中文題目：在結核病盛行的國家，Rifampin 的使用可能會減弱 crizotinib 在 ALK 陽性的第四期肺癌病患的臨床效益

英文題目：Rifampin May Decline the Effect of Crizotinib in Patients with Stage IV Lung Adenocarcinoma Harbored Anaplastic Lymphoma Kinases (ALK) Rearrangement in Tuberculosis Endemic Country.

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Introduction

Crizotinib is an anti-cancer drug acting as an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor and it had been demonstrated a marked therapeutic efficacy in non-small cell lung cancer harbored ALK rearrangement. Therefore, crizotinib was approved by the US Food and Drug Administration (FDA) in 2011.

In the aspect of pharmacology, crizotinib is a CYP3A substrate, moderate time-dependent inhibitor. Therefore, co-administration of crizotinib dose and a strong CYP3A inducer such as rifampin, may decrease the plasma concentration of crizotinib and further decline the efficacy of crizotinib.

Taiwan is a tuberculosis endemic country and coincidence of lung cancer and tuberculosis is possible. Herein, we present a Taiwanness who had coincidence of lung adenocarcinoma harbored ALK and pulmonary tuberculosis.

We prescribed crizotinib as the 1st line therapy according to the rule of Taiwan National Health Insurance Bureau. In the meanwhile, he was diagnosed as a pulmonary tuberculosis and he had to start rifampin contained four-combined antituberculosis therapy 2 weeks later after we initiated crizotinib. He had rapidly tumor remission but unfortunately, tumor recurrence one month later. We believe drugs interaction between crizotinib and rifampin play an important role in the story.

Case Report

A 66-year-old Asian, never-smoker male, with history of Type 2 diabetes mellitus, Hypertension, early chronic kidney disease and coronary artery disease, presented with progressive dyspnea about 2 weeks.

The chest radiography which show right pleural effusion. After right chest tube insertion and drainage, Chest computed tomography (CT)-scan showed a contrast - enhanced 6.2 cm consolidation mass in the right upper lobe with invasion to right hilum. Bronchoscopic biopsy disclosed lung adenocarcinoma, grade 2. The immunohistochemical study revealed TTF-1(+), p40(-). In addition, her specimen also showed an immunoreactive to ALK using D5F3 clone antibody. Programmed death-ligand 1 (PD-L1) tumor proportion scores (TPS) were 65%. No Brain

metastasis but multiple bone metastases under a series of exam.

Since the diagnosis of Lung adenocarcinoma T3N2Ma, Stage IVA was made, the patient started to take oral Crizotinib 250mg twice daily since Mar 19 2018. The Follow- up chest X ray two weeks later showed dramatic resolution one week later.

In addition, the respiratory specimens yielded positive for Mycobacteria Growth Indicator Tube (MGIT) and four combined anti -tuberculosis medicine (Epbutol +Isoniazid +Rifampin+ Pyrazinamide) was initiated since Apr 2 2018. Unfortunately, his lung cancer became unexpectedly larger since the co-administration of both drugs. Since the drugs interaction was highly suspected, we replaced crizotinib by Alectinib 600mg twice daily since Jun 21 2018. His lung tumor and effusion became marked resolution 2 weeks later and the efficacy lasted till now.

Discussion

This is the first clinical case report to describe a coincidence of lung cancer and tuberculosis and co-administrated with crizotinib and antituberculosis agent rifampin may decline the efficacy of crizotinib in Taiwan, one of the tuberculosis endemic countries.

Since Tuberculosis is one of the most widespread communicable diseases in the world, tuberculosis has had the highest incidence and mortality rate among all communicable diseases in Taiwan. Rifampin is the most important drug of combination therapy in first-line antituberculosis therapy. However, Rifampin is a potent inducer of drugs undergoing metabolism by the cytochrome P450 enzyme system (notably CYP3A4), which can lead to markedly reduced bioavailability and enhanced clearance of some medications, included crizotinib.

In a pharmacokinetic study, co-administration of a single 250-mg crizotinib dose with the strong CYP3A inducer rifampin caused an 82 % decrease in crizotinib in an area under the plasma–concentration curve extrapolated to infinity (AUC0−inf), indicates that concurrent crizotinib with CYP3A4 inducer such as rifampin should be avoided. Alectinib, the 2nd generation ALK inhibitor may be an alternative choice due to no prominent interaction between rifampin and Alectinib.

Some limitations in this case had to be discussed. First, we didn't perform next-generation sequencing (NGS) nor reverse transcription polymerase chain reaction (RT-PCR) for genotype analysis of Anaplastic Lymphoma Kinases (ALK) kinase domain mutation and second, we didn’t check serum concentration of crizotinib or it’s metabolites after rifampin use.

Nevertheless, in addition to different effect in genotypes of ALK and different effects in ALK inhibitors, we proposed that rifampin, the most effective antituberculosis agent, may decline the effect of crizotinib in tuberculosis endemic countries.