ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Second-Generation ALK Inhibitors

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H&O What is the mechanism of action for second-generation anaplastic lymphoma kinase (ALK) inhibitors?

HM Most of the currently available second-generation ALK inhibitors are ATP-competitive reversible inhibitors. The second-generation inhibitors were designed to be effective against tumors that acquire resistance to crizotinib (Xalkori, Pfizer), the first ALK inhibitor.

In 2010, we published a study in the *New England Journal of Medicine* that describes the mechanism by which *EML4-ALK*–positive tumors acquire resistance to crizotinib. We found that different subclones within the same tumor independently acquired secondary mutations in *EML4-ALK* that changed Cys-1156 to Tyr or Leu-1196 to Met. Both mutations conferred drug tolerance and are within the catalytic domain of *EML4-ALK*. Interestingly, Leu-1196 corresponds to Thr-790 in the epidermal growth factor receptor (EGFR) or to Thr-315 in *BCR-ABL*, the so-called "gatekeeper" site. Thr-790–to–Met is the most frequent mutation in EGFR-positive lung cancer that confers resistance to gefitinib, and Thr-315–to–Ile is the most frequent mutation in *BCR-ABL*–positive chronic myeloid leukemia that confers resistance to imatinib (Gleevec, Novartis).

Second-generation ALK inhibitors are designed to be effective even if the tumors acquire the Leu-1196–to–Met mutation in *EML4-ALK*. To the best of my knowledge, a total of 8 such inhibitors are available: ceritinib (Zykadia, Novartis) has been approved by the US Food and Drug Administration (FDA), alectinib has been approved in Japan, and 6 others are currently in clinical trials.

H&O Could you describe the second-generation ALK inhibitors that are currently FDA approved?

HM Ceritinib was approved by the FDA in April 2014 as a drug for crizotinib-resistant *EML4-ALK*–positive non–small cell lung cancer (NSCLC). Shaw and colleagues published the phase 1 data for this drug in the *New England Journal of Medicine* in 2014. The overall response rate to this drug was 58%, and the median progression-free survival was 7.0 months. Interestingly, ceritinib showed an equivalent response rate of 56% in crizotinib-resistant NSCLC.

Though not approved in the United States, alectinib was approved in Japan in July 2014 for the treatment of *ALK* fusion–positive NSCLC. The results of the phase 1/2 study were published by Seto and colleagues in 2013 in *The Lancet Oncology*. This study demonstrated a remarkable overall response rate of 93.5%, with 4.3% complete responses and 89.1% partial responses. An ongoing trial (NCT01801111) presented by Ou and colleagues at the most recent American Society of Clinical Oncology (ASCO) meeting found an overall response rate of 49.2% and a disease control rate of 79.5% for crizotinib-resistant tumors. For patients with previous chemotherapy and crizotinib, these rates were 43.8% and 78.1%, respectively. The central nervous system overall response rate was 55.9%, with 5 complete responses.

H&O What are the side effects of the second-generation ALK inhibitors?

HM Dose-limiting toxicities for ceritinib included diarrhea, vomiting, dehydration, liver toxicity, and hypophosphatemia. All events resolved after discontinuing treatment, and all but 1 patient resumed treatment.

Alectinib did not reach the maximum tolerated dose in clinical trials, but low-grade toxicities included neutropenia, increased creatine kinase, and liver toxicity. Treatment-related adverse events occurred in 26% of patients, and 11% of patients had serious adverse events. No grade 4 adverse events or deaths were reported.

H&O What is EML4-ALK–positive lung cancer?

HM *EML4-ALK*–positive lung cancer is enriched in adenocarcinoma and tends to occur in nonsmokers, light smokers, and relatively young patients. EML4 is a microtubule-associated protein, and ALK is a receptor-type protein tyrosine kinase. Both *EML4* and *ALK* genes are mapped within the same short arm of human chromosome 2. We found that 4% to 5% of patients with NSCLC harbor the *EML4-ALK* fusion-type oncogene generated by the intrachromosome inversion inv(2)(p21p23). This chromosomal rearrangement results in the fusion of the N-terminal half of EML4 to the kinase domain of ALK. Our study—published in *Nature* in 2007—was the first example of a recurrent kinase fusion in major epithelial carcinoma. This study, together with the discovery of *ETS* gene fusions in prostate cancer, provided strong evidence against the common notion that chromosomal translocation is not involved in the carcinogenesis of epithelial carcinoma. Reviews on this subject were published by our group in *Cancer Science* in 2008 and by Ramalingam and colleagues in *Cancer Discovery* in 2014.

H&O How many patients could benefit from ALK inhibitors?

HM Approximately 1.6 million people die of lung cancer every year worldwide, 4% to 5% of whom have this gene fusion. Therefore, 60,000 to 80,000 patients die of *EML4-ALK*–positive NSCLC and could be rescued with ALK inhibitors.

Furthermore, ALK inhibitors should be effective in any tumors with an *ALK* gene fusion. In addition to *EML4-ALK*, *ALK* fuses with *KIF5B* in NSCLC, nucleophosmin (*NPM*) in anaplastic large cell lymphoma, *TPM3/4* in inflammatory myofibroblastic tumor, vinculin (*VCL*) in renal medullary carcinoma, and fibronectin (*FN1*) in ovarian stromal sarcoma. All *ALK* gene fusions are most likely potent oncokinases that support tumor growth. Indeed, a study by Gambacorti-Passerini and colleagues found that crizotinib was effective in *ALK* fusion–positive lymphoma, and a study by Butrynski and colleagues found the drug to be effective in inflammatory myofibroblastic tumor, albeit in a small cohort.

In a review published in *Cancer Discovery* in 2012, I proposed that such tumors collectively be called "ALKoma," because single ALK inhibitors are effective against all of them, regardless of the organ of origin. The designation of ALKoma is an early example of a beyond-organ cancer classification scheme.

H&O What is the future of ALK inhibition?

HM Brain metastasis is a frequently observed and often fatal complication of lung cancer. Therefore, second-generation ALK inhibitors should have a high blood-brain barrier penetration ratio so that brain metastases can be controlled. Alectinib and ceritinib seem to be effective against brain metastases and therefore are promising.

Given the high response rate of alectinib, ALK inhibitors may be one of the most effective drugs against epithelial tumors if they have less toxicity and can be effective against brain metastases. I believe that combination therapies with ALK inhibitors and any modality acting on nondividing cancer stem cell fractions are likely to become the gold standard in future cancer treatment.

Suggested Readings

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