The Abundance of EGFR Mutations Could Be More Better Predictor for EGFR-TKI Therapy in Advanced Non-Small Cell Lung Cancer

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Background: Incresing data show advanced non-small cell lung cancer (NSCLC) patients with EGFR activating mutant have discrepant response to EGFR-TKI. The abundance of EGFR mutations may be a powerful explanation for the uneven clinical benefit. This study was designed to investigate the influence of EGFR mutant abundance on efficacy of EGFR-TKI by a quantitative method. Methods: 201 NSCLC patients treated with EGFRTKI with available tissue samples for EGFR mutation test were enrolled into the study. EGFR common mutations were detected by amplification refractory mutation system (ARMS) and percentage of mutant EGFR was tested with the method of an Allele Specific Quantitative PCR with Competitive Blocker (ASB-qPCR). In this assay, the copies of all mutations and EGFR locus were calculated by standard curve respectively. The cutoff values were obtained by the receiver operating characteristics (ROC) curve in training set. Further, the cutoff values were confirmed in validation set and the whole population.The relationship between the abundance of EGFR mutations and efficacy of EGFR-TKIwas statistically analyzed. Results: Of the 201 samples, 72 harbored 19DEL mutation,63 carried L858R mutant, and 66 with wild-type. The cohort was randomly divided into training and validation sets. The cutoff values of 19DEL and L858R mutation abundance were 4.84% and 9.47% determined by ROC curve in training set. 9.7% of patients with 19DEL positive were low abundance (<4.84%, LA group), while 33.3% of L858R-positive patients were LA (<9.47%).High abundance (HA) group, regardless of 19DEL or L858R positive had more longer median progression free survival (PFS) compared with LA and wild-type groups in either validation set or the whole population (15.0 vs 2.0 vs 1.9, 8.0 vs 1.9 vs 1.9; 15.0 vs 4.0 vs 2.0, 12.0 vs 2.0 vs 2.0; p<0.001). COX regression analysis showed that EGFR mutation abundance, together with smoking status, were independent factors of response to EGFR-TKI. Conclusion: The abundance of EGFR mutation could more precisely predict EGFR-TKI efficacy. NSCLC patients with LA mutation had inferior clinical benefit with EGFR-TKI. The heterogeneity in EGFR mutant abundance partly explain the efficacy discrepancy in patients with 19DEL or L858R positive.

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