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Beyond the Common Mutation: Examining Chemotherapy Success in Uncommon EGFR Mutations

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Abstract

Background: Second-generation tyrosine kinase inhibitors (TKIs) have demonstrated enhanced efficacy in managing non-small cell lung cancer (NSCLC) patients harboring uncommon epidermal growth factor receptor (EGFR) mutations. However, there is limited research comparing the effectiveness of second-line chemotherapy in NSCLC patients with common and uncommon EGFR mutations. This retrospective study aims to evaluate treatment outcomes in these patient groups.

Methods: This retrospective analysis examined patients with advanced-stage EGFR-mutated NSCLC who had received first-line EGFR-TKIs at a tertiary referral center from January 2010 to August 2022. Patients who tested negative for the T790M mutation at disease progression and subsequently received second-line chemotherapy were included. Progression-free survival (PFS) and overall survival (OS) were compared between NSCLC patients with common and uncommon EGFR mutations using Kaplan–Meier survival analysis and log-rank tests. **Results:** Of the 209 patients meeting the inclusion criteria, 192 (91.8%) had common EGFR mutations (exon 19 deletion or exon 21 L858R substitution), while 17 (8.2%) had uncommon EGFR mutations. Patients with common EGFR mutations exhibited significantly longer PFS compared to those with uncommon EGFR mutations (4.57 vs. 2.57 months, p = 0.031). Cox proportional hazard regression analysis, controlling for potential confounding factors, indicated that an uncommon EGFR mutation independently predicted shorter PFS.

Conclusion: Our study highlights that NSCLC patients with uncommon EGFR mutations experience reduced chemotherapy responses and shorter survival when compared to those with common EGFR mutations. There is an unmet need for the development of novel treatment strategies tailored to this patient subgroup.

Methods

This retrospective study investigated patients diagnosed with advanced-stage non-small cell lung cancer (NSCLC) at a tertiary referral center from 2010 to 2022. After excluding patients who did not undergo EGFR testing at initial diagnosis, those with negative EGFR mutation results, those who did not receive first-line EGFR-TKI therapy, and those with missing data or lost follow-up, the study focused on patients with advanced EGFR-mutant NSCLC who received first-line EGFR-TKI therapy. Subsequently, in cases of disease progression during first-line therapy, a subset of patients underwent rebiopsy and T790M testing to determine further treatment. Patients with a negative T790M test at disease progression who received second-line chemotherapy were included. Demographic and clinical data, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, tumor characteristics, EGFR mutation status, tumor size, lymph node involvement, and distant metastasis sites, were recorded and anonymized following ethical guidelines. The study received approval from the Institutional Ethics Committee of National Cheng Kung University Hospital. Informed consent was waived due to the retrospective nature of the study. After commencing second-line chemotherapy, all patients underwent regular imaging assessments every three months to evaluate treatment response based on Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PFS) was defined as the time from initiating second-line chemotherapy to radiological evidence of disease progression, while overall survival (OS) was measured from the start of second-line treatment to death. In cases without disease progression or death, censoring was applied using the last follow-up date..

EGFR mutation analysis was conducted on tumor tissues obtained from various sources, including primary lung masses, metastatic lymph nodes, or pleural tumors, following microscopic examination with hematoxylin and eosin staining to confirm eligibility. Tumor DNA extraction and EGFR mutation detection were performed using Therascreen EGFR RGQ PCR Kit (EGFR IVD Kit; Qiagen). Statistical analysis included presenting categorical variables, estimating progression-free survival (PFS) and overall survival (OS) with Kaplan–Meier methods, and identifying prognostic factors through univariate and multivariate Cox proportional hazards regression analysis. A p-value less than 0.05 was considered statistically significant, and proportional hazards assumptions were assessed using R software.

Figure 1. Study flowchart.

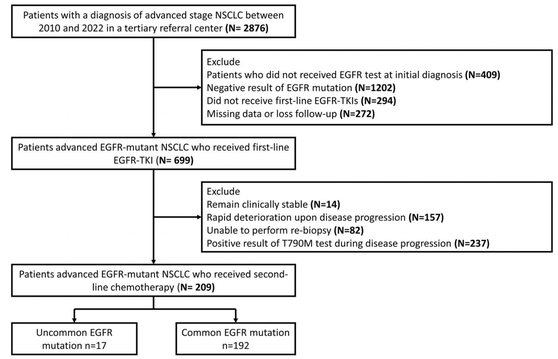

Table1 . Baseline patient characteristics.

Variable	Common *EGFR* mutation (n = 192)	Uncommon *EGFR* mutation (n = 17)	All patients (n = 209)	p-values
Age (years), median (interquartile range)	63.3 (56.6–70.5)	68.4 (61.4–75.8)	64.0 (56.1–71.3)	
<65, n (%)	105 (54.7%)	6 (35.3%)	111 (53.1%)	0.1246
>65, n (%)	87 (45.3%)	11 (64.7%)	98 (46.9%)	
Gender, n (%)				
Female	104 (54.2%)	12 (70.6%)	116 (55.5%)	0.1916
Male	88 (45.8%)	5 (29.4%)	93 (44.5%)	
Histological subtype, n (%)				
Adenocarcinoma	183 (95.3%)	15 (88.2%)	198 (94.7%)	0.2217
Nonadenocarcinoma	9 (4.7%)	2 (11.8%)	11 (5.3%)	
Stage, n (%)				
III	14 (7.3%)	1 (5.9%)	15 (7.1%)	0.6503
IV	178 (92.7%)	16 (94.1%)	194 (92.9%)	
Performance score, n (%)				
0/1	188 (97.9%)	17 (100%)	205 (98.1%)	1.0000
2/3/4	4 (2.1%)	0 (0%)	4 (1.9%)	
Brain metastasis, n (%)				
No brain metastasis	141 (73.4%)	11 (64.7%)	152 (72.7%)	0.4385
Brain metastasis	51 (26.6%)	6 (35.3%)	57 (27.3%)	
Liver metastasis, n (%)				
No liver metastasis	167 (87.0%)	14 (82.4%)	181 (86.6%)	0.4048
Liver metastasis	25 (13.0%)	3 (17.6%)	28 (13.4%)	

Figure 2. The progression-free survival of patients refractory to first- line EGFR-TKIs with second-line chemotherapy.

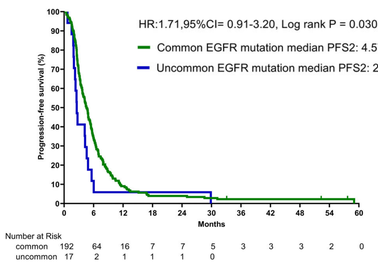

Figure 3. The overall survival of patients refractory to first-line EGFR-TKIs with second-line chemotherapy.

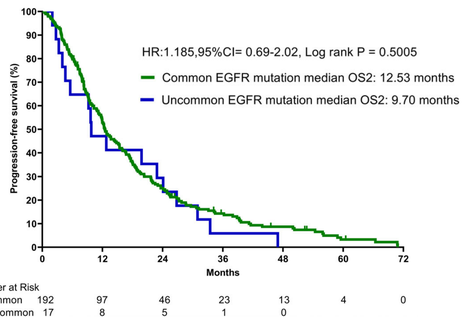

Table 2. Cox proportional hazard regression analysis identifying prognostic factors for PFS.

Variable	Univariate Hazard ratio (95% CI)	p-value	Multivariate Hazard ratio (95% CI)	p-value
Age(years)				
<65	Reference		Reference	
>65	0.748 (0.563–0.994)	0.0453	0.655 (0.477–0.899)	0.0087
Gender				
Female	Reference		Reference	
Male	1.077 (0.815–1.424)	0.6018	1.146 (0.858–1.530)	0.3572
Histologicaltype				
Adenocarcinoma	Reference		Reference	
Nonadenocarcinoma	1.396 (0.735–2.654)	0.3083	1.670 (0.850–3.281)	0.1366
Stage				
III	Reference		Reference	
IV	1.649 (0.938–2.898)	0.0820	1.734 (0.984–3.124)	0.0566
EGFR mutation				
Common	Reference		Reference	
Uncommon	1.724 (1.045–2.846)	0.0331	2.146 (1.267–3.635)	0.0045
Performance score				
0/1	Reference		Reference	
2/3/4	1.614 (0.952–2.737)	0.0755	1.761 (1.023–3.032)	0.0412
Brain metastasis				
No brain metastasis	Reference		Reference	
Brain metastasis	1.142 (0.839–1.555)	0.3984	0.968 (0.696–1.346)	0.8457
Liver metastasis				
No liver metastasis	Reference		Reference	
Liver metastasis	1.357 (0.905–2.035)	0.1393	1.152 (0.749–1.770)	0.5199

Table 3. The Cox proportional hazard regression analysis identifying prognostic factors for OS.

Variable	Univariate Hazard ratio (95% CI)	p-value	Multivariate Hazard ratio (95% CI)	p-value
Age(years)				
<65	Reference		Reference	
>65	0.965 (0.727–1.281)	0.8047	1.019 (0.745–1.396)	0.9043
Gender				
Female	Reference		Reference	
Male	1.508 (1.135–2.004)	0.0046	1.640 (1.218–2.208)	0.0011
Histologic type				
Adenocarcinoma	Reference		Reference	
Non-adenocarcinoma	1.560 (0.819–2.969)	0.1761	1.504 (0.757–2.988)	0.2443
Stage				
III	Reference		Reference	
IV	1.469 (0.813–2.653)	0.2026	1.548 (0.848–2.828)	0.1548
EGFR mutation				
Common	Reference		Reference	
Uncommon	1.187 (0.720–1.956)	0.5013	1.277 (0.769–2.120)	0.3440
Performance score				
0/1	Reference		Reference	
2/3/4	1.333 (0.785–2.263)	0.2870	1.176 (0.674–2.052)	0.5669
Brain metastasis				
No brain metastasis	Reference		Reference	
Brain metastasis	1.209 (0.883–1.656)	0.2367	1.094 (0.779–1.537)	0.6041
Liver metastasis				
No liver metastasis	Reference		Reference	
Liver metastasis	1.636 (1.083–2.472)	0.0194	1.639 (1.043–2.575)	0.0322