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Crizotinib-Induced Large Bowel Perforation: A Rare Adverse Event

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Case Report

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Abstract

Crizotinib is a tyrosine kinase inhibitor approved for use in the treatment of anaplastic lymphoma kinase positive, advanced non-small cell lung cancer. This targeted therapy improved clinical outcome and prolonged responses. However, potentially serious adverse effects may occur. We report a case of Crizotinib-induced large bowel perforation.

Keywords: Lung cancer; Crizotinib; Bowel perforation

Introduction

Crizotinib is a multi-target inhibitor approved for the treatment of patients with ROS1 rearrangement or anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) patients. Crizotinib was approved in patients with locally advanced and/or metastatic lung adenocarcinomas with a clinical benefit and improvement of median survival. It is generally well tolerated .The most frequently occurring side effects are gastrointestinal events and visual disorders. We report a case of an exceptional large bowel perforation probably Crizotinib-induced.

Case Report

A 40-year-old woman with no medical comorbidities was diagnosed with metastatic non-small-cell lung cancer (NSCLC). Histological examination revealed adenocarcinoma positive anaplasic lymphoma kinase (ALK) and negative for epidermal growth factor receptor (EGFR) gene mutation. A computed tomography (CT) scan was performed. It revealed bone metastases and pleural effusion. First-line chemotherapy with a doublet protocol (Cisplatin combined with Gemcitabine) was carried out from the time of diagnosis without clinical benefit. Given the presence of ALK gene rearrangement, the patient was started on tablet Crizotinib 250 mg twice per day. *She experienced* disease *progression* three months later, and started receiving third-line *treatment* with Cisplatin combined with Pemetrexed for three cycles with clinical benefit. Fourth-line treatment with Lorlatinib was carried out. A clinical and radiological progression was noted six months after the beginning of Lorlatinib. Our patient was rechallenged with Crizotinib. Three weeks after the beginning of Crizotinib, she presented to the emergency department with complaints of acute abdominal pain. *Physical examination revealed rebound tenderness* .Contrast-enhanced abdominal CT showed a large bowel perforation. Laparoscopic and *open surgical treatments* were performed. Crizotinib was stopped.

Discussion

We report an exceptional and unusual observation of Crizotinib–induced large bowel perforation. Crizotinib is generally well tolerated and has superior efficacy compared to chemotherapy for treatment of patients with advanced NSCLC with ALK rearrangement. Clinical trials showed this targeted therapy prolonged progression free survival, increased response rates, and improved the quality of life in patients [1]. The majority of adverse events are moderate. The most frequently occurring side effects are gastrointestinal (GI) events (abdominal pain, diarrhea, constipation, nausea, anorexia), visual disturbances, fatigue, peripheral edema, altered taste, neuropathy, and rash

[2]. Gastrointestinal (GI) perforation in an extremely rare adverse event. Yanagisawa et al reported the first case of Crizotinib-induced rectal perforation. We find only one case similar to our observation, concerning a 86 year-old man that developed after 6 days of Crizotinib, concomitantly to a disease response, a dysgeusia, nausea, fever, vomiting and diarrhea on day 9 leading to Crizotinib discontinuation. Symptoms and fever persisted despite antibiotics and symptomatic treatment with increased abdominal pain and appearance of tenderness in the right lower abdomen. A CT scan was performed. The diagnosis of rectal perforation and subsequent abscess were confirmed. He was treated by radiology-controlled drainage with success [3]. The mechanism of Crizotinib-induced large bowel perforation remains unknown. GI metastasis can cause perforation.GI metastases of lung cancer are rare. They occur in 0.19% of patients in lung cancer [4]. Our patient showed no evidence of bowel metastasis, according to radiologic findings at initial diagnosis or during administration of Crizotinib. Two cases of epidermal growth factor receptor (EGFR) inhibitors associated with GI perforation were reported in the literature [5,6]. There were no GI metastases in these cases.

Criztotinib-induced mucosal damage and increased intraluminal pressure may explain GI perforation [3].

Conclusion

Crizotinib is generally well tolerated. However, physicians should be aware of severe adverse effects like bowel perforation following administration of Crizotinib even in patients without GI metastases. Further work should explore underlying mechanisms of these severe toxicities to identify risk factors that can induce large bowel perforation.

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