 42.80 months, respectively) was superior to that of first-line EGFR-TKI and second-line GP in 26 cases of patients (median PFS and OS were 9.70 and 34.46 months, respectively) ( $P<0.05$ ). Additionally, subgroup analysis of the pemetrexed monotherapy group of 61 cases showed that the long-term efficacy of first-line GP and second-line EGFR-TKI in 34 patients (median PFS and OS were 13.80 and 38.72 months, respectively) was better than that of first-line EGFR-TKI and second-line GP in 27 patients (median PFS and OS were 8.80 and 32.94 months, respectively) ( $P<0.05$ ) (Table 2).

## Discussion

In the current retrospective study of 116 cases of EGFR mutation-sensitive patients with the application of GP chemotherapy and EGFR-TKI in a different first- and second-line order and the third-line application of pemetrexed with or without bevacizumab, the impact of different medication orders and combinations of these lines



**Figure 2** The median overall survival time of third-line pemetrexed monotherapy (P) in 61 cases was 36.22 months, the median survival time of third-line pemetrexed plus bevacizumab (P + A) in 55 cases was 38.76 months ( $P=0.04$ ).

of drugs on patient outcomes was preliminarily investigated.

For patients with advanced EGFR mutation-sensitive lung cancer, EGFR-TKI treatment must be considered. In 2004, it was reported that very promising results were achieved after the administration of gefitinib in a patient with ineffective multi-line chemotherapy; this case study set the prelude to targeted therapy use in lung adenocarcinoma (12). Subsequent studies including IPASS, NEJ002, WTJOG3405, EURTAC and OPTIMAL (3-5,13,14), all found in subgroup analysis that for EGFR mutation-sensitive patients, regardless of first-line EGFR-TKI or first-line chemotherapy, the survival time was the longer in patients who had received both treatments. However, how to choose third-line medication after second-line treatment, or whether the order of the former two-line therapy would affect the third-line therapy, has not yet been reported.

Pemetrexed was originally used for the treatment of pleural mesothelioma (15) and has achieved remarkable results. Subsequent studies have also confirmed its position in the treatment of lung adenocarcinoma (16-18). Bevacizumab, a recombinant vascular endothelial growth factor (VEGF) monoclonal antibody, is the world's first VEGF inhibitor approved for marketing and may be combined with all VEGF isoforms (19). In terms of the range optimization of treatment, for patients with advanced EGFR mutation-sensitive lung adenocarcinoma, after first- or second-line use of three generations of cisplatin dual-

drug and EGFR-TKI, third-line bevacizumab may be a choice for the treatment plan. Studies on bevacizumab and pemetrexed have indicated that both drugs may have advantages in lung adenocarcinoma and are safe with low toxicity (16,20). The previous studies indicated that the application of the pemetrexed and bevacizumab combination regimen maybe a better choice as a third-line treatment for patients with a poor performance status (PS) score and advanced EGFR mutation-sensitive lung adenocarcinoma (20).

In the current study, we found that regardless of the order of first- and second-line chemotherapy and TKI therapy, as long as bevacizumab was added to the third-line therapy, the pemetrexed in combination with bevacizumab regimen was superior to pemetrexed monotherapy. At present, or even in the future, it may be difficult to carry out prospective studies on multi-line treatment for patients with advanced EGFR mutation-sensitive lung cancer in terms of full-range optimized therapy. However, we may be inspired from the existing first- or second-line so-called alternate treatment patterns. Similar results were obtained from previous studies (21,22) as well as this multi-line retrospective study. The reason can be explained from a biological evolution perspective. When the patients are continuously treated with the same class of drugs, due to the evolution of tumor cells, which have adapted to this environment, the tumor cells are more resistant to the same type of treatment; however, when an entirely different treatment approach is applied, due to the tumor cells failing to adapt to the new environment, the possibility of resistance may be lower. Over time, however, when the tumor cells have adapted to the new environment and become resistant and a treatment approach similar to the prior environment is re-applied, then the old treatment has to some extent become a new environment; thus, an alternative treatment strategy may be a better choice.

In conclusion, regardless of the order of the first- and second-line chemotherapy and TKI therapy, the pemetrexed plus bevacizumab regimen was superior to the pemetrexed monotherapy as the third-line therapy in patients with advanced EGFR mutation-positive lung adenocarcinoma. However, this strategy is worth further investigation in prospective studies.

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