—Case Reports—

# A Drug Interaction between Crizotinib and Warfarin in Non-Small-Cell Lung Cancer: A Case Report

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We report a case of increased prothrombin time-international normalized ratio (PT-INR) when crizotinib and warfarin were co-administered. A 74-year-old Japanese woman presented to the hospital with dyspnea, and was diagnosed with anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC). Three years after surgical resection of the tumor, the patient started crizotinib because of the recurrence of NSCLC. She received 2 mg/day warfarin due to a medical history of cerebral infarction and chronic atrial fibrillation. Before crizotinib initiation, the patient's PT-INR was 2.60. After 7 days of daily doses of crizotinib, the patient's PT-INR increased to 3.65. This case report provides the first evidence of a drug interaction between crizotinib and warfarin. (J Nippon Med Sch 2017; 84: 291–293)

**Key words:** crizotinib, warfarin, drug interaction, prothrombin time-international normalized ratio (PT-INR), non-small-cell lung cancer (NSCLC)

## Introduction

Cancer chemotherapy has been developing rapidly, especially in the field of molecular-targeted and immuno-oncology agents[1]. Although individual gene profiling of patients plays an important role in producing significant benefits[2], many patients with cancer are elderly and have comorbidities that are being treated concomitantly with other drugs. Consequently, effective management of adverse drug reactions and interactions by pharmacists is required.

Crizotinib, an oral small-molecule tyrosine kinase inhibitor (TKI) of anaplastic lymphoma kinase (ALK), mesenchymal-epidermal transition (MET) and c-ROS oncogene 1 (ROS1) kinases, was shown to be more effective than pemetrexed or docetaxel in patients with ALK-positive non-small-cell lung cancer (NSCLC) who had previously been treated with platinum-based chemotherapy[3]. Crizotinib is metabolized and excreted via O-dealkylation by cytochrome P-450 (CYP) isoenzyme 3A4/5. Crizotinib is also an inhibitor of CYP3A4/5; therefore, it has the potential for many drug interactions, including confirmed interactions with ketoconazole and rifampin[3,4].

Warfarin, an anticoagulant, is a racemic mixture of two enantiomers, (S)- and (R)-warfarin. The potency of the (S)-enantiomer is greater than that of the (R)-enantiomer, and the (S)-enantiomer is primarily metabolized by CYP2C9, whereas the (R)-enantiomer is metabolized by CYP3A4, CYP1A2, and other isozymes[5,6].

Some studies have indicated that TKIs (gefitinb, erlotinib, and cabozantinib) exhibit drug interactions with warfarin, resulting in an increased prothrombin time-international normalized ratio (PT-INR)[7–9]. However, to date there have been no investigations into drug interactions between warfarin and crizotinib. Furthermore, a possible interaction is not mentioned in the Japanese package insert. In the present study, we report a case of increased PT-INR when crizotinib and warfarin were co-administered.

## Case Report

A 74-year-old Japanese woman presented to the hospital with dyspnea, and was diagnosed with ALK-positive NSCLC (pT2aN0M0, Stage IB). She underwent right upper lobectomy. Without adjuvant chemotherapy, she re-

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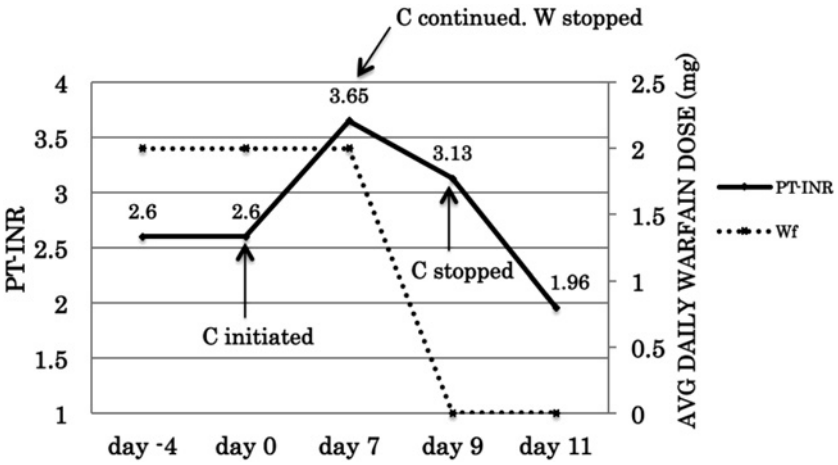


Fig. 1 Changes in Prothrombin Time-International Normalized Ratio (PT-INR) of warfarin (W) after the start of crizotinib (C) therapy. The average daily doses of warfarin are also shown. Arrows denote treatment change along the period shown.

ceived 2 mg/day warfarin (Warfarin® tablets: Eisai Co., Tokyo, Japan) due to a medical history of cerebral infarction and chronic atrial fibrillation. Three years after surgical resection of the tumor, the patient started crizotinib (Xalkori® capsules: Pfizer Co., Tokyo, Japan) because of the recurrence of NSCLC. Pharmacists recommended periodic monitoring of PT-INR to the attending physician because of the possibility of a drug interaction between crizotinib and (R)-warfarin through CYP3A4. Before crizotinib, the patient's PT-INR was 2.60. After 7 days of daily doses of crizotinib, the patients PT-INR increased to 3.65.

Warfarin was immediately stopped. Because the patient developed loss of appetite and delirium 2 days after stopping warfarin administration, crizotinib was also stopped. The patient died because of a rapid increase in carcinomatous lymphangiomatosis (**Fig. 1**) 13 days after starting crizotinib.

## Discussion

In the present case, PT-INR was increased by the administration of warfarin in combination with crizotinib. This case report provides the first evidence of a drug interaction between crizotinib and warfarin. Crizotinib is an inhibitor of CYP3A4/5 and (R)-warfarin is metabolized by CYP3A4[3,4]. Therefore, it is suggested that the pharmacological effect of warfarin was potentiated by crizotinib-induced inhibition of CYP3A4.

Unfortunately, the patient died of a rapid progression of NSCLC, suggesting intrinsic resistance to crizotinib. No severe adverse events as a result of the increased PT-INR were observed.

The present case report has several limitations. First, it cannot be ruled out that the findings presented herein represent an accidental phenomenon because no other studies have reported a possible interaction between warfarin and crizotinib. Second, it is unknown whether crizotinib increased blood concentrations of warfarin because these were not measured. Third, we did not investigate potential polymorphisms for warfarin, which may have affected the pharmacokinetics of warfarin[10]. Further investigations are needed to elucidate these drug interactions.

In conclusion, PT-INR was increased in a patient following combined administration of warfarin and crizotinib. Periodic monitoring of PT-INR should be undertaken when crizotinib and warfarin are administered together.

**Conflict of Interest:** We received a research grant and lecture fee.

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