Clinical utility of target selector ctDNA testing: detection of EGFR mutations via liquid biopsy enabled targeted therapy selection for patients with advanced NSCLC

Abstract

Background: Molecular profiling of tumors provides information key for devising personalized therapeutic strategies for managing disease in cancer patients. Liquid biopsy is emerging as a sensitive means to evaluate biomarker status without the complications and costs associated with surgical biopsies, particularly for patients unable or unwilling to undergo invasive procedures.

Materials and methods: Patient blood specimens were collected in Biocept’s proprietary Blood Collection Tubes for liquid biopsy testing in Biocept’s CLIA-certified, CAP-accredited laboratory. Dual circulating tumor cell (CTC) and circulating tumor DNA (ctDNA) platforms were utilized to detect ALK or ROS1 gene rearrangements by FISH, or EGFR mutations, respectively.

Results: Described are three metastatic NSCLC patients for which liquid biopsy guided the selection of a targeted therapy when a standard tissue biopsy was inadequate to assess biomarker status. All three patients were prescribed EGFR tyrosine kinase inhibitor (TKI) treatment after an activating EGFR mutation was detected via liquid biopsy. One patient exhibited complete response for approximately two years. Two patients received osimertinib following emergence of the EGFR T790M resistance mutation, which was also detected via liquid biopsy.

Conclusion: Liquid biopsy analyses of ctDNA and CTCs can complement tumor testing, identifying potential drivers of a patient’s cancer. Clinical utility of liquid biopsy is demonstrated where first line and subsequent targeted treatments were prescribed based on the identification of genomic alterations in blood. Each patient received therapeutic benefit that significantly extended survival and enhanced their quality of life.

Keywords: liquid biopsy, EGFR, targeted therapy, NSCLC

Introduction

Lung cancer is the leading cause of cancer death in the USA, with an estimated 154,000 deaths predicted for 2018. To improve patient outcomes, molecular profiling of a patient’s tumor can guide the selection of a personalized treatment strategy. For example, non-small cell lung cancer (NSCLC) represents over 80% of lung carcinomas and EGFR tyrosine kinase activating mutations are observed in 15–20% of NSCLC adenocarcinomas in the USA. Treating these patients with an EGFR tyrosine kinase inhibitor (TKI) can extend progression-free-survival (PFS) and quality of life compared to platinum-based chemotherapy. Unfortunately, tissue biopsies performed for initial cancer diagnosis often do not yield sufficient amounts of tissue for biomarker analysis. In addition, some patients are either unable or unwilling to tolerate these invasive procedures. In recent years, technological platforms for performing “liquid biopsies” have emerged, complementing traditional tumor-based diagnostic testing. Recent technological advances in liquid biopsy offer health care providers with sensitive and viable molecular profiling options through the analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) from a peripheral blood draw. This non-invasive approach permits efficient serial specimen collection for tracking tumor characteristics (e.g., emergence of resistance mutations at signs of progression), and can detect actionable genetic alterations missed by solid tissue tests. Here we describe three NSCLC cases for which liquid biopsies identified EGFR activating and resistance mutations. Based on liquid biopsy results, targeted therapies were prescribed that dramatically extended patient survival. All patients (or next of kin for the deceased) provided written consent to present their medical information (excluding private information) in this publication.

Materials and methods

Liquid biopsy blood samples were collected into 10-mL Biocept CEE-Sure Blood Collection Tubes (Biocept, Inc.) and maintained at ambient temperature until processed. Specimens were shipped to Biocept’s CLIA-certified, CAP-accredited laboratory for processing within 24 hours of receipt. ctDNA extracted from blood plasma was subjected to Target Selector™ assays specific for the EGFR activating mutations, L858R and exon 19 deletion (Del19), or the T790M mutation, which confers resistance to EGFR TKIs. Proprietary Target Selector™ switch blocker methodology enriches mutant target sequences by specifically blocking PCR amplification of the wild-type allele. Subsequent Sanger sequencing of the Target Selector™
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Discussion

Reflecting improved understanding of the genetic causes of NSCLC and the rapid development of therapies targeting these mutations, the National Comprehensive Cancer Network (NCCN) now recommends EGFR mutation and ALK testing (category 1), as well as ROS1, BRAF, and PD-L1 testing (category 2A), for metastatic non-squamous NSCLC patients, and suggests consideration to test for these biomarkers in a subset of squamous-cell carcinoma patients. However, significant risk and cost are associated with acquiring sufficient tissue for these molecular analyses. Poor patient health, reluctance to undergo invasive surgical procedures, and inaccessible metastatic lesions are additional barriers to obtaining tissue for molecular profiling. Tumor heterogeneity may also preclude correct assessment of a patient’s biomarker status. Thus, relying solely on tissue testing may misclassify patients. Emerging liquid biopsy technologies enable molecular characterization via a simple, peripheral blood draw, affording more comprehensive analysis of tumor DNA derived from various regions within a tumor and metastatic sites. Furthermore, a recent analysis by the International Association for the Study of Lung Cancer (IASLC) has concluded that technologies for detecting EGFR mutations in peripheral blood are now so reliable that their implementation in the clinic is highly recommended.

Here we have presented three cases of metastatic NSCLC for which traditional biopsy procedures did not provide sufficient tissue for biomarker testing. Recognizing the potential of liquid biopsy, the physician submitted patient blood samples to Biocept to test clinically actionable biomarkers associated with FDA approved therapies. For all three patients, EGFR TKI therapy was initiated upon detecting an activating EGFR mutation via liquid biopsy across a range of mutant allele frequencies. For one patient, EGFR TKI administration resulted in approximately two years of complete response, a remarkable improvement over typical chemotherapy outcomes. When the other two patients eventually exhibited signs of progression, additional Biocept liquid biopsy testing identified the EGFR T790M resistance mutation; these patients were placed on T790M-specific inhibitors, further extending quality of life and survival. This case series highlights the clinical utility of liquid biopsy in both identifying the molecular drivers of a tumor at diagnosis when traditional biopsies fail to recover sufficient tissue for molecular analysis (as was the case for the three patients discussed here), and in monitoring the evolution of tumor mutations to identify drivers of drug resistance and disease progression (resistance to targeted therapies inevitably emerges).

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Whereas the serial collection of tissue biopsies is frequently infeasible, the longitudinal evaluation of blood samples is well tolerated and can be used to identify changes in mutation frequencies and the emergence of drug-resistant clones. This enables the rapid switching to TKIs that target acquired resistance EGFR mutations (e.g., osimertinib and fourth generation EGFR TKIs that are on the way). It should be noted, however, that a negative liquid biopsy result derived from current technologies should not be considered conclusive, but instead should trigger conventional tissue analyses. Thus, the paired implementation of tissue and liquid biopsies offers the best chance to understand and treat a patient’s disease.

Applicable to a wide range of cancers, liquid biopsies represent a state-of-the-art technology for the non-invasive, real-time, and cost-effective identification of genetic drivers of a patient’s disease. Importantly, emerging technologies promise to increase the clinical utility of liquid biopsies by enabling, for example, the analysis of other fluids (urine, cerebrospinal fluid and saliva), the capture and analysis of RNA, and the monitoring for residual disease. Analysis of a single liquid biopsy specimen provides a snapshot of the molecular profiling landscape of both primary and metastatic tumors, including intra- and inter-tumor heterogeneities. These data equip physicians with information valuable for devising optimal, personalized therapeutic strategies that can extend patient survival – as seen for the three NSCLC patients in this case series.

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Conflict of interest

Author declares that there is no conflict of interest.

References