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Predictors of Acquired *T790M* Mutation in Patients Failing First- or Second-Generation *Epidermal Growth Factor Receptor*-Tyrosine Kinase Inhibitors

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Background: This study aims to determine the predictors of acquired *exon 20 T790M* mutation in advanced non-small cell lung cancer (NSCLC) patients harbouring sensitizing *epidermal growth factor receptor* (*EGFR*) mutation following the failure of first- or second-generation *EGFR* tyrosine kinase inhibitor (TKI).

Methods: This is a retrospective observational study of NSCLC patients with sensitising *EGFR* mutation experiencing disease progression (PD) whilst on first- or second generation *EGFR*-TKIs with subsequent investigations to detect acquired *T790M* mutation at the University of Malaya Medical Centre from 1st January 2015 to 31st December 2017.

Results: A total of 87 patients were included. Upon PD, acquired *T790M* mutation was found in 55 (63.2%) patients and was significantly more common in patients who achieved partial response (PR) whilst on the *EGFR* TKIs ($p = 0.008$) or had new lung metastasis upon PD ($p = 0.048$). It was less frequent in patients who developed new symptomatic brain lesions ($p = 0.021$). Patients with *exon 19* deletion were more likely to acquire *T790M* mutation compared to those with *exon 21 L858R* point mutation ($p = 0.077$). Multivariate analysis revealed PR whilst on *EGFR*-TKI treatment was an independent predictor of acquiring *T790M* mutation ($p = 0.021$), whereas development of new symptomatic brain lesions ($p = 0.034$) or new lymph node metastases ($p = 0.038$) upon PD was independently against acquiring *T790M* mutation. Patients with *exon 19* deletion were more likely to acquire *T790M* mutation compared to those with *exon 21 L858R* point mutation (odds ratio: 2.3, 95% confidence interval: 0.84–6.25, $p = 0.104$).

Conclusion: The best tumour response of PR to first- or second-generation *EGFR* TKI treatment independently predicts acquired *T790M* mutation. Patients with *exon 19* deletion are likely to acquire *T790M* mutation. This would prove useful for clinicians to prognosticate and plan subsequent treatments for patients with advanced NSCLC harbouring *EGFR* mutations.

Keywords: non-small cell lung cancer, epidermal growth factor receptor, acquired *T790M* mutation, independent predictor, tyrosine kinase inhibitor

Introduction

Lung cancer, 85% of which are non-small cell lung cancer (NSCLC), remains the leading cause of cancer mortality globally.[1] Upon diagnosis, the majority of NSCLC patients have locally advanced or metastatic disease. Conventional first-line chemotherapy in these patients confers a dismal median overall survival of 8–10 months and a 2-year survival rate of 11%.[2,3]

The discovery of mutations of the *epidermal growth factor receptor* (*EGFR*) has completely revolutionized the management of patients with advanced NSCLC.

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