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Original Article

Efficacy and mechanism of osimertinib combined with bevacizumab in the treatment of postoperative EGFR positive stage II-IIIA lung adenocarcinoma

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Abstract: Objective: To explore the efficacy and mechanism of osimertinib combined with bevacizumab in treating postoperative epidermal growth factor receptor (EGFR) positive stage II-IIIA lung adenocarcinoma. Methods: In this retrospective study, one hundred and thirty patients with postoperative EGFR positive stage II-IIIA lung adenocarcinoma were divided into two groups according to different treatment methods. Patients treated with osimertinib alone were included in the single group (65 patients). Patients treated with bevacizumab on the basis of the single group were included in the joint group (65 patients). The short-term efficacy, side effects and survival results of the two groups were counted. The changes of serum vascular endothelial growth factor, serum tumor markers and life quality before and after the treatment were observed. Results: The ORR (66.15%) and DCR (86.15%) in the joint group were significantly higher than those in the single group (47.69% and 70.77%) (both $P<0.05$). The serum levels of VEGFA, VEGFB, VEGFC, BFGF, HDGF, SDF-1, CEA, CA153, CYFRA21-1 and CA199 in the joint group were lower than those in the single group after the treatment (all $P<0.05$). No significant difference was shown in the incidence of adverse reactions such as rash, diarrhea, constipation, albuminuria, hypertension and interstitial pneumonia between the joint group and the single group (all $P>0.05$). After the treatment, the ZPS score of the joint group was lower than that of the single group, and the KPS score was higher than that of the single group (both $P<0.05$). There was no significant difference in the two-year median DFS and the one or two-year DFS rate between the joint group and the single group (all $P>0.05$). Conclusion: Osimertinib combined with bevacizumab in the treatment of postoperative EGFR positive stage II-IIIA lung adenocarcinoma has evident short-term efficacy and mild side effects, which is helpful in improving the disease control rate and life quality. The mechanism may be related to the regulation of serum CEA, CA153, CYFRA21-1, CA199 levels and inhibition of VEGFA, VEGFB, VEGFC, BFGF, HDGF, and SDF-1 levels.

Keywords: EGFR mutation, stage II-IIIA, lung adenocarcinoma, osimertinib, bevacizumab, efficacy, tumor marker, vascular endothelial growth factor

Introduction

The most common pathological type of non-small cell lung cancer is lung adenocarcinoma, accounting for about 1/2 of all lung cancers. In the past, radiotherapy, chemotherapy and surgery were the primary treatments. Unfortunately, the overall survival rate was low, with a high recurrence rate [1, 2]. In recent years, with the discovery of lung cancer-driving genes and the progress of pharmacochemistry, the focus of treatment for lung adenocarcinoma has gradually changed from cellular level to molecular targeted therapy based on gene mutation and histomorphology.

More and more driving genes, such as K-ras, human epidermal growth factor receptor-2 (HER2) and epidermal growth factor receptor (EGFR), have been proved to play a role in the occurrence and proliferation of lung adenocarcinoma [3]. EGFR is one of the critical regulatory

proteins in the growth of epidermal cells. According to the 2018 edition of CSCO Guidelines for Diagnosis and Treatment of Primary Lung Cancer, EGFR is a common mutant gene in lung adenocarcinoma [4]. The EGFR mutation can participate in the process of inhibiting tumor cell invasion, apoptosis, proliferation and angiogenesis by blocking the signal transduction mediated by EGFR. At present, a study has confirmed that first-generation tyrosine kinase inhibitors (TKI), such as gefitinib and erlotinib, can significantly benefit patients with lung adenocarcinoma and positive driving genes, but the problem of drug resistance has become increasingly prominent [5]. Osimertinib is a third-generation TKI drug, which can selectively act on lung adenocarcinoma with EGFR mutation and inhibit tumor cell proliferation and invasion [6]. Bevacizumab is a recombinant human derived monoclonal antibody targeting vascular endothelial growth factor (VEGF). It can inhibit VEGF/VEGFR signal pathway, block downstream signal pathway and inhibit neovascularization [7]. Seto et al. reported in the J025567 phase II clinical trial that erlotinib combined with bevacizumab improved the median progression-free survival time of non-small cell lung cancer patients with positive EGFR mutation compared with erlotinib alone [8]. Therefore, we speculate that as a therapeutic drug for EGFR gene mutation with potential acquired drug resistance, osimertinib combined with antivascular therapy may further improve the efficacy of the single drug. Based on this, this study retrospectively analyzed the efficacy and mechanism of osimertinib combined with bevacizumab in the treatment of postoperative EGFR positive stage II-IIIA lung adenocarcinoma, which may provide reference for clinical application.

Materials and methods

General information

One hundred and thirty patients with EGFR positive stage II-IIIA lung adenocarcinoma from May 2017 to July 2019 were selected, including 68 males and 62 females, aged from 43 to 81 years (61.99±4.72). The patients were divided into two groups according to different treatment methods. Patients treated with osimertinib alone were included in the single group (65 patients). Patients treated with bevacizumab on the basis of the single group were included in the joint group (65 patients). This study was approved by the ethics committee of our hospital (approval No. 20190117). The patients had signed the written consent voluntarily.

Inclusion and exclusion criteria

Inclusion criteria: The patients with confirmed unresectable stage II-IIIA non-small cell lung cancer by histology or cytology; The patients with pathological type of lung adenocarcinoma; The patient whose condition met the relevant diagnostic criteria in the 2011 IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma [9]; The patients with positive mutation of EGFR gene detected by the amplification refractory mutation system (ARMS); The patients with a predicted survival time of more than three months; The patients with at least one measurable lesion which had not been irradiated before; The patients who underwent standard posterolateral thoracic lobectomy combined with systematic lymph node dissection, and the patients with the American Eastern Cancer Cooperative Group (ECOG) score of 0-2.

Exclusion criteria: The patients who used antineoplastic drugs in previous treatment; The patient with radiation lung disease, interstitial pneumonia or chronic obstructive pulmonary disease; The patients with coagulation dysfunction, immune dysfunction or bone marrow dysfunction; The patients with wildtype EGFR gene; The patients with a history of allogeneic organ transplantation; The patients with diseases in the blood system, severe hypofunction of liver and kidney or severe cardio-cerebrovascular diseases; The patients with allergy to the drugs involved in the study; The patients with mental disorders, and the patients in pregnancy or lactation period.

Methods

Single group: The single group was treated with osimertinib alone. Patients were orally given osimertinib (specification: 40 mg; manufacturer: AstraZeneca AB; approval number: H20170166), 80 mg/time, once per day. Patients were treated for two cycles, with three weeks as a cycle.

Joint group: The joint group was treated with bevacizumab based on the single group. Patients were given intravenous infusion of bevacizumab injection (specification: 400 mg (16 mL)/bottle; manufacturer: Roche Pharma (Schweiz) Ltd; approval number: S20170036), 15 mg/kg/time. The treatment was repeated once every three weeks, three weeks as a cycle, with a total of two cycles.

Outcome measures

Short-term clinical efficacy: The evaluation of short-term clinical efficacy was based on the efficacy standard of solid tumors [10]. Complete remission (CR): all target lesions disappeared completely, and the short diameter of all pathological lymph nodes was reduced to <10 mm. Partial remission (PR): the total diameter of target lesions decreased by more than 30% compared to before treatment. Stable disease (SD): the diameter of target lesion decreased but did not reach the standard of CR or PR. Progressive disease (PD): the diameter of target lesion increased by >20%, or the absolute value of total diameter increased by >5 mm. Disease control rate (DCR) = (cases of CR, PR and SD)/total cases ×100%. Objective remission rate (ORR) = (cases of CR and PR)/total cases ×100%.

VEGF and serum tumor markers: Three milliliters of fasting venous blood were collected before treatment and after two cycles of treatment in both groups. The blood samples were centrifuged for 5 min using Hettich MIKRO220/220R centrifuge (Germany). The supernatant was collected. The levels of VEGF subtypes VEGFA, VEGFB, VEGFC, hepatoma-derived growth factor (HDGF), basic fibroblast growth factor (BFGF) and stromal cell-derived factor-1 (SDF-1) were detected by the enzyme-linked immunosorbent assay (ELISA). The ELISA kit was provided by Kebang Xingye (Beijing) Technology Co., Ltd., (catalog number: SBJ-H0094, RP300109, RP300098, IB-E10044, FNAb03809 and IB-E10090). The levels of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) and carbohydrate antigen 153 (CA153) were detected by electrochemiluminescence immunoassay (kits provided by Shanghai Hegao Biotechnology Co., Ltd., catalog number: YX-E10327, PL0301683, elisa2013-11697 and EK-H12457).

Toxic side effects: During the treatment, patients were observed for adverse reactions such as skin rash, diarrhea, constipation, proteinuria, hypertension, and interstitial pneumonia.

Life quality: Before treatment and after two cycles of treatment, the Zubrod performance status (ZPS) and the Karnofsky performance scale (KPS) were used to assess the life quality of the patients. The ZPS scale adopted a 5-point scale, where lower scores indicated better life quality. The KPS scale adopted a 100-point scale, where lower scores indicated poorer life quality.

Survival results: The patients were followed up for two years. The disease-free survival (DFS) was observed, which was the time from randomization to the recurrence of the disease or death due to the disease progression.

Statistical analysis

Data were analyzed by the SPSS 23.0 software. The Shapiro-Wilk test was used for normality test. Measurement data in accordance with normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm sd$). The paired-sample t-test was adopted for intra-group comparison, and the independent-sample t-test for inter-group comparison. The enumeration data were expressed as percentage and analyzed by the χ^2 test. For survival analysis, Kaplan-Meier curve method and the log rank test were used. A difference was considered significant with $P<0.05$.

Results

Comparison of general information

No significant difference was shown in general information between the joint group and the single group (all $P>0.05$). See **Table 1**.

Comparison of therapeutic efficacy

Compared with the single group, the ORR and DCR of the joint group were higher, with a significant difference (both $P<0.05$). See **Table 2**.

Table 1. Comparison of general information between the two groups (n, $\bar{x} \pm sd$)

		Single group (n=65)	Joint group (n=65)	χ^2/t	P
Male Female		35/30	33/32	0.123	0.725
Age (years)		62.4±5.1	61.9±4.9	0.570	0.570
Course of disease (years)		5.03±2.15	4.96±2.02	0.191	0.849
TNM staging (n)	Stage III/stage IIIA	28/37	31/34	0.279	0.597
Histological differentiation degree (n)	Low/moderate/high differentiation	16/31/18	13/30/22	0.432	0.499
Lymph node metastasis (n)		31	35	0.492	0.483

Table 2. Comparison of therapeutic efficacy between the two groups (n (%))

	Single group (n=65)	Joint group (n=65)	χ^2	P
CR	8 (12.31)	15 (23.08)		
PR	23 (35.38)	28 (43.08)		
PD	15 (23.08)	13 (20.00)		
SD	19 (29.23)	9 (13.85)		
ORR	31 (47.69)	43 (66.15)	4.012	0.045
DCR	46 (70.77)	56 (86.15)	4.840	0.028

Note: CR: complete remission; PR: partial remission; PD: progressive disease; SD: stable disease; ORR: objective remission rate; DCR: disease control rate.

Comparison of serum VEGF levels

No significant difference was shown in the levels of serum VEGFA, VEGFB and VEGFC between the joint group and the single group before the treatment (all P>0.05). After the treatment, the levels of serum VEGFA, VEGFB and VEGFC in the joint group were lower than the single group (all P<0.001). See **Table 3**.

Comparison of serum BFGF, HDGF and SDF-1 levels

The BFGF, HDGF and SDF-1 levels in the serum before the treatment showed no significant difference between the joint group and the single group (all P>0.05). The serum BFGF, HDGF and SDF-1 levels in the joint group after the treatment were lower than those of the single group, and the difference was statistically significant (all P<0.001). See **Table 4** and **Figure 1**.

Comparison of serum tumor marker levels

No significant difference was shown in serum tumor marker levels between the joint group and the single group before the treatment (all P>0.05). The serum CEA, CA153, CYFRA21-1, CA199 and CYFRA21-1 levels in the joint group after the treatment were lower than the single group (all P<0.001). See **Table 5** and **Figure 2**.

Comparison of toxic side effects

No significant difference was shown in the incidence of adverse reactions such as rash, diarrhea, constipation, albuminuria, hypertension and interstitial pneumonia between the two groups (all P>0.05). See **Table 6**.

Comparison of life quality

No significant difference was shown in ZPS scores and KPS scores between the two groups before treatment (P>0.05). The ZPS scores of the joint group were lower, and the KPS scores were higher than those of the single group after treatment (both P<0.001). See **Table 7**.

Comparison of survival result

The median two-year DFS after treatment in the joint group was 21.06 months (95% CI: 19.708-22.415). The median two-year DFS in the single group was 18.99 months (95% CI: 17.255-20.714). No significant difference was shown between the two groups (Log rank =2.098, P=0.148). There was no statistically significant difference in the one and two-year DFS rate after treatment between the joint group and the single group (both P>0.05). See **Table 8** and **Figure 3**.

Discussion

A domestic study has found that molecular targeted drugs can prolong the progression-free survival time and improve the disease control rate of lung adenocarcinoma to some extent. However, many patients will develop acquired drug resistance 9-13 months after receiving EGFR inhibitors, which leads to disease progression [11]. Therefore, how to optimize the

Table 3. Comparison of serum VEGF levels between the two groups ($\bar{x}$ ± sd, pg/mL)

		Single group (n=65)	Joint group (n=65)	t	P
VEGFA	Before treatment	203.65±29.58	205.59±30.02	0.371	0.711
	After treatment	135.19±20.13***	68.95±16.64***	20.448	<0.001
VEGFB	Before treatment	172.28±30.02	170.03±28.46	0.439	0.661
	After treatment	126.65±16.32***	78.20±9.16***	20.872	<0.001
VEGFC	Before treatment	169.62±25.56	172.43±24.03	0.646	0.519
	After treatment	88.86±13.37***	63.37±15.19***	10.156	<0.001

Note: VEGFA: vascular endothelial growth factor A; VEGFB: vascular endothelial growth factor B; VEGFC: vascular endothelial growth factor C. Compared with before treatment in the same group, ***P<0.001.

Table 4. Comparison of serum BFGF, HDGF, and SDF-1 levels between the two groups ($\bar{x}$ ± sd)

		Single group (n=65)	Joint group (n=65)	t	P
BFGF (ng/L)	Before treatment	27.65±5.57	28.03±4.61	0.424	0.672
	After treatment	20.13±3.19***	16.75±2.98***	6.242	<0.001
HDGF (ng/mL)	Before treatment	20.46±4.26	20.98±4.58	0.670	0.504
	After treatment	14.16±3.38***	10.76±2.94***	6.119	<0.001
SDF-1 (pg/mL)	Before treatment	6423.52±522.74	6419.72±530.12	0.041	0.967
	After treatment	5821.46±468.21***	5203.65±399.75***	8.091	<0.001

Note: BFGF: basic fibroblast growth factor; HDGF: hepatoma-derived growth factor; SDF-1: stromal cell-derived factor-1. Compared with before treatment in the same group, ***P<0.001.

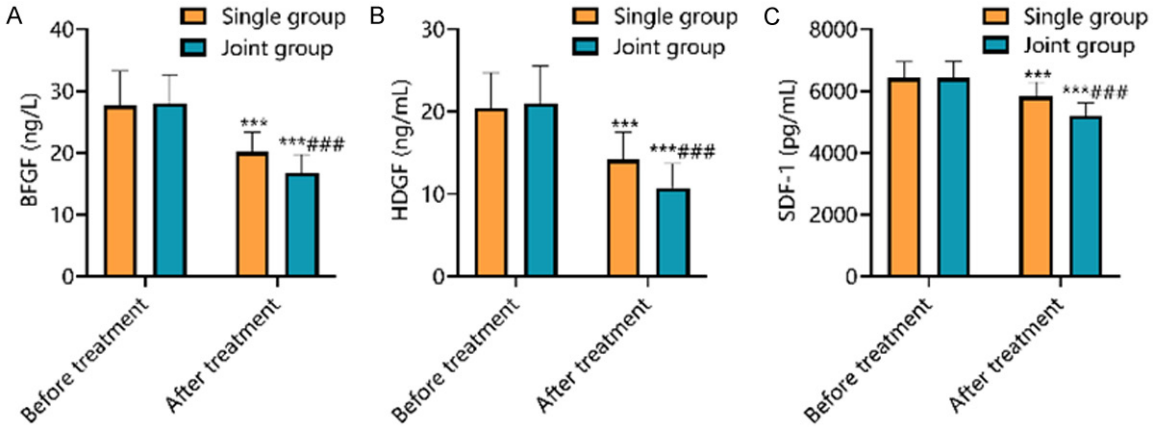

Figure 1. Comparison of serum BFGF, HDGF and SDF-1 levels between the two groups. A: BFGF levels; B: HDGF levels; C: SDF-1 levels. Compared with before treatment, ***P<0.001. Compared with single group, ###P<0.001.

Table 5. Comparison of serum tumor marker levels between the two groups ($\bar{x}$ ± sd)

		Single group (n=65)	Joint group (n=65)	t	P
CEA (ng/mL)	Before treatment	16.32±4.02	15.83±3.94	0.702	0.484
	After treatment	12.06±2.31**	9.03±2.11***	7.808	<0.001
CA153 (U/mL)	Before treatment	43.34±6.03	44.05±5.73	0.688	0.493
	After treatment	36.02±5.13***	30.08±5.91***	6.119	<0.001
CYFRA21-1 (μg/L)	Before treatment	3.93±0.46	3.86±0.37	0.956	0.341
	After treatment	2.41±0.29***	1.32±0.19***	25.347	<0.001
CA199 (U/mL)	Before treatment	48.52±7.16	47.29±7.03	0.988	0.325
	After treatment	32.46±5.02***	25.59±4.03***	8.604	<0.001

Note: CEA: carcinoembryonic antigen; CA253: carbohydrate antigen 153; CYFRA21-1: cytokeratin 19 fragment antigen 21-1; CA199: carbohydrate antigen 199. Compared with before treatment in the same group, **P<0.01, ***P<0.001.

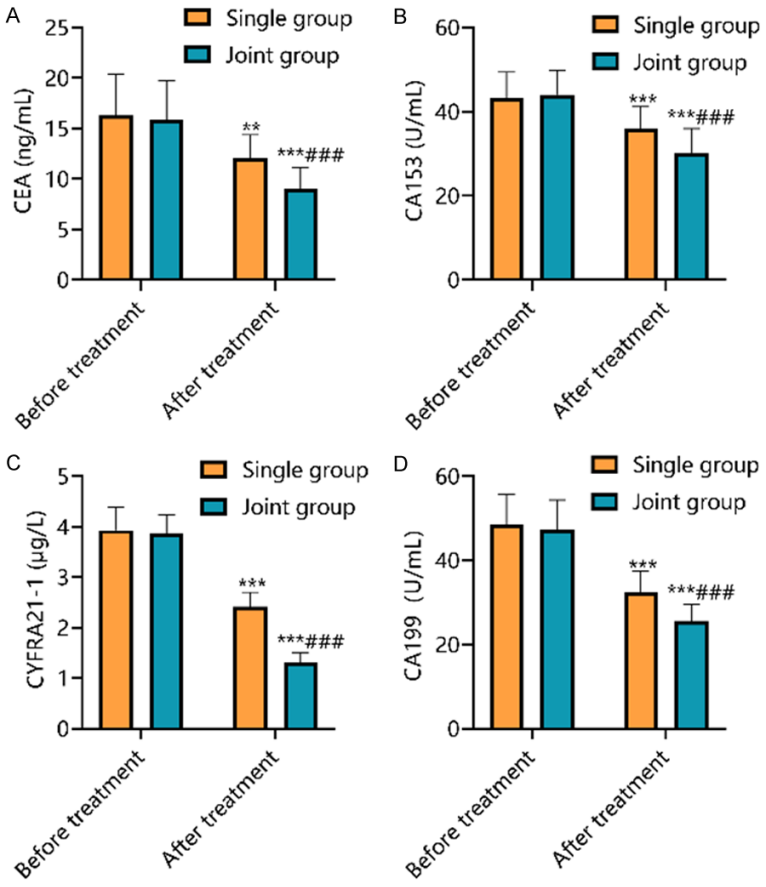

Figure 2. Comparison of serum tumor marker levels between the two groups. A: CEA levels; B: CA153 levels; C: CYFRA21-1 levels; D: CA199 levels. Compared with before treatment, **P<0.01, ***P<0.001. Compared with single group, $^{###}$P<0.001.

Table 6. Comparison of toxic side effects between the two groups (n (%))

	Single group (n=65)	Joint group (n=65)	X^2	P
Rash	9 (13.85)	16 (24.15)	2.427	0.119
Diarrhea	11 (16.92)	17 (26.15)	1.639	0.201
Constipation	9 (13.85)	12 (18.46)	1.311	0.252
Albuminuria	13 (20.00)	15 (23.08)	0.182	0.670
Hypertension	6 (9.23)	13 (20.00)	3.020	0.082
Interstitial pneumonia	2 (3.08)	4 (6.15)	0.699	0.403

treatment for EGFR drug-resistant and sensitive mutations is the focus of current research. The combination of drugs can reduce the resistance to targeted drugs and improve the efficacy by preventing the signal pathway on which tumor occurrence and development depend. The downstream signal transduction pathway of HER-1/EGFR is the same as that of VEGF. Blocking VEGF can affect the autocrine signal of HER-1/EGFR, while inhibition of HER-1/EGFR can reduce VEGF expression. It can be seen that double blockage of molecular targets can have a synergistic or additive effect [12, 13].

The results of the phase AURA1 trial showed that the DCR and ORR of 127 T790M positive patients treated with osimertinib were 61% and 95%, respectively. The median PFS was 9.6 months. The ORR of 61 patients without T790M mutation was only 21%, with a median PFS of 2.8 months. The result showed that osimertinib has a good curative effect on non-small cell lung cancer with T790M mutation [14]. Another AURA1 trial reported that osimertinib had higher clinical efficacy in advanced non-small cell lung cancer with EGFR-TKIs drug resistance and T790M mutation [15]. In a phase IIIb/IV randomized trial, 72 patients with IIIb/IV stage non-small cell lung cancer were randomly divided into two groups. After three treatment cycles, it was found that ORR (58.33%) and DCR (86.11%) in bevacizumab + docetaxel group were higher than those in docetaxel + cisplatin chemotherapy group (27.78% and 61.11%). The result indicates that bevacizumab combined chemotherapy has more advantages than chemotherapy alone. It is speculated that the inhibition of PKC/MAPK/NF-kB pathway may be involved [16]. This study showed that ORR and DCR in the joint group were significantly higher than those in the single group. The ZPS scores in the joint group were lower than those in the single group, and the KPS score was higher than that in the single group. The result indicates that osimertinib combined with bevacizumab can improve the

Table 7. Comparison of ZPS scores and KPS scores between the two groups ($\bar{x} \pm sd$, point)

		Single group (n=65)	Joint group (n=65)	t	P
ZPS	Before treatment	2.65±0.32	2.59±0.41	0.930	0.354
	After treatment	1.86±0.28***	1.06±0.31***	15.440	<0.001
KPS	Before treatment	58.46±5.18	59.93±4.86	1.669	0.098
	After treatment	67.73±4.68***	73.34±5.82***	6.056	<0.001

Note: ZPS: Zubrod performance status; KPS: Karnofsky performance scale. Compared with before treatment in the same group, ***P<0.001.

Table 8. Comparison of DFS rate between the two groups (n (%))

Group	One year after treatment	Two years after treatment
Single group (n=65)	48 (73.85)	39 (60.00)
Joint group (n=65)	54 (83.08)	47 (72.31)
χ^2	2.784	2.199
P	0.095	0.138

Note: DFS: disease-free survival.

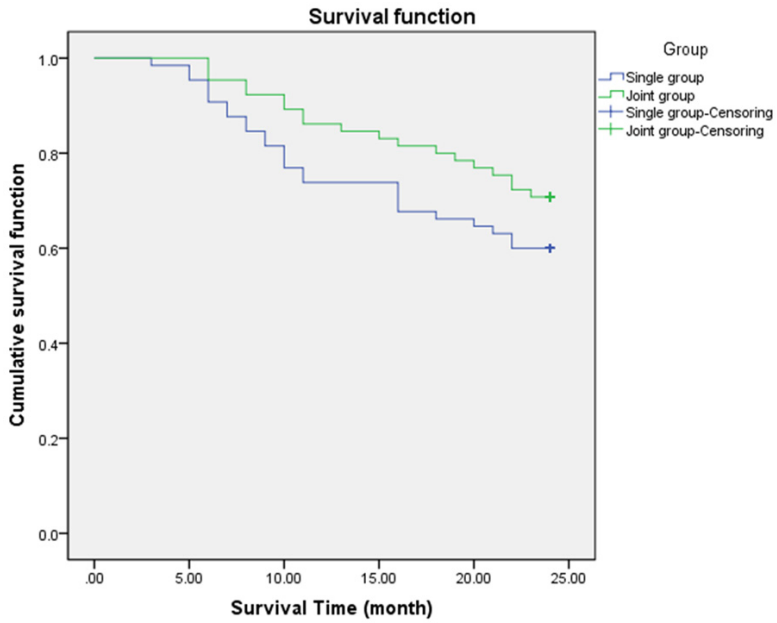

Figure 3. Comparison of DFS survival function between the two groups.

disease control rate of EGFR positive stage II-III A lung adenocarcinoma, reduce the tumor volume, inhibit the disease progression and improve life quality. The reason could be that osimertinib belongs to a monoaniline pyrimidine compound, which can pass through the blood-brain barrier. It can inhibit EGFR target activation and tyrosine kinase phosphorylation, block mutant EGFR homodimerization, interfere with the phosphorylation of downstream signal substrates ERK and AKT, and induce apoptosis of T790M mutant cells. As a result, osimertinib can inhibit carcinomatous cell differentiation, proliferation and metastasis [17]. In addition, osimertinib can inhibit EGFR and its downstream Ras-Raf-MAPK and PI3K/AKT/mTOR signal pathways. When combined with bevacizumab, osimertinib can regulate the microenvironment of tumor tissue, further inhibit the above two signal pathways, and then obtain a more efficient tumor cell killing effect.

CEA has the effects of inhibiting cell adhesion and cell apoptosis. CEA helps tumor cells escape the body's immunity, interferes with the adhesion between cells and promotes the separation between cells and tumors, which continue to infiltrate surrounding tissues, and even promote metastasis. When lung adenocarcinoma progresses to the advanced stage, cancer cells lose their polarity and cause a large amount of CEA to be released, which promotes the increase of CEA expression in serum. CA153 is a gland-associated antigen. Cell carcinogenesis activates glycosyltransferase and causes changes in cell surface carbohydrates, which are released from cancer cells into the blood circulation. Therefore, it has strong organ specificity, and its level is positively correlated with the patient's condition. CYFRA21-1 is a cytoskeletal marker. When cells undergo necrosis and dissolution, cytoglial proteins are released into body fluids, resulting in high expression of CYFRA21-1 in the serum. The positive rate of tumor diagnosis can reach 76% [18]. CA199 is

an oligosaccharide antigen. Its abnormal increase may be related to the secretion of tumor cells entering the blood after degeneration and necrosis. CA199 is highly expressed in the serum of patients with cholangiocarcinoma, gallbladder cancer, pancreatic cancer and many other tumors. This study found that the serum levels of CEA, CA153, CYFRA21-1, and CA199 after treatment in the joint group were lower than those in the single group. It suggests that osimertinib combined with bevacizumab can inhibit the progression of postoperative EGFR positive stage II-IIIA lung adenocarcinoma and regulate the level of serum tumor markers.

Angiogenesis is important for tumor cell proliferation, invasion and metastasis. When the tumor volume expands, the tumor can rob the body of nutrition through neovascularization, thus aggravating the disease. The process of angiogenesis is complicated, involving many factors, among which VEGF can accelerate the proliferation of vascular endothelial cells and angiogenesis and promote lymphangiogenesis. BFGF can promote the growth of cell fibers, interact with VEGF and enhance the ability of angiogenesis [19, 20]. HDGF is a proliferative heparin-binding protein, and its overexpression is related to tumor differentiation, lymph node metastasis and recurrence [21]. VEGF and its receptor (VRGFR) belong to an important signal pathway, which can promote the abnormal migration and proliferation of tumor vascular endothelial cells. Thus, VEGF monoclonal antibodies help regulate the imbalance of inhibitors and prevent angiogenesis [22]. This study showed that the serum levels of VEGFA, VEGFB, VEGFC, BFGF and HDGF in the joint group were lower than the single group, indicating that osimertinib combined with bevacizumab can inhibit tumor neovascularization and exert the anti-tumor effect in patients with EGFR positive stage II-IIIA lung adenocarcinoma. The reason may be that bevacizumab can target VEGF, competitively antagonize the combination of VEGF and VRGFR, improve vascular permeability, reduce angiogenic factors stimulating vascular endothelium, normalize survival vessels and then inhibit the physiological effects of VEGF and neovascularization [23, 24]. In addition, bevacizumab can reduce microvascular density, vascular permeability, blood volume and blood flow, which can directly act on tumor microenvironment, lead to tumor vascular system degeneration and delay tumor growth [25].

No significant difference was shown in the median two-year DFS and the one and two-year DFS rate after treatment between the joint group and the single group. The treatment of osimertinib combined with bevacizumab did not significantly prolong the survival time of the patients. It may be that the number of cases included in the study is relatively small. Therefore, it is necessary to expand the sample size and extend the follow-up time in the future studies to further analyze the impact of the program on the survival rate of patients. From the view of safety, the main adverse reactions in the joint group were rash, diarrhea, albuminuria and hypertension. No significant difference was shown in adverse reactions between the joint group and the single group, indicating that the treatment of osimertinib combined with bevacizumab did not significantly increase the adverse reactions. Thus, patients can tolerate the combined use of the two drugs.

There are some limitations in this study. We did not discuss the specific molecular mechanism of osimertinib combined with bevacizumab in the treatment of postoperative EGFR-positive stage II-IIIA lung adenocarcinoma. In the next step, we will expand the number of cases and further detect Ras-Raf-MAPK and other downstream signal pathway related factors to investigate specific mechanisms.

To conclude, osimertinib combined with bevacizumab in the treatment of postoperative EGFR positive stage II-IIIA lung adenocarcinoma has obvious short-term efficacy and mild side effects, which is helpful for improving the disease control rate and the quality of life. The mechanism may be related to regulating the level of serum tumor markers and inhibiting tumor neovascularization.

Disclosure of conflict of interest

None.

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