Identification of Therapeutically Relevant Mutations in Circulating Tumor DNA at Baseline to Assist in Treatment Decision Making

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Background & objectives

According to current guidelines, molecular tumor profiling is performed on tumor cells of lung cancer patients to facilitate treatment decision making. Liquid biopsy approaches, especially the detection of circulating tumor DNA (ctDNA) in the bloodstream, are emerging as sensitive and reliable surrogates for routine diagnostic testing relying on tumor tissue biopsy specimens. Here, we analyze serially collected baseline plasma samples of lung cancer patients to determine the agreement between tumor tissue-based and ctDNA-based molecular tumor profiling and the consequent clinical implications. Additionally, as molecular profiling of the tumor fails in 10-20% of the cases, we determine the additional value of liquid biopsy testing when tumor tissue next-generation sequencing (NGS) data is unavailable.

Methods

Between July 2018 and December 2021, 180 serially collected baseline plasma samples were included. Using 2mL of plasma, circulating cell-free DNA (ccfDNA) was extracted and analyzed with the UltraSEEK® Lung Panel v2 on the MassARRAY® System (Agena Bioscience, San Diego, USA), which detects 78 common (actionable) mutations in *BRAF*, *EGFR*, *ERBB2*, *KRAS* and *PIK3CA*. CcfDNA are retrospectively quantified using the LiquidIQ® Panel (Agena Bioscience) to evaluate discrepant results.

Results

Tumor tissue NGS analysis was available for 132 NSCLC patients (73%). An 82% concordance has been observed between mutations detected in tumor tissue and plasma. More mutations were reported with tumor tissue NGS in 19 patients, while in 4 patients additional have been found in plasma. In the absence of tumor tissue NGS data, five therapeutically targetable mutations were detected. Molecular tumor profiling based on tissue allocated 60 patients eligible for TKI treatments of which 15 (8%) for rearrangements not covered by the UltraSEEK Lung Panel. Forty-one patients (23%) were eligible for TKI against mutations in *BRAF*, *EGFR* and *KRAS* based on ctDNA analysis.

Conclusion

Molecular tumor profiling using circulating tumor DNA (ctDNA) with the UltraSEEK Lung Panel identified therapeutically relevant mutations at a comparable rate as tumor tissue NGS and might therefore serve as a prescreening tool for baseline actionable variant identification in absence of tumor tissue, or as a complementary test in addition to tumor tissue NGS.