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Commentary

cfDNA testing for monitoring response to EGFR tyrosine kinase inhibitors: Time for clinical implementation?

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the recommended first-line treatment for patients with EGFR-mutant advanced non-squamous non-small-cell lung cancer (NSCLC) [1]. However, a fraction of patients do not respond to EGFR TKIs and the duration of the response itself is highly variable. These observations suggest that additional biomarkers are needed to better define the patient population with higher sensitivity to TKIs. In addition, the availability of different TKIs and combination strategies makes it even more important to define the prognosis of EGFR-mutant patients, for the purpose of evaluating the balance between efficacy and toxicity of the various therapeutic options.

Analysis of plasma-derived circulating cell-free DNA (cfDNA) for EGFR mutation status is recommended only when tumour tissue is not available, because of the relatively low sensitivity of the test [2]. In fact, in most studies carried out, a proportion of EGFR-mutant patients with a negative cfDNA EGFR test are identified. This observation led to the conclusion that there is a subpopulation of "non-shedders" in NSCLC patients, who have tumours that do not release cfDNA or otherwise release it in extremely limited quantities. This hypothesis is supported by the study of Fukuhara and collaborators published in this issue, in which they describe the results of cfDNA testing in the NEJ026 Phase 3 trial that compared erlotinib (E) vs erlotinib plus bevacizumab (BE) in EGFR-mutant advanced NSCLC [3].

The low sensitivity of cfDNA testing has always been presented as a limitation of this approach. However, it contains highly relevant prognostic information. In fact, EGFR-mutant NSCLC patients with a negative cfDNA test for EGFR mutations show a much better median progression free survival (mPFS) as compared with EGFR-mutation positive patients, in different studies and independently from the type of treatment [3-5]. This finding probably reflects the clinical and pathological characteristics of the disease. The negativity of cfDNA has in fact been associated with a lower tumour burden. However, data suggest that the amount of cfDNA is also related to indices of biological aggressiveness such as the level of differentiation and Ki67 expression [6].

While these data are in line with previous reports, the study by Fukuhara and collaborators provides novel and relevant data on the use of liquid biopsy in monitoring the response to TKIs. Although previous reports have addressed this issue, it is the first time that monitoring through cfDNA testing has been explored within a randomized phase III clinical trial.

By testing patients' cfDNA at baseline (P0) and 6 weeks after the start of the treatment (P1), three groups of patients with different prognoses were identified. Patients in group A, with both P0 and P1 negative tests, had mPFS of 18.1 months (m) and 16.7 m (HR 0.805) in the BE and E arms, respectively. We can hypothesize that these patients have a very good prognosis and a tumour highly dependant on the EGFR pathway. In group B, patients had a positive EGFR cfDNA test at P0 and negative at P1. The mPFS was 15.5 m in the BE arm and 11.1 m in the E arm (HR 0.613). This subgroup of patients had a relatively poor prognosis and benefited from combined treatment of anti-EGFR and anti-angiogenic drugs. In this respect, the synergism of these two agents might be due to several different mechanisms: i) the contemporary blockade of two pathways that are both important for tumour progression, i.e. cell proliferation and survival and angiogenesis; ii) the "normalizing" effect of anti-angiogenic drugs that favour a better diffusion of drugs in the tumour mass; iii) the role of VEGF-signalling in the acquired resistance to EGFR TKIs; iv) the immunosuppressive activity of VEGF [7].

Finally, group C patients with a positive EGFR cfDNA test both at P0 and P1, had an mPFS of 6.0 m and 4.3 m (HR 0.781) in the BE and E arms, respectively. These patients are likely to carry a tumour that is not dependant or at least not completely dependant on EGFR signalling and do not benefit from EGFR TKIs. Data suggest that some EGFR-mutant tumours have intra-tumour heterogeneity that might affect response to TKIs [8].

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Are the data presented by Fukuoka and collaborators going to change clinical practice? The main limit of the proposed test is that it seems to be prognostic, rather than predictive. Nevertheless, a negative EGFR cfDNA test at baseline might indicate a good prognosis and single agent TKI could be the best therapeutic approach in this setting because of the better toxicity profile. In the cfDNA positive group, BE or other EGFR TKI-based combinations could be the standard approach. However, if the cfDNA test does not become negative after a few weeks of treatment, the switch to chemotherapy could be the best choice in this EGFR TKI-refractory sub-population. Prospective trials are needed to confirm such hypothesis, as well as a standardized and quantitative testing for EGFR on cfDNA.

Declaration of Competing Interest

Dr. Normanno reports personal fees from MSD, grants and personal fees from Qiagen, grants and personal fees from Biocartis, personal fees from Incyte, grants and personal fees from Roche, grants and personal fees from BMS, grants and personal fees from MERCK, grants and personal fees from Thermofisher, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Astrazeneca, personal fees from Sanofi, personal fees from Eli Lilly, personal fees from Bayer, personal fees from ArcherDX, grants and personal fees from Illumina, personal fees from Amgen, outside the submitted work. Dr. De Luca has nothing to disclose. Dr. Perrone reports personal fees from Bayer, personal fees from Ipsen, personal fees from Astra Zeneca, personal fees from Bristol Myers Squibb, personal fees from Sandoz, personal fees from Incyte, personal fees from Celgene, personal fees from Pierre Fabre, personal fees from Janssen Cilag, outside the submitted work.

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