When not having a tissue may not be an issue in advanced lung cancer

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Tissue biopsy and histopathological diagnosis remain the gold standard for establishing a diagnosis of lung cancer. For patients who are able to undergo a tissue biopsy, up to 20% of biopsies are insufficient for additional molecular testing (1). As a result, patients with advanced lung cancer whose tumor potentially carry actionable mutations may not receive targeted therapies they would have been eligible for. While this challenge in this particular population has been addressed with the emergence of liquid biopsy that could identify the actionable mutations through circulating tumor DNA (ctDNA) testing, there is a different patient population that exist in real world practice, and pose a real challenge that has not been well addressed. That patient population is those patients who have clinical evidence of metastatic lung cancer but do not undergo invasive tissue sampling due to various reasons (2). Those patients are usually left untreated with cancer-directed therapy and often have poor prognosis. Those patients could similarly have a tumor with an actionable mutation and are missing on a treatment that could prolong survival and improve quality of life. This challenge is more encountered in regions with high prevalence of EGFR mutations, such as East Asia.

To address this challenge and find a treatment strategy for the subpopulation of patients who do not have a confirmed tissue diagnosis of lung cancer, Xu *et al.* (3) conducted a prospective phase 2 clinical trial (CHALLENGE) for patients with clinically diagnosed advanced lung cancer without tissue biopsy and offered icotinib treatment to those who are positive for EGFR mutation in ctDNA testing. This trial was a multicentered, open-label, single-arm, phase 2 clinical trial conducted in 19 institutions in China between July 1, 2017, and July 31, 2019. Patients were eligible if they have clinically diagnosed advanced lung cancer without histopathological diagnosis and have positive ctDNA EGFR sensitizing variants, namely exon 19 deletion and/or L858R mutation. The ctDNA EGFR mutation status was measured by three platforms: Super amplification refractory mutation system (SuperARMS) polymerase chain reaction (PCR), droplet digitalPCR (ddPCR), or next-generation sequencing (NGS). Among 391 patients who underwent screening, a relatively high percentage of them (35.8%, n=140) were found to have sensitizing EGFR mutations and 116 of them were included in the trial and received icotinib, an EGFR-tyrosine kinase inhibitor. The objective response rate (ORR) was 52.6% (95% CI: 43.1–61.9%). The median progression-free survival (PFS) and overall survival (OS) were 10.3 months (95% CI: 8.3–12.2) and 23.2 months (95% CI: 17.7–28.0), respectively. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 6.9% patients (3).

Icotinib is a first-generation EGFR tyrosine kinase inhibitor (TKI) developed and widely used in China. It was initially approved by the State Food and Drug Administration of China in 2011 (4). In the phase 3 CONVINCE trial, icotinib showed a better ORR and a longer PFS compared with platinum-based chemotherapy (64.8% *vs.* 33.8%, P<0.001, 11.2 *vs.* 7.9 months, P=0.006, respectively) as the first line therapy for patients with

advanced EGFR-mutant lung adenocarcinoma (5,6). The Chinese Society of Clinical Oncology (CSCO) guidelines recommend icotinib as one of the TKIs options that could be used as a first line therapy for patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC). Recently, icotinib was also shown to improve DFS as an adjuvant therapy in resected EGFR-mutated stage IB NSCLC (7). Notably, the ORR and PFS are slightly lower in the CHALLENGE trial compared with the CONVINCE trial (52.6% *vs.* 64.8% and 10.3 *vs.* 11.2 months). The authors of the CHALLENGE trial attributed the differences to a slightly higher proportion of patients with older age and poorer performance status (3). Having said that, cross-trials comparison is always a tricky task and must be taken with a grain of salt and looked at with caution. Overall, the CHALLENGE trial suggested that icotinib, when used in patients with ctDNA EGFR-positive lung cancer without tissue diagnosis, resulted in similar clinical outcomes compared to patients with confirmed tissue diagnosis. The outcomes were also similar to a real world study of 6,087 patients with advanced NSCLC treated with icotinib (8).

In this trial, 54.3% patients were unable to obtain tissue diagnosis due to non-medical reasons (either cultural tradition or simply advanced age). These reasons are less common in the US but seem to be prevalent in certain parts of the world (9,10). Those patients can be otherwise medical fit for cancer-directed treatment. In fact, 90% of patients in this trial had Eastern Cooperative Oncology Group (ECOG) score 0 or 1. The less medically fit or unfit patients with ECOG score 2 or above were underrepresented in this trial. In another study conducted by Deng *et al.* (11), 30 patients with ECOG score 3 or 4 and unable to undergo tissue biopsy were screened for EGFR mutations by ctDNA testing. Among them, 20 patients were found to have sensitizing EGFR mutations and treated with EGFR TKIs. The ORR was an impressive 90%, and the median PFS and OS were significantly higher than the other 10 EGFR-negative untreated patients (11 *vs.* 1 months, P<0.001 and not reached *vs.* 3 months, P<0.001, respectively) (11). This study complements the CHALLENGE trial demonstrating improved outcomes by using ctDNA testing as a bridge to targeted therapy while bypassing tissue biopsy in medically unfit frail patients with suspected advanced lung cancer.

In practice, brain metastases are usually difficult to biopsy and they can be commonly seen in patients with lung cancer who lack tissue biopsy, particularly in those without other accessible lesions. In the CHALLENGE trial, 31.9% patients had brain metastases, however, the outcomes of this subgroup were not reported. In patients with tissue-diagnosed advanced EGFR-positive NSCLC, icotinib is effective against brain metastases with a median intracranial PFS of 10 months compared with 4.8 months in the whole brain irradiation group (12). It will be important to know whether icotinib or other EGFR TKIs have the same efficacy against brain metastases in patients with ctDNA EGFR-positive lung cancer but without tissue diagnosis.

ctDNA testing is a form of liquid biopsy that detects tumor DNA fragments released in bloodstream following tumor cell death. It is used in different aspects of lung cancer management, including screening actionable tumor mutations complementary to tissue biopsies, assessing treatment responses, and detecting resistance mutations after disease progression. Generally speaking, however, ctDNA cannot replace tissue biopsy and cannot be used to diagnose lung cancer due to its limitations. ctDNA cannot determine the histological subtype of lung cancer. The false negative rate of ctDNA testing is relatively high at 30%. Further, the genomic variants detected by ctDNA testing are not always related to the tumor, but can be from other conditions such as clonal hematopoiesis of indeterminate potential (CHIP) (13,14). Having said that, expanding the application of ctDNA can be clinically beneficial in the subpopulation of patients who have suspected lung cancer and are ineligible for tissue biopsy. EGFR mutations are found in several types of cancer, but the exon 19 deletion and L858R mutation, so called sensitizing mutations, are highly specific to lung cancer. Studies have shown that EGFR mutation detection by ctDNA has high specificity (close to 100%) and high positive predictive value (98.6%) (15). In patients with radiographic evidence of advanced lung cancer along with ctDNA-detected sensitizing EGFR mutations, the chance of misdiagnosis is minimal. EGFR TKIs, such as icotinib, are more tolerable than platinum-based chemotherapy, and as shown in the CHALLENGE trial, can improve clinical outcomes in these patients who are otherwise usually left untreated.

Worldwide, there is an unmet need for treatment options for patients with clinically suspected advanced lung cancer who are unable to obtain histopathological diagnosis. The study by Xu *et al.* provides a new strategy by using non-invasive ctDNA testing to identify those with sensitizing EGFR mutations who can benefit from icotinib with improved clinical outcomes. This trial leads

to some questions. It is important to investigate whether similar benefits can be achieved with more widely used TKIs, such as osimertinib, which is a 3rd generation TKI that has become the standard of care 1st line treatment for patients with advanced EGFR mutant lung cancer in many parts of the world based on the results of the FLAURA trial (16). Finally, future trials are needed to know whether targeted therapy can be used for patients without tissue biopsy but have other ctDNA-detected actionable genetic alterations, such as ALK, ROS1, MET, etc. More broadly, it will be interesting to know whether ctDNA can guide targeted therapies based on pan-solid tumor biomarkers including NTRK and RET fusions, without tissue diagnosis of primary tumor. Traditionally, obtaining tumor tissue has been an essential issue that dictates cancer-directed therapy. With new technological advances and wider applications of liquid biopsy, we may see some more exceptions to this doctrine with a mutual goal to improve survival and quality of life in patients with advanced lung cancer.

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