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Elevated Prothrombin Time/International Normalized Ratio after Concomitant Administration of Erlotinib in Patients Receiving Warfarin: A Report on Two Cases

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Abstract

Adverse interactions between warfarin and cytotoxic agents are well documented; however, interactions between warfarin and erlotinib are not well characterized. Here we report two patients with non-small cell lung cancer in whom concomitant treatment with erlotinib and warfarin resulted in elevated prothrombin time-international normalized ratio (PT-INR) values. In the first case, the PT-INR value increased from 2.24 to 2.73 9 days after initiating erlotinib treatment in a 59-year-old Japanese man receiving prophylactic warfarin therapy for cardiovascular disease. However, erlotinib did not adversely affect the hepatic function in this patient. In the second case, the PT-INR value increased from 1.58 to 7.54 7 days after initiating erlotinib treatment in a 61-year-old Japanese man receiving prophylactic warfarin therapy for cerebral infarction; this was accompanied by bleeding diathesis (purpura). In both cases, PT-INR was well maintained by warfarin therapy prior to initiating erlotinib treatment.

Our experience with these cases underlines the importance of the careful monitoring of the PT-INR value and appropriate adjustment of warfarin dosage in patients receiving concomitant erlotinib and warfarin therapy.

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Introduction

Drug interactions can cause many clinical complications, particularly when drugs are co-administered with anticancer agents. Erlotinib, a reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) is commonly used to treat advanced non-small cell lung cancer (NSCLC). Warfarin, an anticoagulant, interacts with various drugs, resulting in altered effects.

Thromboembolic phenomena, such as deep vein thrombosis and pulmonary embolism, commonly occur in cancer patients and often necessitate prophylactic anticoagulant therapy with warfarin [1]. Owing to the interaction of several drugs with warfarin and the large inter-individual variability in pharmacodynamics, warfarin dosage must be adjusted according to the prothrombin time-international normalized ratio (PT-INR) in individual patients.

The prescription information for erlotinib treatment includes a precaution for patients on concomitant warfarin therapy owing to the associated risk of elevated PT-INR values. However, the underlying mechanism of this interaction is unknown. Although a few reports have described the interaction between gefitinib and warfarin [2], the interaction between warfarin and erlotinib is not well characterized. Here we report two patients with lung cancer, who exhibited an increase in the PT-INR values after concomitant administration of erlotinib and warfarin.

Case Presentation

Case 1

A 59-year-old Japanese man was diagnosed as having lung non-squamous cell adenocarcinoma (stage IV: T1N3M1). He was maintained on a regular warfarin therapy (3.5 mg daily) for prophylaxis from cardiac infarction. After three courses of chemotherapy with carboplatin and pemetrexed, he exhibited a grade 3 reduction in hemoglobin and a decline in renal function. Therefore, second-line chemotherapy was initiated with erlotinib at the dose of 150 mg daily (day 1). His PT-INR

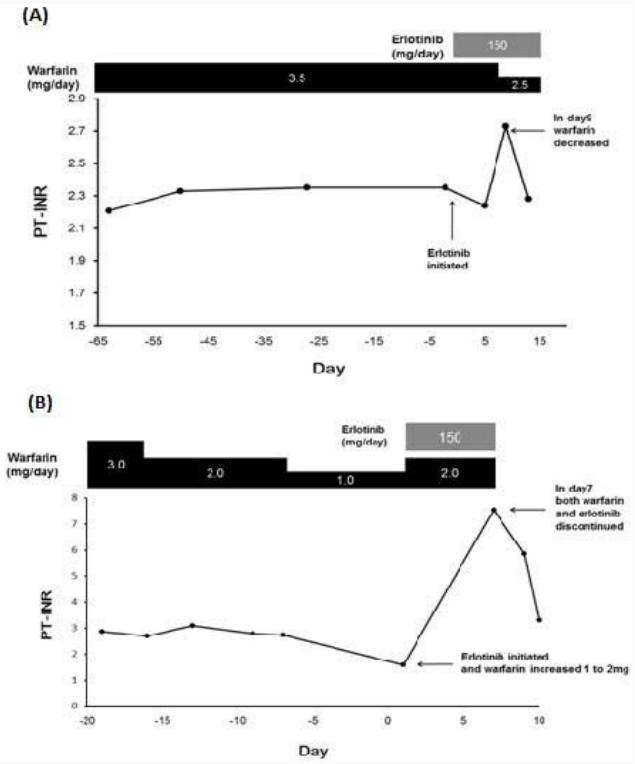

Figure 1: Changes in prothrombin time/international normalized ratio (PT-INR) after concomitant administration of erlotinib and warfarin (A) Clinical case 1. The patient had been receiving warfarin at a dose of 3.5 mg/day for 4 months before initiating erlotinib treatment. (B) Clinical case 2. The patient was administered warfarin at a dose of 3 mg/day for 6 months before initiating erlotinib treatment.

value was relatively stable (2.1-2.4) and the daily warfarin dosage was maintained at 3.5 mg for at least 3 months before erlotinib was initiated. Nine days after initiating erlotinib therapy, the patient's PT-INR value increased from 2.24 to 2.73. Therefore, starting from day 9, the warfarin dose was decreased to 2.5 mg daily. On day 13, his PT-INR value restored to 2.24, and he continued receiving warfarin at the dose of 2.5 mg (Figure 1A). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (SCr), and serum albumin (Alb) levels did not change after treatment with erlotinib. There were no changes in diet or severe episodes of nausea or vomiting.

Case 2

A 61-year-old Japanese man was diagnosed as having lung non-squamous cell adenocarcinoma (stage IV: T4N3M1). He was on warfarin therapy for multiple cerebral infarcts. Warfarin dosage was adjusted to maintain a target PT-INR value of 2.0-2.5. His PT-INR value was relatively stable (1.8-2.5) when 3 mg warfarin was administered daily for at least 1 month before initiating the sixth-line chemotherapy comprising a daily dose of 150-mg erlotinib (day 1). On day 19, before initiating erlotinib therapy, his PT-INR value was 2.86; thus, warfarin dose was reduced to 2 mg. On day 9, before initiating erlotinib therapy, the PT-INR value was still high (2.79), which warranted a further dose reduction to 1 mg. On day 1, after initiating erlotinib, the PT-INR value decreased to 1.58; thus, from day 2, warfarin dosage was increased to 2 mg daily.

However, 7 days after initiating erlotinib therapy, the PT-INR value increased to 7.54 (Figure 1B). The patient developed purpura on the arms. Warfarin was discontinued, and the anticoagulant effect was rapidly reversed by administering subcutaneous phytonadione. Owing to the decline in the renal and hepatic functions (day 1: SCr, 1.09 mg/dL; AST, 49 U/mL; ALT, 29 U/mL → day 7: SCr, 1.52 mg/dL; AST, 99 U/mL; ALT, 46 U/mL), erlotinib treatment was discontinued. Three days later (day 10), the PT-INR value decreased to 3.3. Both patients took the prescribed warfarin dose every day without fail.

Discussion

Owing to the relatively advanced age at the diagnosis of lung cancer, most patients are likely to receive anticoagulant therapy for pre-existing cardiovascular diseases [1,2]. Prophylactic or therapeutic warfarin therapy is often recommended for cancer patients. Warfarin has a narrow therapeutic index, which makes it the third most common drug responsible for hospital admissions because of adverse drug effects [3]. The interaction of several drugs with warfarin elevates the risk of thrombotic or hemorrhagic events in such patients [4-5]. We report two cases wherein the co-administration of erlotinib and warfarin potentiated the effect of warfarin.

In case 1, the PT-INR value increased 9 days after initiating erlotinib treatment. Kelly S et al. [6] demonstrated an increase in the PT-INR value 7 days after initiating erlotinib, which necessitated a decrease in the warfarin dose. As a result, in this case, the first blood examination was performed on day 5, when the PT-INR value was relatively stable. However, blood examination at an earlier stage is required to establish the time-point at which the PT-INR value begins to rise after initiating erlotinib along with warfarin therapy. In case 2, warfarin dosage was increased at the time of initiating erlotinib, which resulted in a sudden increase in the PT-INR value. If a sudden decline in the renal or hepatic functions causes a sudden rise in the PT-INR value, as in this case, it is necessary to consider an increase in the warfarin concentration in the blood.

The exact mechanism underlying this interaction is yet unknown; however, it is possibly related to a decrease in warfarin metabolism via the inhibition of the cytochrome P450 (CYP) enzyme system by erlotinib or one of its metabolites. Warfarin is present as a racemic mixture, with each enantiomer differentially metabolized by the liver microsomal system. The R-enantiomer is metabolized by CYP1A2/3A4, whereas the S-enantiomer is primarily metabolized by CYP2C9. The efficacy of warfarin is mainly affected by the altered metabolism of the S-enantiomer; however, the R-form has a longer half-life and is a noncompetitive inhibitor of S-warfarin metabolism by CYP2C9 [7-8]. Erlotinib is metabolized in the liver, mainly by cytochrome CYP 3A4/3A5, and to a lesser extent, by CYP1A1/1A2. Because the metabolizing enzyme of erlotinib resembles that of the R-form of warfarin, it is likely that the competitive inhibition of warfarin metabolism is responsible for the increase in the warfarin concentration in the blood. It is interesting that afatinib was hardly metabolized by CYP, unlike other EGFR-TKIs. Future data on the concomitant administration of afatinib and warfarin may help elucidate the mechanism of interaction between warfarin and EGFR-TKIs.

According to the package inserts of warfarin and erlotinib, both drugs are highly plasma protein bound (warfarin: 97%, erlotinib: 95%). According to the product information of erlotinib, an *in vitro* study that examined the impact of erlotinib on the plasma protein binding of warfarin showed a little effect on the binding capacity of warfarin; the underlying mechanism of this interaction is unclear. It is

likely that erlotinib may also compete with warfarin for the albumin-binding sites, which may result in elevated levels of unbound warfarin, and a consequent potentiation of hypoprothrombinemia. Therefore, pharmacokinetic and pharmacodynamic interactions seem to occur between erlotinib and warfarin. Liver disease, kidney disease, and hypoalbuminemia are known risk factors for bleeding in patients on warfarin therapy [9,10]. In the phase I pharmacokinetic studies of erlotinib, patients with renal dysfunction could tolerate 150 mg of erlotinib daily and were found to have erlotinib clearance similar to that in patients with normal renal function. However, patients with hepatic dysfunction should receive a lower dose consistent with their reduced clearance [11]. In case 1, the co-administration of warfarin and erlotinib did not affect the renal and hepatic functions; however, in case 2, a decline in the renal and hepatic functions occurred after initiating erlotinib. Therefore, this probably shows the potential influence of erlotinib on the decline in the hepatic functions. Camidge et al. [12] demonstrated an increase in the area under the curve of warfarin when warfarin and capecitabine were co-administered. We did not measure the warfarin concentrations in the blood in the two cases. It is likely that erlotinib increased the warfarin concentrations in the blood via the inhibition of its metabolism by CYP 3A4, which potentiated its anti-coagulant effects. Warfarin therapy has a detrimental effect on cancer patients. During warfarin maintenance therapy, approximately one-third of the patients experience side effects, such as recurrence and bleeding [13]. In a recent study, erlotinib alone or in combination with bevacizumab, as the first-line therapy, was shown to have a favorable effect in patients with advanced NSCLC [14]. Bevacizumab therapy is associated with a risk of bleeding. Therefore, the screening of patients on warfarin therapy is of key importance prior to initiating erlotinib. The concomitant administration of erlotinib and warfarin requires patient education regarding the risk of bleeding and the need for a close monitoring of PT-INR for necessary warfarin dose adjustment.

Conclusion

The concomitant administration of erlotinib and warfarin resulted in an increase in the PT-INR values, which suggests the need for the careful monitoring of the PT-INR values and appropriate adjustment of warfarin dosage.

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