Case Reports

Drug Interaction Between Gefitinib and Warfarin

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Gefitinib is a synthetic, oral anilinoquinazoline specifically designed to inhibit the epidermal growth factor receptor tyrosine kinase, and is the first targeted drug to demonstrate reproducible activity in non-small cell lung cancer patients who do not respond to platinum-based chemotherapy. In this report, we present two cases of an interaction between gefitinib and warfarin which has not been reported previously. Because of the potentially serious consequences of this interaction, close monitoring of the International Normalized Ratio and warfarin dosage adjustment are recommended for patients receiving warfarin together with gefitinib.

Key words: gefitinib – warfarin – drug interaction – International Normalized Ratio – non-small cell lung cancer

INTRODUCTION

Gefitinib is an orally active, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that was found to exhibit antitumor activity in vitro and in vivo (1). Gefitinib has shown excellent activity in heavily pre-treated patients with non-small cell lung cancer (NSCLC), attaining median survival durations of 6.5–7.6 months and 1-year survival rates of 29–35% (2,3). In addition, gefitinib administration resulted in rapid, sustained and clinically significant improvements in symptoms and quality of life among 40% of the patients.

Deep-vein thrombosis is one of the well recognized complications of cancer (4,5). It is also known that the incidences of both atrial fibrillation and lung cancer increase with age. Warfarin is the treatment of choice for long-term oral anticoagulation in patients with these diseases, because other coumarins are poorly absorbed. Warfarin is well absorbed orally and is highly but reversibly bound (>99%) to albumin; it is a racemic mixture of two optical isomers (enantiomers) R(+) and S(–) warfarin. These enantiomers are metabolized via different pathways and have different half-lives and potencies: the S(–) enantiomer is 3- to 5-fold more potent but has a shorter half-life (6). The interactions of warfarin with other drugs have been well documented, which put patients at risk for thrombotic or hemorrhagic events (7,8). However, there are few reports describing the interaction between anticancer agents and warfarin (9–12). Specifically, an interaction between warfarin and the target-based agent gefitinib has not been reported to date. Here, we report two cases of patients who received gefitinib and warfarin simultaneously, which resulted in the potentiation of the effect of the latter.

CASE REPORTS

CASE 1

For a 74-year-old female patient, patent ductus arteriosus was surgically ligated in 1985. Two years after the operation, she complained of palpitation, dyspnea on exertion, and light-headedness with a diagnosis of persistent atrial fibrillation and mitral valve prolapse. Warfarin was started to prevent thromboembolic events, with a target International Normalized Ratio (INR) of approximately 2. In April 2003, she was diagnosed with stage IV bronchioloalveolar carcinoma of the lung. We decided to introduce gefitinib therapy for her, because her cardiac function did not allow for cisplatin-based chemotherapy and the drug had been showing encouraging results for bronchioloalveolar carcinoma patients. She started gefitinib therapy at a daily dose of 250 mg/m² in June 2003. She did not take any other new agents, vitamins or herbal preparations, and there were no changes in warfarin brand or diet therapy.

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The patient’s daily warfarin dose had been 4 mg (INR of approximately 2) immediately before the gefitinib therapy was started. Her INR was monitored at least twice weekly. The daily warfarin dose was decreased to 3 mg after the start of gefitinib therapy, but the INR increased to 2.4. Therefore, the daily warfarin dose was decreased further to 2.5 mg, which returned the INR to the therapeutic range (Fig. 1A). Her dyspnea was promptly improved, and a chest X-ray taken 6 months after the initiation of treatment revealed a considerable improvement of the disease (Fig. 2). This patient is still under treatment, with no evidence of treatment failure after >12 months. Gefitinib therapy was generally well tolerated, with grade 1 skin toxicity, transient grade 2 diarrhea and temporal elevation of aspartate aminotransferase up to 83 U/l.

**CASE 2**

A 56-year-old female patient presented with complaints of swelling of the left supraclavicular node and dry cough. A computed tomography (CT) scan of the lung showed a left

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**Figure 1.** Changes in International Normalized Ratio (INR) of warfarin after the start of gefitinib therapy. (A) Case 1. The patient had been receiving warfarin at 4 mg/day for 16 years before the initiation of gefitinib therapy with stable INR values in the therapeutic range. (B) Case 2. The patient was administered warfarin at 5 mg/day for 3 months before the start of gefitinib therapy. Patient 2 showed minimal elevation in INR with co-administration of gefitinib.
upper lobe mass and mediastinal lymphadenopathy. Multiple tiny bilateral pulmonary nodules were also found. An aspiration cytology of the supravacuicular node revealed adenocarcinoma consistent with pulmonary origin. Irinotecan/amrubicin chemotherapy was started. She tolerated this chemotherapy well, and a chest X-ray showed that the primary lesion had decreased slightly in size from $3.2 \text{ cm} \times 3.0 \text{ cm}$ to $3.0 \text{ cm} \times 2.8 \text{ cm}$. On day 6 of the second cycle, the patient developed deep-vein thrombosis of the left lower limb. A Greenfield caval filter was placed in the inferior vena cava through the right internal jugular vein under ultrasonic guide, and thrombolysis was begun with tissue plasminogen activator. She was then treated with intravenous heparin followed by oral warfarin at $5 \text{ mg}$ per day. The anti-cancer treatment was discontinued. One month after stopping irinotecan/amrubicin therapy, chest X-ray demonstrated an increase in size of the left upper lobe mass. Her treatment was changed to two cycles of carboplatin/paclitaxel, which stabilized the disease. A CT scan obtained 2 months later demonstrated an increase in size of the primary lesion and mediastinal lymphadenopathy, as well as marked progression of the multiple bilateral pulmonary nodules and a new lesion of the liver (Fig. 3A). She began to take gefitinib at a daily dose of $250 \text{ mg/m}^2$. There were no other changes in her medication, diet or clinical status. Based on the previous experience, the daily warfarin dose was decreased to $3 \text{ mg}$, but the INR did not increase to the expected level. Therefore, the warfarin dose was returned to the previous $5 \text{ mg}$, which resulted in the INR returning back to the therapeutic range (Fig. 1B). The degree of the potentiation of warfarin effects by gefitinib was minimal in this patient compared with that of case 1. A follow-up CT demonstrated good partial response, with marked decrease in the primary lesion and complete disappearance of bilateral pulmonary metastases (Fig. 3B). Because of the sustained marked response to therapy, she continues to receive gefitinib therapy without any toxic reactions, including liver dysfunction. Both patients were non-smokers. Both patients took the prescribed warfarin dose every day without fail.
DISCUSSION

Lung cancer is the leading cause of death in most developed countries. Approximately 80% of lung cancers are NSCLC. Approximately one-third of the patients with NSCLC are in the advanced stages of the disease. Palliative chemotherapy thus remains the mainstay of treatment for these patients. Because patients with lung cancer are relatively advanced in age, they may have already been put on medications for co-morbid diseases. Drug interactions can cause many clinical problems, particularly when the drugs are administered in combination with anticancer agents. Ideally, all this knowledge should be available before a new anticancer agent is introduced into clinical practice. However, the situation is far from ideal available before a new anticancer agent is introduced into clinical practice. However, the situation is far from ideal.

Whereas the more potent S(−) enantiomer of warfarin is metabolized mainly by CYP2C9, the less active R(+) enantiomer is metabolized by CYP1A2, CYP3A4 and other isozymes (13).

After single-dose oral administration of gefitinib to the patients, plasma concentrations were observed to peak within 3–7 h; the absolute bioavailability of gefitinib was 60%. Ninety-one percent of gefitinib was bound to serum albumin and 1/1-acid glycoprotein. Gefitinib is also metabolized extensively in the liver, predominantly by CYP3A4 (86% in feces, <4% in urine). The identified metabolic pathways include O-demethylation, dealkylation and oxidative defluorination. As the R(+) enantiomers of warfarin and gefitinib are metabolized by the same CYP3A4, the metabolic pathway of gefitinib appears to be similar to that of warfarin. Thus, there is a theoretical possibility that gefitinib could compete with the less active isomer of warfarin. Furthermore, gefitinib has been reported to have a weak inhibitory effect on CYP1A2, CYP2C9 and CYP3A4 activities (14). These results suggest that at least in some patients gefitinib would inhibit the metabolism of warfarin, which is a substrate of CYP1A2, CYP2C9 and CYP3A4. As gefitinib and warfarin are both highly protein bound, gefitinib will also compete with warfarin for albumin-binding sites, resulting in elevated levels of unbound warfarin, with potentiation of hypoprothrombinemia. Therefore, pharmacokinetic and pharmacodynamic interactions seem to occur between gefitinib and warfarin. On the other hand, it seems unlikely that the results are explained for the reason that gefitinib is a basic drug, and the protein binding displacement of warfarin is more strongly associated with acidic drugs than with basic ones (15).

Pharmacological studies have indicated that patients with moderately and severely elevated liver function tests have gefitinib pharmacokinetics comparable with those of patients without liver abnormalities. However, it has also been shown that gefitinib causes asymptomatic increases in liver transaminases in approximately 20% of Japanese patients (3). This liver dysfunction may impair both the metabolic function of the CYP enzyme system and the synthesis of clotting factors. Therefore, this hepatic toxicity also contributes to the increase in the INR. Furthermore, the gastrointestinal toxic effects of gefitinib may also affect the absorption of warfarin and vitamin K.

Williams et al. (16) reported that the binding of the S(−) enantiomer of warfarin to CYP2C9 generates the allosteric alteration of CYP2C9 to make a new binding pocket of CYP2C9 for a second drug, and that CYP2C9 may have the capacity to bind multiple substrates simultaneously. The degree of the allosteric alteration in CYP2C9 may vary from patient to patient. This may explain the inter-patient variability of the INR change. However, further studies are needed to elucidate the exact mechanism of the potentiation of the effect of warfarin by gefitinib. At the same time, it is necessary to carry out a pharmacokinetic study of gefitinib when these drugs are administered simultaneously.

In summary, one patient showed potentiation of the effect of warfarin with the simultaneous administration of gefitinib, whereas the other patient did not. Marked inter-individual variability in the interaction was observed in our cases. Thus, when gefitinib therapy is started (or discontinued) in patients receiving warfarin, close monitoring of anticoagulant control is recommended. Warfarin dose should be adjusted quickly if any altered responses are observed for the drug.

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References