ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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ROS1-Targeted Therapy in Non–Small Cell Lung Cancer

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H&O What is ROS1, and what is its mechanism of action?

LS ROS1 is a receptor tyrosine kinase of the insulin receptor family. Chromosomal rearrangement is the primary mechanism that activates ROS1 in lung cancer and other cancers, and a number of ROS1 rearrangements can occur in nonsquamous lung cancer. These rearrangements lead to aberrant expression of ROS1 and constitutive activation of its tyrosine kinase. Signaling downstream of ROS1 fusions results in activation of cellular pathways that are known to be involved in cell growth and proliferation.

H&O How common are ROS1 rearrangements in non–small cell lung cancer (NSCLC)?

LS Genomic alterations in ROS1 have previously been noted in gliomas and were first reported in an Asian patient with NSCLC. Subsequent studies have revealed ROS1 translocations in approximately 1–2% of patients with NSCLC. However, little is known about the signaling pathway from activated ROS1 kinase. Even though this genomic subset comprises a small percentage of all adenocarcinomas, lung cancer is a common disease, so this finding will translate to 3,000–4,000 new patients diagnosed annually with ROS1-rearranged NSCLC in the United States alone.

H&O What are the characteristics among NSCLC patients with ROS1 rearrangement?

LS In our large group experience at Massachusetts General Hospital (MGH), we screened tumor samples from more than 1,000 NSCLC patients treated at MGH, Vanderbilt University, the University of California at Irvine, and Fudan University in Shanghai, China. ROS1 rearrangement was identified in 18 tumor samples (1.7%). Patients whose tumors harbored ROS1 translocations were more likely to have adenocarcinoma and to be Asian, younger, and never-smokers. These are clinical features that are also associated with both epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) rearrangements. However, more data are needed in order to confirm these early findings.

H&O How are patients with ROS1-positive NSCLC identified?

LS The standard approach thus far has involved the use of fluorescence in situ hybridization (FISH) to test for rearrangement. However, FISH is quite challenging to think about performing on a widespread basis in every hospital. It requires specialized technical resources and expertise, and is not cost-effective. As such, other diagnostic modalities are being developed, including reverse transcriptase-polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC). If a reliable IHC test can be developed, that would be easier to implement on a larger scale. Generally, IHC is easy to perform and interpret, and it is cost-effective. However, technical problems and false-positive results make this method less robust than FISH. Ideally, there would be a validated test that is both highly sensitive and specific, yet relatively inexpensive and not overly technical to perform. This would enable widespread adoption and implementation of particular treatments and ensure that the maximum number of patients to benefit from such therapy can be identified.

H&O What have recent study data demonstrated regarding the role of crizotinib (Xalkori, Pfizer) in ROS1-positive NSCLC?

LS Due to a high degree of homology between the ALK and ROS tyrosine kinase domains, the ROS1 tyrosine kinase has been shown to be highly sensitive to crizotinib in preclinical models.

The safety of crizotinib has already been demonstrated in ALK patients and the drug has received approval from the US Food and Drug Administration in that population. As such, the use and approval of a drug for patients with ROS1-positive NSCLC is likely not too far away. We have already treated a number of patients with ROS1 rearrangements using crizotinib as part of a phase I clinical trial, and some of the preliminary results are very promising.

H&O What are the biggest remaining challenges?

LS Over the last few years, there have been major strides in the understanding of molecular abnormalities, the identification of molecular targets, and the development of molecular-targeted therapies in NSCLC. However, despite such advances, the reality is that these treatments are not cures, and such therapies tend to control the disease for approximately 1 year. Therefore, it is critical that we continue improving upon current treatments, develop new therapeutic strategies, and learn how to combat drug resistance.

H&O What does the future hold?

LS I think the future will be heavily based on molecular tests. In some ways, the future is already here, but the availability of such tests varies at each institution. The availability and scope of molecular testing will continue to increase in the future. We will also work toward preventing the emergence of drug resistance in these patients. Ideally, combination treatments, including those up front, will prove to be even more effective than these single-targeted therapies.

Suggested Readings

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