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Icotinib alone or with bevacizumab as first-line therapy in Chinese patients with advanced nonsquamous non-small cell lung cancer and activating *EGFR* mutations: A retrospective study

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Abstract

Background: This study focused on comparing the safety and therapeutic effects between icotinib monotherapy and icotinib plus bevacizumab combined therapy in non-small cell lung cancer (NSCLC) cases harboring *EGFR* mutations.

Methods: Data were collected retrospectively from the Cancer Institute and Hospital of Tianjin Medical University between October 2018 and December 2019, where the NSCLC cases that harbored *EGFR* mutations underwent first-line therapy with icotinib in the presence or absence of bevacizumab. This study included 90 cases, of which 60 patients were in the icotinib group (I) and 30 in the icotinib plus bevacizumab group (IB).

Results: The follow-up period to evaluate median PFS in our study was 18 months. Median PFS was 18.0 months (95% confidence interval [CI]: 14.7–21.3) with icotinib plus bevacizumab and 11 months (95% CI: 8.9–13.1) with icotinib alone (hazard ratio 0·54, 95% CI: 0.31–0.92; $p = 0.029$). According to the subgroup analyses based on the type of *EGFR* genomic aberration, a prolonged median PFS was observed in the cases harboring exon 21 point mutation (Ex21.L858R) in the IB group compared to the I group (not reached vs. 11 months [8.8–13.2], $p = 0.021$). However, the difference between the cases harboring exon 19 deletions in the *EGFR* gene was not significant. The DCR and ORR were comparable between both groups. Substantially higher incidences of hypertension and proteinuria were observed in the combined group compared to the icotinib monotherapy group.

Conclusions: This is the first study to provide further evidence of the benefits of applying icotinib in combination with bevacizumab as first-line treatment for advanced NSCLC cases harboring *EGFR* mutations. However, these findings need to be verified through prospective phase 3 clinical studies.

KEYWORDS
bevacizumab, combination therapy, epidermal growth factor receptor (EGFR), icotinib, non-small cell lung cancer (NSCLC)

INTRODUCTION

Epidermal growth factor receptor (*EGFR*) mutation represents a critical and frequently occurring mutation in the driver gene of nonsquamous non-small cell lung cancer

†All authors have contributed equally to the present study and are deemed as the co-first authors.

(NSCLC), especially in Asians.[1] Approximately 90% of *EGFR* mutations occur within the exon 21 point mutation (Ex21.L858R) and exon 19 deletion (Ex19del).[2] At present, some EGFR-tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, afatinib, osimertinib, and dacomitinib are used as mainstream first-line treatments to treat advanced NSCLC harboring *EGFR* mutations. Although first-line EGFR-TKIs may achieve a greater tumor response rate, many cases still show resistance to first-generation EGFR-TKIs after just one year of treatment.[3–5] Simultaneous suppression of vascular endothelial growth factor (VEGF) and the EGFR signal transduction pathways, verified through preclinical as well as clinical studies,[6–9] may serve as the candidate mechanisms to enhance the therapeutic efficacy in NSCLC cases harboring *EGFR* mutations.

Icotinib is a first-generation, selective, and reversible EGFR-TKI of Chinese origin which has been approved only in China for patients with advanced or metastatic *EGFR*-mutated NSCLC.[5,10,11] As a result, it is important to explore the effect of bevacizumab on improving the therapeutic effect of icotinib in *EGFR* mutation cases who do not actually receive any systemic therapy. Based on the above situation, the present retrospective work focused on analyzing the effect of icotinib in the presence or absence of bevacizumab on advanced NSCLC cases harboring *EGFR* mutations.

METHODS

Patient eligibility

Stage IIIB/IV NSCLC eligible cases harboring *EGFR* mutations (Ex19del and Ex21.L858R), which were confirmed by ARMS or next-generation sequencing (NGS) from the Cancer Institute and Hospital of Tianjin Medical University between October 2018 and December 2019 (Figure 1), were included in the study. None of the patients had received any systemic therapy for advanced or metastatic disease. The inclusion criteria were as follows: patients had been administered at least two courses of bevacizumab plus icotinib or icotinib alone; patients had been regularly imaged for the effective analysis based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1); and patients had a complete record of any adverse reactions. Cases excluded from the study were those receiving combined anticancer treatment or with additional cancers.

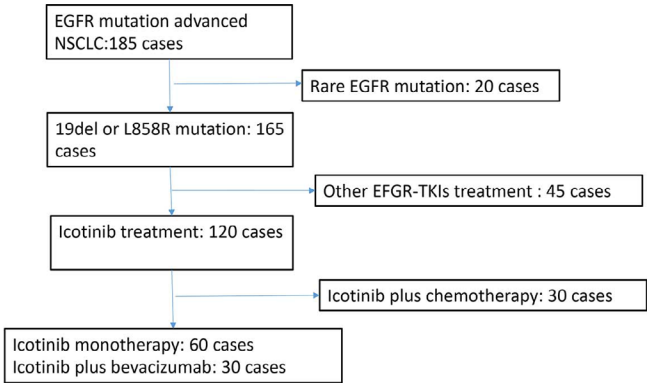

FIGURE 1 The flow diagram representing patient enrollment in the study

Treatment schedule

Patients received icotinib (125 mg per os TID) in the presence or absence of 7.5 mg/kg bevacizumab, which was intravenously injected at an interval of 21 days for at least one cycle. Treatment lasted until there was cancer progression, the occurrence of unacceptable adverse reactions, or if discontinuation of treatment was requested by the physician or the patient. All patients were asked to evaluate their blood pressure while receiving treatment with bevacizumab.

Study endpoints and assessment

Progression-free survival (PFS) was defined as the primary endpoint, which represented the time between treatment initiation and the last follow-up or cancer progression. In addition, treatment-related adverse events (TRAEs), disease control rate (DCR), and objective response rate (ORR) were deemed as secondary endpoints. Typically, we assessed TRAEs through clinical observation, questionnaires, or laboratory examination as per the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events ([NCI CTCAE], version 4.0). Meanwhile, we evaluated DCR through the partial response (PR), complete response (CR), and stable disease (SD) rates, while ORR was evaluated based on PR and CR.

Statistical analysis

The last follow-up in this study was conducted in December 2020. Subgroup analyses were conducted based on age, sex, clinical stage, smoking status, brain metastasis, and *EGFR* mutation type. Fisher's exact test or chi-square test was used to analyze TRAEs, DCR, and ORR. Kaplan–Meier (KM) curves were plotted to analyze PFS, after which the median together with the relevant 95% confidence intervals (CIs) were determined. SPSS 19.0 (IBM Corp.) was employed for statistical analysis. The significance level was set at $p < 0.05$ (two-sided). Since the historical data suggested a significant difference in the efficacy between bevacizumab plus EGFR-TKIs and only EGFR-TKIs, we were prompted to carry out a retrospective study even with such a small sample size.

RESULTS

Clinical characteristics of patients

A total of 90 NSCLC cases harboring *EGFR* mutations were included in this study. Sixty patients underwent icotinib

treatment (I group) while 30 patients underwent icotinib combined with bevacizumab treatment (IB group). A similar proportion of patients were present in both groups based on clinical stage, *EGFR* mutation status, and brain metastases. Considering the side effects of both drugs, we selected patients that were younger and in better physical conditions for the IB group compared to those included in group I (Table 1).

Efficacy

Those patients in B group showed markedly prolonged PFS compared to the I group (median, 18 months vs. 11 months; $p = 0.037$) (Figure 2). Also, the prediction of the 12-month PFS rate in the IB group was 73.3%, while in the I group, it was 44.2%. According to the subgroup analysis based on the type of *EGFR* mutation, the IB group harboring the Ex21. L858R mutation showed dramatically improved PFS compared to the I group with Ex19del (Figure 3). For the IB group and I group, we predicted the median PFS time for the Ex19del subgroup as 17 (14.2–20) versus 12 (7.5–16.5) months ($p = 0.499$), while for the Ex21.L858R subgroup, it was predicted as NR (not reached) versus 11 (8.8–13.2) months ($p = 0.021$), respectively. However, upon the deadline, mature overall survival data could not be obtained.

TABLE 1 Baseline clinical characteristics of patients

Characteristics	No. of patients (%)		*p*-value
	I ($n = 60$)	IB ($n = 30$)	
Age, years			
Median	57	54	
Range	32–75	35–70	
Sex			0.353
Male	24(40%)	9(30%)	
Female	36(60%)	21(70%)	
ECOG PS			0.290
0	12(20%)	9(30%)	
1	48(80%)	21(70%)	
Smoking status			0.750
Non-smoker	40(66.7%)	21(70%)	
Former-smoker	20(33.3%)	9(30%)	
Clinical stage			0.370
IIIB	15(25%)	5(16.7%)	
IV	45(75%)	25(83.3%)	
EGFR mutation status			0.643
Exon 19del	39(65%)	18(60%)	
Exon 21L858R	21(35%)	12(40%)	
Brain metastases			0.626
Yes	17(28.3%)	10(33.3%)	
No	43(71.6%)	20(66.7%)	
Median treatment cycles	16	25	

Abbreviations: B, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; I, icotinib; TKIs, tyrosine kinase inhibitors.

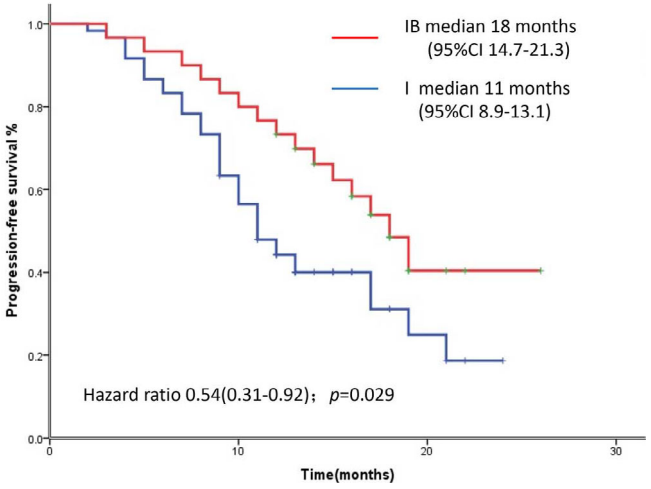

FIGURE 2 KM curves plotted to calculate PFS of the overall population. I, icotinib; B, bevacizumab

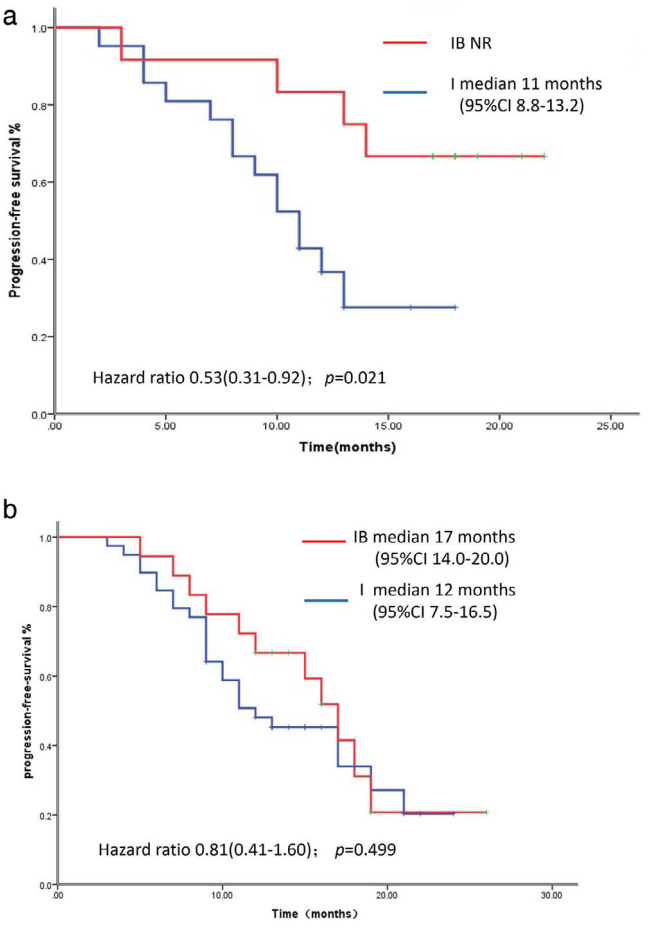

FIGURE 3 KM curves plotted to calculate progression-free survival (PFS) in patients harboring baseline mutations Ex21.L858R (a) or Ex19del (b). I, icotinib; B, bevacizumab

The ORR (73.3% vs. 68.3%) and DCR (91.7% vs. 90%) were found to be similar between the IB and I groups (Table 2). The post-progression results were available for the 54 cases with *EGFR* mutations detected for the second time; thus, accessible analysis data were obtained after progression. In such a patient population, the T790M mutation rate was comparable between both groups (IB group, 7/15 patients, 46.7%; I group, 18/39 patients, 46.2%).

Safety

Treatment-related adverse events (TRAEs) of the hematological and nonhematological cases are shown in Table 3. The frequently occurring TRAEs in IB and I groups included rash (70% vs. 66.7%), diarrhea (41.7% vs. 40%), and anorexia (41.7% vs. 43.3%). A marked change was observed in the grade ≥ 3 TRAEs in the IB group, such as hypertension (10%) and proteinuria (10%), which were both common adverse events related to bevacizumab.

TABLE 2 Treatment response of patients

	Case number (%)		
Response	**I ($n = 60$)**	**IB ($n = 30$)**	***p*-value**
CR	2(3.3%)	2(6.6%)	
PR	39(65%)	20(66.7%)	
SD	14(23.3%)	5(16.7%)	
PD	5(8.3%)	3(10%)	
ORR	41(68.3%)	22(73.3%)	0.628
DCR	55(91.7%)	27(90%)	0.795

Abbreviations: B, bevacizumab; CR, complete response; DCR, disease control rate; I, icotinib; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Discussion

According to our results, the IB group with advanced or metastatic NSCLC cases harboring *EGFR* mutation that received bevacizumab plus icotinib were associated with a prolonged duration of 18 months PFS (95% CI: 14.7–21.3) compared to that of the median PFS of 11 months (95% CI: 8.9–13.1) in the group receiving icotinib alone (I group). In the Ex21.L858R subgroup, the IB group showed prominently prolonged mPFS compared to the I group (mPFS: NR vs. 11 months, $p = 0.021$). In the Ex19del subgroup, although the PFS in the IB group was prolonged, the difference was not significant compared to the I group. Since the overall survival data remained immature upon reaching the deadline, we were unsure whether the IB group had prolonged OS or not.

Several studies have verified that simultaneous suppression of the VEGF and EGFR signal transduction pathways improved the outcome of patients with *EGFR* mutation. Phase 2 JO25567 trial[9] assessed and compared the efficacy of first-line bevacizumab plus erlotinib with only erlotinib in 154 NSCLC cases harboring *EGFR* mutation (median PFS of 16.0 months for the combination group vs. 9.7 months for the erlotinib group). Thereafter, bevacizumab was applied in combination with EGFR-TKIs as first-line therapy to treat patients with NSCLC harboring *EGFR* mutation, although this combination did not show significant improvement in OS.[12] Phase 3 NEJ026 trial[7] further verified the above findings in 228 cases (median PFS was 16.9 for the combination arm vs. 13.3 months for the erlotinib arm). The phase

TABLE 3 Adverse events in patients

	I ($n = 60$)		**IB ($n = 30$)**		
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	***p*-value[a]**
Rash	42 (70%)	9 (15%)	20 (66.7%)	5 (16.7%)	0.747
Paronychia	19(31.7%)	2(3.3%)	9(30%)	0	0.872
Diarrhea	25 (41.7%)	2 (3.3%)	12 (40%)	2 (6.6%)	0.880
Mucositis	18 (30%)	1(1.7%)	10 (33.3%)	1 (3.3%)	0.747
Neutropenia	3 (5%)	0	3 (10%)	0	0.654
Anemia	6 (10%)	0	2 (6.6%)	0	0.896
Thrombocytopenia	4 (6.7%)	0	3 (10%)	0	0.889
Hypertension	12 (20%)	2(3.3%)	24 (80%)	3 (10%)	<0.001
Proteinuria	3 (5%)	1(1.7%)	18 (60%)	3 (10%)	<0.001
Anorexia	25 (41.7)	3 (5%)	13 (43.3%)	2 (6.7%)	0.880
Fatigue	21 (35%)	6 (10%)	9 (30%)	2 (6.7%)	0.635
AST increased	16 (26.7%)	1(1.7%)	8 (26.7%)	0	0.614
ALT increased	17(28.3%)	1(1.7%)	8 (26.7%)	0	0.493

Abbreviations: B, bevacizumab; I, icotinib.
[a]Statistical values were calculated based on the results of any grade.

3 international trial RELAY[13,14] evaluated the efficacy of ramucirumab combined with erlotinib as first-line therapy compared to using erlotinib alone in 449 NSCLC cases harboring *EGFR* mutation (median PFS was 19.4 months for the combination arm vs. 12.4 months for the erlotinib arm). Our study shows results (median PFS of 18 months vs. 11 months) that are very close to these conclusions. Also, a meta-analysis summarized that the antiangiogenic agent combined with EGFR-TKI treatment can serve as a novel choice in the treatment of advanced NSCLC cases with *EGFR* mutation.[15] In addition to combination therapy with bevacizumab, another study also demonstrated that icotinib combined with chemotherapy can improve the survival efficacy in advanced NSCLC cases with sensitive *EGFR* mutations.[16,17]

It is a well-known fact that patients with Ex21.L858R mutation experience lower efficacy and poorer survival compared to the patients harboring Ex19del mutation after treatment with EGFR TKIs alone.[18,19] However, this difference seems to be reversed by the synergistic inhibition of EGFR and VEGF. In the RELAY study, the median PFS time between the cases that received ramucirumab plus erlotinib for both Ex19del and Ex21.L858R subgroups were comparable in the East Asian subset[13] (19.4 vs. 19.2 months) as well as in the general study population[14] (19.4 vs. 19.6 months). Notably, the Ex21.L858R subgroup showed the most prolonged PFS (19.4 months) among the existing first-line therapies for such a population. The median PFS time with only first-line EGFR TKI treatment (FLAURA,[18] ARCHER 1050,[20] EURTAC[21]) for the Ex21.L858R subgroup ranged between 7.1 and 14.4 months, while the combination with bevacizumab (JO25567[9] and NEJ026[7]) showed a median PFS time ranging between 13.9 and 17.4 months. Our data also showed that patients in the Ex21.L858R mutation subgroup experienced a significant benefit in PFS when treated with combination therapy as compared to icotinib alone ($p = 0.021$); however, because of the short follow-up period and the low sample size, the final PFS value could not be reached. An interesting study, INCREASE,[22] demonstrated that compared to that of the routine dose (125 mg, TID), a high-dose of icotinib (250 mg, TID) showed better efficacy (12.9 vs. 9.2 months) and moderate toxicity in cases harboring Ex21.L858R mutation. Thus, the regimen bevacizumab combined with a high dose of icotinib may be a potential choice for Ex21.L858R mutation in NSCLC.

A point mutation in EGFR T790M is the most frequently occurring cause for first- and second-generation resistance against EGFR TKIs, which takes place in 30%–60% of patients.[23,24] A study also found that patients receiving bevacizumab combined with EGFR TKI treatment showed a lower frequency of T790M.[25] At the opposite end of the spectrum was the RELAY study, wherein the treatment groups had a comparable mutation rate in the EGFR T790M at the time of PD, which suggested that adding ramucirumab showed no preventive effect on the occurrence of T790M in patients that received erlotinib.[14] Consistent with the RELAY study, our findings showed no difference in EGFR T790M mutation rates between both groups (46.7% vs. 46.2%).

IB treatment was expected to increase the TRAE rates compared to the treatment with icotinib only. The IB group also showed increased hypertension and proteinuria rates than the I group. Similar grade 3 icotinib-associated toxicities occurred (rash, diarrhea, fatigue, and anorexia) in both groups. A recent study further revealed that icotinib was well-tolerated both overall and in elderly NSCLC patients.[26]

However, several limitations were noted in this study. First, this single-center study enrolled patients at an unmatched ratio. Second, the baseline features were poorly matched in both arms. For example, the IB group constituted an increased ratio of younger patients with good ECOG PS and stage IV morbidity compared to the I group. Third, there was only a small number of samples in this retrospective study. As a result, the findings have revealed great discrepancies, particularly in the PFS data.

Together, bevacizumab plus icotinib achieved better efficacy than icotinib alone, and can be adopted as first-line treatment for advanced NSCLC cases harboring *EGFR* mutation. Nonetheless, such a treatment strategy needs to be further confirmed by carrying out more prospective clinical studies.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in the present study.

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