Antibiotic use is a negative predictor of the efficacy and toxicity of epidermal growth factor receptor-targeted therapy in advanced non-small cell lung cancer

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Abstract. Non-small cell lung cancer (NSCLC) is closely associated with inflammation and chronic infection. Antibiotics are frequently prescribed for NSCLC patients in combination with epidermal growth factor receptor (EGFR)-targeted treatment in the presence of infection. The association between antibiotic use and the efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) has not previously been thoroughly investigated. Therefore, the present study investigated whether antibiotics could affect the efficacy and toxicity of EGFR-TKI treatment, with the aim of restricting the use of antibiotics in combination with targeted therapy in patients with advanced NSCLC in the near future. All patients received treatment with EGFR-TKIs until disease progression, unacceptable toxicity or other factors, including death, pregnancy or unwillingness to further receive targeted therapy, were observed. Patients were retrospectively divided into two groups: Group A, which was treated with EGFR-TKIs and antibiotics; and Group B, which was treated with EGFR-TKIs alone. Patients having used antibiotics 6 months prior to EGFR-TKI therapy were also included in the study. Antibiotic use negatively affected the median progression-free survival (PFS) following EGFR-TKI treatment in NSCLC compared with that in patients not treated with antibiotics; median PFS in Group A was 6.6 months, whereas median PFS in Group B was 10.1 months. Antibiotics also increased the toxicity of targeted therapy for advanced NSCLC. There were significant statistical differences between the two groups in the occurrence of the adverse events of diarrhea and dyspnea. In conclusion, antibiotics decreased the efficacy of first-line targeted therapy in advanced NSCLC and increased incidences of diarrhea and dyspnea. Large randomized studies are needed to identify the impact of antibiotic use on EGFR-TKI treatment for NSCLC.

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Abbreviations: DCR, disease control rate; EGFR, epidermal growth factor receptor; NCI-CTCAE 3.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TKIs, tyrosine kinase inhibitors

Key words: antibiotics, targeted therapy, first-line therapy, non-small cell lung cancer

Introduction

Lung cancer is the most commonly diagnosed cancer worldwide, and is generally classified into small-cell lung cancer and non-small cell lung cancer (NSCLC); the latter accounts for ~80% of all cases of lung cancer (1-3). NSCLC is an aggressive carcinoma with poor prognosis; it accounted for ~27% of all cases of cancer associated-mortality in the United States in 2017 (1). Previously, unresectable NSCLC was primarily treated by chemotherapeutic methods, with a median overall survival (OS) time of 8-10 months (4). Advanced NSCLC with epidermal growth factor receptor (EGFR) gene mutation, which accounts for 30-50% of NSCLC cases in East Asia, is often treated using several small tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, which results in a median OS of ~2 years (5-7).

Previous studies have also revealed that NSCLC was closely associated with inflammation and chronic infection (8,9). Obstructive pneumonia frequently occurs in patients with advanced NSCLC, and obstruction of a proximal airway may lead to recurrent pneumonias in the same location of the lung lobe (10). Since pneumonia can be a considerable cause of mortality in patients with lung cancer, antibiotics may be used for those patients in clinical settings (10). However, an association between antibiotic use and inferior efficacy of antitumor drugs in advanced NSCLC has been reported (11). Chemotherapy may alter microbiotic distribution in the gut as a result of gastrointestinal mucositis, which may cause bacterial translocation to the bloodstream; and thus, may cause severe infection requiring antibiotic treatment (12,13).

Targeted therapies, such as EGFR-TKIs, often have fewer and relatively mild side effects compared with chemotherapy and immunotherapy (14,15). Unlike chemotherapy, targeted treatment rarely causes myelosuppression-related infection. However, antibiotic use is very prevalent in the clinic for several reasons, and it is unknown whether antibiotics may influence the efficacy of targeted therapy in patients with advanced NSCLC. Since multidrug-resistance of antibiotics is currently emerging as a major challenge, it is important to investigate the relationship between antibiotics and EGFR-TKI treatment.

Therefore, the present study was performed to investigate whether antibiotics could affect the efficacy and toxicity of EGFR-TKI treatment, with the aim of restricting the use of antibiotics in combination with targeted therapy in patients with advanced NSCLC in the near future, thus reducing the probability of treatment failure and the associated healthcare costs.

Materials and methods

Patients and data collection. The present study was approved by the Ethics Committee of Dongguan People's Hospital (Dongguan, China) and was conducted according to the Declaration of Helsinki. Patients provided informed written consent at the time of data collection. A total of 102 patients with EGFR mutations, treated with EGFR-TKIs at Dongguan People's Hospital, Southern Medical University (Dongguan, China) between May 2014 and December 2017 were included in this study. The inclusion criteria were: i) Patients who were ≥18 years old; ii) patients with cytological or histological confirmation of stage IIIB and IV EGFR gene-mutated NSCLC based on The International Association for the Study of Lung Cancer 7th edition of Tumor Node Metastasis Staging classification; iii) patients who had not previously received any antitumor regimens. The exclusion criteria were: i) Patients who were pregnant; ii) patients who were allergic to the drugs; iii) patients who had primary organ failure; iv) patients whose clinical information could not be obtained in full.

Patients with different Eastern Cooperative Oncology Group Performance Status were investigated in the present study (16). A score of 0 meant that patients had completely normal activity. A score of 1 meant that patients had the ability to move about freely and engage in light physical activities, including general household or office work, but not heavier physical activities. A score of 2 meant that patients had the ability to walk freely and take care of themselves, at least half of the time during the daytime, but lost the ability to work. A score of 3 meant that patients could take care of themselves partially, and spent more than half of the day in bed or in a wheelchair. A score of 4 meant that patients were usually bedridden, and unable to take care of themselves at all. Clinical data, such as patient history, physical examination and hematological examination were recorded within 1 week prior to EGFR-TKI treatment. Antibiotic types and treatment time were also recorded. Tumor response was evaluated by computed tomography scans, according to the Response Evaluation Criteria in Solid Tumors criteria. Disease control was defined as complete response, partial response or stable disease. Further disease progression was defined as progressive disease. Adverse events were recorded and classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE 3.0) (17).

Progression-free survival (PFS) was defined as time between the start of the treatment and disease progression or death, with censoring for patients alive without progression at last contact. The cutoff date for PFS data was 28 June, 2018, when the last patient had undergone treatment for 6 months. By that time, enough data were collected to analyze the efficacy and adverse events for each arm of the study.

EGFR status and grouping. EGFR mutations were identified in tumor tissues using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (Sanger), the scorpion amplification refractory mutation system method or next-generation sequencing technology, as previously described (18). Patients were retrospectively divided into two groups: Group A, which were treated with EGFR-TKIs and antibiotics, and Group B, which were treated with EGFR-TKIs alone. Antibiotic use 6 months prior to EGFR-TKI therapy was included in Group A.

Statistical analysis. The aim of this retrospective study was to compare the efficacy of EGFR-TKI co-treatment with antibiotics with that of EGFR-TKI treatment alone as a first-line therapy for patients with advanced NSCLC. The primary endpoint was PFS. The secondary end points were objective response rate (ORR) and disease control rate (DCR). All patients with EGFR-TKI treatment were evaluable for response. The safety population consisted of all patients who received at least one week of treatment. Average response rate and 95% confidence intervals were calculated separately for each arm of the study.

Statistical analyses were performed using SPSS 22.0 software (IBM Corp.). The relationships between treatment groups and patient characteristics were performed using Pearson's χ^2 test or Fisher's exact test. Estimates of PFS and OS were calculated using the Kaplan-Meier method and two-sided 95% confidence intervals were obtained. A two-sided Breslow test was used to compare PFS between the study groups. The Cox proportional hazards model was used to estimate the hazard ratios for each study group.

Results

Baseline characteristics and treatment. A total of 102 eligible patients with NSCLC were treated with EGFR-TKIs at Dongguan People's Hospital, Southern Medical University (Dongguan, China). The clinicopathological characteristics of the patients are presented in Table I; no statistically significant differences were identified between the two study groups. The median age of Group A was 63 years (range, 36-83 years) and 52.3% patients were women, and that of Group B was 62 years (range, 27-82 years) and 63.8% were women. The majority of patients had an Eastern Cooperative Oncology Group Performance Status of 0-2 and had sensitive EGFR mutations, including Exon 19 deletion, Exon 21 L858R and Exon 18 G719X. All patients with advanced NSCLC received treatment with first-line EGFR-TKIs: Gefitinib (250 mg/day), icotinib (375 mg/day), erlotinib (150 mg/day) or afatinib (40 mg/day) until disease progression, unacceptable toxicity or

Table I. Patient clinicopathological characteristics.

Characteristic	Group A (n=44)	Group B (n=58)	P-value
Age (years)			
Median	63	62	
Range	36-83	27-82	
Age groups (years)			0.22
18-39	5 (11.4%)	2 (3.4%)	
40-64	20 (45.5%)	33 (56.9%)	
65-85	19 (43.1%)	23 (39.7%)	
Sex			0.24
Male	21 (47.7%)	21 (36.2%)	
Female	23 (52.3%)	37 (63.8%)	
ECOG PS			0.57
0	1 (2.3%)	3 (5.2%)	
1-2	38 (86.3%)	51 (87.9%)	
≥3	5 (11.4%)	4 (6.9%)	
Lung cancer stage			1.00
IIIB or lower	1 (2.3%)	2 (3.4%)	
IV	43 (97.7%)	56 (96.6%)	
Smoking			0.46
Yes	11 (25)	11 (18.9%)	
No	33 (75%)	47 (81.1%)	
Number of metastases			0.81
0-1	13 (29.5%)	20 (34.5%)	
2	12 (27.3%)	13 (22.4%)	
≥3	19 (43.2%)	25 (43.1%)	
Brain metastasis			0.27
Yes	15 (34.1%)	26 (44.8%)	
No	29 (65.9%)	32 (55.2%)	
EGFR mutation status			0.34
Exon 19 deletion	22 (48.9%)	24 (41.5%)	
Exon 21 L858R	17 (45.7%)	31 (53.4%)	
Exon 18 G719X	1 (2.9%)	1 (1.7%)	
Other	4 (2.9%)	2 (3.4%)	
Drugs			0.46
Gefitinib	20 (45.5%)	31 (53.4%)	
Erlotinib	5 (11.4%)	7 (12.1%)	
Icotinib	17 (38.6%)	20 (34.5%)	
Afatinib	2 (4.5%)	0 (0%)	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; Group A, EGFR-TKI co-treatment with Antibiotics; Group B, EGFR-TKI treatment alone; TKIs, tyrosine kinase inhibitors.

other factors, including death, pregnancy or unwillingness to further receive targeted therapy, were observed.

Of the 102 patients with EGFR mutations, 44 patients received antibiotic treatment prior to or during the targeted therapy period. Antibiotic therapy rarely exceeded three types of drug in these patients (Fig. 1A). Only six patients (13.6%) received ≥4 types of antibiotics. The majority of patients (77.3%) received antibiotic treatment for ≤1 month when co-treated with EGFR-TKIs (Fig. 1B). In addition, 26 different antibiotic types were used in the present study, the most commonly prescribed of which was cefmetazole, followed by imipenem-cilastatin and moxifloxacin (data not shown).

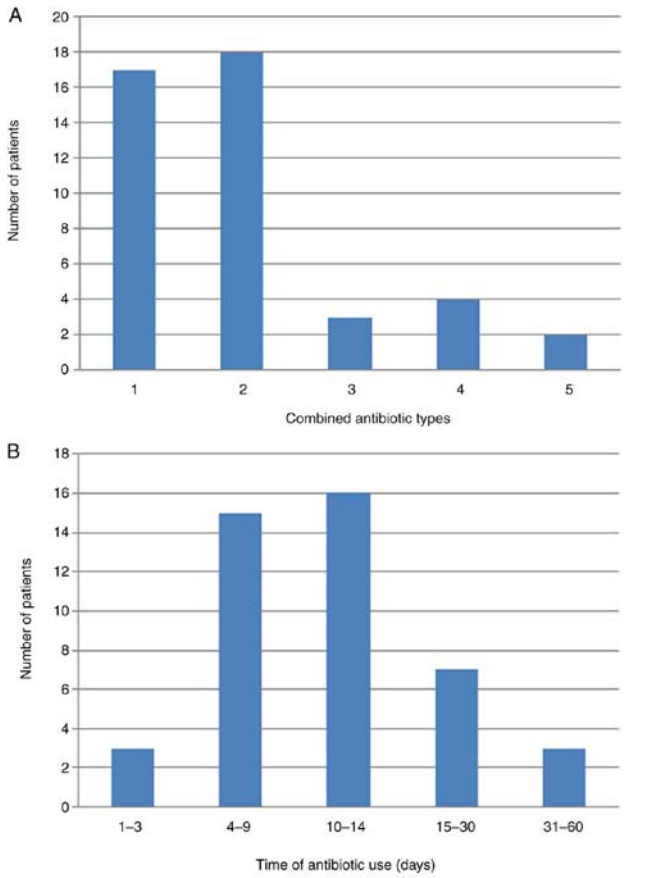

Figure 1. Use of antibiotics during the epidermal growth factor receptor-tyrosine kinase inhibitor therapeutic period. (A) Use of combined antibiotics in patients with advanced non-small cell lung cancer. (B) Duration of antibiotic use.

Treatment efficacy. The response rate of patients with NSCLC co-treated with EGFR-TKIs and antibiotics (Group A) was 52.3%, whereas that of patients treated with EGFR-TKIs alone (Group B) was 56.9% (Table II). No significant differences in ORR or DCR were observed between the two groups. However, the median PFS of Group A was 6.6 months compared with 10.1 months in Group B (P=0.02; Fig. 2). The 1-year PFS rates in the two groups were 20.5% and 37.9%, respectively (P=0.03). The effects of different numbers of antibiotics and the duration of the treatment period among patients in group A were also investigated; analyses of PFS revealed that there were no statistically significant differences between the patient subgroups (Fig. 3A and B).

Adverse events. The most common side effects that were possibly related to the treatment are presented in Table III. The majority of the adverse events in the two study groups were mild; no patients in the present study exhibited severe adverse events. The most common grade 1/2 adverse events

Table II. Treatment efficacy.

Variable	Group A (n=44)	Group B (n=58)	P-value
Response			
PR (%)	23 (52.3%)	33 (56.9%)	
SD (%)	13 (29.5%)	18 (31.0%)	
PD (%)	8 (18.2%)	7 (12.1%)	
Response rate (%)	52.3	56.9	0.64
95% CI	37.3-67.2	44.1-69.8	
Disease control rate (%)	81.8	87.9	0.39
95% CI	70.3-93.3	79.5-96.4	
Median PFS (months)	6.6	10.1	0.04
95% CI	4.7-8.4	6.4-13.8	
1-year PFS rate (%)	20.5	37.9	0.03

Group A, EGFR-TKI co-treatment with antibiotics; Group B, EGFR-TKI treatment alone; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; PR, partial remission; SD, stable disease; PD, progressive disease; PFS, progression-free survival.

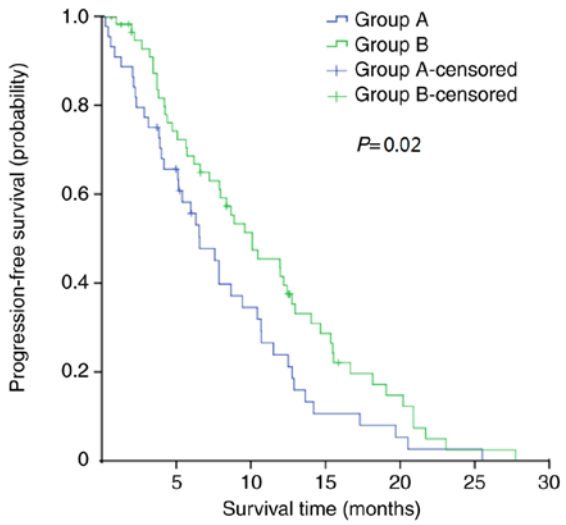

Figure 2. Kaplan-Meier curves for progression-free survival. Patients with advanced non-small cell lung cancer were treated with the epidermal growth factor receptor-tyrosine kinase inhibitor; Group A were co-treated with antibiotics, whereas Group B did not receive antibiotics during or 6 months prior to the treatment.

(NCI-CTCAE 3.0) in Group A were anorexia, rash, raised aminopherase and fatigue, whereas those in Group B were raised aminopherase, rash, anorexia and nausea; no statistically significant differences in treatment-related toxicities other than fever were observed between the two groups. In the EGFR-TKIs treatment without antibiotic treatment group, the incidence of fever was relatively low.

A total of 20 episodes of grade 3/4 adverse events occurred in Group A, including diarrhea (15.9%), rash (11.4%), dyspnea (11.4%), fatigue (4.5%) and hemorrhage (2.3%), whereas only nine episodes occurred in Group B, including rash (12.1%), raised aminopherase (1.7%) and diarrhea (1.7%). The adverse events of diarrhea and dyspnea were significantly more common in Group A compared with Group B ($P<0.05$).

Discussion

Advanced NSCLC is closely associated with chronic and acute infection (8,9). A previous study revealed that the tumor itself causes immunosuppression, which may lead to severe infection (8). In addition, chemotherapy has a myelosuppressive effect; therefore, the incidence of infection is high in patients with NSCLC. Thus, antibiotics are extensively used in the clinic to decrease the mortality rate in patients with advanced NSCLC (19). However, antibiotics may negatively impact the therapeutic efficacy of antitumor agents in NSCLC (11). A previous study has shown that antibiotics inhibit the clinical benefit of these agents by changing the gut microbiome composition of patients with advanced cancer, which further reduces the recruitment of $CCR9^{+}CXCR3^{+}CD4^{+}$ T lymphocytes into the tumor beds (20).

EGFR-TKIs are a standard treatment method for patients with EGFR mutated advanced NSCLC (7). Compared with patients receiving chemotherapy, serious infection caused by myelosuppression rarely occurs in patients during the targeted therapeutic period (6). However, EGFR-TKI treatment may damage the gastrointestinal mucosa, inducing side effects such as nausea, vomiting and diarrhea; this may promote bacterial translocation and lead to bloodstream infection (21). Therefore, antibiotics are still frequently prescribed for patients undergoing EGFR-TKI treatment in the presence of infection.

In the present study, a similar phenomenon was observed with antibiotic use in patients with targeted therapy. During different periods of the antitumor treatment, ~43.1% of patients who chose EGFR-TKIs as their initial therapy received one or more types of antibiotics. Additionally, 25.5% of these patients received prophylactic or empirical treatment with several antibiotics for >10 days. Further analysis displayed that cefmetazole, imipenem-cilastatin and moxifloxacin were the most frequent antibiotic types used in patients who participated in this study. Similar to previous studies, antibiotics also exerted a negative impact on targeted therapy for the first-line treatment of advanced NSCLC (20,22).

In the present study, antibiotics did not change the ORR or DCR. However, antibiotic administration was associated with shorter median PFS of EGFR-TKI treatment for NSCLC of only 6.6 months, which is lower compared with the results from multiple randomized clinical trials (PFS, 9-10 months) (5,6). For the patients who did not receive antibiotics, the median PFS was 10.1 months, which is similar to the results of previous clinical trials (5,6). The 1-year PFS rates of the two study groups were also significantly different. Since the basic patient characteristics in the two groups were well balanced, it is possible that antibiotics weakened the long-term efficacy of the EGFR-TKI treatment, rather than altering the partial response to the antitumor agents, which was commonly obtained after a few months of targeted therapy. Antibiotics affect the number of lymphocytes around the tumor (20); this process requires a relatively long time, thus the effect of antibiotics on EGFR-TKI therapy may present in a chronic way, which corresponds with the results of PFS and 1-year PFS.

Table III. Treatment-related toxicity.

	Grade 1/2			Grade 3/4		
Toxicity	Group A (n=44) (%)	Group B (n=58) (%)	P-value	Group A (n=44) (%)	Group B (n=58) (%)	P-value
Rash	15 (34.1)	15 (25.9)	0.37	5 (11.4)	7 (12.1)	0.91
Pruritus	8 (18.2)	6 (10.3)	0.26	0	0	
Dizziness	6 (13.6)	5 (8.6)	0.42	0	0	
Fever	8 (18.2)	2 (3.4)	**0.01**	0	0	
Diarrhea	7 (15.9)	7 (12.1)	0.58	7 (15.9)	1 (1.7)	**0.008**
Fatigue	9 (20.5)	8 (13.8)	0.38	2 (4.5)	0	0.10
Nausea	8 (18.2)	9 (15.5)	0.72	0	0	
Vomiting	8 (17.1)	8 (13.7)	0.55	0	0	
Anorexia	16 (36.4)	13 (22.4)	0.12	0	0	
Raised aminopherase	14 (31.8)	16 (27.6)	0.65	0	1 (1.7)	0.380
Dyspnea	6 (13.6)	7 (12.1)	0.82	5 (11.4)	0	**0.008**
Hemorrhage	2 (4.5)	4 (6.9)	0.62	1 (2.3)	0	0.25

Group A, EGFR-TKI co-treatment with antibiotics; Group B, EGFR-TKI treatment alone.

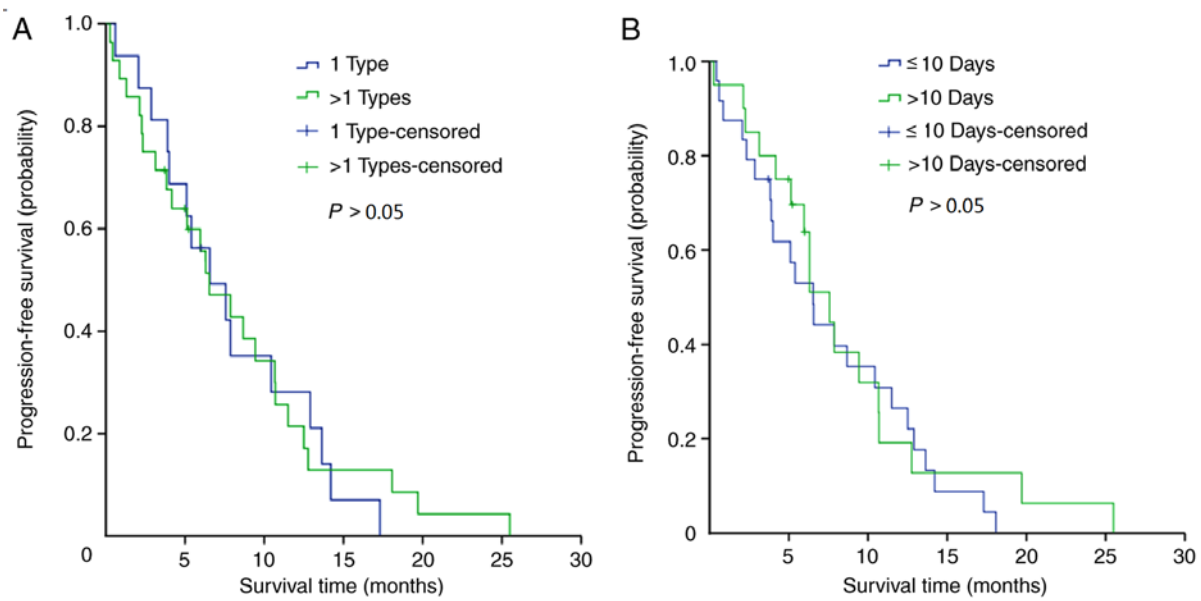

Figure 3. Kaplan-Meier curves for progression-free survival of different application of antibiotics. (A) Survival of patients with non-small cell lung cancer treated with one or more types of antibiotics. (B) Survival of patients with non-small cell lung cancer treated with antibiotics for ≤10 or >10 days.

The impact of the number of antibiotics and treatment duration on targeted therapy for advanced NSCLC was also investigated in the present study. No significant differences were observed among these factors. These results suggested that the administration of antibiotics may decrease the therapeutic efficacy of EGFR-TKI independently of antibiotic number and treatment time. These results are consistent with a previous study, which demonstrated that antibiotics lead to long-term microbial shifts in feces, which in turn may influence antitumor outcomes (22). As the number of patients in the present study was relatively small, additional studies are necessary to further clarify the relationship between antibiotic use and EGFR-TKI efficacy.

Antibiotics may also influence the adverse events associated with targeted therapy for advanced NSCLC. However, the statistical difference of the grade 1/2 incidence rate of fever may be unrelated to the different treatment arms. It was observed in the medical records of these patients that the majority of them already exhibited symptoms of fever associated with infection prior to antibiotic treatment. In the present study, the incidence rates of grade 3/4 diarrhea and dyspnea in group A were increased compared with group B. Previous studies demonstrated that the use of antibiotics is associated with an altered composition of the gut microbiome and increased occurrence of ectopic diseases, such as asthma and eczema (23-26). Diarrhea accounts for the majority of adverse events associated

with targeted treatment, and dyspnea is a severe symptom of advanced NSCLC. Therefore, it is strongly suggested that the use of antibiotics without evidence should be prohibited and that prophylactic use should be applied with caution for patients with NSCLC receiving EGFR targeted treatment.

In conclusion, antibiotics may lead to a long-term decrease the efficacy of first-line targeted therapy in advanced NSCLC, with increased adverse events of diarrhea and dyspnea. Further large randomized studies are necessary to evaluate the impact of antibiotic use on EGFR-TKI treatment for NSCLC. Basic research is also suggested to clarify the mechanism of this clinical phenomenon.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

KL, WZ and QT interpreted the patient data regarding antibiotic use and EGFR targeted therapy in advanced NSCLC, and participated in drafting and revising the manuscript. GJ and JJ designed and supervised the analysis of this retrospective study. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work presented in the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Dongguan People's Hospital (Dongguan, China) and was conducted according to the Declaration of Helsinki. Patients provided informed written consent at the time of data collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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