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Treatment of Non-Small Cell Lung Cancer (NSCLC) With Activating Mutations Considering ctDNA Fluctuations

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Abstract : Analysis of ctDNA in patients with NSCLC is an emerging biomarker. Multiple research efforts of quantitative or at least qualitative analysis before and during the first periods of treatment with TKI showed the prognostic value of ctDNA clearance. Still, these important results are not incorporated in clinical standards. We evaluated the role of ctDNA in EGFR-mutated NSCLC receiving first-line TKI. Firstly, we analyzed sequential plasma samples from 30 patients that were collected before intake of the first tablet (at baseline) and at 6, 12, 24, 36, and 48 hours after the “starting point.” EGFR-M+ allele was measured by ddPCR. Afterward, we included sequential qualitative analysis of ctDNA with cobas® EGFR Mutation Test v2 from 99 NSCLC patients before the first dose, after 2 and 4 months of treatment, and on progression. Early response analysis showed the decline of EGFR-M+ level in plasma within the first 48 hours of treatment in 11 subjects. All these patients showed objective tumor response. 10 patients showed either elevation of EGFR-M+ plasma concentration (n = 5) or stable content of circulating EGFR-M+ after the start of the therapy (n = 5); only 3 of these patients achieved an objective response (p = 0.026) when compared to the former group). The rapid decline of plasma EGFR-M+ DNA concentration also predicted for longer PFS (13.7 vs. 11.4 months, p = 0.030). Long-term ctDNA monitoring showed clinically significant heterogeneity of EGFR-mutated NSCLC treated with 1st line TKIs in terms of progression-free and overall survival. Patients without detectable ctDNA at baseline (N = 32) possess the best prognosis on the duration of treatment (PFS: 24.07 [16.8-31.3] and OS: 56.2 [21.8-90.7] months). Those who achieve clearance after two months of TKI (N = 42) have indistinguishably good PFS (19.0 [13.7 – 24.2]). Individuals who retain ctDNA after 2 months (N = 25) have the worst prognosis (PFS: 10.3 [7.0 – 13.5], p = 0.000). 9/25 patients did not develop ctDNA clearance at 4 months with no statistical difference in PFS from those without clearance at 2 months. Prognostic heterogeneity of EGFR-mutated NSCLC should be taken into consideration in planning further clinical trials and optimizing the outcomes of patients.

Keywords : NSCLC, EGFR, targeted therapy, ctDNA, prognosis
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