EDITORIAL

Overcoming Drug Resistance in *ALK*-Rearranged Lung Cancer

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Approximately 4 to 15% of lung adenocarcinomas harbor a genomic rearrangement in the anaplastic lymphoma kinase gene (*ALK*) that creates a gene fusion activating the tyrosine kinase ALK.[1-4] Treatment of patients with *ALK*-rearranged lung cancer with the MET and ALK inhibitor crizotinib induces responses[5] and confers a benefit in progression-free survival.[6] In a nonrandomized registry study, crizotinib also improved overall survival.[4]

Unfortunately, all patients who have *ALK*-rearranged lung cancer will have a relapse eventually, after a response that typically lasts for 8 months.[6] Thus, drugs that are capable of suppressing the growth of recurrent tumors are urgently needed. In the phase 1 trial by Shaw and colleagues[7] reported in this issue of the *Journal*, one of these drugs, ceritinib, induced remissions in almost 60% of patients with *ALK*-rearranged lung cancer. More striking, however, is the fact that responses were independent of whether patients had been treated with crizotinib previously. Thus, patients appear to have a second chance of response after relapse occurs following crizotinib treatment.

Thus far, data suggest that acquired resistance to crizotinib may emerge by means of second-site mutations affecting the binding of the drug in the kinase domain or by means of the activation of pathways that bypass the original oncogenic kinase signal.[8] Since ceritinib is several times as potent as crizotinib,[9] interindividual variations of drug levels in plasma, which may cause insufficient inhibition of the target by crizotinib in some patients, could be less of a problem with ceritinib, which may still be able to shut down the oncogenic kinase. Moreover, the higher potency of ceritinib may often be sufficient to inhibit the mutant ALK causing crizotinib resistance.[10] Of note, one of the mutations that led to crizotinib resistance, but was overcome by ceritinib, was the mutation at the so-called gatekeeper position of the kinase domain, L1196M. Mutations of the gatekeeper in ABL or epidermal growth factor receptor (EGFR) cause resistance to ABL inhibitors in chronic myeloid leukemia and to EGFR inhibitors in lung cancer and are among the most difficult to overcome.

So, why is ceritinib still active against gatekeeper mutations? A possible explanation may be rooted in the chemical architecture of these compounds. The polar aromatic amine in the 2-position of the pyridine scaffold of crizotinib may not be ideal to make interactions with a large lipophilic residue at the gatekeeper position, such as methionine. By contrast, the chlorine in the 5-position of the pyrimidine of ceritinib may interact more favorably with a methionine gatekeeper in crizotinib-resistant ALK. Thus, similar to other second-generation kinase inhibitors such as WZ4002 or CO-1686, which are designed to target drug-resistant mutant EGFR and which carry halide substituents in their pyrimidine rings, ceritinib appears to be ideally suited to interact with large and lipophilic gatekeeper mutants.

A major advantage of this phase 1 trial lies in its large size. With 114 patients having received at least 400 mg of ceritinib, this study is a first proof of concept for the successful targeting of ALK, beyond the establishment of safety and a maximum tolerated dose. Thus, the response rates and progression-free survival times are already more than an initial glimpse regarding the efficacy of ceritinib.

Since response rates were almost identical in the cohorts of patients who had received crizotinib previously and those who had not, ceritinib is another example for the ongoing debate regarding the context in which second-generation inhibitors should be applied. The most intuitive scenario may be second-line treatment after relapse following crizotinib treatment. It is plausible that the progression-free survival of these two lines of therapy may simply be added to ultimately confer a prolongation of overall survival. Furthermore, the early signs of activity against brain metastases define this important cohort of patients as another target population of ceritinib, independent of the line of treatment.

Alternatively, the higher potency of ceritinib, as compared with crizotinib, may be exploited to achieve an increase in progression-free survival during front-line treatment. Shaw et al. observed a progression-free survival that was a median of 3 months longer among patients who had not received crizotinib previously than among patients who had — a finding that supports such a front-line treatment scenario. To establish such a strategy, however, a head-to-head comparison of both drugs is required. One caveat of this approach, though, is that the front-line application of ceritinib could lead to inferior outcomes if ceritinib resistance cannot be overcome by existing drugs.

Some questions remain. For example, what was the drug exposure and degree of target inhibition in patients with a response, as compared with those without a response? In addition, given the indirect measure of ALK fusions by means of fluorescence in situ hybridization with the use of break-apart probes, it would be helpful to determine the presence or absence of the fusion in patients with a response and in those without a response by means of direct sequencing in order to validate the true performance of this critical test. Finally, were responses also observed in patients with primary crizotinib resistance?

The study by Shaw and colleagues is good news for patients with *ALK*-rearranged lung cancer. It is also an example of how mechanistically inspired and rationally designed trials involving large, genotypically defined patient cohorts[4] can lead to dramatic steps forward in the care of patients with cancer.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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