Comprehensive genomic profiling NSCLC patients with leptomeningeal metastases through circulating tumor DNA in cerebrospinal fluid

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INTRODUCTION

Leptomeningeal metastases occur in more than 3% of patients diagnosed with non-small-cell lung cancer (NSCLC) through the whole course of disease, resulting in poor clinical outcomes and limitations on therapies. The cerebrospinal fluid (CSF) is a direct liquid biopsy for pathological diagnosis of leptomeningeal metastases. However, traditional clinical methods of detecting tumor cells in CSF showed limited sensitivity. Meanwhile, the unique genomic aberrations of leptomeningeal metastases remain unknown. Here we report the prospective clinical study aiming to identify genomic aberrations carried by NSCLC patients with leptomeningeal metastases through circulating tumor DNA (ctDNA) in CSF.

METHODS

The study planned to enroll 50 NSCLC patients diagnosed with leptomeningeal metastases. In the pilot study, 13 patients were enrolled and CSF samples were collected after diagnosis of metastases. Among them, PBMC samples were collected from 11 patients as germline control materials. PredicineWES™, a low-pass whole-genome sequencing (LP-WGS) assay, was performed to identify copy number variations and tumor fraction in CSF samples from all 13 patients. Furthermore, PredicineWES+™, a boosted whole exon sequencing assay, was performed on paired CSF and PBMC samples from 11 patients.

RESULTS

Fig. 2. The genome-wide landscape of copy number variations in CSF. ctDNA fractions were identified in all 13 CSF samples through PredicineWES™ assay. Gene copy variants related to NSCLC were also detected such as copy gain of EGFR/7p, BRAF/5p5ts, MET/5p5ts, KRA/S2/2p5ts, ERBB2/2p5ts, ROS1/1p5ts, ALK/1p5ts and copy loss of RB1/4p5ts, Pten/2p5ts, TP53/1p5ts.

Fig. 3. The genome-wide mutational landscape in CSF. PredicineWES+™, the boosted whole exome sequencing, identified 1493 somatic variants in 11 CSF samples, among which 97 variants were previously reported as possibly pathogenic by public clinical database. For NSCLC-specific biomarkers, 7 out of 11 patients carried EGFR variants including 3 Exon19del incidents, 1 Exon20ins incident, 1 L858R mutation, and other gain-of-function mutations.

Fig. 4. The detection of EML—ALK fusion in CSF. PredicineWES+™ identified EML4-ALK fusion event in one patient (P012).

Table 1: Copy number burden(CNB) and tumor fraction (TF) identified by PredicineCBN.

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<th>P001</th>
<th>P002</th>
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CONCLUSIONS

This study demonstrated the clinical utility of PredicineWES™ and PredicineCBN™ liquid biopsy NGS assays in comprehensive genome-wide molecular profiling using CSF samples from patients with NSCLC leptomeningeal metastases. More importantly, this study identified 1396 novel biomarkers beyond 97 variants that were previously reported as possibly pathogenic by public clinical database, providing additional insights for clinical diagnosis, drug resistance mechanism study and minimal residual disease (MRD) monitoring in NSCLC leptomeningeal metastases.