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Clinical significance of detecting EGFR and KRAS mutations in plasma/pleural effusion in patients with advanced NSCLC

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Objective: We attempted to detect EGFR and KRAS mutations in plasma/pleural effusion in patients with advanced non-small-cell lung cancer (NSCLC) by pyrosequencing, to investigate whether plasma and pleural effusion DNA can replace tumor tissues for detecting gene mutations, and to explore the correlation of EGFR/KRAS mutations with the efficacy of the epithelial growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) as well as with the survival in TKI-treated patients.

Methods: Blood, pleural effusion and tumor tissues were obtained from 146, 64 and 63 patients with advanced NSCLC, of whom there were 40 matched tissue and plasma samples, and 24 matched tissue and pleural effusion samples. The exons 19, 20 and 21 of EGFR were amplified by mutant-enriched PCR using selective restriction enzyme digestion, and exon 2 of KRAS in plasma was amplified by nested-PCR. Then mutations were detected by pyrosequencing. The association between mutations and the patients' survival was analyzed using Kaplan-Meier.

Results: EGFR mutations were detected in 34.38% tumor tissues (22/64), 24.24% plasma samples (24/96) and 30.16% pleural effusion samples (19/63). KRAS mutations were detected in 4.69% tissues (3/64), 6.16% plasma samples (9/146) and 7.93% pleural effusion samples (5/63). No statistical significance was found in EGFR/KRAS mutations between plasma/pleural effusion and tumor tissues ($p>0.05$). The same EGFR genes were observed in plasma and the matched tissues in 34 patients (consistency: 85%). The sensitivity of detecting circulating EGFR mutations was 73.33% and the specificity was 92 %. Only one KRAS mutation was detected in the 40 tissues, but no mutation was detected in the matched plasma (consistency: 97.5%). The same EGFR/KRAS genes were observed in 21, 23 pleural effusion and matched tissues respectively (consistency: 87.5%, 95.83%). The sensitivity of detecting EGFR/KRAS mutations was 77.78% and 66.67%. The specificity was 93.33% and 100%. Significant correlation existed between EGFR mutations in tumor tissue/pleural effusion in patients with advanced NSCLC and a smoking history as well as the histopathologic type ($p<0.05$). Among the 38 TKI-treated patients, the disease control rate (DCR) and objective response rate (ORR) were 90% and 60%, respectively;in patients with EGFR mutation in plasma, DCR and ORR were 53.57% and 17.86%, respectively;in patients with wide-type EGFR (DCR, $p=0.059$; ORR, $p=0.019$). The DCR and ORR were 66.67% and 33.33%, respectively, in patients with wide-type KRAS in plasma, and 40% and 0%, respectively, in patients with KRAS mutation. However, no statistical significance was found ($p>0.05$). Patients with EGFR-activating mutations in plasma had a favoring median PFS of 10.5 months, significantly longer than that of the patients with wild-type EGFR (5.0 months) ($p=0.228$). The median PFS was 2.5 months for patients with KRAS mutation and 9 months for patients with wild-type KRAS, respectively ($p=0.000$).

Conclusion: A high consistency exists between EGFR/KRAS mutation detection in plasma/pleural effusion and tumor tissues. Plasma/pleural effusion can replace tumor tissues for detecting gene mutations. EGFR and KRAS mutations in plasma are highly associated with the treatment response and prognosis of TKI-treated patients. It is feasible to detect EGFR and KRAS mutations in plasma/pleural effusion by pyrosequencing, a simple and high-throughput method. The detection sensibility of EGFR mutations can be increased by ME-PCR, facilitating choosing patients for TKI treatment

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