Refining precision cancer therapy in ALK-positive NSCLC

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The treatment approach to advanced anaplastic lymphoma kinase fusion-positive (ALK-positive) non-small cell lung cancer (NSCLC) serves as a paradigm for precision oncology. To date, five ALK-tyrosine kinase inhibitors (TKIs)—crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib—have been approved by the US Food and Drug Administration. Although each TKI has significant efficacy in ALK-positive NSCLC, the duration of benefit is invariably limited by the development of acquired resistance.

Alectinib, a second-generation ALK-TKI, is the current standard initial therapy for advanced ALK-positive NSCLC. Once patients develop alectinib resistance, second-line options include lorlatinib, chemotherapy, or a clinical trial. Lorlatinib is a potent, brain-penetrant, third-generation ALK/ROS1-TKI with efficacy against most known ALK resistance mutations including G1202R, the most common alectinib-resistant mutation. Based on phase II results demonstrating its activity in patients who progressed on second-generation ALK-TKIs, lorlatinib recently received FDA approval for second- or third-line treatment of ALK-positive NSCLC. Sequential therapy with alectinib followed by lorlatinib is therefore anticipated to be a common treatment approach. Yet, resistance to lorlatinib invariably develops, and thus, elucidating mechanisms of resistance to lorlatinib is critical to developing effective next-line treatments.

In this issue of EBioMedicine, Okada and colleagues report the identification of 14 lorlatinib-resistant compound ALK mutations. Using an ENU mutagenesis screen of Ba/F3 cells expressing EML4-ALK-I1171N or G1202R—the most common alectinib-resistant mutations—the authors identified nine I1171N-based and four G1202R-based double mutants. A G1202R/G1269A double mutant was additionally identified in an EML4-ALK-G1202R mouse model made lorlatinib-resistant. Indeed, three of these compound mutations (G1202R/G1269A, G1202R/L1196M, and I1171N/L1198F) had previously been reported based on lorlatinib-resistant tumour biopsies. The ALK mutations identified herein expand upon those reported in an independent mutagenesis study, suggesting lorlatinib resistance may emerge from a diverse array of compound ALK mutations as patients receive sequential alectinib then lorlatinib.

Importantly, the authors evaluated the in vitro sensitivity of several compound ALK mutants to approved ALK inhibitors. Interestingly, certain I1171N-based double mutants could be overcome by earlier-generation ALK-TKIs. For example, I1171N/L1256F was sensitive to alectinib; I1171N/L1196M and I1171N/G1269A were sensitive to brigatinib or ceritinib. These findings are reminiscent of a prior report on a lorlatinib-resistant ALK C1156Y/L1198F compound mutation, which re-sensitised tumour cells to crizotinib. Okada et al. similarly found double ALK mutants containing L1198F (G1202R/L1198F and I1171N/L1198F) to be sensitive to crizotinib. Collectively, these results highlight that structurally distinct, even earlier-generation, ALK-TKIs may be useful at different time points during the disease course as patients receive sequential ALK targeted therapies.

It should be noted that a significant fraction of lorlatinib-resistant compound ALK mutations are not sensitive to earlier-generation ALK-TKIs. In this study, G1202R-based double mutants G1202R/L1196M, G1202R/F1174C, and G1202R/F1174L were refractory to all approved ALK inhibitors. While G1202R/G1269A was moderately sensitive to brigatinib in vitro, the IC50 was modestly higher than that for G1202R. As ALK G1202R has been detected in brigatinib-resistant biopsies, it is unclear to what degree brigatinib will prove clinically effective against G1202R/G1269A. For these refractory compound ALK mutations, novel rationally designed inhibitors are urgently needed.

Overall, the current study contributes to the growing understanding of lorlatinib-resistant compound ALK mutations. The observation that specific compound mutations are sensitive versus refractory to earlier-generation ALK inhibitors in vitro could help inform practice, and underscores the importance of repeat biopsies in identifying resistance mutations, some of which may predict sensitivity to alternative TKIs. However, this study raises several important questions. First, can these compound ALK mutations be reliably identified in the clinic by tumour or liquid biopsies? While the individual mutations themselves may be readily detected, determining the allelic context of the ALK mutations (i.e., whether the ALK mutations reside on the same or different alleles) can be much more challenging and will often not be feasible using the standard next-generation sequencing assays on genomic DNA. Second, will earlier-generation ALK inhibitors induce meaningful clinical benefit in lorlatinib-resistant patients harbouring sensitive compound ALK mutations? In patients relapsing after multiple sequential therapies, tumours may harbour a greater degree of genomic complexity and heterogeneity that tempers the efficacy of any single ALK-TKI and effectively dampens the ALK-dependent phenotype. CNS disease status will further influence the extent of clinical benefit from earlier-generation TKIs which are generally less active in the CNS than lorlatinib.
lorlatinib. Third, will upfront treatment with lorlatinib result in more durable benefit than a sequential approach which fosters the accumulation of genetic changes including ALK resistance mutations? Lorlatinib is potent against most known single ALK resistance mutations; hence, upfront lorlatinib may delay or suppress the emergence of refractory compound ALK mutations [8]. A phase III trial (ClinicalTrials.gov identifier NCT03052608) is evaluating the first-line efficacy of lorlatinib compared to crizotinib.

Finally, although not addressed in this study, ALK-independent mechanisms of resistance such as bypass signaling or lineage changes remain a major therapeutic hurdle in ALK-positive NSCLC. In an analysis of 20 lorlatinib-resistant tumour biopsies, 65% did not harbour compound ALK resistance mutations [8], implicating ALK-independent resistance. The prevalence of ALK-independent resistance mechanisms will likely rise as strategies to overcome ALK mutations continue to improve. Thus, effective combinatorial approaches that address both ALK-dependent and ALK-independent resistance are needed. Together, these endeavours will help fine-tune our treatment approach to ALK-positive NSCLC to more precisely match the biology of the tumour.

Disclosures

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