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The Use of Crizotinib in Late Stage Lung Cancer Patients with an Abnormal ALK Gene

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Abstract
The relatively new anti-cancer drug, crizotinib (Xalkori®, Pfizer), has created excitement in the research community. This drug has exhibited dramatic clinical benefits for select non-small cell lung cancer patients showing evidence of a mutation in the EML4-ALK gene. This gene mutation is present in 4 to 5 percent of non-small cell lung cancer patients. Crizotinib acts through a tyrosine kinase inhibition pathway, targeting the ALK and MET tyrosine kinases, to inhibit phosphorylation of activated ALK, which halts the ALK gene mutation and impedes metastasis. In phase I clinical trials, a 57 percent overall response rate was shown, and researchers calculated that the six-month progression-free survival was 72 percent. Therefore, patients treated with crizotinib had an increased survival rate when compared to conventional chemotherapy. Although the success rate of crizotinib is high, the mutated ALK gene has been shown to develop resistance to it. However, the predicted impact of this drug is still promising.

Background
Lung cancer is the leading cause of cancer-related death in the United States, with a five-year survival rate of approximately 15.6 percent. The World Health Organization divides lung cancer into two major classes based on biology, therapy, and prognosis: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts for more than 85 percent of lung cancer cases and presents as either a locally advanced or metastatic disease. Recently, malignancies have been attributed to genetic alterations in a single gene causing the cancer to become reliant on signaling from the encoded protein, usually a receptor tyrosine kinase. Therefore, current treatments for NSCLC have focused on the use of targeted drug therapy, namely the epidermal growth factor receptor (EGFR) inhibitors, gefitinib and erlotinib, and the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab. Recently, a new type of targeted drug therapy for NSCLC has emerged. This therapy targets mutations of the anaplastic lymphoma kinase (ALK) and the echinoderm microtubule-associated protein-like 4 (EML4) genes. Crizotinib (Xalkori®) is an inhibitor of ALK and MET tyrosine kinases, allowing for effective control of the disease state.

Mutation of the ALK Gene, Prevalence, and Testing
The EML4-ALK mutation was first discovered in 1997 from a lung adenocarcinoma. This mutation is a fusion-type protein tyrosine kinase that is present in 4 to 5 percent of NSCLC cases. Of these cases, a total of approximately 10,000 patients within the United States are affected each year. The EML4-ALK fusion gene is more prevalent in nonsmokers, in patients with a history of light smoking and in patients with adenocarcinomas. Therefore, evidence suggests that the ALK gene rearrangement is a distinct subgroup of lung cancer that is not related to smoking. Additionally, patients with the EML4-ALK gene are typically younger than the average NSCLC patient. While genetic alterations involving ALK have been identified in other malignancies, the EML4-ALK fusion is unique to NSCLC. The EML4-ALK mutation is produced as the result of a small inversion within the short arm of human chromosome 2. ALK undergoes dimerization through interaction within the coiled-coil domain at the EML4 regions of each monomer, activating ALK. Activated ALK is involved in the promotion of cellular growth and the inhibition of apoptosis, generating oncogenic activity.

Before the FDA approved crizotinib, the Vysis ALK Break Apart Fluorescent in situ hybridization (FISH) Probe Kit detected chromosomal rearrangements in the ALK gene. This test utilizes fluorescent-labeled DNA probes to indicate the existence of the ALK gene chromosomal rearrangement found via lung biopsy. If the test is positive for an ALK gene rearrangement, the patient may benefit from crizotinib treatment. A limitation of the Vysis ALK Break Apart FISH method is the detection of only ALK gene rearrangements versus identification of actual EML4-ALK fusion genes. Some other diagnostic methods for the EML4-ALK gene mutation are immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR), but the Vysis ALK Break Apart FISH method is most widely used.

Crizotinib and Clinical Trials
As an oral receptor tyrosine kinase inhibitor, crizotinib is used in the treatment of locally advanced and metastatic NSCLC. Crizotinib inhibits ALK and Hepatocyte Growth Factor Receptor (HGFR, c-Met) tyrosine kinases by preventing their phosphorylation and halting tumor cell growth.

In the phase I trial conducted by Kwak et al., the efficacy and adverse events of crizotinib were tested in an expanded cohort study. Eighty-two patients with ALK-rearranged advanced NSCLC cancer participated in the trial. The subjects were tested for ALK-gene rearrangements using the FISH method. FISH positive samples had split ALK 5' and 3' DNA probe signals or single 3' signals in more than 15 percent of the tumor cells. For evaluation, patients had a baseline tumor assessment, received a dose of oral crizotinib on day one of the first 28-day cycle, and then completed a minimum of one post-baseline tumor assessment. Patients received 250 mg of crizotinib twice daily. Patient safety was monitored every two weeks during the first two cycles and every four weeks.
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The majority of side effects related to crizotinib were ophthalmic in nature and usually not life-threatening, but crizotinib does have some adverse reactions that are potentially very serious and require monitoring by health care professionals. These adverse effects of crizotinib included visual impairment, photopsia, blurred vision, vitreous floaters, photophobia, and diplopia in 62 percent of patients during the first two weeks of crizotinib administration. Neuropathy, bradycardia, and complex renal cysts have also been observed. Crizotinib has the potential to cause life-threatening pneumonitis; therefore, patients should be monitored for symptoms of pneumonitis while taking crizotinib. This drug has also been associated with QT interval prolongation and should be avoided in patients with congenital long QT syndrome and should not be combined with drugs that may prolong the QT interval such as clarithromycin, moxifloxacin, amiodarone, sotalol, procainamide or quinidine. Patients suffering from congestive heart failure, bradyarrhythmias, electrolyte irregularities and those patients taking medications that prolong the QT interval should be monitored. Crizotinib is a CYP3A4 inhibitor. Common drug interactions with crizotinib include drugs that alter crizotinib plasma concentrations, such as other CYP3A4 inhibitors (clarithromycin and ketoconazole) and CYP3A4 inducers (phenytoin and carbamazepine), and their concomitant use should be monitored. Crizotinib’s absorption is pH dependent, and drugs increasing gastric pH reduce its solubility and bioavailability. Crizotinib is classified as a pregnancy category D drug and should be avoided unless benefit substantially outweighs the risk. 

Resistance to crizotinib

Despite crizotinib’s effectiveness in patients with EML4-ALK gene fusions, the cancer usually becomes resistant within the first year. According to Katayama et al., a patient who became resistant to crizotinib after five months of treatment was found to have two common secondary mutations in the kinase domain of the EML4-ALK gene, C1156Y, and a gatekeeper mutation, L1196M. These mutations are also resistant to other more potent ALK tyrosine kinases. When tumors show secondary mutations in the kinase domain of a gene, drug resistance is common. Other methods of drug resistance include amplification of the gene targeted by the kinase or activation of a different signaling mechanism bypassing the kinase activation. Due to these genetic mutations conferring drug resistance, new drugs are being developed to help treat patients who acquire tyrosine kinase inhibitor resistance.

Conclusion

Lung cancer continues to be one of the leading causes of cancer-related death, with NSCLC affecting the majority of patients. The discovery of the EML4-ALK gene mutation and crizotinib’s ability to target this gene offers another treatment option. More research, as well as advancing technologies in targeted drug therapy, shows promise in the development of future cancer drug therapies. With this knowledge, researchers are able to learn more about cancer pathogenesis, targeted drug therapy and drug resistance with the ultimate goal of improving patient outcomes.

References

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