Commentary

Differential crizotinib response duration among ALK fusion variants in ALK-positive non–small-cell lung cancer

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EML4-ALK is a fusion-type protein-tyrosine kinase generated through a recurrent chromosome rearrangement, a small inversion within the short arm of chromosome 2, inv(2)(p21p23) (1).

The identification of ALK rearrangements, found in approximately 5% of non-small-cell lung cancers (NSCLCs), and the success of tyrosine-kinase inhibitor (TKI) (crizotinib, ceritinib, alectinib and brigatinib) treatment, have achieved a breakthrough similar to the discovery of EGFR mutations and treatment (2). Rapid clinical development with effective TKI treatments has perhaps meant that less attention has been paid to ALK variants.

The most frequent among more than 13 variants (3) is variant 1, where exon 13 of EML4 is fused to exon 20 of ALK (E13; A20) and represents about 30% of all ALK rearrangements; in variant 2, exon 20 of EML4 is fused to exon 20 of ALK (E20; A20), and in variant 3a/b, exon 6a or 6b of EML4 is fused to exon 20 of ALK (E6a/b; A20).

Yoshida *et al*. have published a study evaluating whether the efficacy of crizotinib differs among ALK variants (4). They were able to retrospectively evaluate 35 patients and detected ALK variants by RT-PCR on the basis of patient characteristics, initial response to crizotinib, and progression patterns. Seven (20%) of the patients presented brain metastasis prior to treatment with crizotinib. ORR was 69% and the median PFS in all patients was 9.7 months. The most frequent ALK-variants were variant 1 in 19 patients (54%), followed by variant 2 in five (14%), variant 3a/3b in four (12%), and other variants in seven patients (20%). Patients were divided into ALK variant 1 and non-variant 1 groups and similar clinical characteristics were observed in both groups. Differences were found in the median PFS, which was significantly longer in patients with variant 1 than in patients with non-variant 1 (11.0 *vs*. 4.2 months, respectively; P<0.05), and the disease control rate (DCR) 95% *vs*. 63% (P=0.03), but not in the objective response rate (ORR) (74% *vs*. 63%, respectively). The multivariate analysis identified two factors associated with the duration of PFS; these were ALK variant 1 and advanced stage.

There are *in vitro* observations that could generate doubts about some differences between variant and drug sensitivity, however these are inconclusive.

In this study, the ORR was similar but DCR was longer, in addition, PFS was longer in variant 1. However, these two aspects could be affected, more than any other, by the retrospective nature of the study and because the imaging studies were not conducted at consistent intervals. The authors also recognized this fact and we believe that classifying cases between variant 1 and other variants is arbitrary because there are actually more than 10 different variants.

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Recently, Cha *et al*. (5) reported the results of a study using a similar approach. They studied the clinical outcomes of 52 patients according to ALK fusion variants. No clinical pathological distinction was found between the different ALK fusion variants. Treatment response rates for each therapeutic agent did not differ according to the ALK fusion variant. However, EML4 variants, especially variant 1, showed significantly longer progression-free survival on pemetrexed treatment. With respect to ALK fusion variants, no significant difference was found in PFS of patients treated with crizotinib or ceritinib. However, in the multivariate analysis variant 1 was the only statistically significant predictive factor of longer PFS.

Both studies had similar limitations that could have affected the results: their retrospective nature and small sample size. Our knowledge of these aspects is very limited in part due to the use of FISH or immunohistochemistry to diagnose ALK rearrangement, and these techniques are not able to detect these variants, nevertheless there are some interesting data. First, variant 1 is the most common subtype, and second, it has a tendency to longer PFS.

We need a rational explanation for these results. In the study by Takeuchi *et al*. (3), all EML4-ALK variants manifested marked differences in the size and domain structure of the EML4 portions of these chimeric proteins and the domain of EML4 may play an essential role in the dimerization and activation of EML4-ALK variants and the binding to specific subcellular components. But this seems insufficient because ALK positive tumors are a very special, complex, heterogeneous process (6). Most patients with ALK NSCLC initially respond to treatment with crizotinib then inevitably, after 1 or 2 years, relapse with multiple mechanisms of resistance and distinct patterns that depend on each ALK inhibitor (7,8).

It is clear that we need more studies to know the frequency of ALK variants in different populations. The study by Yoshida *et al*. (4) has been performed in Japanese population and it is not clear from the paper if these patients were mainly ex-smokers or never smokers. The first table showed that the median smoking index was 0 but there were also smokers. The frequency of ALK translocations is higher in never smokers and also in Asian populations compared to Caucasian populations and has a range of 5% (9) to 15% (10). Therefore, it could be expected that the frequency of different ALK variants might differ between Caucasian and Asian populations. More research is needed to have a clearer picture on this issue.

In EGFR, Del 19 mutations are associated with more effective EGFR-TKI (11) therapy than L858R point mutation and exon 20 insertion (12). In contrast, in EGFR mutation, T790M predominates as the mechanism of resistance, however in ALK it is more similar to the broad spectrum of mutations observed in BCR-ABL given that this is similarly related to chromosome rearrangement. The influence of ALK variants in response to TKIs and survival need to be clarified, therefore further studies are required to analyze these factors as well as the relationship with mutations of secondary resistance. Furthermore, it appears that those patients with variant 1 seemed to have higher toxicity than those with other variants, though toxicity broken down by ALK variant has not been analyzed in detail. This aspect is relevant and must be counterbalanced with the better effectiveness observed for those carrying ALK+ variant 1.

Next-generation sequencing (NGS) can reveal additional information even in tissues that were previously negative (13). In the near future, it could be that genotyping with clinical information and personalized medicine with NGS could transform our perspective about these and other variants (14).

To conclude, the study by Yoshida *et al*. has shown that the clinical effectiveness for treatments directed to ALK+ patients might be different depending on ALK translocation variant. Nevertheless, this pilot study only included 35 Japanese patients. There is room for clinical trials that, though complicated from a logistical point of view given the low prevalence of ALK+ patients, could compare the clinical effectiveness of different available treatments for the most frequent ALK+ variants. In these future clinical trials differential toxicity between variants cannot be neglected and ideally should have the necessary power to address this question.

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Footnote

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