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PLASMATIC TUMOR DNA ASSESSMENTS PREDICT CLINICAL OUTCOME IN EGFR-MUTATED NON-SMALL CELL LUNG CANCER PATIENTS TREATED BY EGFR INHIBITORS

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Aim: We aimed to study the dynamics of plasmatic EGFR mutations by qualitative (Q-PCR) and quantitative (droplet PCR) methods in EGFR-mutated lung cancer patients treated by EGFR tyrosine kinase inhibitors (EGFR-TKI).

Methods: We investigated a single-institution cohort of patients treated by EGFR-TKI. Plasma blood samples and RECIST assessments were repeated every 2 months. Plasmatic cell-free DNA extraction was performed with the QIAsymphony DSP Virus/Pathogen kit (Qiagen). EGFR mutations were assessed in plasmatic DNA using Q-PCR and droplets digital PCR with CAST probes (L858R and Del19). The rate of EGFR mutant/wild-type droplets was used for normalization. The prediction of plasmatic DNA changes between two consecutive samples on treatment outcome was evaluated by Receiver Operator Characteristic (ROC). Survival was estimated with the Kaplan-Meier method.

Results: 22 EGFR-mutated patients treated by EGFR-TKI underwent plasmatic DNA follow-up. Patients were stage IV (n = 22), TKI naive (n = 17), or TKI pre-treated (n = 5). Median follow-up, progression-free survival (PFS) and overall survival were 19.0, 4.7 and 15.8 months, respectively. At baseline, tumor plasmatic DNA was found by Q-PCR, droplets or one of the two technics in 14, 15 and 16/20 (80%) patients, respectively. Droplet changes under treatment were more accurate than bulk PCR changes to predict RECIST outcome (progressive disease vs. clinical benefit, ie stable disease or partial response): ROC area under the curve (AUC) 0.92 and 0.35, respectively. Droplet changes also predict 2-month RECIST outcome, ROC AUC 0.94. According to ROC Youden indexes, a droplets increase of +19% best predicts immediate (sensitivity 0.90, specificity 0.84) and 2-months RECIST outcome (sensitivity 0.88, specificity 0.96). Median PFS assessed by droplets was 3.4 months (cut off +19%). Mean time from droplets increase (cut off +19%) to RECIST progression was 42 ± 23 days.

Conclusions: In this feasibility cohort, droplets increase under EGFR-TKI predicts immediate and 2-month treatment outcomes. Plasmatic tumor DNA monitoring could anticipate the radiological tumor progression, allowing clinicians to change treatment before a symptomatic or lethal tumor progression occurs. The threshold of +19% droplets increase will be prospectively tested in an on-going biomarker trial.

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