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# Can Nutritional Supplementation Increase the Risk of Crizotinib-Associated Hepatotoxicity: A Clinical Case Example

**Zenzri Y*, Daoud N, El Benna H, Berrazaga Y and Boussen H**

*Medical oncology department, Abderrahmen Mami Hospital Ariana, Tunisia*

***Corresponding author:** Yosr Zenzri, Medical oncology department, Abderrahmen Mami Hospital Ariana, Tunisia; E-mail: yosr-zenzri [at] live [dot] fr

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## Abstract

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death. The identification of oncogene tic driver mutation in lung cancer led to a therapeutic revolution by the discovery of targetable genetic alterations including the anaplastic lymphoma kinase (ALK) fusion oncogene and ROS1. The tyrosine kinase inhibitor "Crizotinib" improved clinical outcome and prolonged responses. Severe hepatotoxicity is a rare adverse event. We report a case of Crizotinib-induced acute hepatitis with a probable drug-bergamot interaction.

**Keywords:** Crizotinib; Bergamot; Hepatotoxicity

## Introduction

Crizotinib is a targeted therapy, tyrosine kinase inhibitor that proved its efficacy in advanced non-small cell lung cancer (NSCLC). At a conventional oral dose of 250 mg, twice daily, it is well-tolerated and the most frequently occurring adverse events graded 1, 2 are visual disorders, gastrointestinal symptoms (diarrhea, nausea-vomiting, anorexia, and constipation), peripheral edema and neutropenia [1]. The mechanism of Criztotinib hepatotoxicity is unknown. Grade 3-4 liver toxicity is an unusual side effect. We present here a case of Crizotinib-induced severe hepatotoxicity.

## Case Presentation

A 61–year-old nonsmoker woman, without medical comorbidities or hepatic previous disease, presents with a 4-months history of isolated dry cough. Physical examination was normal. Etiological work-up showed the presence on CT-scan of a bulky right lung lesion, with contralateral axillary and supraclavicular lymph nodes with right pleural effusion. Bronchoscopy showed tumor localized to right upper lobar bronchus and biopsies have concluded a primary lung adenocarcinoma with positive TTF1 on immunohistochemistry (IHC). We performed a screening for anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR) and ROS 1. ROS1 rearrangement was identified. Additional work-up showed the presence on brain magnetic resonance imaging (MRI) of cerebral, bone and lymph nodes metastases. She was diagnosed with stage IV lung cancer in February 2019. The patient's full blood count, renal and liver function tests were normal. The patient was started on tablet Crizotinib 250 mg twice per day ten days after diagnosis. Crizotinib was given as monotherapy for front line management. During the follow-up, 53 days after the beginning of Crizotinib, she presented to the emergency department with complaints of fatigue, vomiting, anorexia and nausea since 2 days. The clinical examination was normal. There was neither hepatomegaly nor jaundice. A complete blood count, kidney and liver tests were performed. Liver tests showed highly increased ALT at 2413 IU/l (45 times the upper limit of normal), AST at 1062 IU/l ( 25 times the upper limit of normal), prothrombin time (PT) at 62%, while ALP, GGT and bilirubin were normal. She was admitted to the hospitalist team for management of acute hepatitis. An abdominal ultrasound was normal for liver parenchyma and bile ducts without obstruction or ischemic hepatitis. Hepatitis B markers were negative for HBs Antigen and HBc antibodies as well as PCR testing for HCV, cytomegalovirus, herpes simplex virus and Epstein–Barr virus. The patient reported having consumed

Bergamot orange during Crizotinib treatment. We decided to stop the treatment and the bergamot intake. One month after livers tests normalization, we decided to restart it at a half dose of 250 mg once daily. However, 2 days after drug reintroduction, liver tests showed hepatic cytolysis and we stopped definitely Crizotinib. Ceritinib was the second-line drug received during three months. Treatment was started at a dose of 750 mg/day. Regular liver enzyme testing was carried out during treatment. The tests were normal. A progression of the disease was noted after 3 months of Ceritinib. The patient is on third line chemotherapy by pemetrexed and carboplatin.

## Discussion

This report describes a durg –induced acute hepatitis by Crizotinib, a small molecule inhibitor with multiple targets, including ALK, c-MET, and ROS1. Crizotinib is approved for the treatment of a distinct subgroup of NSCLC mediated by rearrangements of ALK or ROS1 [2,3]. The PROFILE 1 and subsequent randomized studies proved Crizotinib efficacy, safety and its superiority compared with chemotherapy. The most common adverse events of Crizotinib include diarrhea, constipation, abdominal pain, anorexia, nausea, visual disturbances, fatigue and peripheral edema. Potentially serious adverse effects include interstitial lung disease and QT prolongation [4]. In a recent meta-analysis about 1,908 patients from 10 clinical trials, ALT and AST all-grades increase were observed in 25.2 and 26%, respectively, while grade 3 and 4 were reported in 7 and 9.9%. Sub-group analysis showed a higher incidence of liver toxicities for ceritinib compared to Crizotinib and alectinib [5]. Renault et al reported the first case with crizotinib-induced acute hepatitis, who relapsed after reintroduction of the treatment [6-10]. Profile 1014, a phase 3 study has demonstrated that grade 3 or 4 elevated aminotransferases were noted in 24 patients receiving Crizotinib. A majority of these adverse events were reversible on dose interruption. Four cases of fatal hepatic failure have been reported in the literature (Table 1).

***Table 1**: Case reports of Crizotinib-induced fatal hepatic failure.*

| Autours | Dose of Crizotinib | Therapy line | Occurrence time of fulminant liver failure |
|---|---|---|---|
| Sato | 400 mg every day | First line | Day 29 |
| Van Geel | 250 mg twice a day | Second line | Day 24 |
| Adhikari | 250 mg twice a day | First line | Day 39 |
| Zhang | 250 mg twice a day | First line | Day 46 |

That the underlying mechanism was partly an allergic reaction to Crizotinib or its metabolites. Dose reduction associated with oral steroids following crizotinib-induced hepatotoxicity did not improve the hepatitis. Oral desensitization may be considered as a good option following hepatitis [11]. Moreover, Ceritinib which is a small molecule tyrosine kinase receptor inhibitor could be an alternative treatment when crizotinib causes hepatotoxicity [12]. Specific risk factors for Crizotinib-induced hepatitis remain unclear. General risk factors of drug-induced hepatotoxicity are reported to be female sex, pregnancy, older age, excessive alcohol intake, smoking, HBV or HCV infection, HIV infection and genetic variability [13,14]. The use of CYP3A inducers and inhibitors like grapefruit juice must be interrupted since it may increase the plasma concentration of Crizotinib [15]. In our case, the patient reported having consumed Bergamot orange during treatment. Bergamot tin is a natural furanocoumarin found in the pulp of pomelos and grapefruits. It is also found in the peel and pulp of the bergamot orange. Bergamot tin was tested for its inhibitory effects on hydroxylase and O-dealkylase activities of human cytochrome P450 is enzymes CYP 3A4 and CYP 1B1 [16]. This could explain the enhancement of liver toxicity observed in our patient. Crizotinib-induced hepatotoxicity usually occurs within the first two months of treatment. Monitoring liver function tests every two weeks is mandatory during this period. A thorough knowledge of the metabolism and pharmacologic properties of the treatment is important to prevent side effects.

## Conclusion

Although Crizotinib is usually well tolerated, it can cause acute hepatitis in lung cancer patient. Regular liver enzyme testing should be carried out during the first two months of Crizotinib treatment. Further work should explore underlying mechanisms of these severe cases to identify risk factors that can induce hepatotoxicity.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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