Genetic testing

CHALLENGES AND PROGRESS

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TRIAL SUMMARY: Testing ctDNA in non-small cell lung cancer

Wang Y, Ho C, Vandt S, et al. EGFR and KRAS mutations in archival tissue (atDNA) and circulating tumour DNA (ctDNA): the impact of tumour heterogeneity. Abstract 5, Canadian Association of Medical Oncology Annual Meeting, April 27, 2017, Toronto.

In non-small cell lung cancer (NSCLC), ctDNA is a potential alternative to tissue biopsies in identifying targetable mutations. Individual ctDNA platforms have varying abilities to detect specific mutations. This prospective, multicentre study was conducted to determine concordance, sensitivity and specificity of ctDNA and atDNA genotyping. Patients with advanced NSCLC at the BC Cancer Agency were enrolled over 14 months. Next-generation sequencing (NGS) and high-throughput multiplex amplification of a 27-gene panel (Raindance) were used for atDNA analysis, and concordance, sensitivity and specificity were analyzed with atDNA as the reference standard.

Results: In the 76 patients, 26 EGFR mutations in 22 atDNA samples, and 12 mutations in 11 ctDNA samples were detected, with a concordance of 78%, sensitivity of 39%, and specificity of 98%. One EGFR T790M mutation was positive by ctDNA alone. Twenty-one KRAS mutations in 21 atDNA samples were detected and, within this subgroup, 10 ctDNA samples had KRAS mutations, with a concordance of 76%, sensitivity of 50%, and specificity of 80%. The interval between archival tissue and ctDNA collection, and time between treatment and ctDNA collection, did not significantly impact the rate of concordance ($p>0.05$). Although the sensitivity is low, the OnTarget ctDNA analysis is specific in identifying clinically relevant EGFR mutations and has acceptable concordance rates between ctDNA and atDNA testing. Targetable EGFR and KRAS mutations were detected in ctDNA but not atDNA, which may reflect site of biopsy and tumour heterogeneity.

COMMENTARY: Advances in genetic testing have allowed the discovery of multiple targetable mutations. This is particularly true in advanced adenocarcinoma of the lung, a subtype of NSCLC. Patients with driver mutations (including EGFR, ALK and ROS1) can be treated with targeted therapy, which improves outcomes. Therefore, broader molecular testing is now recommended in NSCLC.[1] Precision medicine needs accurate and efficient diagnostic tools to help identify mutations. Screening methods are constantly evolving, with NGS now becoming the technique of choice[2]. NGS allows for parallel testing and rapid evaluation of genomic alterations. However, it is not commonly used in routine clinical practice.

Molecular testing is usually performed on tumour tissue. An emerging technique is liquid biopsy, a blood-based assay studied to replace or complement tissue biopsy. ctDNA or circulating tumour cells can be detected in patients with malignancies. This is an active research field, with multiple assays being developed. Dr. Wang and colleagues conducted a study to determine the concordance, sensitivity and specificity of ctDNA and atDNA genotyping in NSCLC. This type of study is important to better assess the precision of ctDNA testing. The authors reported a low sensitivity of the OnTarget ctDNA test, but found it to be specific in identifying EGFR mutations. They also found acceptable concordance rates between ctDNA and atDNA testing. An interesting finding is that one targetable mutation could be detected in ctDNA, but not atDNA. This is often due to intratumoural and intermetastatic heterogeneity. A liquid biopsy may give a global picture of the mutational burden.[3] We know that patients with mutations detectable only by ctDNA can respond to targeted therapy.[4]

Given the development of clonal evolution and tumour resistance, some patients will need more than 1 biopsy over the course of their disease. For EGFR+ adenocarcinoma, a repeat biopsy at disease progression is needed to assess for mechanisms of resistance to gefitinib/afatinib. Over 50% of patients will acquire a T790M mutation, which responds to a third-generation EGFR inhibitor, osimertinib.[4,5] Repeat biopsies can be challenging, as the availability and safety of biopsy need to be taken into account. Liquid biopsy is quicker and less invasive than a standard tumour biopsy. Patients with a negative result on ctDNA may need a tissue biopsy, if possible.[4,6] Liquid biopsies could also be potentially used for disease monitoring and early detection of resistance to therapy.[3,6]

In conclusion, advances in molecular genotyping include NGS and liquid biopsies. Different assays are being developed and validated. They are still mostly used in a research setting. Nonetheless, we can expect these techniques to become more widely available in the near future.

References:

1. National Comprehensive Cancer Network. *Non-Small Cell Lung Cancer* (Version 5.2017).
2. Xue Y, Wilcox WR. Changing paradigm of cancer therapy: precision medicine by next-generation sequencing. *Cancer Biol Med.* 2016;13(1):12-18.
3. Hiley CT, Le Quesne J, Santis G, et al. Challenges in molecular testing in non-small-cell lung cancer patients with advanced disease, *Lancet.* 2016 Sep 3;388(10048):1002-11.
4. Oxnard GR, Thress KS, Alden RA, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer, *J Clin Oncol.* 2016 34:28,3375-3382.
5. Mok TS, Wu YL, Ahn MJ, et al for the AURA3 Investigators. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *NEJM.* 2017; 376:629-640.
6. Mino-Kenudson M. Cons: Can liquid biopsy replace tissue biopsy? the US experience. *Transl Lung Cancer Res.* 2016;5(4):424-427.