Analysis and Monitoring CTCs and ctDNA in CSF Demonstrates Clinical Concordance in Tesevatinib Treated NSCLC Patients with LM

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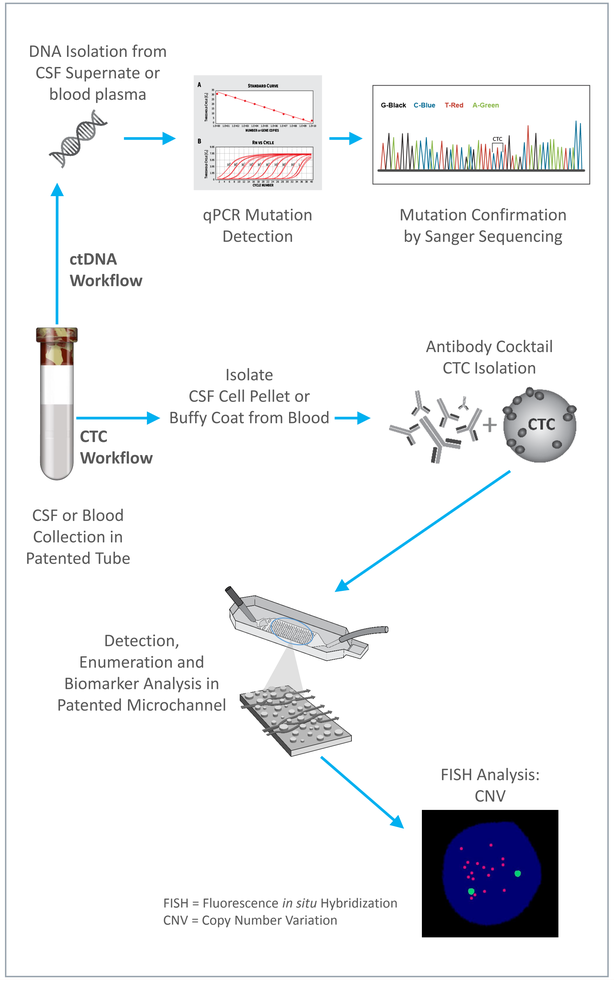
Background

Liquid biopsy using blood has emerged as a non-invasive and economical method to assess cancer biomarkers. Applying liquid biopsy methods to evaluate cerebrospinal fluid (CSF) is less well documented and provides key information to supplement routine cytology in patients with brain metastases or leptomeningeal metastases (LM). Current first line tyrosine kinase inhibitor (TKI) therapy of non-small cell lung cancer (NSCLC) patients with activating EGFR mutations, exhibits poor penetration to the central nervous system (CNS). About 28% of patients treated with erlotinib or gefitinib progress with CNS involvement. Here we present liquid biopsy evaluation of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) in the CSF of NSCLC patients with LM, who were treated with the TKI, tesevatinib (KD019-206 clinical trial).

Methods

CSF samples were collected in patented tubes validated to preserve CTCs for up to 96 hours and ctDNA for up to 8 days. The platform utilized in this work for CTC capture and biomarker analysis employs a 10 antibody capture cocktail targeting a wide spectrum of CTC phenotypes. CTC capture and identification of both cytokeratin positive (epithelial) and cytokeratin negative (mesenchymal, stem cell) CTCs were undertaken in a patented microchannel. The quantitative ctDNA platform incorporates switch-blockers, real time PCR and sequencing to detect a mutant allele frequency down to 0.05% against wildtype. CTC analyses included enumeration and *EGFR* gene amplification status determination; ctDNA testing was used to detect *EGFR* activating mutations L858R and Exon19 deletions, as well as the T790M resistance mutation.

ctDNA and CTC Analyses from a Single Specimen



Results

CSF collections from 20 NSCLC patients with LM were obtained at baseline. When possible, CSF was collected after 14 and 56 days of tesevatinib therapy. For a subset of 8 patients, blood was also collected prior to tesevatinib treatment.

Pretreatment tesevatinib CTC counts were higher in CSF vs. blood in 75% (6 of 8) patients with both collections.

In 3 of 5 patients with baseline or emergent T790M ctDNA in CSF, detection paralleled progression; T790M emerged after tesevatinib therapy in the patient whose CTCs decreased at progression. CTC enumeration mirrored response to therapy, decrease of symptoms, or progression in 11 of 13 patients where CTCs were present and sufficient clinical information was available. Serial CSF CTC and ctDNA analyses were consistent with the overall clinical course of disease.

CSF CTC Detection: Baseline and All Time Points

	Specimens Tested (N)	Specimens with Detectable CTCs	CTC Detection Rate
Baseline	20	16	80.0%
All Time Points	48	38	79.0%

Results

All LM Patients: CSF CTC and Biomarker Detection

	Patients Tested (N)	Patients with Detectable Biomarkers	Biomarker Detection Rate
CTCs Detected at ≥ 1 Time Point	20	17	85.0%
EGFR Gene Amplification Detected at ≥ 1 Time Point	20	7	35.0%
EGFR Activating Mutation at First Available Time Point	20	19	95.0%

Conclusions

- Dual platform liquid biopsy technology for CSF analysis demonstrates highly sensitive detection of both CTCs and mutant ctDNA in NSCLC patients with LM.
- CSF results were highly concordant with tissue analysis and clinical course of disease.
- Serial monitoring of CSF with CTCs and ctDNA can be utilized to evaluate drug response and disease progression, providing pertinent, vital information for disease management and care of LM patients.