A case of successful concomitant administration of warfarin and uracil-tegafur/leucovorin achieved by self-measurement of INR

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Abstract
A woman in her seventies who was started on warfarin after heart valve replacement began outpatient adjuvant chemotherapy with tegafur-uracil/leucovorin for rectal cancer. The patient performed weekly INR self-measurements at a health insurance pharmacy between outpatient visits. Results recorded in her personal medicine notebook were shared between her physician, a hospital pharmacist, and a pharmacy pharmacist. When INR values were outside the therapeutic target range, doses were altered according to the physician’s instruction. Our approach enables the fine adjustment of warfarin doses according to changes in INR and contributes to the maintenance of the therapeutic target range and safe and appropriate outpatient chemotherapy.

KEYWORDS
INR self-measurement, tegafur-uracil/leucovorin, time in the therapeutic range, warfarin

1 | INTRODUCTION
Enhancement of the anticoagulant action of warfarin (WF) by concomitant administration with a fluorouracil antitumor agent has been reported. However, the mechanisms and timing of their interaction remain unclear, and thus, regular blood coagulation tests are recommended to adjust WF dosing based on INR values while continuing anticaner treatment.1-3

In this study, we implemented a collaborative outpatient medication management system for a patient who had concomitant administration of WF and a combination of a fluorouracil agent tegafur-uracil and leucovorin (UFT/LV). A health insurance pharmacy-based pharmacist assisted the patient to perform point-of-care testing (POCT) for INR self-measurement between outpatient visits. Information on appropriate WF doses deduced from the results of INR self-measurement, the situation regarding adverse effect, and medication status were shared between the health insurance pharmacy-based pharmacist, a hospital-based physician, and a hospital-based pharmacist. Herein, we report our implementation and outcomes of this system that aimed to provide appropriate WF therapy.

2 | CASE
A woman in her seventies had undergone artificial heart valve replacement for valvar disease complicated by atrial fibrillation in October year X. WF therapy (2.0 mg daily) was started after surgery.

Following an investigation into melena, rectal cancer was diagnosed in February in year (X+9) and laparoscopic abdominoperineal resection was performed in December in the same year. Postoperative histology revealed rectal cancer of Rb, type 2, tub2>tub1, pT3, ly1, v1, pN0 (0/9), pPM0, pDM0 (pStage II). Although histology results indicated Stage II cancer, both lymphatic and venous invasion were...
positive, and thus, the risk of recurrence was expected to be high in accordance with the colorectal cancer treatment guidelines. After providing sufficient explanation and obtaining consent from the patient, outpatient adjuvant chemotherapy with UFT/LV (six cycles of a 35-day regimen: UFT 500 mg daily plus LV 75 mg daily for 28 days followed by a 7-day break) was started.

2.1 | Procedures of the collaborative outpatient medication management system

The procedure of the collaborative outpatient medication management system was established based on the outcomes of the meeting held between a hospital physician, a hospital-based pharmacist (hereinafter referred to as the hospital pharmacist), and a health insurance pharmacy-based pharmacist (hereinafter referred to as the pharmacy pharmacist). Major outcomes of the meeting were the following: once weekly self-measurement of INR at a health insurance pharmacy (except the week of the outpatient visit); 3-day withholding of WF therapy when self-measured INR values exceeded the target therapeutic range (1.5-2.5); and re-start of WF therapy with an altered daily dose in accordance with the physician’s advice. The workflow depicting the procedure of the collaborative outpatient medication management system is shown in Figure 1.

1. The hospital pharmacist recorded the information about the UFT/LV treatment schedule and INR values (measured at the hospital) in the patient’s personal medicine notebook and shared it with the pharmacy pharmacist.
2. The patient visited the insurance pharmacy weekly to perform POCT for INR between outpatient visits.
3. The pharmacy pharmacist objectively evaluated whether INR measurements were within the therapeutic target range or in the adverse effect-causing range, obtained the information on medication status and adverse effects from the patient, and provided the patient with an instruction on medication accordingly. When INR values (measured at the health insurance pharmacy) were outside the therapeutic target range, the pharmacy pharmacist called the hospital pharmacist to inform the patient’s conditions and appropriate WF doses.
4. Based on the information passed by the hospital pharmacist, the physician gave instruction (withholding or adjusted doses of WF) to the hospital pharmacist, who then called the pharmacy pharmacist to inform the physician’s instruction.
5. The pharmacy pharmacist instructed the patient according to the adjusted medication (withholding or alteration of WF doses).

2.2 | POCT for INR self-measurement

Point-of-care testing for INR self-measurement was performed by the patient using the CoaguChek® XS (EIDIA Co. Ltd, Tokyo, Japan). Instructions on machine operation, disinfection of the site of needle insertion, and disposal of biohazardous waste (eg, blood contaminated needles) were given by the pharmacy pharmacist prior to self-measurement.

2.3 | Evaluation of the effect of WF therapy based on the time in the therapeutic range (TTR)

The TTR, which is the percent of time when INR was maintained within the therapeutic range, was used to evaluate the effect of WF therapy. The TTR values during a 24-week period before and a 24-week period after the start of UFT/LV therapy were evaluated.

2.4 | Ethical considerations

This study was performed after obtaining approval from the Clinical Research Ethics Committee of the School of Pharmacy, Aichi Gakuin University.

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**FIGURE 1** The workflow of the procedure of the collaborative outpatient medication management system. The patient performed weekly INR self-measurements at a health insurance pharmacy between outpatient visits. Results recorded in her personal medicine notebook were shared between her physician, a hospital pharmacist, and a pharmacy pharmacist. When INR values were outside the therapeutic target range, doses were altered according to the physician’s instruction. INR, international normalized ratio; UFT/LV, tegafur-uracil and leucovorin; WF, warfarin

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**Between outpatient visits**

- **Patient**
  - INR self-measurement
  - Health insurance pharmacy-based pharmacist
    - Checking INR values
    - Medication status
    - Adverse effect status
    - Dispensing
    - Instruction on medication
- INR values outside the therapeutic target range

**Day of an outpatient visit**

- **Patient**
  - Physician
    - Checking INR values and other information
    - Consultation
    - WF prescription
- **Hospital-based pharmacist**
  - INR values (measured at the hospital)
  - UFT/LV treatment schedule
- **Physician**
  - Phone call
  - Instructing to withhold or change WF doses
2.5 | Clinical course

Before receiving adjuvant chemotherapy with UFT/LV, INR values were maintained within the target therapeutic range (1.5-2.5) with oral anticoagulation therapy (WF 2.0 mg daily) (Figure 2). Upon the start of UFT/LV chemotherapy, the daily WF dose was reduced from 2.0 to 1.5 mg. The INR value (measured at the hospital) at day 36 of UFT/LV chemotherapy was increased to 4.35, but a bleeding tendency was absent. Thus, after withholding WF for 3 days, WF therapy was restarted with a reduced daily dose (1.0 mg). The INR value (measured at the hospital) at day 43 of UFT/LV chemotherapy was within the target range. WF therapy with a reduced WF dose (1.0 mg) was continued, but the INR value (measured at the hospital) at day 85 dropped to 1.34. The daily WF dose was increased to 2.0 mg from the next day, but the INR value (measured at the hospital) at day 92 was increased to 3.4. The pharmacy pharmacist reported the INR, WF administration status, and the absence of a bleeding tendency to the physician via the hospital pharmacist. According to the physician’s advice, the pharmacy pharmacist explained to the patient about the change in the WF regimen (3-day withdrawal and reduced daily dose from 2.0 to 1.0 mg). The INR (measured at the hospital) was within the target therapeutic range at day 99 of UFT/LV chemotherapy.

After this time point, WF doses were adjusted in the range between 0.5 and 1.0 mg in accordance with INR values measured at the hospital or at the pharmacy.

The patient on WF therapy performed INR self-measurement at the pharmacy three times on average during one cycle of UFT/LV chemotherapy. WF doses were adjusted eight times in total (after four measurements at the hospital and four measurements at the pharmacy) when INR values did not fall within the target therapeutic range.

The TTR during the 24-week period before the concomitant administration of WF and UFT/LV was 94.0%, while that during the 24-week period after concomitant administration was 75.6%.

There were no adverse effects during the combination treatment with WF and UFT/LV.

3 | DISCUSSION

A possible mechanism for increases in INR, which occur when WF is used with fluorouracil antitumor agents, is enhancement of the WF action via inhibition of a WF-metabolizing enzyme CYP2C9A by fluorouracil antitumor agents, but the details of the mechanism have not yet been elucidated.1,2
In the present case, increases in INR were observed around 2 weeks after concomitant administration of WF and UFT/LV, and INR values remained high even when WF was withhold. Also, as UFT/LV therapy progressed toward the final sixth cycle, INR values exceeded the upper limit of the target therapeutic range, but reduced WF doses successfully reverted INR values to the target range within 1 week.

Previous studies that examined interaction between WF and a concomitant S-1 (combination of fluorouracil prodrug tegafur, gimecaril, and oteracil potassium) showed increases in INR values within 1-3 weeks in all cases, marked differences in the range of INR fluctuation among individuals, and bleeding diathesis\(^4,5\). Also, problems regarding the lack of INR measurement in the early stage of outpatient treatment with concomitant S-1 were reported, suggesting the possible danger of missing signs of drug interaction when subjective signs of adverse effect (eg, bleeding) are absent.

We also found increases in INR values 2 weeks after concomitant administration and beyond. However, therapy was continued without causing adverse effects (eg, bleeding) in our case, owing to the collaboration between the hospital and the health insurance pharmacy, enabling once weekly INR measurement, objective evaluation of INR values (falling within the therapeutic target range or the adverse effect-causing range), and swift adjustment of WF doses according to the evaluation.

Although the precise INR measurement schedule was not stated in these reports, INR measurements around 1-2 weeks after the start of concomitant administration of WF and S-1 and subsequent adjustment of WF dosing were recommended\(^4,6\).

Thus, in this study, we employed the POCT-based INR monitoring system reported by Yamanura et al.,\(^7\) wherein health insurance pharmacies play an important role. More precisely, the patient visited a health insurance pharmacy for self-measurement of INR once a week between outpatient visits, and the pharmacy pharmacist examined the INR values and objectively judged whether WF dosing would result in an INR in the therapeutic range or in the adverse effect-causing range. Such information was shared with the physician and the pharmacist in charge at the hospital, and it successfully enabled the establishment of the collaborative outpatient medication management system as well as on-time WF adjustment. With this system, the TTR in the 24-week periods before and after concomitant administration of WF and UFT/LV were 94.0% and 75.6%, respectively; both are above 65%, which is the lowest TTR value indicating appropriate dosing of WF.

Fluorouracil antitumor agents such as UFT and S-1 have been commonly used in outpatient treatment in recent years. However, the mechanism underlying the increases in INR due to their interaction with WF and the timing of INR elevation remains unclear, and thus, regular INR measurement and subsequent adjustment of WF doses, as well as checking the WF administration status and adverse effects (eg, bleeding), are important to achieve the target therapeutic range in WF therapy.

The collaborative outpatient medication management system, involving physicians, hospital pharmacists, and pharmacy pharmacists, enables fine adjustment of WF dosing according to the changes in INR caused by concomitant administration of UFT/LV with WF and will be beneficial in the maintenance of the WF therapeutic target range and safe and appropriate outpatient adjuvant chemotherapy with UFT/LV.

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**CONFLICT OF INTEREST**

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

**REFERENCES**

1. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. Clin Colorectal Cancer 2005;5:175–80.
2. Giunta G. Warfarin-5-FU interactions. Ann Oncol 2006;17:176.
3. Yamamura K, Yano K, Hirooka Y, et al. A successful case of a patient undergoing warfarin and S-1 therapy using internet-based control of home-measured PT-INR. Yakugaku Zasshi 2015;135:925–7.
4. Yamada T, Watanabe H, Yano T, et al. Timing of expression of blood coagulation abnormality in patients treated with warfarin and s-1 concomitantly. Yakugaku Zasshi 2010;130:955–60.
5. Igarashi H, Maeda Y, Kasamatsu Y, et al. Drug Interaction between S-1 and warfarin. J Jpn Soc Hosp Pharm 2009;45:1321–4.
6. Watanabe H, Itoh H, Tsuchiya Y, et al. Reinforcement of warfarin action in a patient administered S-1. Jpn J Cancer Chemother 2015;42:131–3.
7. Yamamura K, Kurata H, Shigeno K, et al. Establishment of a new function for pharmacies: sharing of patient-monitored warfarin PT-INR information with clinics: case report on successful control of PT-INR. J Jpn Prim Care Assoc 2012;35:45–8.

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