Patients Harboring Uncommon EGFR Exon 19 Deletion-insertion Mutations Respond Well to First-generation EGFR Inhibitors and Osimeritinib Upon Acquisition of T790M

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Research Article

Keywords: EGFR exon 19 deletion-insertion, EGFR TKI, Clinical outcomes, Resistance mechanism, NSCLC

Posted Date: April 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-423015/v1>

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Version of Record: A version of this preprint was published at BMC Cancer on November 13th, 2021. See the published version at <https://doi.org/10.1186/s12885-021-08942-x>.

Abstract

Background: This study is to investigate the effects and resistance mechanisms of first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC) patients carrying rare EGFR exon 19 deletion-insertion (19delins) mutations.

Methods: The next generation sequencing (NGS) data of 1783 patients diagnosed as advanced NSCLC from November 2017 to September 2020 were successively and retrospectively reviewed. 41 patients with EGFR 19delins and 41 patients with EGFR exon 19 deletion (19del) were enrolled in this study, who were given first generation EGFR TKIs as first-line therapy.

Results: 17 mutation types of EGFR 19delins were identified in this study, L747_P753delinsS (10/41) and L747_A750delinsP (9/41) were the most frequent mutation types, followed by L747_T751delinsP (6/41) and E746_S752delinsV (3/41). Under the same baseline characteristics, median progression-free survival (mPFS) was similar in patients with EGFR 19delins to those with EGFR 19del (10.4 months vs. 13.1 months, $p=0.1076$). Interestingly, patients with L747_T751delinsP had a better mPFS than those with other variants (18.7 months vs. 13.1 months, $p=0.035$). No significant difference in mPFS was found among the three groups of gefitinib, icotinib, and erlotinb with 14.7 months, 10.9 months, and 13.1 months ($p>0.05$). After progression from first-line EGFR TKIs, both EGFR 19delins and EGFR 19del had similar rates of developing resistance mechanisms including EGFR T790M mutation (45.8% vs. 57.8%). Patients acquiring T790M mutation received osimertinib as second-line treatment, and the mPFS was similar between the groups of EGFR 19delins ($n=8$) and EGFR 19del ($n=10$): 12.0 months vs. 12.2 months ($p=0.97$).

Conclusion: Our results indicate that patients with uncommon EGFR 19delins can also benefit from first-generation EGFR TKIs treatment, having similar treatment responses and survival outcomes to those with EGFR 19del, even similar clinical outcomes from osimertinib upon acquiring T790M resistance mutation.

Introduction

Non-small cell lung cancer (NSCLC), accounts for 85–90% of all lung cancers, is the leading cause of cancer-related mortality in China and worldwide (1). Epidermal growth factor receptor (EGFR) mutations are one of the most frequent oncogenic driver events in NSCLC. Among them, exon 19 deletions and the L858R point mutation comprise up to 90% EGFR mutations and confer hypersensitivity to EGFR tyrosine kinase inhibitors (TKIs) (2). With the increasing use of next-generation sequencing (NGS) in clinical practice, more rare and low frequency mutations have been identified, such as EGFR 19 deletion-insertion (19delins) (3). However, our understanding of their biology and clinical response to EGFR TKIs is poorer than that of classical mutations. In particular, few large-scale studies focused on treatment strategies of these rare EGFR mutations due to the low frequency of these rare mutations and difficulty in trial recruitment.

The clinical responses of EGFR 19delins to EGFR TKIs are reported to be different. Truini et al proved that patients with L747_A750delinsP had significantly worse PFS and OS than those with common 19del and L747_P753delinsS (4). In addition, some reports revealed EGFR 19delins confer primary resistance to gefitinib or erlotinib (5–7). On the contrary, some researchers reported that patients with EGFR 19delins mutation, such as L747P, had favorable outcomes upon EGFR-TKI therapy (8, 9). However, the above results are based on limited cases and inconsistent. Furthermore, the resistance mechanisms to first-generation EGFR-TKIs are not studied in the population of EGFR 19delins. The study from Peng et al including 93 cases with EGFR 19delins has shown that first-line EGFR TKIs bring better survival benefits to these patients than those with EGFR 19del, but once upon the acquisition of T790M resistance mutation, the outcomes of EGFR 19delins group are poor (10). However, different from their findings, our research demonstrated that patients carrying EGFR 19delins mutation can also benefit from first-generation EGFR TKIs (gefitinib and icotinib) equally to those carrying EGFR 19del mutation. Besides, we also analyzed the resistance mechanism of EGFR 19delins to first-generation TKIs and the outcomes of those receiving second-line osimertinib upon acquisition of T790M mutation.

Materials And Methods

Patients

The NGS molecular testing data of 1783 patients diagnosed as advanced NSCLC were retrospectively screened successively between November 2017 and September 2020. And 82 treatment-naïve patients at diagnosis met the inclusion criteria: 41 with EGFR 19 delins mutation and 41 with EGFR 19del mutation. All these patients were given gefitinib (250 mg once daily) or icotinib (125 mg three times a day) or (erlotinib 150 mg once daily) orally as first-line therapy. Clinical outcomes of these patients were evaluated (Fig. 1). The inclusion criteria for patients in the study were: beyond 18 years, stage IV disease according to the 8th American Joint Committee on Cancer Staging System, lung carcinoma or squamous carcinoma confirmed by immunohistochemistry, first-line standard EGFR TKI therapy, EGFR 19delins or EGFR 19del status confirmed by NGS, radiographic images data available at baseline and progression per Response Evaluation Criteria in Solid Tumors, version 1.1. Patients with baseline EGFR T790M mutation and other systematic antitumor treatment were excluded. The Ethics Committee of First Affiliated Hospital of Zhengzhou University approved this retrospective analysis and waived informed consent.

Next-generation sequencing (NGS)

DNA processing and sequencing methods were described as below. In brief, at least 20 ng DNA was extracted from tissue or liquid biological samples and processed for NGS library construction. Then the profiling was performed on Illumina HiSeq 4000 (Illumina, San Diego, CA) using commercially available hybrid-capture sequencing panels including 8, 14 or 56 genes (GeneseeqOne, Nanjing Geneseeq Technology Inc., China; Burning Rock Biotech Ltd., Guangzhou, China). All the above panels covered the

whole exons and relevant introns of the below 8 driver genes: EGFR, KRAS, ALK, ROS1, RET, MET, ERBB2 and BRAF. And the NGS data were mapped to the human genome 19 (hg19), which enabled accurate detection of mutations covering point mutation, insertion-deletion mutation, copy number variants and chromosome structural abnormality.

Evaluation

Clinical information was retrieved retrospectively from the medical records, including demographic characteristics, response rate, progression-free survival (PFS) and NGS-detected mutations. Tumor specimens were profiled at baseline and progression from first-line EGFR TKI therapy with NGS. Tumour tissue was obtained at the initial diagnosis by resection or biopsy and stored as formalin-fixed paraffin-embedded samples.

Statistical analysis

The baseline data was compare by chi-square test. Propensity score (PS) correction method was used for controlling confounding factors (11), such as age, gender, ECOG score, T stage, N stage, brain metastases, first line TKIs. The survival analysis was performed using the Kaplan-Meier method with the statistical packages R (The R Foundation; <http://www.r-project.org>; version 3.4.3) and Empower (R) (www.empowerstats.com, X&Y solutions, inc. Boston, Massachusetts). Two sided p values less than 0.05 were considered statistically significant.

Results

Patients' baseline characteristics

Among 1783 patients diagnosed as advanced NSCLC, 41 treatment-naive patients with EGFR 19delins mutation were enrolled in this study, with 41 patients carrying EGFR 19del mutation as control cohort. Patients with EGFR 19delins were mostly women (24/41), non-smokers (34/41), stage IV disease (41/41) and adenocarcinoma histology (40/41). The clinical baseline characteristics of the cohorts of uncommon EGFR 19delins and EGFR 19del were matched and summarized in Table 1.

Table 1
Baseline characteristics of the NSCLC patients with EGFR 19 delins or EGFR 19 del

Characteristics		19delins (n = 41)	19del (n = 41)	P value
Age, years	Median (range)	60 (30–75)	60 (34–76)	0.638
Sex	Male	17	11	0.162
	Female	24	30	
Smoking status	Never	34	34	1.000
	Smoker	7	7	
Histological type	Adenocarcinoma	40	41	1.000
	Squamous carcinoma	1	0	
TNM stage	IIIB	0	0	1.000
	IV	41	41	
ECOG PFS score	0 or 1	34	31	0.414
	2	7	10	
Brain metastases	No	25	27	0.647
	Yes	16	14	
EGFR 19delins variants	p.L747_P753delinsS	10		
	p.L747_A750delinsP	9		
	p.L747_T751delinsP	6		
	p.E746_S752delinsV	3		
	Other EGFR 19delins	13		
EGFR 19del variants	p.E746_A750del		36	
	p.L747_S752del		3	
	P.L747_T751del		2	
First-line treatment	Gefitinib	24	25	0.973
	Icotinib	15	14	
	Erlotinib	2	2	
19delins: EGFR exon 19 deletion-insertion; 19del, EGFR exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group performance status.				

Baseline mutation profile

At baseline, 8-gene panel for 26.8% (11/41), 14-gene panel for 36.6% (15/41), and 56-gene panel for 36.6% (15/41) were used for tissue or liquid sample genotyping in the patients with EGFR 19delins receiving first-line EGFR-TKI therapy. And, the patients with EGFR 19del were profiled using 8-gene panel for 24.4% (10/41), 14-gene panel for 41.5% (17/41), and 56-gene panel for 31.1% (14/41). In our study, no other classic oncogenic driver mutations were detected from both cohorts. EGFR amplification and TP53 mutation were the most frequent concurrent mutations identified with 17.1% (7/41) and 9.8% (4/41) in the EGFR 19delins cohort, and 17.1% (7/41) and 17.1% (7/41) in EGFR 19del cohort. No classic oncogenic driver mutations other than EGFR 19del or 19delins were detected in either cohort. No significant difference was observed in sequencing methods and concurrent mutations between the two cohorts.

The variants detected in uncommon EGFR 19delins cohort

A total of 17 different EGFR 19delins mutation types were identified in the EGFR 19delins cohort (Fig. 2). Among them, 3 were novel and not published in previous literatures and somatic mutation database (Catalogue of Somatic Mutations in Cancer, COSMIC), such as L747_K754delinsSR, A750_I759delinsPS, and L747-T751delinsAI. The most frequent mutation types in the EGFR 19delins cohort were L747_P753delinsS (n = 10, 24.4%), L747_A750delinsP (n = 9, 22.0%), L747_T751delinsP (n = 6, 14.6%), and E746_S752delinsV (n = 3, 7.3%, Fig. 2B). Distribution of EGFR 19delins mutation types have been illustrated using Pie charts Figure. And EGFR amplification was the most common concurrent mutation in both uncommon EGFR 19delins and common EGFR 19del groups, with equal percentage of 17.1% (7/41).

Treatment response to first-line EGFR TKI therapy

The effects of first-line EGFR TKI treatment in the patients with EGFR 19delins and EGFR 19del are evaluated. The clinical baseline characteristics of the two cohorts were similar (Table 1). The patients with EGFR 19delins were given gefitinib (n = 24, 58.5%), icotinib (n = 15, 36.6%), and erlotinib (n = 2, 4.9%), respectively. Similarly, the patients with EGFR 19del were given gefitinib (n = 25, 58.5%), icotinib (n = 14, 36.6%), and erlotinib (n = 2, 4.9%), respectively.

The best changes of tumor size from baseline after first-line TKI treatment in the two cohorts were estimated (Fig. 3A and 3B). The objective response rate (ORR) was similar between the two cohorts (EGFR 19delins vs. EGFR 19del: ORR 75.6 % vs. 78.0 %; DCR 97.6 % vs. 100 %). Among the patients with EGFR 19delins, 31 patients achieved partial response (PR; 75.6%), 9 patients had stable disease (SD;

22.0%) and one patient had progressive disease (PD, 2.4%) after first-line EGFR TKI. Likewise, in the patients carrying EGFR 19del, the rates of PR, SD, and PD were 78.0% (32/41), 22.0% (9/41) and 0.

PS correction method was used for controlling confounding factors, such as age, gender, ECOG score, T stage, N stage, brain metastases, first line TKIs (the binary logistic regression model: $PS = -1.345 + 0.569 \times \text{sex} - 0.015 \times \text{age} + 0.411 \times \text{ECOG score} - 0.305 \times \text{T stage} + 1.126 \times \text{N stage} - 0.216 \times \text{brain metastases} - 0.020 \times \text{first line TKIs}$). The distribution of PS between the cohorts of EGFR 19delins and EGFR 19del showed no significance (Figure S1). Then survival analysis was performed under the adjustment of PS. The median PFS (mPFS) was 10.4 month in patients with EGFR 19delins, similar to 13.1 months in those with EGFR 19 del (HR: 0.6527; 95% CI: 0.3885–1.0983; $p = 0.1076$; Fig. 4A). Interestingly, the outcomes of patients with different EGFR 19delins mutation types are not exactly same. As shown in Fig. 4B and 4C, patients harboring L747_T751delinsP had a longer mPFS than those harboring L747_P753delinsS, L747_A750delinsP, and other variants (18.7 months vs 13.1 months, HR: 0.3318; 95% CI: 0.1193–0.9232; $p = 0.035$). There is no significant difference between patients with L747_A750delinsP and L747_T751delinsP (Fig. 4B). Then, we analyzed the effects of three first-generation EGFR TKIs in patients with EGFR 19delins. And no significant difference in mPFS was found among the three groups of gefitinib, icotinib, and erlotinb with 14.7 months, 10.9 months, and 13.1 months ($p > 0.05$; Fig. 4D). No serious adverse events (grade 3/4) were reported by the two cohorts.

3.5. The Mechanisms of resistance to first-generation EGFR TKIs

At the data cut-off of January 17, 2021, a total of 34 patients carrying EGFR 19delins and 32 patients carrying EGFR 19del had PD. At progression, 64.7% (22/34) in EGFR 19delins cohort and 78.1% (25/32) in EGFR 19del cohort performed re-biopsies and NGS test. And EGFR T790M was the main resistance mechanism in two cohorts without statistical significance (EGFR 19delins vs. EGFR 19del: 54.5% (12/22) vs. 60.0% (15/25)). The resistance mutation was not identified in 22.7% (5/22) and 24.0% (6/25) of the patients with EGFR 19delins and EGFR 19del, respectively. Besides, one case had sarcomatoid carcinoma transformation and two cases had squamous transformation from adenocarcinoma in EGFR 19 delins cohort. Comparatively, in EGFR 19del cohort, there was one each case had small-cell lung cancer transformation and squamous transformation from adenocarcinoma. MET amplification was acquired in (2/22) EGFR 19delins group and ERBB2 amplification was acquired in 1/25 of EGFR 19del cohort (Fig. 5A and 5B).

3.6. The efficacy of second-line osimertinib therapy in patients acquiring EGFR T790M

The effects of osimertinib as second-line therapy was compared between the groups of EGFR 19delins ($n = 8$) and EGFR 19del ($n = 10$) acquiring EGFR T790M mutation after progression with first-generation

TKI treatment. The therapeutic responses were similar in both EGFR 19delins and EGFR 19del groups: ORR 62.5% vs 30.0%, DCR: 100.0% vs 80.0% (Table 2). There was also no significant difference in mPFS between EGFR 19delins and EGFR 19del groups (mPFS: 12 months vs. 12.2 months; Log-rank test, p = 0.97; Fig. 5C).

Table 2
Clinical responses of third-generation EGFR-TKI as second line therapy in patients with EGFR 19delins and E EGFR 19del

	19delins (n = 8)	19del (n = 10)
ORR, n (%)	5 (62.5)	3 (30.0)
DCR, n (%)	8 (100.0)	8 (80.0)
Best objective response, n (%)		
CR	0	0
PR	5 (62.5)	3 (30.0)
SD	3 (37.5)	6 (50.0)
PD	0	2 (20.0)
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate		

Discussion

The present study analyzes the variants and treatment outcomes to first-generation EGFR TKIs as first-line therapy in Chinese patients with rare EGFR 19delins mutation. After progression, the resistant mechanisms to first-generation EGFR TKIS and the effects of osimertinib on patients with EGFR T790M mutation have also been investigated. A total of 17 mutation types of uncommon EGFR 19delins are identified and 3 are previously unpublished in any literatures and COSMIC database.

EGFR 19del is the most common variant type of EGFR mutation in NSCLC (12). Clinically, EGFR genotyping methods include amplification refractory mutation system (ARMS)-polymerase chain reaction (PCR), Sanger sequencing, and NGS. Despite the most common use in clinical practice, ARMS-PCR can't cover the entire spectrum of EGFR mutations based on the current mutation-specific PCR kits, therefore some potentially treatable variants are inevitably missed by this approach (13–15). Sanger sequencing can identify all mutations in a given gene region, however, false negatives still occur especially when tumor cells are insufficient. For this problem, NGS can profile all types of EGFR mutations and concurrent mutations with high sensitivity. To this end, NGS method was used for screening patients in our study. We have reviewed the NGS records of 1783 NSCLC untreated patients, and 41 objects with EGFR 19delins were enrolled, compared by 41 baseline-matchable objects with EGFR 19del. The present study shows that the treatment response and PFS in the population with EGFR 19delins mutation are not worse than

those with common EGFR 19del when using first-generation EGFR TKIs. Interestingly, our results demonstrate that gefitinib can bring a better survival benefit to those patients with uncommon EGFR 19delins mutation than icotinib can. Among the more frequent EGFR 19delins mutation types, L747_T751delinsP group has a better PFS data after the therapy of first-generation TKIs. At progression, the main resistant cause is EGFR T790M mutation with similar rates both in EGFR 19delins and 19del groups. Moreover, the clinical outcomes including disease control rate and PFS are not significantly different.

Previous studies suggest that patients with some subtypes of EGFR 19delins mutation have poorer clinical outcomes than those with EGFR 19del (16). For example, afatinib can inhibit phosphorylation of EGFR in both L747_P753delinsS and L747_A750delinsP subtypes, whereas erlotinib and osimertinib only inhibit that in L747_P753delinsS mutation (16). As for mechanisms underline, Simona Coco et al consider that E746V-L747P (E746_L747delinsVP) variant confers resistance to gefitinib by mediating N terminal rearrangement of EGFR kinase domain, which leads to high affinity with ATP and EGFR activation (7). However, another large scaled research has reported that patients with EGFR 19delins have longer PFS than that of common EGFR 19del population (10). The mechanism may be that the insertion of one or more amino acids changes the conformation of EGFR kinase domain and enhances its binding to EGFR TKIs (10). Interestingly, our data provide different views that the population with EGFR 19delins mutation has a good response to first-generation EGFR-TKIs and similar PFS outcomes to patients with common EGFR 19del mutation. And we speculate that only some deletion-insertion mutations cause conformational changes that affect their binding to EGFR TKIs, while others are not significantly different from the common deletion variants in exon 19 of EGFR gene on the therapeutic mechanisms of EGFR TKIs. For example, among the more frequent EGFR 19delins mutation types, L747_T751delinsP group has a better PFS data than L747_P753delinsS group. However, the exact mechanism underline still needs more preclinical experiments to illustrate. After disease progression on first-generation EGFR-TKIs, the acquired resistance mechanisms in this study are consistent with the published data (17), including EGFR T790M mutation, MET amplification, ERBB2 amplification, activation of EGFR downstream signaling, and histological transformation to small-cell or squamous cell carcinoma, even sarcomatoid carcinoma, and so on. Given that, tissue re-biopsy are strongly recommended for histological analysis and genotyping when disease progressed. In our research, EGFR T790M is still the major resistant mechanism. The efficacy of osimertinib as second-line therapy is also similar between the groups of EGFR 19 delins and 19del.

As a retrospective investigation, there are inevitably some limitations and mixed factors. In this regard, the cases are collected successively during a period and PS correction method was used for controlling confounding factors, such as age, gender, ECOG score, T stage, N stage, brain metastases, first line TKIs. In this study, NGS approach is adopted for screening patients due to possible missed detection of some mutations by PCR. However, PCR remains the primary genotyping method in clinical practice currently, which means that a larger portion of the population was excluded. So whether our results are representative of the whole population with EGFR 19delins needs further verification in the future larger scaled and prospective trials.

In conclusion, this study demonstrates that patients with rare EGFR 19delins have equal treatment response and similar survival outcomes to those with common EGFR 19del population to first-line EGFR TKIs. Compared to icotinib, gefitinib seems to bring better benefits to the EGFR 19delins mutant population. Of note, patients with L747_T751delinsP mutation have a significant better survival outcome than those with other variants. At disease progression, EGFR T790M mutation is still the prevalent resistance mechanism of patients with EGFR 19delins and also sensitize to third-generation EGFR TKI osimertinib, similar to the population with EGFR 19del. Given that the most frequent and sensitive mutation in NSCLC, EGFR 19 del (especially E746_A750del) is an indicator for good response to EGFR TKIs. Our results provide a proof that EGFR 19delins mutation also can serve as one good predictor for response to first-generation EGFR TKIs.

Declarations

Author contributions

Yurong Wang, Ruipan Zheng, Shujing Shen, and Xingya Li contributed to the conception and design of the work. Yurong Wang, Peizhu Hu, Ziheng Zhang contributed to data collection. Yurong Wang and Ruipan Zheng contributed to data analysis, interpretation, and graphics presentation. Yurong Wang and Ruipan Zheng, Shujing Shen, and Xingya Li contributed to constructive discussions and manuscript writing. All authors reviewed and approved the final version of the manuscript.

Acknowledgements

Not applicable.

Data Sharing Statement

The authors would like to share data collected for our study to others.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics

committee of First Affiliated Hospital of Zhengzhou University and individual consent for this retrospective analysis was waived.

Funding

This work was supported by the Youth Innovation Fund of the First Affiliated Hospital of Zhengzhou University (2019-70885, 2019-70967). The funding source had no role in the study design, data collection, analysis, results interpretation, manuscript drafting and decision to submit the paper for publication.

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Figures

Figure 1

Flow chart of the study design. 1783 patients with NSCLC performing NGS molecular test in our center were successively screened. 41 patients with uncommon EGFR 19delins and 41 common EGFR 19del were identified, receiving first-generation EGFR TKI gefitinib or icotinib as first-line therapy. At progression, the resistance mechanisms are analyzed. And the PFS and response rates after second-line osimertinib are also evaluated.

Figure 2

Variants and their proportion identified in the cohort of uncommon EGFR 19delins mutatio. Pie charts illustrating the distribution of EGFR 19delins variants among 41 patients.

Figure 3

Best changes from baseline in tumor-size since treatment of first-generation EGFR TKIs in cohorts of EGFR 19delins (A) and EGFR 19del (B)

Figure 4

Patients with uncommon EGFR 19delins had similar median PFS to those with EGFR 19del mutation since first-generation EGFR TKI as first-line treatment. Kaplan-Meier curves were drawn for comparing the PFS (A) between patients with uncommon EGFR 19delins and common EGFR 19del, PFS (B and C) among patients with different variants in EGFR 19delins cohort, and PFS (D) between patients receiving gefitinib and icotinib in EGFR 19delins cohort.

Figure 5

Resistance mechanisms of first-line EGFR TKIs and survival outcomes of patients developing T790M and receiving osimertinib as second-line treatment. Resistance mutations were described by Pie charts between the cohort of EGFR 19delins (A) and EGFR 19del (B). (C) Kaplan-Meier curves comparing the PFS of patients with EGFR 19delins and those with EGFR 19del who were receiving osimertinib therapy when developing EGFR T790M from first-generation EGFR TKIs.

Supplementary Files

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