Medicine®

OPEN

Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) combined with bevacizumab for advanced non-squamous non-small-cell lung cancer patients with gradual progression on EGFR-TKI treatment
A cohort study

Yuman Yu, MD, Yuehong Wang, MD, Linying Wu, PhD, Xuanli Xu, PhD, Hua Zhou, PhD, Qing Wang, PhD, Jianying Zhou, MD* 🆔

Abstract
Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) significantly improve outcomes of patients with EGFR-mutated non-small-cell lung cancer (NSCLC). However, acquired resistance inevitably emerges and remains a major challenge. The present study aimed to evaluate the efficacy of EGFR-TKIs plus bevacizumab in advanced non-squamous NSCLC patients with gradual progression on EGFR-TKIs.

Advanced non-squamous EGFR-mutated NSCLC patients with gradual progression on EGFR-TKIs were administered bevacizumab while EGFR-TKIs were continued until disease progression occurred. Tumor lesions were assessed, and blood samples were collected at the start of the combination treatment and every 6 weeks until disease progression.

Among the 15 included patients, there were no grade 3 or higher adverse events (AEs). Partial response (PR) and stable disease (SD) were achieved in 1 and 13 patients, respectively, with an objective response rate (ORR) of 6.7% and a disease control rate (DCR) of 93.3%. The median progression-free survival 2 (PFS2), defined as the time from the initiation of combination treatment to disease progression, was 5.0 (95% confidence interval [CI]: 4.0–6.0) months. Additionally, Spearman correlation analysis revealed that PFS2 was positively correlated with the serum vascular endothelial growth factor (VEGF) level at baseline ($r = 0.7212$, $P = .0234$). Patients with high baseline serum VEGF levels showed a better median PFS2 than those with low baseline serum VEGF levels (5.5 months vs 3.6 months, $P = .0333$).

EGFR-TKIs plus bevacizumab led to a durable prolongation of PFS in non-squamous NSCLC patients with gradual progression on EGFR-TKIs. This therapeutic regimen was well tolerated and could be a promising strategy for these patients. Serum VEGF could be a potential biomarker to predict a subset of patients who are likely to benefit from EGFR-TKIs combined with bevacizumab.

Abbreviations: AE = adverse event, CI = confidence interval, CR = complete response, DCR = disease control rate, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, ELISA = enzyme-linked immunosorbent assay, FDA = Food and Drug Administration, HGF = hepatocyte growth factor, NSCLC = non-small-cell lung cancer, ORR = objective response rate, PD = progressive disease, PFS = progression-free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.

Keywords: acquired resistance, bevacizumab, epidermal growth factor receptor mutation, epidermal growth factor receptor tyrosine kinase inhibitor, non-small-cell lung cancer

1. Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have achieved remarkable clinical responses in advanced non-small-cell lung cancer (NSCLC) patients harboring activating EGFR mutations.[1–3] Lung adenocarcinoma patients with EGFR mutations had a response rate as high as 80% to EGFR-TKI treatment and approximately 9 to 13 months of progression-free survival (PFS).[4–7]

However, despite the excellent therapeutic effect of EGFR-TKIs in the treatment of patients with EGFR-mutated NSCLC, almost all patients develop progressive disease (PD) due to acquired resistance.[8] The management of NSCLC patients who acquire resistance to EGFR-TKIs remains an ongoing challenge. In current clinical practice, EGFR-TKI acquired resistance can be divided into 3 clinical types based on different durations of disease control, the evolution of tumor burden, and clinical symptoms: dramatic progression, gradual progression, and local progression. For patients with gradual progression, the continuation of EGFR-TKIs as an optimal treatment strategy has been recommended.[9]

Tumor angiogenesis is indispensable for tumor proliferation and metastasis, and abnormalities in the vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) pathway are recognized as a key factor in tumor angiogenesis.[10] The VEGF and EGFR pathways are known to be extensively interrelated.[11] In xenograft models, VEGF was greatly reduced by erlotinib in the erlotinib-sensitive phase but significantly elevated in the erlotinib-refractory phase.[12] Since an overactive VEGF pathway plays a crucial role in the resistance to EGFR-TKIs, the dual targeting of both the VEGF and EGFR pathways may prevent resistance through VEGF.[13]

Bevacizumab, a recombinant, humanized monoclonal antibody directly targeting VEGF, received Food and Drug Administration (FDA) approval for the treatment of non-squamous NSCLC in 2006. This treatment causes preexisting tumor blood vessels to regress and blocks the formation of new vessels.[14] In the randomized Phase 2 JO25567 trial in Japan, first-line treatment with bevacizumab plus erlotinib significantly prolonged PFS in advanced non-squamous NSCLC patients with EGFR mutations compared with erlotinib alone.[15] Additionally, the BELIEF trial in European countries further validated the PFS benefit of erlotinib combined with bevacizumab as a first-line treatment for NSCLC patients with activating EGFR mutations.[16] Recently, another randomized Phase 3 trial in Japan (NEJ026) corroborated these findings and demonstrated that bevacizumab combined with erlotinib significantly improved PFS compared with erlotinib alone in patients with EGFR-mutated NSCLC.[17] For a real-world population with EGFR-mutated NSCLC, first-line treatment with EGFR-TKIs and bevacizumab significantly extended PFS as well.[18] A significantly extended PFS of approximately 16 months in EGFR-mutated patients was achieved in response to the first-line use of EGFR-TKIs with bevacizumab, which suggested the synergistic effects of bevacizumab and EGFR-TKIs. However, the fact that long-term combination therapy may result in increased toxicity, particularly hypertension, proteinuria, and hemorrhagic events, remains a concern. Instead of first-line treatment of EGFR-TKIs with bevacizumab, the addition of bevacizumab upon the development of acquired resistance to EGFR-TKIs is much more acceptable and safer for patients with EGFR-mutant NSCLC.

Nonetheless, it remains largely unknown whether bevacizumab still acts synergistically with EGFR-TKIs after acquired resistance develops. Hence, it is worthwhile to explore the potency of combined bevacizumab treatment upon EGFR-TKI resistance.

In a preclinical study that established a xenograft model with acquired resistance to erlotinib, the addition of bevacizumab to erlotinib treatment showed enhanced antitumor activity and prolonged efficacy in the erlotinib-refractory phase.[12] Thus, we hypothesized that combination treatment with EGFR-TKIs and bevacizumab in patients with gradual progression on EGFR-TKIs might be beneficial. The aim of this study was to evaluate the clinical efficacy of this combination treatment strategy in advanced non-squamous NSCLC patients after gradual progression on EGFR-TKI treatment.

2. Patients and methods

2.1. Patient eligibility

This was a cohort study at our center. Eligible patients with cytologically or histologically confirmed stage IIIB/IV or postoperative recurrent non-squamous NSCLC with an activated EGFR mutation (exon 19 deletion, exon 21 L858R, exon 18 G719X, or exon 20 S768I) who experienced gradual progression on EGFR-TKIs (gefitinib, icotinib, or afatinib) were enrolled from August 2018 to August 2019. The definition of gradual progression on EGFR-TKI treatment was based on a study by Yang et al.[9] The criteria for gradual progression were as follows: disease control for ≥6 months with EGFR-TKI treatment; minor increase in tumor burden compared with the previous assessment; and a symptom score ≤1.[9] Clinical symptoms, including cough, hemoptysis, chest pain, fever, dyspnea, and metastatic lesion-related symptoms, were quantified, and symptom scores of 0, 1, and 2 were quantified based on the asymptomatic status, stability of the pre-existing item, and deterioration of any pre-existing item or new item, respectively.[19] The radiographic response to EGFR-TKI treatment was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1). The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University and was conducted according to the Declaration of Helsinki. All participating patients provided written informed consent.

2.2. Treatment

Gefitinib and afatinib were prescribed orally at dosages of 250 and 40 mg once daily, respectively, and the dose of oral icotinib was 125 mg 3 times daily. After gradual progression, bevacizumab was intravenously administered at 7.5 mg/kg every 3 weeks with the continuation of previous EGFR-TKI treatment until disease progression or unacceptable toxicity was observed.

2.3. Evaluation

Tumor lesions were assessed by computed tomography 2 months before gradual progression on EGFR-TKI treatment, at baseline (the start of combination treatment), and every 6 weeks thereafter until disease progression on combination treatment. The primary endpoint was progression-free survival 2 (PFS2), defined as the time from the date of combination treatment initiation to disease progression. The secondary endpoints were the objective response rate (ORR) and disease control rate (DCR). Tumor

rebiopsy was performed after disease progression on combination treatment to examine the EGFR T790 M status.

2.4. Serum analyses

Blood samples were obtained at baseline, 6 weeks thereafter and at disease progression. These samples were incubated at room temperature for 30 minutes and centrifuged at $1000 \times g$ for 15 minutes. The top layer of serum was aliquoted into three fresh tubes and stored at $-80\,°C$ until use. Enzyme-linked immunosorbent assay (ELISA) (BioLegend, San Diego, CA) for human VEGF was used to quantify each serum analyte according to the manufacturer's instructions. Serum hepatocyte growth factor (HGF) concentrations were determined using a Human HGF ELISA Kit (Thermo Fisher Scientific, Waltham, MA). All the samples were tested in triplicate.

2.5. Statistical analysis

Tumor response was evaluated according to RECIST 1.1. Progression-free survival 1 (PFS1) was defined as the time from the beginning of EGFR-TKI treatment to gradual progression. PFS2 was calculated from the date of combination treatment initiation to disease progression. The ORR was defined as the rate of complete response (CR) + partial response (PR). The DCR was defined as the rate of CR+PR + stable disease (SD). PFS was analyzed using the Kaplan–Meier method to estimate the median points with 95% confidence intervals (CIs). Comparisons of PFS2 between subgroups were conducted using a log-rank test. Hazard ratios (HRs) and corresponding 95% CIs were estimated from the Cox model. Spearman's test was applied to assess the correlation between serum VEGF or HGF levels and PFS2. Statistical analyses were conducted using SPSS 23.0 software (IBM Corporation, Chicago, IL).

3. Results

3.1. Patients

A total of 15 EGFR-mutated non-squamous NSCLC patients with gradual progression on EGFR-TKI treatment were enrolled.

Table 1

Patient characteristics (n = 15).

Characteristics	No. of patients (%)
Age, y	
Median (range)	64 (47–83)
Sex	
Male, N (%)	7 (46.7%)
Female, N (%)	8 (53.3%)
ECOG PS	
0	5 (33.3%)
1	10 (66.7%)
Smoking history	
Never	9 (60.0%)
Former/current	6 (40.0%)
Stage	
IIIB	2 (13.3%)
IV	13 (86.7%)
Relapse after surgery	1 (6.7%)
Histology	
Adenocarcinoma	15 (100%)
Primary EGFR mutation status	
Exon 21 (L858R)	5 (33.3%)
Exon 19 (deletion)	8 (53.3%)
Exon 18 (G719X)	1 (6.7%)
Exon 20 (S768I)	1 (6.7%)
Previous EGFR-TKIs	
Gefitinib	5 (33.3%)
Icotinib	9 (60.0%)
Afatinib	1 (6.7%)

ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

The patient characteristics are shown in Table 1. The median age was 64 years (range, 47–83 years). Females (8 of 15, 53.3%) and individuals who had never smoked (9 of 15, 60.0%) were dominant. The primary EGFR mutation status was an exon 19 deletion in 8 patients (53.3%), exon 21 L858R in 5 (33.3%), exon 18 G719X in 1 (6.7%), and exon 20 S768I in 1 (6.7%). Patients received gefitinib (5 of 15, 33.3%), icotinib (9 of 15, 60.0%), and afatinib (1 of 15, 6.7%). During the follow-up period, 2 patients were lost to follow-up.
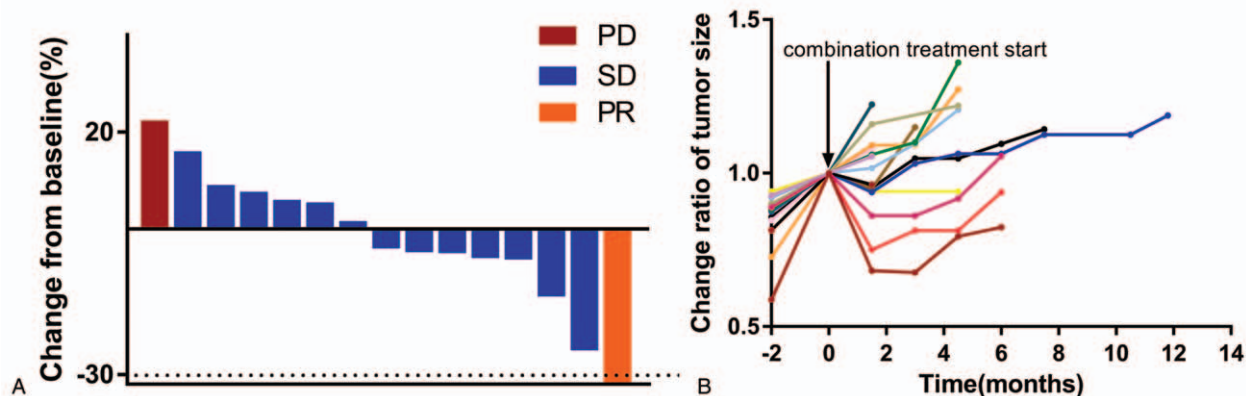

Figure 1. Change in tumor size after combination treatment with EGFR-TKIs and bevacizumab. (A) Waterfall plot of the best percentage change from baseline (the start of combination treatment) for the sum of the longest tumor diameters. Tumor response to combination therapy with EGFR-TKIs and bevacizumab was confirmed according to RECIST version 1.1. (B) Dynamic changes in tumor size in individual patients before and after receiving combination treatment with EGFR-TKIs and bevacizumab. The arrow indicates the time when combination treatment was initiated. EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; RECIST = Response Evaluation Criteria in Solid Tumors.
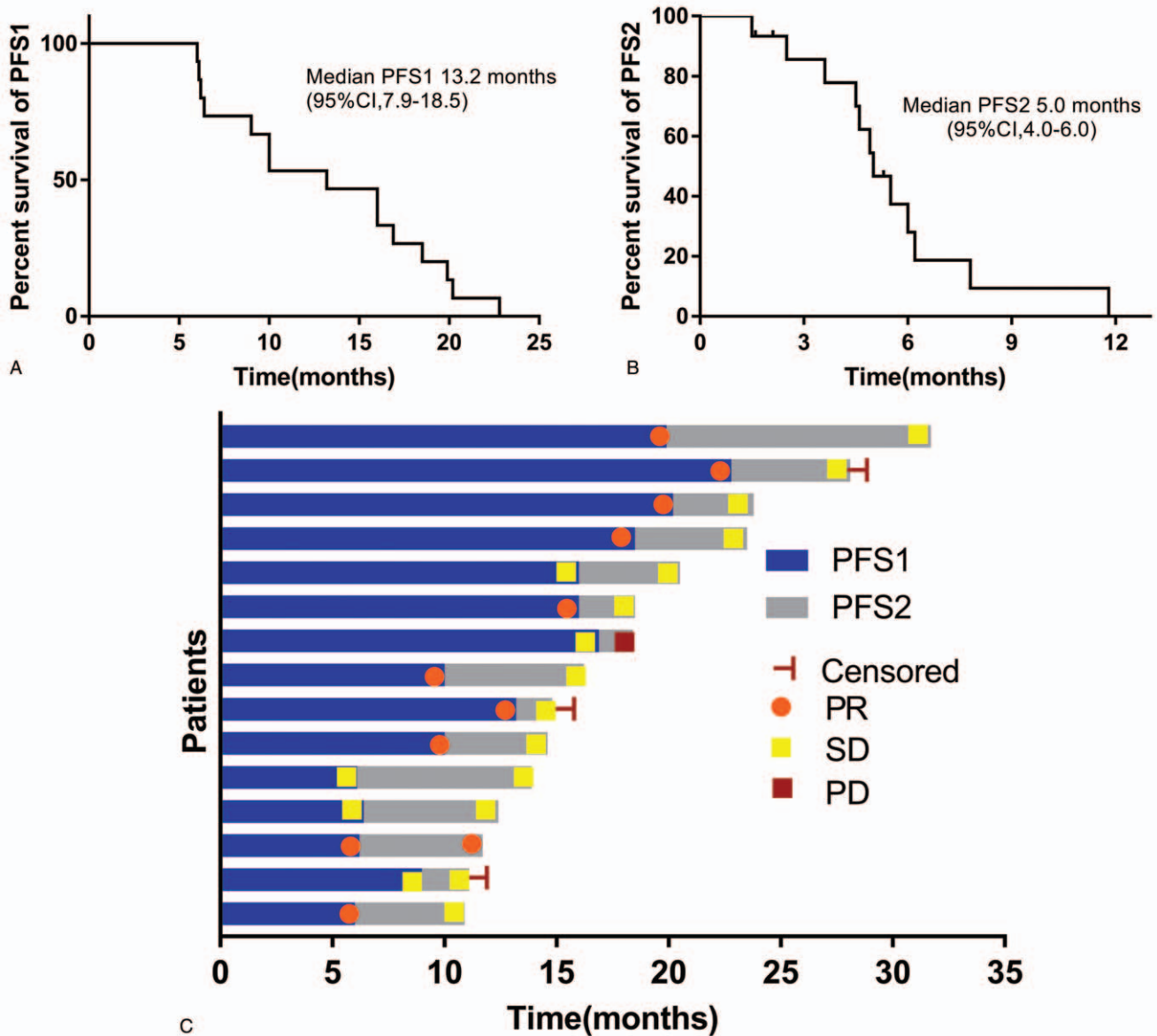
Figure 2. PFS for all patients who received combination treatment with EGFR-TKIs and bevacizumab (n = 15). (A) Kaplan–Meier estimate of PFS1 for all patients (n = 15). The median PFS1 was 13.2 [95% CI 7.9–18.5] months. (B) Kaplan–Meier estimate of PFS2 for all patients (n = 15). The median PFS2 was 5.0 (95% CI: 4.0–6.0) months. (C) Individual swimmer plot for each patient. Each bar depicts PFS1 on the initial EGFR-TKI treatment (blue) and PFS2 on combination treatment with EGFR-TKIs and bevacizumab (gray). The yellow square, red square, and orange circle represent the best responses to the initial EGFR-TKI treatment and combination treatment, respectively. EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; PFS = progression-free survival.

3.2. Efficacy and safety

The waterfall plot in Fig. 1A shows the change in tumor size from baseline (the start of combination treatment) for each patient. No CR was confirmed. PR and SD were achieved in 1 and 13 patients, respectively, with an ORR of 6.7% and a DCR of 93.3%. Figure 1B shows the changes in tumor size for each patient before and after receiving combination treatment with EGFR-TKIs and bevacizumab. Tumor shrinkage was observed in 8 (53.3%) patients. The median PFS1 on the initial EGFR-TKI treatment was 13.2 (95% CI: 7.9–18.5) months (Fig. 2A), and the median PFS2 on combination treatment was 5.0 (95% CI: 4.0–6.0) months (Fig. 2B). The swimmer plot in Fig. 2C shows PFS1

on the initial EGFR-TKI treatment and PFS2 on combination treatment with EGFR-TKIs and bevacizumab for each patient. Figure 3 shows representative imaging of 3 patients.

No grade 3 or higher adverse events (AEs) were observed. One case of (6.7%) grade 2 hypertension, 1 case of (6.7%) grade 1 proteinuria, and 1 case of (6.7%) grade 1 rash were observed.

3.3. Efficacies in EGFR T790M-positive and EGFR T790M-negative patients

Rebiopsy was performed on 12 patients after progression on combination therapy with EGFR-TKIs and bevacizumab. Seven
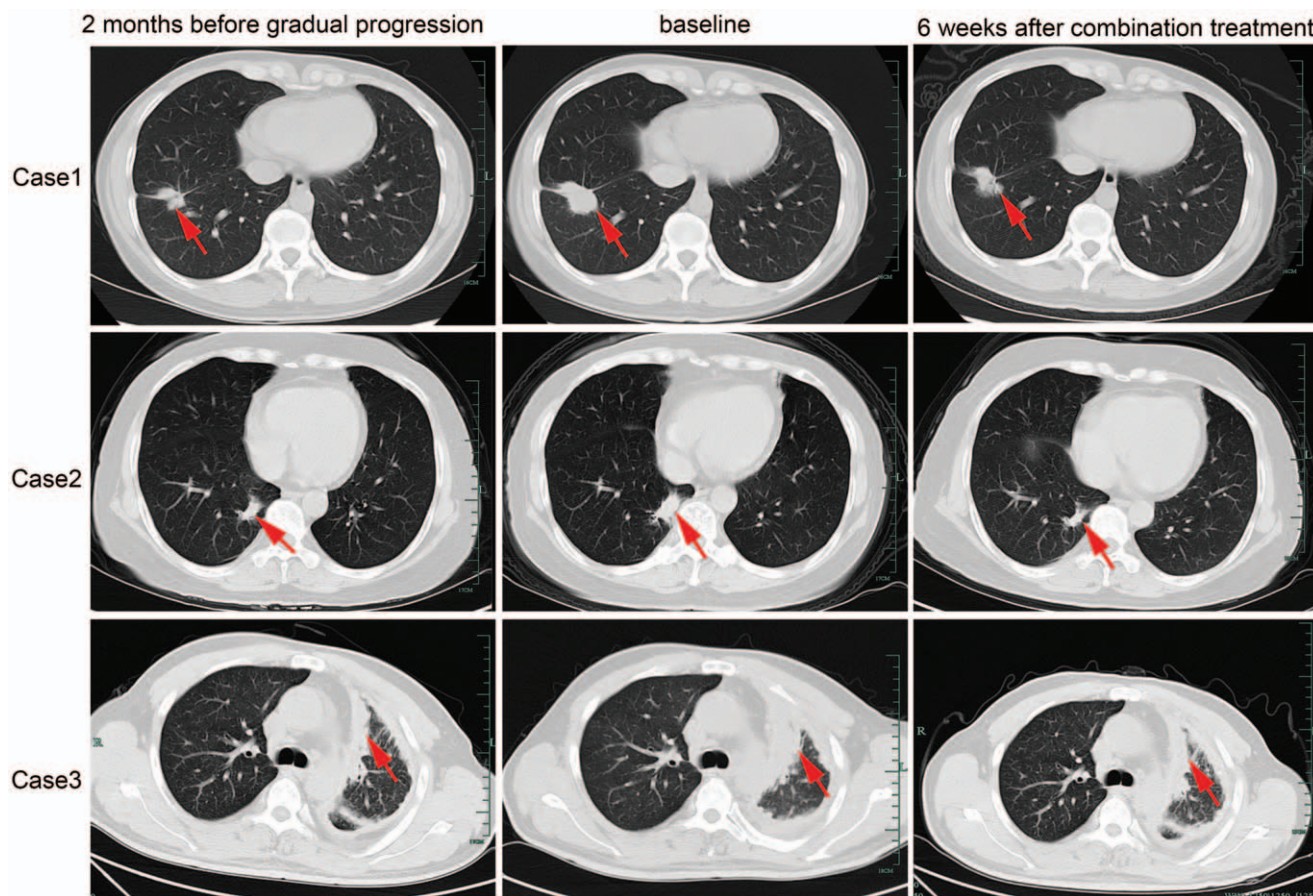
Figure 3. Representative chest CT images show the tumor size 2 months before gradual progression, at the start of combination treatment and 6 weeks after combination treatment. Chest CT scans in 3 patients showed gradual progression on the initial EGFR-TKI therapy and tumor shrinkage after combination therapy with EGFR-TKIs and bevacizumab. CT = computed tomography; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

(58.3%) patients were EGFR T790M-positive, and 5 (41.7%) patients were EGFR T790M-negative. The median PFS2 of T790M-positive patients and T790M-negative patients was 4.9 (95% CI: 4.4–5.4) months and 4.5 (95% CI: 2.1–6.9) months (HR 1.77, 95% CI: 0.51–6.12, P = .3028), respectively (Fig. 4).

3.4. Correlation between PFS2 and serum protein levels at baseline

Blood samples were obtained at baseline (the start of combination treatment), 6 weeks thereafter and at disease progression in 10 patients. To explore biomarkers that were predictive of clinical benefit from combination treatment with EGFR-TKIs and bevacizumab after developing acquired resistance, we investigated associations between serum VEGF and HGF levels and PFS2 by using Spearman test. Figure 5A demonstrates that PFS2 was positively correlated with the serum VEGF level at baseline (r = 0.7212, P = .023). Baseline serum VEGF levels were relatively low in the patient who experienced PD (110.9 pg/mL). As shown in Fig. 5B, after 6 weeks of combination treatment with bevacizumab and EGFR-TKIs, the serum VEGF levels in all patients were significantly decreased and remained low at disease progression. We selected the median baseline serum VEGF level among the 10 patients to classify those patients. Patients with high baseline serum VEGF levels (n = 5) showed a better median

PFS2 than those with low baseline serum VEGF levels (n = 5) (5.5 months vs 3.6 months, P = .0333) (Fig. 5C). However, no significant correlation (r = −0.1758, P = .6321) was observed
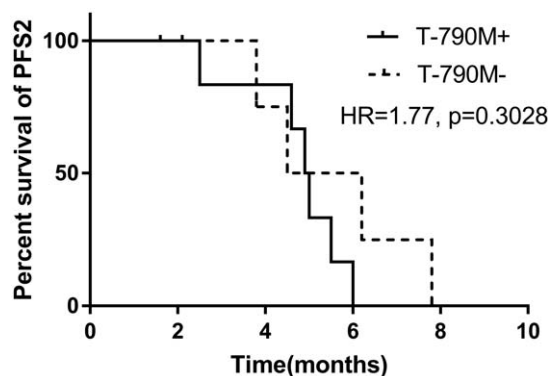

Figure 4. Comparison of PFS2 between T790M-positive and T790M-negative populations. The median PFS2 of T790M-positive patients (n = 7) and T790M-negative patients (n = 5) was 4.9 months (95% CI: 4.4–5.4 months) and 4.5 months (95% CI: 2.1–6.9 months) (HR 1.77, 95% CI: 0.51–6.12, p = 0.3028), respectively. CI = confidence interval; HR = Hazard ratio; PFS = progression-free survival.
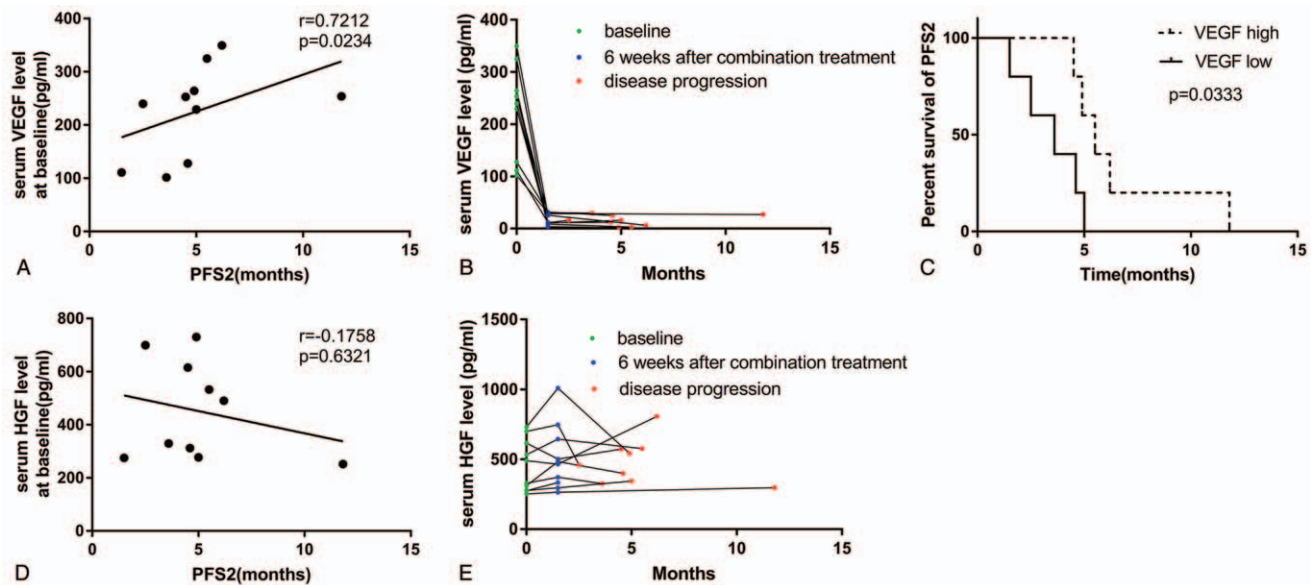
Figure 5. Correlation between PFS2 and serum protein levels at baseline. (A) Correlation between serum VEGF levels at baseline (the start of combination treatment) and PFS2 (n = 10). Spearman correlation analysis revealed that serum VEGF levels at baseline were positively correlated with PFS2 (r = 0.7212, P = .0234). (B) Dynamic changes in serum VEGF levels at baseline, 6 weeks after combination treatment and at disease progression (n = 10). After 6 weeks of combination treatment with bevacizumab and EGFR-TKIs, the serum VEGF levels of all patients were significantly decreased and remained low at disease progression. (C) PFS2 classified by high and low baseline serum VEGF levels. Patients were divided into high and low VEGF groups by a median baseline serum VEGF value (246.3 pg/mL). Patients with high baseline serum VEGF levels (n = 5) showed a better median PFS2 than those with low baseline serum VEGF levels (n = 5) (5.5 months vs 3.6 months, P = .0333). (D) Correlation between serum HGF levels at baseline and PFS2 (n = 10). Spearman correlation analysis revealed that there was no significant correlation between serum HGF levels at baseline and PFS2 (r = −0.1758, P = .6321). (E) Dynamic changes in serum HGF levels at baseline, 6 weeks after combination treatment and at disease progression (n = 10). EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; HGF = hepatocyte growth factor; VEGF = vascular endothelial growth factor.

between PFS2 and serum HGF levels at baseline (Fig. 5D). Dynamic changes in serum HGF levels are shown in Fig. 5E.

4. Discussion

The occurrence of acquired resistance is a major obstacle to the successful long-term treatment of patients with EGFR-mutant NSCLC. In this study, the combination of continued EGFR-TKIs with bevacizumab after gradual progression on EGFR-TKI treatment demonstrated an ORR of 6.7% and a DCR of 93.3%. The ORR seems relatively low, but most patients achieved a certain extent of tumor shrinkage or a diminished tumor growth rate. Importantly, combination treatment with EGFR-TKIs and bevacizumab prolonged PFS2 with a median PFS2 of 5.0 months, and there were no grade 3 or higher AEs. Our findings were consistent with those of a previous study that retrospectively evaluated EGFR-TKI rechallenge with bevacizumab in NSCLC patients who developed acquired resistance to EGFR-TKIs.[20] The combination of EGFR-TKIs and bevacizumab was administered after an EGFR-TKI-free interval in their study, however we continued treatment with EGFR-TKIs and bevacizumab without an EGFR-TKI-free interval.[20] The clinical efficacy was not exactly comparable between the 2 studies due to different study designs. However, a similar PFS prolongation was observed in both studies (5.0 months and 4.1 months).[20] In addition, the Japanese ABC Study evaluated afatinib-bevacizumab combination therapy after acquired resistance to EGFR-TKI treatment developed and also observed a PFS prolongation with a median PFS of 6.3 months.[21] Thus, EGFR-TKIs combined with bevacizumab achieved longer disease control and were well tolerated by patients.

The mechanism driving the enhanced therapeutic efficacy of combination treatment with EGFR-TKIs and bevacizumab may be related to the blockade of the VEGF signaling pathway by bevacizumab. VEGF is an important regulator of angiogenesis and a confirmed target for NSCLC.[22,23] EGFR-TKI resistance is associated with increased tumor-derived and host stromal-derived VEGF.[24] By inhibiting VEGF, bevacizumab blocks tumor angiogenesis and normalizes aberrant tumor vessels, thereby improving tumor oxygenation and restoring the intra-tumoral delivery of EGFR-TKIs.[25–27] Thus, elevated VEGF facilitates tumor growth through various mechanisms, and the combined blockade of both VEGFR and EGFR may overcome resistance to EGFR-TKIs.

Although bevacizumab combined with EGFR-TKIs enhanced antitumor effects via VEGF pathway inhibition, not all cases with acquired resistance benefited from combination therapy. Our study demonstrated that patients with higher serum levels of VEGF showed a longer PFS2, suggesting that the efficacy of bevacizumab differs among patients with different VEGF levels. This finding is consistent with a preclinical in vivo study that demonstrated that the efficacy of erlotinib-bevacizumab combination therapy differs among EGFR-TKI-resistant NSCLC xenografts expressing distinct levels of VEGF and that combination therapy partially reversed resistance to EGFR-TKIs in H157 xenografts expressing high levels of VEGF protein.[28]

To the best of our knowledge, our study is the first to identify VEGF as a predictive biomarker for evaluating the efficacy of EGFR-TKIs combined with bevacizumab. It might be confusing that the VEGF level was not identified as a biomarker in previous clinical trials evaluating first-line treatment with bevacizumab

and EGFR-TKIs in EGFR-mutant NSCLC patients.[15–18] One possible explanation for this discrepancy is that tumor VEGF levels are lower in the EGFR-TKI-sensitive phase. Tumor VEGF levels were reported to be reduced by erlotinib in the erlotinib-sensitive phase but significantly increased after acquired resistance developed in a preclinical model.[12] When tumor VEGF increases after acquired resistance to EGFR-TKIs develops, tumors expressing higher levels of VEGF are potentially more dependent on VEGF signaling. Overall, VEGF levels may be a potential biomarker to predict a subset of patients who are likely to benefit from bevacizumab treatment. However, this finding needs further confirmation in a large-scale study due to the small sample size of our study cohort.

The EGFR T790 M mutation status was examined after progression on the continuation of EGFR-TKIs with bevacizumab. We observed a survival benefit in both T790M–positive and T790M–negative patients with median PFS2 of 4.9 months and 4.5 months, respectively. This finding is consistent with that of a preclinical study using T790M-induced and non-T790M-induced erlotinib-resistant in vivo models that demonstrated that erlotinib-bevacizumab combination therapy enhanced antitumor activity compared with each single agent.[29] Therefore, for patients with gradual progression on EGFR-TKIs, the addition of bevacizumab led to a longer PFS regardless of the T790 M status, and this result is valuable for patients without the secondary detection of the genotype profile after progression. Currently, there are fewer therapeutic options for T790M-negative populations after resistance to first- or second-generation EGFR-TKI therapy.[30] This result indicates that the combination of continued EGFR-TKIs with bevacizumab after gradual progression on EGFR-TKIs could be a promising therapeutic option for T790M-negative populations.

Our study had several limitations. First, the size of our study cohort was small. There was no defined cutoff value for the serum VEGF concentration. Therefore, further larger scale studies should be performed to determine an optimal cutoff value for serum VEGF. In addition, additional studies comparing the efficacy of EGFR-TKIs plus bevacizumab for EGFR T790M-positive and EGFR T790M-negative populations should be conducted.

In conclusion, EGFR-TKIs combined with bevacizumab resulted in a durable prolongation of PFS in non-squamous NSCLC patients with gradual progression on EGFR-TKI treatment. This combination treatment was well tolerated and could be a promising strategy for these patients. Serum VEGF concentrations could be a potential biomarker for identifying a subset of patients who are likely to benefit from combination treatment with EGFR-TKIs and bevacizumab. Further large-scale prospective studies are needed to confirm our findings in NSCLC patients with gradual progression on first- or second-generation EGFR-TKI treatment.

Acknowledgments

Author contributions

Conceptualization: Jianying Zhou.
Data curation: Yuman Yu, Linying Wu, Hua Zhou, Qing Wang.
Formal analysis: Yuman Yu, Linying Wu.
Investigation: Yuman Yu, Yuehong Wang.
Methodology: Yuman Yu, Yuehong Wang.
Project administration: Xuanli Xu, Hua Zhou, Qing Wang.
Resources: Xuanli Xu, Hua Zhou, Qing Wang.
Software: Yuman Yu, Linying Wu.
Supervision: Yuman Yu, Yuehong Wang, Jianying Zhou.
Validation: Yuman Yu, Yuehong Wang, Jianying Zhou.
Visualization: Yuman Yu, Yuehong Wang, Linying Wu.
Writing – original draft: Yuman Yu, Yuehong Wang.
Writing – review & editing: Yuman Yu, Yuehong Wang, Jianying Zhou.

References

[1] Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
[2] Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
[3] Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306–11.
[4] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
[5] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735–42.
[6] Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213–22.
[7] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EUR-TAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.
[8] Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 2010;28:i re3j357–60.
[9] Yang JJ, Chen HJ, Yan HH, et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. Lung Cancer 2013;79:33–9.
[10] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
[11] Byers LA, Heymach JV. Dual targeting of the vascular endothelial growth factor and epidermal growth factor receptor pathways: rationale and clinical applications for non-small-cell lung cancer. Clin Lung Cancer 2007;8(suppl):S79–85.
[12] Masuda C, Yanagisawa M, Yorozu K, et al. Bevacizumab counteracts VEGF-dependent resistance to erlotinib in an EGFR-mutated NSCLC xenograft model. Int J Oncol 2017;51:425–34.
[13] Tabernero J. The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents. Mol Cancer Res 2007;5:203–20.
[14] Assoun S, Brosseau S, Steinmetz C, Gounant V, Zalcman G. Bevacizumab in advanced lung cancer: state of the art. Future Oncol 2017;13:2515–35.
[15] Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014;15:1236–44.
[16] Rosell R, Dafni U, Felip E, et al. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. Lancet Respir Med 2017;5:435–44.

[17] Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol 2019;20:625–35.

[18] Zeng L, Xiao L, Jiang W, et al. Investigation of efficacy and acquired resistance for EGFR-TKI plus bevacizumab as first-line treatment in patients with EGFR sensitive mutant non-small cell lung cancer in a Real world population. Lung Cancer 2020;141:82–8.

[19] van Puijenbroek R, Bosquee L, Meert AP, et al. Gefitinib monotherapy in advanced nonsmall cell lung cancer: a large Western community implementation study. Eur Respir J 2007;29:128–33.

[20] Otsuka K, Hata A, Takeshita J, et al. EGFR-TKI rechallenge with bevacizumab in EGFR-mutant non-small cell lung cancer. Cancer Chemother Pharmacol 2015;76:835–41.

[21] Hata A, Katakami N, Kaji R, et al. Afatinib plus bevacizumab combination after acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer: multicenter, single-arm, phase 2 trial (ABC Study). Cancer 2018;124:3830–8.

[22] Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.

[23] Frezzetti D, Gallo M, Maiello MR, et al. VEGF as a potential target in lung cancer. Expert Opin Ther Targets 2017;21:959–66.

[24] Naumov GN, Nilsson MB, Cascone T, et al. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. Clin Cancer Res 2009;15:3484–94.

[25] Dickson PV, Hamner JB, Sims TL, et al. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. Clin Cancer Res 2007;13:3942–50.

[26] Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Discov 2011;10:417–27.

[27] Viallard C, Larrivee B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. Angiogenesis 2017;20:409–26.

[28] Li H, Takayama K, Wang S, et al. Addition of bevacizumab enhances antitumor activity of erlotinib against non-small cell lung cancer xenografts depending on VEGF expression. Cancer Chemother Pharmacol 2014;74:1297–305.

[29] Furugaki K, Fukumura J, Iwai T, et al. Impact of bevacizumab in combination with erlotinib on EGFR-mutated non-small cell lung cancer xenograft models with T790 M mutation or MET amplification. Int J Cancer 2016;138:1024–32.

[30] Suda K, Rivard CJ, Mitsudomi T, Hirsch FR. Overcoming resistance to EGFR tyrosine kinase inhibitors in lung cancer, focusing on non-T790 M mechanisms. Expert Rev Anticancer Ther 2017;17:779–86.