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CASE STUDY

ENHANCEMENT OF WARFARIN ANTICOAGULANT ACTIVITY BY S-1

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Abstract S-1, an oral prodrug of 5-fluorouracil, has been employed in treatment of solid tumors in Japan. We report two patient cases whose international normalized ratio (INR) increased due to concomitant treatment with warfarin and S-1. In case 1, a 63-year-old man, who had taken 3.5 mg/day warfarin for dilated cardiomyopathy, had a subcutaneous hematoma in a left lower eyelid on the ninth course of combination chemotherapy with S-1 and docetaxel for metastatic gastric cancer. His INR increased to 3.68 despite careful monitoring of coagulation parameters. In case 2, a 68-year-old man, who received combination chemotherapy with S-1 and irinotecan for metastatic colorectal cancer, had to reduce the dose of warfarin twice during the same chemotherapy courses because of repeated prolongation of INR. We speculate that multiple mechanisms of unstable INR are involved in strengthening the anticoagulant effect of warfarin. Frequent monitoring of INR is required to prevent unexpected adverse events of coagulation abnormality induced by the interaction between S-1 and warfarin.

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Key words: coagulation; S-1; warfarin.

症例研究

S-1によるワーファリン抗凝固作用の増強

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抄録　5-FU の Prodrug である S-1 は，日本において，固形腫瘍に広く使われている．著者らは，S-1 とワーファリンを同時に使用することにより，international normalized ratio（INR）の延長を来たした 2 例を報告する．第 1 例は，63歳男性．拡張型心筋症でワーファリン3.5 mg 内服しており，進行期胃癌のためドセタキセル＋S-1 併用化学療法施行 9 コース後に左眼の下に血腫が出現した．慎重な INR モニターにも関わらず INR は3.68と延長していた．第 2 例は68歳の女性．進行期大腸癌で，S-1+塩酸イリノテカン併用化学療法を受けていたが，治療中 INR の延長を来たし，2 回ワーファリンの減量が必要であった．S-1 投与中の INR の不安定さは，ワーファリンの効果増強には複数の機序が関わっていることを示唆する．S-1 とワーファリンの同時使用時には，予期しない抗凝固能の異常を予防するため，頻回の INR の測定が重要であると考えられる．
international normalized ratio（INR）

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キーワード：相互作用；S-1；ワーファリン．

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Introduction

S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-fluorouracil (5-FU), with gimeracil, an inhibitor of dihydropyrimidine dehydrogenase, and oteracil, an inhibitor of fluorouracil phosphorylation, in a molar ratio of 1:0.4:1. S-1 is used widely in digestive tract, lung, head and neck, and breast cancer in Japan[1-3] and is one of the key drugs in chemotherapy of digestive tract cancer in particular.

Warfarin is used frequently for ischemic heart diseases or thrombogenic disorders because of its strong anticoagulant activity. The international normalized ratio (INR) is one of the parameters calculated from prothrombin time, and it is affected by drug interaction and absorption of vitamin K. Enhancement of activity is known to occur as a result of interaction between warfarin and several anticancer drugs including 5-fluorouracil prodrug[4]. In addition, vitamin K1 taken from food and vitamin K2 produced by enteric bacteria are absorbed in the alimentary canal. Decreased oral intake of vitamin K and episodes of diarrhea cause INR elevation in patients receiving warfarin[5]. Gastrointestinal toxicity of S-1 is often observed, and the occurrence of grade >1 nausea, vomiting, and diarrhea is 22.3%, 7.8%, and 18.7%, respectively[6]. These gastrointestinal toxicities of S-1 could affect absorption of vitamin K.

We report two cases of elevated INR in patients treated with warfarin and S-1 and discuss possible drug interactions.

Cases Reports

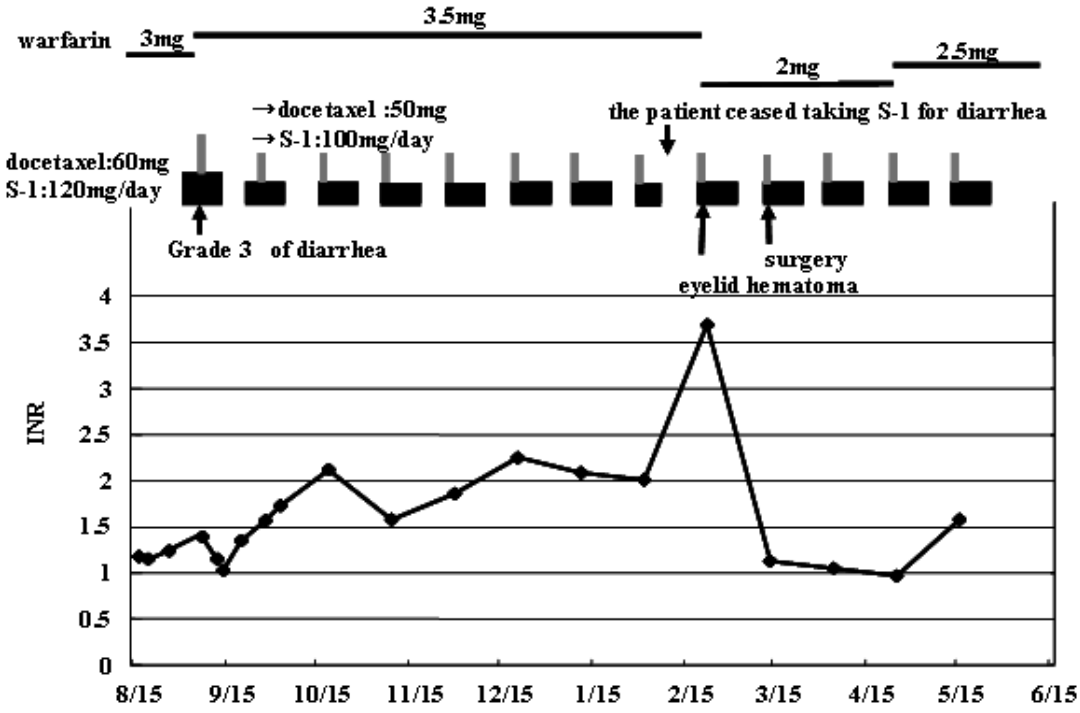
Case 1

A 63-year-old man complained of left upper abdominal discomfort and endoscopic examination revealed advanced gastric cancer at the greater curvature of the stomach. He underwent pylorectomy, D2 nodal dissection, and cholecystectomy. The pathological stage was revealed to be pT3N2M0 (Stage III B). Two months later, he was initiated with combination chemotherapy with S-1 and docetaxel. He continued to receive 3 mg warfarin for dilated cardiomyopathy. Sixty mg of docetaxel was administered intravenously on day 1, and 120 mg/day S-1 was administered orally twice daily for 14 days; this treatment was repeated every 3 weeks. The patient exhibited grade 3 diarrhea, and therefore, the doses of docetaxel and S-1 were reduced to 50 mg and 100 mg/day in the second and following courses. The daily dose of warfarin was increased from 3 to 3.5 mg because of low INR (<1.5) (Figure 1A). INR was maintained in the range of 1.5–2.5 until the eighth course of treatment. Although the patient ceased taking S-1 for diarrhea on day 8 during the eighth course, INR increased to 3.68 on day 1 of the ninth course (Figure 1A). He was found to have a subcutaneous hematoma on the left lower eyelid (Figure 1B). The dose of warfarin was reduced to 2 mg and then INR decreased to 1.13 after 3 weeks. The hematoma was excised by a plastic surgery. The daily dose of warfarin was raised by 2.5 mg during courses 12–14, with 1–1.5 INR. Genotype of the cytochrome P450 (CYP) 2C9, which metabolizes S-warfarin and vitamin K epoxide reductase complex subunit 1 (VKORC1), was analyzed after informed consent was obtained. He was homozygous for *CYP2C9**1/*1 and for G/A of *VKORC1* (–1639G>A).

Case 2

A 68-year-old man complained of edema of both lower extremities and anorexia, and he was diagnosed with sigmoid colon cancer by colonoscopy. The clinical stage was T3N0M1 (Stage IV) with malignant pleural effusion and liver metastasis. He received one course of chemotherapy of modified FOLFOX6 (125 mg L-OHP, 300 mg l-LV, 600 mg 5-FU

A



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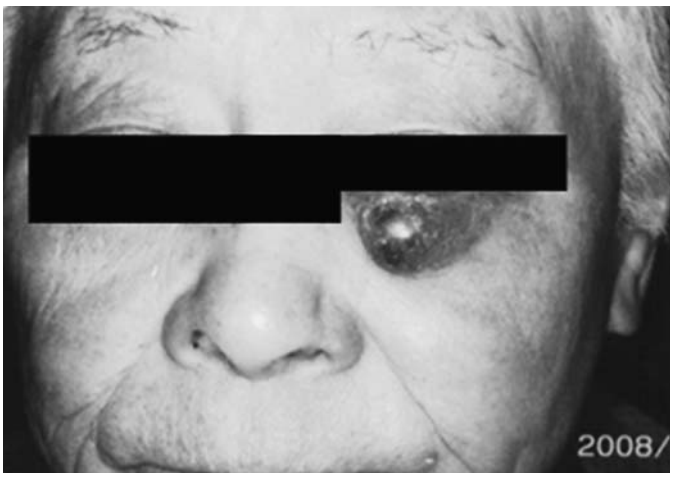

Figure 1 (A) Changes in INR during concomitant therapy with warfarin and S-1 in case 1. (B) Subcutaneous hematoma on the left lower eyelid in case 1.

bolus injection, 3000 mg 5-FU continuous venous infusion for 46 h), and subsequent sigmoidectomy and D2-nodal dissection. During first- and second-line chemotherapy, he suffered cerebral infarction twice. Anticoagulant therapy by warfarin (2 mg/day) was started and continued with an INR range of 1.24–1.48 during second-line chemotherapy with FOLFILI regimen (160 mg irinotecan, 300 mg l-LV, 600 mg 5-FU bolus injection, 3000 mg 5-FU continuous venous infusion for 46 h). After the tumor showed progressive disease,

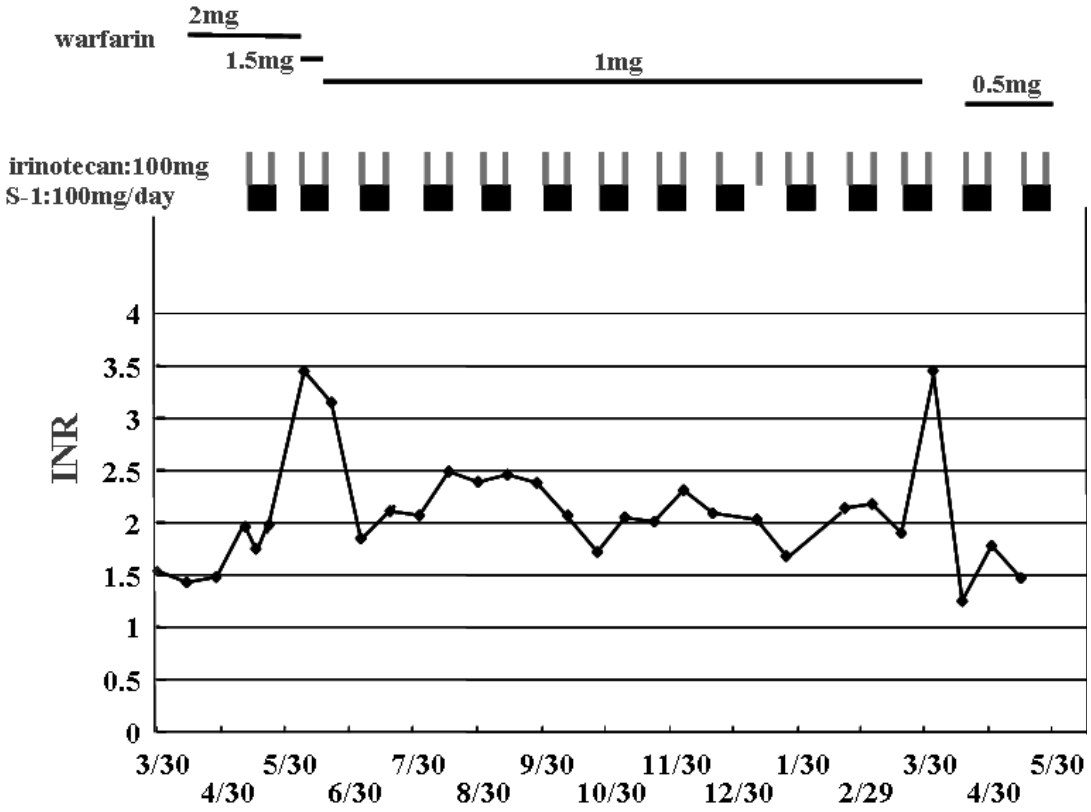

Figure 2 Changes in INR during concomitant therapy with warfarin and S-1 in case 2.

chemotherapy regimen was changed from FOLFILI to combination chemotherapy with S-1 and irinotecan (irinotecan: 100 mg on day 1 and 15, S-1: 100 mg/day from day 1 to 14 every 4 weeks) with warfarin (Figure 2). Because INR rose from 1.96 to 3.45 on day 29 in the first course of irinotecan plus S-1, the dose of warfarin was reduced from 2 to 1.5 mg/day. After 2 weeks, the daily dose of warfarin was further reduced to 1 mg/day because INR remained high (3.15). INR was controlled to 1.68–2.49 during courses 3–11 with 1 mg/day warfarin. However, INR rose again from 1.9 to 3.49 on day 15 of the 12th course, and warfarin administration was discontinued for 2 weeks. To keep INR within the therapeutic dose, warfarin was reduced to 0.5 mg/day during courses 13–22 of combination chemotherapy, and thereafter, no significant change in INR was observed.

Discussion

We report two cases of prolonged INR during concomitant treatment with S-1 and warfarin. Although anticoagulant activity was monitored carefully by INR, case 1 experienced subcutaneous hematoma by overdose of warfarin. The dose of warfarin had to be changed several times because of unstable INR. In case 2, the dose reduction was necessary again 9 months later.

Several publications have reported an interaction between warfarin and anticancer drugs including fluoropyrimidines (5-FU, capecitabine) and gemcitabine[7, 8]. However, the exact mechanisms of increasing activity of warfarin by anticancer drugs are not well understood. CYP2C9 is the principal human liver

enzyme that modulates the *in vivo* anticoagulant activity of warfarin because S-warfarin, which has three times stronger anticoagulation activity than *R*-warfarin, is metabolized mainly by this enzyme, although the CYP isoenzymes involved in the metabolism of warfarin are 2C9, 2C19, 1A2 and 3A4[9]. S-1 and capecitabine are both prodrugs of 5-FU. Arzu et al. reported significant inhibition of CYP2C9 activity at the end of the third course of 5-FU, whereas no inhibitory effect was observed in the first course in patients with colorectal cancer[10]. The area under the plasma concentration time curve from 0 to infinity ($AUC_{0\text{-}\infty}$) of S-warfarin increased by 57% (90% CI, 32–88%) with a 51% prolongation of the elimination half-life ($t_{1/2}$; 90% CI, 32–74%), which increased INR by 2.8 times during capecitabine treatment. Exposure to *R*-warfarin was not affected significantly. The capecitabine–warfarin interaction was significant clinically. The mechanism of action for the interaction might be related to downregulation of CYP2C9 by capecitabine or its metabolites or to a pharmacodynamic interaction with warfarin[11].

In the present two cases, INR elevation was observed again at several months after S-1 initiation. Therefore, mechanisms other than direct pharmacological interaction may be involved. Gene polymorphisms of *CYP2C9* and *VKORC1* greatly affect the response to warfarin. When the *CYP2C9* genotype is *CYP2C9*3*, metabolism of S-warfarin is low[12]. When polymorphism of *VKORC1(–1639G>A)* is located within the promoter region and the *G* allele substitutes for the *A* allele, its transcriptional activity decreases[13]. In a similar case, a bleeding tendency appeared in a patient who was homozygous for *CYP2C9*1/*1* (wild type) and for *A/A* of *VKORC1(–1639G>A)* after 19 days in the second course of combination treatment with warfarin, S-1, and gemcitabine[14]. Gene polymorphisms in case 1 were *CYP2C9*1/*1* (wild type) and G*/A* of *VKORC1(–1639G>A)*.

As another factor, grade 3 diarrhea appeared before INR elevation in case 1 after 6 months chemotherapy with S-1 with warfarin. Vitamin K is an essential dietary element for the normal biosynthesis of coagulation factors. INR elevation is associated with diarrhea in patients receiving warfarin because diarrhea decreases vitamin K absorption[15]. The frequencies of nausea, vomiting, and diarrhea, which are the major gastrointestinal toxicities of S-1, are 22.3%, 7.8%, and 18.7%, respectively[6]. Patient 1 suffered from grade 3 diarrhea during the first course and ceased taking S-1 for 6 days because of diarrhea on day 8 of the eighth course. INR elevation appeared after diarrhea. Therefore, S-1 might inhibit absorption of vitamin K through gastrointestinal toxicity. Management of gastrointestinal toxicity could enable us to prevent an unexpected increase in INR.

In conclusion, metabolism of warfarin could be affected by many factors. The mechanisms of the interaction between S-1 and warfarin are still unclear. However, INR may become unstable after concomitant therapy with S-1 and warfarin, and an increase in INR may appear after more than 6 months. Thus, we need to monitor patients carefully for possible INR elevation.

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