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ORIGINAL ARTICLE

Increased anticoagulant activity of warfarin used in combination with doxifluridine

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Abstract
Purpose The purpose of this article is to report the first case of markedly increased anticoagulant activity of warfarin when used in combination with doxifluridine, given as a replacement for capecitabine.
Methods International normalized ratio (INR) of a 73-year-old female patient receiving warfarin was increased after starting chemotherapy using oral fluoropyrimidines (capecitabine or doxifluridine). Since the concomitant use of warfarin and the oral fluoropyrimidines was unavoidable in this case, the warfarin dosage was adjusted to keep INR within goal range (1.7–2.7). To evaluate the effects of the oral fluoropyrimidines on the anticoagulant activity of warfarin, the INR/Dose (warfarin dose in mg/day) was used.
Results To keep INR within goal range, the maintenance dosage of warfarin was reduced during the treatment with doxifluridine as well as capecitabine. It was finally reduced from 5 mg daily in the absence of oral fluoropyrimidines to 1.5 mg daily during the concomitant use of doxifluridine (600 mg daily). In contrast, the higher INR/Dose (1.03–1.66) was continued during the concomitant use of warfarin and doxifluridine compared with the INR/Dose before the start of chemotherapy (about 0.5). These results clearly indicate that the anticoagulant activity of warfarin was markedly increased by the concomitant use of doxifluridine as well as capecitabine.
Conclusions It is important that physicians closely monitor anticoagulant activity in patients concomitantly receiving doxifluridine and warfarin, and appropriately adjust the dose of warfarin.

Keywords Fluoropyrimidine Antitumor Agent · Doxifluridine (5′-DFUR) · Capecitabine · Warfarin · INR

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Introduction

Doxifluridine (5′-DFUR) is an oral prodrug of fluorouracil (5-FU), a fluoropyrimidine antitumor agent, and has been used for the treatment of breast and colorectal cancer in Japan and other Asian countries for many years. Fluoropyrimidine antitumor agents are often used in combination with warfarin in the clinical setting. As regards oral fluoropyrimidines, sporadic reports suggest that the anticoagulant activity of warfarin was increased after combined administration with a prodrug capecitabine, UFT (tegafur/uracil), and S-1 (tegafur/gimeracil/oteracil potassium), which were designed to increase the plasma concentration of 5-FU [1–8]. In contrast, there have been few reports of interaction between warfarin and oral 5-FU, probably due to low bioavailability.

Doxifluridine is characteristically converted to 5-FU by thymidine phosphorylase, which shows a higher activity in tumor tissues than in normal tissues [9]. Since thymidine phosphorylase is also present in the intestinal epithelium, it

has the dose-limiting toxicity of diarrhea [10, 11]. In contrast, capecitabine is absorbed as the unchanged form and is successively converted to 5′-DFCR, doxifluridine, and finally to 5-FU [9]. As a result, capecitabine can be administered at higher molar doses than doxifluridine [10, 11]. The effect of doxifluridine, which is routinely used at a lower molar dose than capecitabine, on the anticoagulant activity of warfarin remains unknown.

The purpose of this article is to report one case of markedly increased anticoagulant activity of warfarin when used in combination with doxifluridine, which was introduced as a replacement for capecitabine.

Case report

The patient was a 73-year-old woman with a body weight of 53 kg. The patient had a history of atrial fibrillation and mitral valve incompetence, which was controlled by warfarin at a dose of 5 mg/day within INR goal range (1.7–2.7). There was no change in hepatic and renal function parameters throughout the period. The patient had no specific family or allergy history and showed good compliance with treatment and refrained from consumption of chlorella and natto (fermented soybeans).

In April 2003, the patient was diagnosed with left breast cancer and treated with doxifluridine at a dose of 600 mg/day, followed by radical mastectomy in July 2003. In 2005, on March 3, the patient had a high CEA level with a cytological diagnosis of Class V. Capecitabine therapy was started at 2,400 mg/day due to recurrent breast cancer. The cycle of treatment was 3 consecutive weeks of drug administration followed by a 1-week rest period. In addition to warfarin and antitumor drugs, the patient received enalapril maleate tablets, carvedilol tablets, propiverine hydrochloride tablets, cepharanthine tablets, and cimetidine tablets with no change in the regimens during the relevant period. On March 11 (day 9 of the first cycle), the warfarin dose was reduced to 3 mg/day in consideration of a possible interaction with capecitabine, although INR was 2.59 and kept within goal range. In early April (during the 2nd cycle), treatment with capecitabine was discontinued due to adverse reactions (blurred vision and weariness) probably associated with this compound (brain metastasis was excluded by examination). Despite the dosage reduction, INR increased to >5 on April 8. Warfarin treatment was discontinued, and phytonadione was administered during April 9–11. On April 12, warfarin was restarted at a reduced dose of 1 mg/day. On April 22, the dose of warfarin was increased to 2 mg/day, because the INR decreased to 1.25. On April 27 (day 1 of the treatment), treatment with doxifluridine at 600 mg/day was started. When the INR increased from 2.06 on May 20 (day 24 of the treatment) to 3.32 on June 24 (day 59 of the treatment), the dose of warfarin was reduced to 1.5 mg/day. After that, blood coagulability was maintained with warfarin at 1.5 mg/day, within the therapeutic range (INR 1.6–2.4), for over 3 months (Fig. 1).

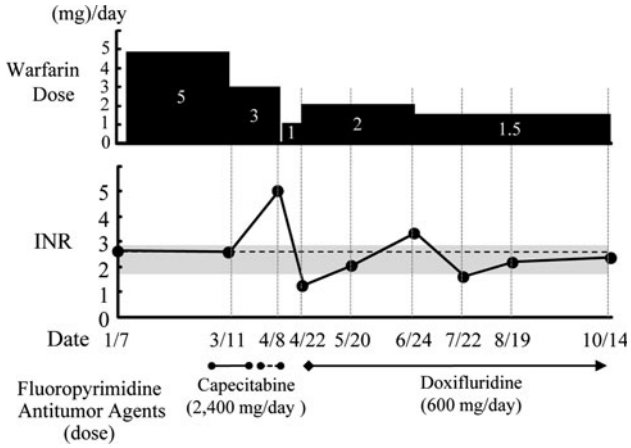

Fig. 1 Clinical course of the present case. Time profiles of warfarin dose and INR were shown in each graph. Since the concomitant use of warfarin and the oral fluoropyrimidines was unavoidable in this case, the warfarin dosage was adjusted to keep INR within goal range (1.7–2.7) (*gray area*)

Discussion

In the present case, the warfarin dosage was adjusted to keep INR within goal range (1.7–2.7), since the concomitant use of warfarin and the oral fluoropyrimidines was unavoidable. The maintenance dosage of warfarin was reduced during the treatment with doxifluridine as well as capecitabine. It was finally reduced from 5 mg daily in the absence of oral fluoropyrimidines to 1.5 mg daily during the concomitant use of doxifluridine (600 mg daily). To evaluate the effects of the oral fluoropyrimidines on the anticoagulant activity of warfarin, the INR/Dose (warfarin dose in mg/day) was used as previously reported [13]. As a result, the higher INR/Dose (1.03–1.66) was continued during the concomitant use of warfarin and doxifluridine compared with the INR/Dose before the start of chemotherapy (about 0.5) (Fig. 2). These results clearly indicate that the anticoagulant activity of warfarin was markedly increased by the concomitant use of doxifluridine as well as capecitabine.

In the present case, the high INR/Dose ($\geq$1.67) was also observed, resulting in the concomitant use of warfarin and capecitabine. The INR/Dose was also as high as 1.25 immediately before the start of combination treatment with doxifluridine. Even at that time, at least 10 days after discontinuation of treatment with capecitabine (the exact number of days was unknown), the effect of capecitabine may

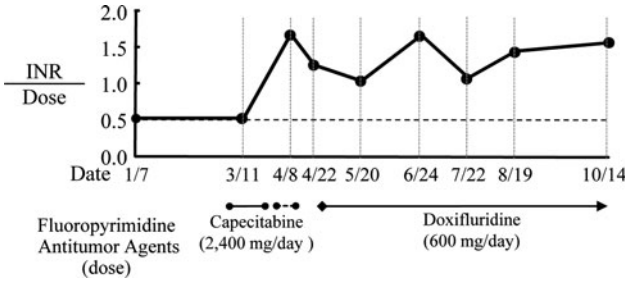

Fig. 2 INR/Dose profile of the present case. In the patient receiving warfarin, the values of INR/Dose (warfarin dose in mg/day) were markedly increased after the start of the combination treatment with doxifluridine or capecitabine compared with that in the absence of doxifluridine and capecitabine administration (*dashed line*)

have persisted. In fact, it was reported that anticoagulant activity was changed for up to 1 month after discontinuation of combination treatment with capecitabine [2]. These phenomena indicate that this interaction should be carefully monitored for some time after discontinuation of capecitabine.

As for the mechanism between warfarin and fluoropyrimidines, it is suggested that fluoropyrimidines inhibit the metabolism of warfarin in the liver [3, 4]. For instance, the previous report showed that the losartan metabolic ratio, which was used as an index of cytochrome P-450 (CYP) 2C9 activity, was significantly decreased in patients treated with 5-FU [12]. In addition, there have been many reports of adverse reactions to phenytoin, which is metabolized by CYP2C9 and CYP2C19, after combined administration with various fluoropyrimidines [14]. CYP2C9 is a major metabolizing enzyme for S-warfarin, the pharmacologically more active form of warfarin [15]. Increased AUC, decreased clearance, and prolonged half-life of S-warfarin were reported in patients concomitantly treated with capecitabine and warfarin [5]. However, neither capecitabine nor its major metabolites (5′-DFCR, doxifluridine, 5-FU, and FBAL) directly inhibited CYPs including CYP2C9 in an in vitro study using human liver microsomes [16]. There was a lag time of several days before the onset of interaction [3], despite a short half-life and no accumulation in plasma after repeated administration [9]. These evidence suggests that synthesis of drug-metabolizing enzymes in the liver may be inhibited by 5-FU, which is known to inhibit DNA synthesis and to cause RNA dysfunction [17]. The interaction between doxifluridine and warfarin may be based on the same mechanism, although no direct evidence is available. In addition, it is unknown whether not only 5-FU, but also unchanged doxifluridine is involved in this phenomenon, and further study is needed to answer this question.

The clinical importance of interaction between warfarin and doxifluridine is interesting issue. It has been reported that the maintenance dosage of warfarin was reduced by 50% or more than 85% in patients by the combination treatment with capecitabine (the dosage of capecitabine was 2,500 mg/m^2/day in one patient and 2,000 mg/m^2/day in the other patient) [6, 7]. The AUC of doxifluridine after the doxifluridine administration (600 mg/day) was appeared to be far lower than that after the capecitabine administration (2,400 mg/day), estimated based on the previous report [9]. In the light of these reports, the interaction between doxifluridine and warfarin may not be very extensive at 600 mg/day used in the patient. Contrary to the expectation, the dosage of warfarin actually had to be reduced by as much as 70% (5–1.5 mg/day) in the present case. The present case revealed that caution is also needed during combination treatment with doxifluridine and warfarin.

In summary, the present case indicates for the first time that the anticoagulant effect of warfarin could be enhanced by the concomitant use of doxifluridine at a lower molar dose than that of capecitabine. Therefore, during combination treatment with doxifluridine and warfarin, it is important that physicians closely monitor the anticoagulant activity in patients and adjust the dose of warfarin as necessary.

Conflict of interest statement None.

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