ALK Rearrangement in Lung Cancer: Is Patients Filtering Possible?

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There is an ongoing discussion about the need to stratify lung cancer patients, in order to establish appropriate target therapeutic strategies. Recently the product of ALK (Anaplastic Lymphoma Kinase) gene rearrangement in lung cancer has been proposed as molecular target for biological therapy. The human ALK (Anaplastic Lymphoma Kinase) gene (2p23), encoding a single-chain transmembrane tyrosine kinase receptor, has been shown to be involved in specific rearrangements producing chimeric proteins with oncogenic activity in many malignancies.

The first translocation described in lung cancer was EML4-ALK fusion gene [1]. Then other less frequent fusion partners have been identified, such as TGF and KIF5B. All chimeric proteins produced show high tumorigenic activities through the ALK constitutive activation.

The high therapeutic value of crizotinib (PF-02341066) [2], a specific inhibitor ALK-MET dual target, breaks new ground for the treatment of patients harboring ALK-Rearrangements (ALK-R). However, despite significant therapeutic advances achieved in the last years, there are many problems associated with the detection of the ALK-R, mainly related to low frequency, to sensitivity/specificity and finally to the costs of the used techniques.

Could these limitations be solved selecting appropriately the potential patients harboring ALK-R?

Several studies have emphasized specific clinicopathological features shared by patients harboring ALK-R, that could constitute a unique subset of Non-Small Cell Lung Cancer (NSCLC) responsive to specific ALK inhibitors.

In most of the cases the patients carrying ALK-R show adenocarcinoma histotype, mainly the mucinous cribriform pattern is more frequent in the Japanese patients and the solid-signet-ring cell pattern in the western patients [3]. Moreover although the ALK-R were initially identified in smokers, generally ALK-R patients are never or lightly smokers [4] and in addition they are younger than ALK wild-type patients [5]; usually ALK-R are mutually exclusive of EGFR and KRAS mutations [1,6].

Recently Kobayashi et al. have proposed the pre-test criteria based on the clinicopathological features to select potential ALK-rearranged patients [7]. The selection of the candidate patients, according to these criteria, resulted in a remarkable increase in the percentage of ALK-R, accounting approximately 29.6% compared to 5-7% in general population of NSCLC patients.

In conclusion ALK status detection in NSCLC patients is needed in consideration of the therapeutic opportunities, but the cost of FISH test could be reduced through a careful filtering of patients potentially harboring ALK-R, from clinic-pathological features to ALK IHC expression.

In addition, the correct diagnosis and management of patients carrying ALK-R needs adequate techniques for screening, such as FISH, RT-PCR and Immunohistochemistry (IHC).

Recently a diagnostic algorithm, similar to HER2 scoring conventionally used in breast cancer, has been proposed to detect ALK-R in NSCLC patients. This algorithm used ALK IHC to predict ALK-R, reserving FISH analysis only to the cases with moderate membrane ALK positivity [5]. Indeed FISH is the only direct method to detect ALK-R although its interpretation requires appropriate experience. Thus FISH analysis is the standard method for enrollment in the clinical trials of crizotinib.

In conclusion ALK status detection in NSCLC patients is needed in consideration of the therapeutic opportunities, but the cost of FISH test could be reduced through a careful filtering of patients potentially harboring ALK-R, from clinic-pathological features to ALK IHC expression.

References


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