Are we ready to introduce T790M plasma analysis in the follow up of patients with NSCLC under treatment with EGFR-TKI?

Estibaliz Alegre[1,2], Débora Martínez[1], Mónica Macías[1], Álvaro González[1,2]

[1]Clínica Universidad de Navarra, Laboratorio de Bioquímica, Av. Pio XII 36, 31008 Pamplona, Spain; [2]IdiSNA, Navarra Institute for Health Research, Irunlarrea 3, 31008 Pamplona, Spain

Correspondence to: Dr. Álvaro González. Clínica Universidad de Navarra, Laboratorio de Bioquímica, Av. Pio XII 36, 31008 Pamplona, Spain. Email: agonzaleh@unav.es.

Provenance: This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).

Comment on: Oxnard GR, Thress KS, Alden RS, *et al*. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:3375-82.

Submitted Oct 18, 2016. Accepted for publication Oct 23, 2016.
doi: 10.21037/atm.2016.11.70
View this article at: http://dx.doi.org/10.21037/atm.2016.11.70

In the last few years, cell free circulating DNA (cfDNA) analysis has advanced from research to clinical laboratory in the case of non-small cells lung cancer (NSCLC), where patients harboring EGFR activating mutations can benefit from treatments with EGFR inhibitors (EGFT-TKIs). Treatment with an EGFR-TKI has been recently approved for patients with activating mutations of EGFR detected in cfDNA when tumor sample is not available for analysis (1). As cfDNA comes from dead cells whose DNA spills out into circulation, tumor cfDNA can provide eventually more information of tumor heterogeneity NSCLC than tissue biopsy.

Although treatment with first-line EGFR-TKIs achieves important response rates, an important percentage of patients develops acquired resistance to this treatment, and in more than 50% of patients is due to the development of the T790M mutation as a mechanism of that acquired resistance (2). However, recently developed third-generation TKIs such as Osimertinib maintain their activity in the presence of T790M mutation (3). Unfortunately, available data on Osimertinib suggest that their response rate and the progression-free survival are reduced in patients without T790M mutation when compared with those harboring that mutation (4). As a consequence, sequential assessment of T790M mutation is crucial during EGFR-TKIs treatment to choose the best EGFR-TKI as part of a personalized medicine. cfDNA analysis would have a crucial role in T790M status assessment, where re-biopsy has some important drawbacks including the impossibility to access to the tumor or to obtain samples with enough quality and, of course, the invasiveness of the procedures.

In their recent work, Oxnard *et al*. proposed an algorithm that includes T790M mutation analysis in cfDNA for the management of NSCLC with acquired resistance to conventional EGFR-TKIs (5). Even more, since response rates were similar in patients with T790M-positive tumor genotyping and in those with T790M-positive plasma genotyping, they proposed non-invasive cfDNA analysis as the initial test instead of tumor biopsy. In this work, T790M mutation was detected in plasma in only 70% of patients with a positive tumor sample. This difference might be derived from the fact that tumor should spill out ctDNA to circulation in enough quantity to be detectable. For that reason, tumor biopsy would be still necessary in those patients with negative results in cfDNA analysis. Nevertheless, the proposed algorithm that limits re-biopsies to those patients where T790M was undetected in plasma, represents an important reduction of re-biopsies. In addition, plasma genotyping may allow the detection of mutations harbored by minor clones that might remain undetected in tumor samples because of the known heterogeneity of tumors, and that can become more predominant in the future as a consequence of clonal selection due to treatments. Another important aspect to consider is that the monitoring cfDNA, can be as frequent

as required because the non- invasiveness of the procedures to obtain it. As the target mutation is known, it enables the use of techniques such as Beaming or Droplet Digital PCR, which are more affordable than other techniques such as NGS, needed when looking for unknown mutations.

Plasma analysis of T790M mutation in Oxnard *et al*. is reduced to a qualitative classification of patients as positive or negative for that mutation but without quantification. However, longitudinal quantification of T790M mutation might be used as a biomarker to monitor treatment efficiency of third-generation EGFR-TKIs. Oxnard *et al*. considered a plasma positive for this mutation when its allelic frequency was higher than 0.06%. This method of analysis might underestimate the percentage of patients positive for this mutation in plasma, since some works report an increase in total copies plasmatic concentrations (6). It might be worthy then, to further study the patients as positive or negative in plasma genotyping, considering T790M mutated copies plasmatic concentrations instead of the allelic fraction of T790M.

The study of Oxnard *et al*. is focused in acquired resistance due to T790M mutation. The existence of this mutation as a primary mutation, prior to EGFR-TKIs treatment, has been traditionally considered as residual (7). However, recent works both in cfDNA (6,8) and tumor tissues (9) reveal that its prevalence as primary mutation can be much higher than thought, probably because of the higher sensitivity of new techniques. This might suppose that more patients might be candidate to receive treatment with third-generation EGFR-TKIs as a first-line treatment, whose usefulness is being evaluated in some on-going studies of Phase I and III (10).

Although the recent development of third-generation EGFR-TKIs, acquired resistance to these treatments has already been reported, with C797S mutation implicated on it. Both C797S and T790M mutations can co-exist in patients. It will be essential in those cases to assess whether these mutations are present in cis or in trans. If the latter, a combination of first-generation and third-generation EGFR-TKIs can be considered, since C797S mutation does not affect first-generation EGFR-TKIs. However, when both mutations are in cis, none of known EGFR-TKIs would be effective (11).

Taking all these data into account, the study of Oxnard *et al*. provides additional evidences that strengthen the usefulness of T790M plasma genotyping in the monitoring of NSCLC patients receiving treatment with EGFR-TKIs. Probably, this and other studies will change treatment guidelines for NSCLC in the future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Electronics Medicines Compendium. IRESSA (gefitinib) 250 mg film- coated tablets. Available from: https://www.medicines.org.uk/emc/medicine/22104
2. Stewart EL, Tan SZ, Liu G, et al. Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations-a review. Transl Lung Cancer Res 2015;4:67-81.
3. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.
4. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015;372:1689-99.
5. Oxnard GR, Thress KS, Alden RS, et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:3375-82.
6. Alegre E, Fusco JP, Restituto P, et al. Total and mutated EGFR quantification in cell-free DNA from non-small cell lung cancer patients detects tumor heterogeneity and presents prognostic value. Tumour Biol 2016;37:13687-94.
7. Siegelin MD, Borczuk AC. Epidermal growth factor receptor mutations in lung adenocarcinoma. Lab Invest 2014;94:129-37.
8. Thress KS, Brant R, Carr TH, et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291. Lung Cancer 2015;90:509-15.
9. Watanabe M, Kawaguchi T, Isa S, et al. Ultra-Sensitive Detection of the Pretreatment EGFR T790M Mutation in Non-Small Cell Lung Cancer Patients with an EGFR-Activating Mutation Using Droplet Digital PCR. Clin Cancer Res 2015;21:3552-60.

10. Zhang H. Osimertinib making a breakthrough in lung cancer targeted therapy. Onco Targets Ther 2016;9:5489-93.
11. Niederst MJ, Hu H, Mulvey HE, et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. Clin Cancer Res 2015;21:3924-33.

Cite this article as: Alegre E, Martínez D, Macías M, González Á. Are we ready to introduce T790M plasma analysis in the follow up of patients with NSCLC under treatment with EGFR-TKI? Ann Transl Med 2016;4(24):504. doi: 10.21037/atm.2016.11.70

