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CLINICAL VIGNETTE

Fatal Interstitial Pneumonitis Following Crizotinib Usage in a Case of EML 4-ALK Rearrangement Non-Small Cell Lung Cancer

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Case Study

A 59-year-old male, a former smoker who quit in 1990, developed back pain and was subsequently diagnosed with widely metastatic non-small cell lung cancer of the right lung with involvement of the vertebral spine, liver, and brain. A needle biopsy had revealed an EML 4-ALK rearrangement. The patient was begun on the ALK tyrosine kinase inhibitor, crizotinib. In addition, he underwent a series of radiation treatments to the vertebral spine and was placed on transdermal fentanyl for control of his back pain.

Three weeks after beginning crizotinib[1-3], the patient was hospitalized for nausea and vomiting associated with severe constipation. He initially denied fever, chills, cough, or dyspnea. His admission vital signs were normal including room air oxygen saturation of 96%. Physical examination was also normal except for moderate abdominal distention. Laboratory findings revealed a white blood count of 14,400. The remainder of the hemogram and the comprehensive chemistry panel were normal. Admission 2V CXR showed no acute lung infiltrates and only right perihilar discoid atelectasis or scar.

By the 7th day of hospitalization, the patient had improved with a bowel regimen that included therapy with methylnaltrexone and lubiprostone. Discharge preparations were underway when he began to complain of shortness of breath and coughing associated with findings of a low grade fever.[4,5] CXR and subsequent CT chest revealed the presence of diffuse ground glass opacities predominantly in both upper lobes, then progressing to involve both entire lungs despite broad spectrum antibiotics (piperacillin/tazobactam, levofloxacin, and fluconazole).[4-6] Crizotinib was immediately stopped and methylprednisolone 80 mg q8 h was added. Additional possible causes of diffuse pulmonary infiltrates were considered including aspiration, opportunistic lung infection, radiation pneumonitis, progression of NSCLC, and sepsis—but were much less likely given the clinical context.

Over the next 2 days, the patient's respiratory status rapidly deteriorated, and he subsequently expired with end of life comfort measures in place.

Discussion

This is a case of a 59-year-old male treated with crizotinib for metastatic adenocarcinoma of the lung who likely developed fatal ALK-TKI induced interstitial lung disease. A previous case report has described a similar fatal outcome in a patient who developed an adult respiratory distress syndrome despite discontinuation of crizotinib, the use of methylprednisolone pulse therapy (1 g once daily for 3 days), and the administration of broad spectrum antibiotics. Postmortem analysis of one lung in that report revealed diffuse alveolar damage.[1]

Safety and tolerability data from the Phase I and Phase II studies presented to the FDA in 2011 described 4 out of 255 (1.6%) patients with crizotinib treatment for ALK rearranged NSCLC who developed severe life-threatening pneumonitis. Although most of the adverse events with these 255 patients were mild including transient visual abnormalities (62%), nausea (53%), and diarrhea (43%), the rapid development of dyspnea and cough associated with findings of diffuse ground glass opacities portends a poor outcome.

Other kinase inhibitors, such as anti-EGFR agents gefitinib and erlotinib, have been reported to lead to various manifestations of lung toxicity.[2] The true incidence of lung toxicity is difficult to ascertain given the lack of clearly defined criteria for drug-induced lung disease and the commonly associated problems of infection and progression of the malignancy. However, the incidence rates for severe lung toxicity with EGFR TK inhibitors appear to be higher in Asians compared to Caucasian or African American populations. Risk factors for developing interstitial lung toxicity with these drugs have been described in a study of Asian patients treated for NSCLC.[3] They included male gender, a history of smoking, a history of prior interstitial fibrosis, and concurrent chest irradiation. The most common

presentation is that of acute dyspnea, low grade fever, and a nonproductive cough occurring within 2-3 months after the initiation of therapy.[7] The mechanism of drug toxicity is poorly understood but appears to be direct cytotoxicity although not dose related. Lung toxicity is fatal in approximately a third of cases of EGFR-TKI interstitial lung disease. Mortality is extremely high in those who present with extensive ground glass infiltrates on CT chest scan. In general, treatment of lung toxicity is supportive with immediate discontinuation of the TKI. The use of glucocorticoids may be efficacious in the initial treatment of drug toxicity but the evidence for this appears to be mainly observational and the results variable. Of some interest, there have been several reports of successful rechallenge with TKIs in patients who have recovered from moderate drug toxicity in which oral glucocorticoids were used empirically.[4,5]

The development of tyrosine kinase inhibitors including crizotinib has had a profound impact on the treatment of patients with adenocarcinoma of the lung. Despite being relatively uncommon, lung toxicity with these agents has the potential to be severe and often fatal. Patients should be instructed to report early symptoms of cough, dyspnea, or low grade fever. Consideration of discontinuation of the drug depends upon the clinical circumstances and the severity of the toxic adverse effect. Despite the reports of successful rechallenge with the EGFR TKIs as well as with crizotinib, it is generally recommended that these drugs be discontinued immediately and permanently when the patient has been diagnosed with severe TKI lung toxicity.

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