translational research

LIQUID BIOPSY TO MONITOR THE EVOLUTION OF NSCLC EGFR+ DURING TREATMENT WITH GEFINTINIB

D. Spada1, M. Del Re2, V. Citi2, S. Guarino2, R. Ficarelli2, E. Testa2, R. Danesi3
1Oncologia Medica, Ospedale Sta Maria della Misericordia, Urbino, ITALY
2Department of Clinical and Experimental Medicine, Clinical Pharmacology Unit, University of Pisa, Pisa, ITALY
3Dept of Internal Medicine, Dept of Oncology, Transplants and New Technologies, Pisa, ITALY

Aim: Resistance to EGFR tyrosine kinase inhibitors (TKI) is a clinically relevant problem that needs to be addressed by the use of appropriate technological platforms to discover the early appearance of mutations during treatment and before clinical disease progression. However, there is a lack of standardised approaches to monitor the molecular evolution of the disease under the selective pressure exerted by targeted treatments. One potential, not yet fully validated approach, is the analysis of gene mutations conferring drug resistance on cell-free circulating tumor DNA (cctDNA) released into the peripheral blood from primary tumor and metastatic sites. Periodic monitoring of the genetic evolution of the tumor, unfeasible with repeated biopsies, will greatly contribute to a better understanding and clinical management of drug resistance in cancer patients.

Methods: In order to validate this approach in real-life conditions, we examined a case of acquired resistance to EGFR TKI to ascertain whether the technical platform chosen to perform this analysis is appropriate in terms of sensitivity and specificity and if it fulfills our need for molecular monitoring of the disease to improve our ability to personalise treatment. Therefore, in order to understand the cause of resistance to EGFR TKIs, a peripheral blood sample (6 ml) was drawn in a patient at first documented complete response to chemotherapy and at the three following disease progression after gefitinib. cctDNA was extracted from plasma with QIAamp Circulating Nucleic Acid Kit (Qiagen®) and molecular analysis of KRAS G12D, G12V, G12A, G12C, G12R, G12S, BRAF V600E, EGFR T790M was performed with a Digital Droplet PCR (Bio-Rad).

Results: At first sampling the patient was wild type for all the tested mutations. At second sampling the patient developed the KRAS G12R and the BRAF V600E mutations. At third sampling also the the EGFR T790M was detected and the analysis confirmed the previous KRAS and BRAF mutations. Finally, the fourth sampling confirmed all three mutations.

Conclusions: The liquid biopsy approach is feasible and uncovers the complexity of secondary mutations occurring in NSCLC patients treated with targeted treatments and underscores the role of the KRAS pathway in the development of resistance.

Disclosure: All authors have declared no conflicts of interest.