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ORIGINAL RESEARCH

Effects of icotinib on early-stage non-small-cell lung cancer as neoadjuvant treatment with different epidermal growth factor receptor phenotypes

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Purpose: Epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR–TKIs) have demonstrated efficacy in treating advanced non-small-cell lung cancer (NSCLC). Preliminary findings suggested that EGFR–TKIs might also be beneficial in neoadjuvant therapy in treating NSCLC. Therefore, this study aimed to evaluate the efficacy and safety of neoadjuvant therapy with icotinib in patients with early-stage NSCLC.

Patients and methods: We retrospectively reviewed the medical history of patients who were initially diagnosed with stage IA–IIIA NSCLC and were under icotinib administration before surgery between December 2011 and December 2014. Tumor assessment was conducted between the second and fourth week from initial icotinib treatment. The association between personal characteristics, smoking status, disease stage, EGFR mutation status, and clinical outcomes were investigated using multivariate logistic regression analysis.

Results: A total of 67 patients with NSCLC were reviewed, and approximately half (38/67) of them were identified as having EGFR-mutant tumors. The overall response rate of all patients was 26.7% at 2–4 weeks' assessment. Multivariate analysis showed that female sex (38.5% versus 10.7% in males, P=0.028) and EGFR mutation status (42.1% versus 6.9% in EGFR wild type, P=0.011) were independent predictive factors. The analysis also showed that the most common adverse effects were rash (43.3%) and dry skin (34.4%), which were tolerable.

Conclusion: Icotinib induced clinical response with minimal toxicity as neoadjuvant treatment in early NSCLC, especially in patients with common EGFR mutations. Further studies are warranted to confirm our findings.

Keywords: non-small-cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor, neoadjuvant

Introduction

Lung cancer is the most commonly diagnosed cancer in the People's Republic of China, with approximately 650,000 new cases diagnosed in 2011.[1] Approximately, 85% of these tumors are non-small-cell lung cancers (NSCLCs), and 25%–30% of the NSCLCs are potentially curable with a multimodality approach.[2] However, the 5-year survival rates still remain low, with 67% for stage I, 54% for stage II, and 40% for stage III.[3]

Neoadjuvant therapy might be considered as effective in reducing tumor size, increasing operability, and eradicating micrometastases. A meta-analysis of 13 randomized trials, which was conducted by Burdett et al, reported that neoadjuvant chemotherapy was associated with improved survival in operable patients, with 5% absolute benefit at 5 years.[4] However, treatment-associated toxicities and a delay in the surgical procedure also limited the use of chemotherapy in a neoadjuvant setting. Since, several

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randomized Phase III clinical trials involving metastatic NSCLC that harbored epidermal growth factor receptor (EGFR) mutations revealed that EGFR–tyrosine kinase inhibitors (TKIs), which function as molecularly targeted agents, are superior to chemotherapy.[5] The National Comprehensive Cancer Network and European Society for Medical Oncology Guidelines recommend EGFR–TKIs as a standard first-line treatment in this population.[6,7] Given their activity in advanced disease and tolerable toxicity profile, EGFR–TKIs could have potential benefits as neoadjuvants and/or adjuvants in treating early EGFR-mutated NSCLC.

Icotinib, which is developed in the People's Republic of China, is a small-molecule EGFR–TKI. A randomized Phase III study demonstrated that the efficacy of icotinib was not inferior to gefinitib.[8] In addition, icotinib was approved by the China Food and Drug Administration as second- or third-line treatment for advanced NSCLC in June 2011 and as a first-line therapy for EGFR-mutant NSCLC recently.

Therefore, the present study aimed to retrospectively evaluate the efficacy and safety of icotinib in treating patients living with early-stage NSCLC during a 2–4 weeks preoperative window. Moreover, potential predictive markers are also investigated in this analysis.

Materials and methods

Study design and patients

A total of 91 patients with a diagnosis of stage IA–IIIA NSCLC and who were administered icotinib (125 mg; Betta Pharmaceuticals Co., Ltd, Hangzhou, People's Republic of China) thrice daily preoperatively were recruited between December 2011 and December 2014 in the People's Liberation Army General Hospital. Eligible patients for this retrospective study were selected in accordance with the following inclusion criteria: patients had dimensionally measurable lesion in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) criteria; had not received chemotherapy or targeted drug; had tumor assessment at 2–4 weeks after receiving icotinib; and had assessed EGFR mutational status. In the end, a total of 24 patients were excluded from this analysis for the following reasons: operations were earlier than planned, the icotinib duration was less than 2 weeks (n=23), and unknown EGFR mutational status (n=1). Accordingly, 67 patients were enrolled in this analysis, 54 of those had surgical resection after 2 weeks' treatment, and 13 patients underwent surgery after the fourth week's evaluation.

This retrospective study was approved by the People's Liberation Army General Hospital Review Board. Patient's clinical records were anonymized and de-identified prior to analysis.

Patient characteristics and evaluation of therapeutic outcomes and toxicity

Patient characteristics, including EGFR mutation status, were retrospectively obtained from medical records. EGFR mutational status was analyzed through the amplification refractory mutation system method (Beijing ACCB Biotech Ltd, Beijing, People's Republic of China) using surgical tissue sample. Tumor responses were interpreted by the same radiologist in accordance with RECIST criteria, version 1.1.[9] Tumor responses were classified as complete response, partial response, stable disease, and progressive disease. Toxicities were categorized into five grades, namely 0–4, in accordance with "Common Terminology Criteria for Adverse Events" (CTCAE4.0), which was established by the National Cancer Institute of America.[10]

Statistical analysis

All the data analyses in this study were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed, and α was set at 0.05 to define statistical significance. Baseline characteristics of the study population were described and compared using independent samples *t*-test. The chi-square test and Fisher's exact test were performed to explore the difference in general characteristics, such as sex, age, smoking history, histology, and staging, between those with EGFR-mutant tumors and wild-type patients. In addition, the correlation between characteristics and objective response rate (ORR) was also investigated. In order to identify independent factors, multivariate logistic regression model was built.

Results

General characteristics of patients and EGFR phenotype

The clinical characteristics of the study population are listed in Table 1. A total of 28 male (41.8%) and 39 female (58.2%) patients with a median age of 59 years were included in the analysis. Among those, 42 (62.7%) were never smokers and 25 (37.3%) had a smoking history. The majority were diagnosed with adenocarcinoma (95.5%). Among the eligible patients, 22 (32.8%) were diagnosed with stage IA, 30 (44.8%) with stage IB, five (7.46%) with stage IIA, and ten (14.9%) with stage IIIA disease. Among the 38 (56.7%) patients harboring EGFR mutations, 15 carried deletion in exon 19, 16 carried the L858R mutation in exon 21, and seven carried the mutation in exon 20, whereas the remaining 29 (43.3%) patients were confirmed as wild-type EGFR. The clinical characteristics showed no significant difference between EGFR-mutated and wild-type patients.

Table 1 General characteristics of the 67 patients

Variables	All patients (n=67)	EGFR mutation (n=38)	EGFR wild type (n=29)	*P*-value
Sex				0.347
Male	28 (41.8%)	14	14	
Female	39 (58.2%)	24	15	
Age				0.352
Median (years)	59 (37–78)	57.5 (43–78)	59 (37–77)	
<65	50 (74.6%)	30	20	
≥65	17 (25.4%)	8	8	
Smoking				0.105
Yes	25 (37.3%)	11	14	
No	42 (62.7%)	27	15	
Histology				0.574
Adeno	64 (95.5%)	37	27	
Squamous	3 (4.5%)	1	2	
Stage				0.58
IA	22 (32.8%)	15	7	
IB	30 (44.8%)	15	15	
IIA	5 (7.5%)	3	2	
IIIA	10 (14.9%)	5	5	
EGFR mutations				NA
Exon 19 deletion	NA	15	NA	
Exon 21 L858R exon 20[a]	NA	16	NA	
	NA	7	NA	

Note: [a]Exon 20 mutation, including 5 Q787Q, 1 V819V, 1 Y774-776ins.
Abbreviations: Adeno, adenocarcinoma; Squamous, squamous-cell carcinoma; EGFR, epidermal growth factor receptor; NA, not applicable.

Evaluation of clinical response

At 2–4 weeks' assessment via computed tomography (CT), 18 out of the 67 patients achieved partial response and 49 had stable disease. The ORR was 26.7%. The association between the clinicopathological factors and early response was analyzed and is presented in Table 2. The ORR was significantly higher among the females (38.5% in females versus 10.7% in males), nonsmokers (35.7% in nonsmokers versus 12% in smokers), patients with EGFR-mutant tumors (42.1% in mutant versus 6.9% in wild-type patients; Table 3), and those with rash (41.4% in rash versus 15.8% in no rash patients) when compared with their counterparts ($P<0.05$). However, the statistical analysis showed no significant association between the clinical response to icotinib administration and some of the patient characteristics, including age, pathological type, and disease stage. Multivariate logistic regression analysis demonstrated that female sex (38.5% versus 10.7% in males, $P=0.028$, 95% confidence interval [CI]: 1.19–22.68) and EGFR mutational status (42.1% versus 6.9% in EGFR wild-type, $P=0.011$, 95% CI: 1.62–42.61) were independent predictive factors. Furthermore, among the 38 patients with an EGFR mutation, the females also showed a better response (54.2%) than their male counterparts (21.4%, $P=0.049$). In addition, the results of the analysis also indicated that patients with common type of EGFR mutation (ORR was 60% in exon 19 deletion and 43.8% in exon 21 L858R mutation) received greater benefits than those with exon 20 mutations (ORR was 0%, $P=0.008$). In addition, no significant difference was observed between patients with exon 19 deletion and those with exon 21 L858R mutation ($P=0.366$).

With regard to the change in tumor's longest diameter, the percentage change upon evaluation at 2–4 weeks from baseline was −19.6%±2% (95% CI: −23.6%, −15.6%) in all the patients. When differences in the EGFR status were compared, we recorded significant percentage changes of −26.15%±2.4% and −10.92%±2.67% in EGFR-mutated and wild-type patients, respectively ($P<0.001$; Table 4). Furthermore, among those with an EGFR mutation, the percentage shrinkage was −28.6%±2.4% (95% CI: −33.7%, −23.5%) in exon 19 deletion, −30.6%±4.13% (95% CI: −39.4%, −21.8%) in exon 21 L858R mutation ($P=0.68$), and −10.6%±4.1% (95% CI: −20.7%, −0.6%) in exon 20 mutation.

Adverse effects of 2–4 weeks' icotinib treatment for patients with early-stage NSCLC

Among the eligible population, 45 (67.2%) patients experienced adverse drug reactions, with the most common adverse effects being skin rash and skin dryness. It was observed that 29 (43.3%) patients had skin rash (27 patients had grade 1

Table 2 Association of clinicopathological factors and molecular characteristics with tumor response to short-term icotinib treatment

Clinical characteristics	Partial response				
	All patients (n=67), n (%)	*P*-value	EGFR mutation (n=38), n (%)	*P*-value	EGFR wild type (n=29), n (%)
Sex		0.011		0.049	
Male	3 (10.7%)		3 (21.4%)		0
Female	15 (38.5%)		13 (54.2%)		2 (13.3%)
Age		0.762		0.767	
<65	13 (26%)		13 (43.3%)		0
≥65	5 (29.4%)		3 (37.5%)		2 (22.2%)
Smoking		0.034		0.237	
Yes	3 (12%)		3 (27.3%)		0
No	15 (35.7%)		13 (48.1%)		2 (13.3%)
Histology		0.558		1	
Adeno	18 (28.1%)		16 (43.2%)		2 (7.4%)
Squamous	0 (%)		0		0
Stage		0.358		0.484	
I	16 (30.2%)		14 (46.7%)		2 (8.7%)
IIA	1 (25%)		1 (33.3%)		0
IIIA	1 (10%)		1 (20%)		0
Adverse effect		0.019		0.154	
Skin rash	12 (41.4%)		11 (52.4%)		1 (12.5%)
No skin rash	6 (15.8%)		5 (29.4%)		1 (4.8%)
EGFR		0.001			NA
Mutations	16 (42.1%)			0.008	NA
19 Del	NA		9 (60%)		NA
21 L858R	NA		7 (43.8%)		NA
20	NA		0		NA
Wild type	2 (6.9%)		NA		NA

Abbreviations: Adeno, adenocarcinoma; Squamous, squamous-cell carcinoma; 19 Del, exon 19 deletion; 21 L858R, exon 21 L858R mutation; EGFR, epidermal growth factor receptor; NA, not applicable.

and two patients had grade 2), 23 (34.3%) had dry skin (22 had grade 1 and one had grade 2), nine (13.4%) had grade 1 diarrhea, three had grade 1 oral ulcer, and one had grade 1 alopecia. However, these adverse drug reactions did not result in the discontinuation of icotinib treatment (Table 5).

Icotinib was administrated until the day before surgery in all the patients. Operations were performed via a video-assisted thoracoscopy or a lateral incision approach. We observed that the main difference from the conventional operation was that neoadjuvant therapy led to tissue adhesion, especially in separating pulmonary vessels and vascular sheath, and vascular fragility increased when ligating blood vessels, but no vascular rupture occurred. However, the surgical incision healed well.

Follow-up

Until the last follow-up on December 31, 2014, the median follow-up time was 20 months (range: 1–36 months). Fifty patients

Table 3 Comparison of overall response between EGFR-mutated and wild-type patients upon evaluation at 2–4 weeks

Best tumor change (RECIST1.1)	EGFR mutation (n=38)	EGFR wild type (n=29)	*P*-value
CR (n)	0	0	
PR (n)	16	2	
SD (n)	22	27	
PD (n)	0	0	
ORR	42.1%	6.9%	0.001

Note: RECIST1.1 signifies "no confirmation measurement".
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; EGFR, epidermal growth factor receptor.

Table 4 Comparison of the tumor shrinkage upon evaluation at 2–4 weeks from baseline between EGFR-mutated and wild-type patients

Percentage tumor change (longest diameter)	EGFR mutation (%), n=38	EGFR wild type (%), n=29	*P*-value
Mean ± SD	−26.15±2.4	−10.92±2.67	<0.001
Min, max	−64.4, 1.8	−52.5, 10.34	
Median	−25.53	−8.7	
Q1, Q3	−27.27, −31.01	−16.39, −5.44	

Abbreviations: EGFR, epidermal growth factor receptor; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Table 5 Summary of the treatment-related adverse events

Adverse events	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Total, n (%)
Acne/rash	27 (40.3)	2 (3)	0	0	29 (43.3)
Dry skin	22 (32.8)	1 (1.5)	0	0	23 (34.3)
Diarrhea	9 (13.4)	0	0	0	9 (13.4)
Oral ulcer	3 (4.5)	0	0	0	3 (4.5)
Alopecia	1 (1.5)	0	0	0	1 (1.5)

received systemic adjuvant therapy, while 17 did not receive any treatment. Only five (7.5%) patients experienced disease progression, and the disease-free survival rate was 10, 15, 16, 18, and 20 months, respectively. Two of them experienced disease relapse, and three had brain/bone metastases. A total of 62 patients remained disease free. The majority of patients are still alive, and the OS data has not matured. Only two died of brain metastases and adverse effects of chemotherapy, with OS being 30 and 24 months, respectively.

Discussion

The present study demonstrated that icotinib induced clinical response with minimal toxicity. In addition, it was associated with no additional surgical risk when utilized as a neoadjuvant therapy in treating early NSCLC. After 2–4 weeks' icotinib administration, the ORR was 26.7% in all the patients, 42.1% and 6.9% in those with an EGFR mutation and wild-type patients, respectively. While a pivotal study has reported on the relationship between EGFR mutations and TKI sensitivity since 2004,[11] multiple Phase III studies have confirmed a striking response and indicated longer progression-free survival (PFS) with EGFR–TKIs than with standard chemotherapy in advanced NSCLC with an EGFR mutation.[5] In neoadjuvant therapy, EGFR–TKI remains hypothetical and needs strong evidence to confirm its efficacy in treating early NSCLC with an EGFR mutation. The results of the current study were consistent with those found in previous Phase II studies. For instance, a number of single arm, Phase II studies showed the benefits of EGFR–TKIs in neoadjuvant therapy. Lara-Guerra et al[12] evaluated 36 patients with 17% EGFR mutations who had been treated with gefitinib 250 mg/day as neoadjuvant therapy for 28 days. The response rate among patients who harbored EGFR mutations was 50%, which was only 11% in all the patients. Similar findings were also reported by Schaake et al,[13] where 60 patients received preoperative erlotinib (150 mg) once daily for 3 weeks.

Traditionally, neoadjuvant chemotherapy is considered as the primary approach in treating NSCLC. Three randomized clinical trials (RCTs) demonstrated that the ORR was 35%, 41%, and 53% in the neoadjuvant chemotherapy arms, respectively.[14–16] A meta-analysis by Pisters et al,[15] which included ten RCTs, showed a significant survival advantage for those who received induction chemotherapy (hazard ratio [HR] 0.89, P=0.02). In addition, the current study further confirmed the findings of earlier studies, where an ORR of 42.1% was reported among those living with EGFR-mutated tumors. We considered EGFR–TKIs warranted evaluation of their potential role as neoadjuvant options by properly designed RCTs in NSCLC EGFR mutation population.

Among the 38 patients with EGFR-mutated lung cancer, 15 harbored exon 19 deletion, 16 had exon 21 L858R mutation, and seven harbored exon 20 mutation. Among those with common type of EGFR mutation, the ORR was 60% in exon 19 deletion and 43.8% in L858R mutation at 2–4 weeks of evaluation. No partial response was observed in patients with exon 20 mutation. The current study revealed a different response rate between exon 19 deletion and exon 21 L858R (60% versus 43.8%, P=0.366) mutation; however, the difference was not statistically significant. Jackman et al and Riely et al indicated that mutations in both exons 19 and 21 were correlated with a promising clinical response to gefitinib or erlotinib. Moreover, patients with exon 19 deletions might show better response than those with exon 21 L858R mutations in terms of response rate, PFS, and OS.[17,18] In CALGB 30406 study, the response rate of exon 19 deletion and exon 21 L858R mutation were 83% and 40%, and the median PFS was 15.7 and 12.6 months, respectively, in erlotinib arm.[19] The variation between exon 19 deletion and exon 21 L858R mutation was further confirmed in a pooled analysis of LUX-Lung 3 and LUX-Lung 6 trials.[20] When compared with traditional chemotherapy, sustainable survival benefits were observed among patients with exon 19 deletions, while no significant improvement was witnessed among those with exon 21 L858R mutations. The current study indicated that a difference might also exist in icotinib treatment and warrants further exploration in neoadjuvant therapy with EGFR–TKIs. Regarding those with exon 20 mutations, none achieved response, which further confirmed the findings from previous research work, where a low efficacy was reported.[21–24]

Neoadjuvant icotinib was generally well tolerated, with rash (43.3%), skin dryness (34.3%), and diarrhea (13.4%) as the most common adverse reactions. All toxicities were mild (ie, at grade 1 or 2). Icotinib was administrated until the day before surgery, and the main change was that it became more difficult to separate vessels and vascular fragility increased; however, these changes did not significantly influence the operational difficulty and wound healing processes.

Conclusion

The role of EGFR–TKIs in neoadjuvant therapy is not well studied. To our knowledge, most trials had small sample size and limited study period. The current study demonstrated the efficacy and tolerability of short-term neoadjuvant therapy with icotinib in patients living with early-stage NSCLC, especially among those with common EGFR mutation type. Future trials should incorporate targeted therapies as part of a neoadjuvant strategy based on molecular profile to provide sufficient consolidated evidence to improve clinical practice.

Disclosure

The authors report no conflicts of interest in this work.

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