Evaluation of liquid biopsies for molecular profiling in untreated advanced non-small cell lung cancer (NSCLC) patients

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BACKGROUND

Approximately 30% of patients with lung adenocarcinoma have an actionable driver mutation1. However, molecular profiling is limited by tissue heterogeneity and access to sufficient tissue for comprehensive analysis. Furthermore, the understanding of the molecular mechanisms of acquired resistance to targeted therapies provides key information for determining subsequent treatment options.

Circulating tumour DNA (ctDNA) can be used as a non-invasive liquid biopsy for mutation detection, quantification and monitoring for personalised treatment strategies.

OBJECTIVES

A prospective study was performed:

• To evaluate molecular profiling using ctDNA compared to tissue (where available)
• To assess correlation of dynamic ctDNA with tissue (where available)

METHODS

We recruited 110 patients into a prospectively-designed study for advanced NSCLC patients intended to initiate 1st line platinum-based chemotherapy. Blood collections (10ml K2-EDTA) were performed prior to treatment and analysed by InVision (enhanced tagged-amplicon sequencing) using a 34-gene panel. Tissue molecular analysis was limited to 97 patients and was performed by Lacroix L, Mezquita L, Jovelet C, Remon J, Howarth K.

RESULTS

cDNA Molecular Profiling

cDNA profiling was performed in 106 patients, with mutations detected in 83 patients (65%, 7 samples failed). Most frequent mutations detected were EGFR (47%), KRAS (26%), STK11 (18%; 11/19 with KRAS/STK11) and EGFR (10%). Additionally, MET (3%), ERBB2 (5%), PIK3CA (5%) and BRAF (5%) mutations and EGFR, MET, ERBB2 amplifications were detected in 4% and patients, respectively. Mutations in this cohort were detected at an allele frequency (AF) range of 0.0375% to 37%. Somatic mutations were detected in 73% of tissue.

Tissue Profiling

Tissue molecular analysis was limited to 97 patients due to insufficient cellularity and/or failed analysis. Somatic mutations were detected in 73% of tissue.

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Population (n=110)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Median 65 (38-84)</td>
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<tr>
<td>Stage (R0/R1)</td>
<td>IB/II/III 51/40/9</td>
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<td>Histology</td>
<td>Adenocarcinoma 76 (69.1%), Squamous 16 (14.5%), Others 18 (16.4%)</td>
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<td>Smoking Status</td>
<td>Never-smoker 15 (13.6%), Former-smoker 40 (36.4%), Smoker 44 (40%)</td>
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Table 1. Patient characteristics

CONCLUSIONS

cDNA can be used as a ‘liquid biopsy’ for molecular profiling of NSCLC patients to detect clinically relevant and actionable mutations when tissue biopsy is unavailable. Liquid biopsies can be used longitudinally as a non-invasive approach to monitoring patient treatment and may provide a surrogate for response evaluation by radiographic RECIST assessment. Further analyses with larger patient cohorts are planned to explore statistical methodology and clinical relevance of cDNA in advanced NSCLC.

For each cancer mutation, cDNA can be quantified either as a fraction of the total amount of DNA (AF%) or as a number of mutant DNA molecules (MM), normalized for variable input volume of plasma and extraction efficiency. These two measurements are correlated (p-value=4.767e-14, CI 0.504, 0.728) but not equivalent (Figure 4). The advantage of evaluating MM is this is not affected by the level of cell-free DNA that is not originating from the tumour. Moreover, by totalling the number of MM across detected cancer mutations, we derive a standard methodology to apply across patients to measure change in disease, including emergence of new / resistance mutations.

Figure 1. a) Distribution of gene mutations and b) genes analysed by InVision (enhanced tagged-amplicon sequencing) using a 34-gene panel.

Figure 2. Number of patients with tissue positive mutations by gene, as compared to cDNA analyses

Figure 3. Mutant event count, sensitivity and specificity were 80.5% and 93.8% respectively.

Figure 4. Correlation between AF with number of MM, normalized per ml of plasma.

Figure 5. Correlation of change in RECIST between D1 and D42 with (a) ratio of total mutant molecules and (b) AF ratio. Figs (c) shows no correlation between D1/D2 total mutation molecule ratio and progression-free survival.

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