Letter to the Editor

Concomitant EGFR mutations/ALK rearrangements: beyond a simple dual target

Domenico Galetta, Annamaria Catino, Andrea Misino

Medical Oncology Unit, Clinical Cancer Center, Istituto Tumori "Giovanni Paolo II", Bari, Italy

Correspondence to: Domenico Galetta, MD. Clinical Cancer Center, Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco 65, 70124 Bari, Italy. Email: galetta@oncologico.bari.it.

Submitted Dec 26, 2015. Accepted for publication Jan 06, 2016.
doi: 10.3978/j.issn.2218-6751.2016.01.09
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2016.01.09

To the Editor,

Despite conventionally considered as mutually exclusive, concurrent EGFR activating mutations and ALK rearrangements in non-small cell lung cancer (NSCLC) are increasingly described, due to more sensitive detection methods (1-3). The rate of double mutations is about 1.3% of NSCLC (2).

Concurrent genic alterations could originate from different cellular clones, so belonging to tumoral heterogeneity, but the coexistence of multiple oncogenetic alterations can be present *ab initio* in the same tumor cells, with different prevalence of a single oncogenic driver during the disease course (1). Furthermore, co-existing gene alterations could express resistance mechanisms occurring in a later phase of treatment, such as *EGFR* mutations occurring in ALK-TKIs acquired resistance (4).

A growing number of reports has been published in the last few years, highlighting this subset of NSCLC harboring concomitant druggable oncogenic drivers, and arising the issue of the therapeutical strategy in these cases.

Some studies underscore a better outcome of these patients if treated with anti-ALK agents (2,3); moreover, a scant response to first-line TKI therapy is reported (1). Globally, the data are conflicting and dysomogeneous with variable responses both to EGFR-TKIs and ALK-TKIs.

As a matter of fact, we herein describe the case of a 76-year-old Caucasian female, never smoker, with metastatic lung adenocarcinoma harboring concomitant EGFR Exon 19 mutation and ALK rearrangement.

After a very good response to chemotherapy with cisplatin plus pemetrexed the patient underwent gefitinib but the treatment response lasted only 6 months.

At disease progression, the patient didn't show any response to crizotinib.

Our experience highlights that the optimal management of these patients is still far from a consensus statement, due to several reasons.

First, despite the increasing detection of EGFR/ALK co-alterations in NSCLC, the number of these cases is too small for ultimate guidelines.

Furthermore, the biological and clinical characteristics of these patients seem to be distinguishing; the response to EGFR-TKIs or ALK-TKIs differs from patients with single oncogenic driver (1) due to reasons to be better explored, such as subtype of rearrangements and/or smoking-related genomic pattern (5).

To test ALK rearrangements also in patients harboring *EGFR* mutations is increasingly important due to the not negligible rate of concurrent alterations (1-3). Moreover, to re-biopsy patients harboring oncogenic drivers is important to re-evaluate the biomolecular profile, in order to detect new gene alterations to be targeted or to assess resistance mechanisms.

The currently available literature data underline that the coexistence of EGFR/ALK alterations is not simply predictive of better response to targeted agents; indeed, in the case described here the presence of two driver mutations is associated to a poor outcome both with EGFR and ALK-TKIs.

Hence, this subset of patients needs to be better studied due to the distinct features and biomolecular patterns, likely correlated with different prognosis and treatment responsivity.

Therefore, in our opinion this is a challenging setting,

still without a standardized management about the combination and the timing of different targeted therapies.

In the future, the improved knowledge of such rare genotypes could lead to a more tailored diagnostic and therapeutical algorithm.

Acknowledgements

None.

Footnote

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

References

1. Baldi L, Mengoli MC, Bisagni A, et al. Concomitant EGFR mutation and ALK rearrangement in lung adenocarcinoma is more frequent than expected: Report of a case and review of the literature with demonstration of genes alteration into the same tumor cells. Lung Cancer 2014;86:291-5.
2. Yang JJ, Zhang XC, Su J, et al. Lung cancers with concomitant EGFR mutations and ALK rearrangements: diverse responses to EGFR-TKI and crizotinib in relation to diverse receptors phosphorylation. Clin Cancer Res 2014;20:1383-92.
3. Won JK, Keam B, Koh J, et al. Concomitant ALK translocation and EGFR mutation in lung cancer: a comparison of direct sequencing and sensitive assays and the impact on responsiveness to tyrosine kinase inhibitor. Ann Oncol 2015;26:348-54.
4. Rossing HH, Grauslund M, Urbanska EM, et al. Concomitant occurrence of EGFR (epidermal growth factor receptor) and KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) mutations in an ALK (anaplastic lymphoma kinase)-positive lung adenocarcinoma patient with acquired resistance to crizotinib: a case report. BMC Res Notes 2013;6:489.
5. Karlsson A, Ringnér M, Lauss M, et al. Genomic and transcriptional alterations in lung adenocarcinoma in relation to smoking history. Clin Cancer Res 2014;20;4912-24.

Cite this article as: Galetta D, Catino A, Misino A. Concomitant EGFR mutations/ALK rearrangements: beyond a simple dual target. Transl Lung Cancer Res 2016;5(1):143-144. doi: 10.3978/j.issn.2218-6751.2016.01.09

