A successful case of a patient undergoing warfarin and S-1 therapy using Internet-based control of home-measured PT-INR

Keiko Yamamura*a, Koji Yanob, Yoshiki Hirookac, Akihiro Hirashikid, Toyoaki Muroharad, Kiyofumiyamad

*aSchool of Pharmacy, Aichi Gakuin University; 1-100 Kusumoto-cho, Chikusa-ku, Nagoya, Aichi 464-8650, Japan: Departments of bPharmacy, cEndoscopy, and dAdvanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine; 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan

e-mail: keiko-y@dpc.agu.ac.jp
Abstract

To avoid major bleeding events in warfarin and S-1 combination therapy, PT-INR levels should be monitored frequently to allow for precise adjustments of the warfarin dose and to verify any side effects reported by the patient. We therefore developed a support system where outpatients obtain a home-measured PT-INR value using the CoaguChek® system and submit it along with details of any side effects to us via the Internet using their mobile phone. A 59-year-old man was started on warfarin (1.5 mg/day) and S-1 (100 mg/day), a combination preparation of tegafur, gimeracil, and oteracil potassium, to treat cholangiocarcinoma. The patient sent his data to the hospital pharmacist every two days after starting S-1 therapy. When the PT-INR was outside the target range of 1.5–2.7, the pharmacist, after consulting the physician, instructed the patient to change his warfarin dose by 0.5 mg. On day 24 after starting S-1, PT-INR had increased from 1.6 to 2.8, so the dose was decreased by 0.5 mg. Thereafter, the dose was adjusted by 0.5–1.0 mg during the observation period so that the patient was able to maintain the therapeutic range approximately 90% of the time. We anticipate this system can be applied to S-1 which interact with warfarin, thereby enabling safer anticoagulation therapy.

Key words: warfarin, S-1, international normalized ratio, home-measured PT-INR prothrombin time, CoaguChek, time in therapeutic range
A 59-year-old man underwent coronary artery bypass graft surgery in September 2004 for severe ischemic heart disease. Coagulation therapy with warfarin (1.5 mg/day) was started after surgery to prevent thrombotic occlusion of the saphenous vein graft. The target range for prothrombin time and international normalized ratio (PT-INR) was set at 1.5–2.7. Single nucleotide polymorphisms related to warfarin therapy were VKORC1 A/A and CYP2C9*1/*3. In January 2012, the patient was diagnosed as having stage IV cholangiocarcinoma and started weekly outpatient treatment of gemcitabine injection. Despite disease progression, the patient and his family requested fewer hospital visits to reduce the burden of pain associated with the injection. We therefore changed weekly gemcitabine injection to monthly oral S-1 administration in August 2012. S-1 (100 mg/day), a combination preparation of tegafur, gimeracil, and oteracil potassium, was started to treat cholangiocarcinoma. Various interactions have been reported between warfarin and fluoropyrimidines such as 5-fluorouracil, tegafur, doxifluridine, and capecitabine, which induce bleeding diathesis due to prolonged prothrombin time.\(^1\) The exact mechanisms of these interactions are unknown but might involve 5-fluorouracil decreasing the expression of CYP2C9, a hepatic drug-metabolizing enzyme that inhibits warfarin metabolism in the liver thereby increasing serum warfarin.\(^2\) To avoid major bleeding events in warfarin and S-1 combination therapy, PT-INR levels should be monitored frequently to allow for precise adjustments of the warfarin dose and verify any side effects reported by the patient. Significant improvements in time to stroke event have been reported in patients with atrial fibrillation taking warfarin whose time in therapeutic range (TTR) is >70% of the time compared with those not receiving warfarin.\(^3\) The indication for warfarin should be regularly monitored based on the patient’s ability to maintain a therapeutic PT-INR.
The present patient was seen at our hospital outpatient clinic for monthly PT-INR measurements. Before concomitant use of S-1, TTR was 86%. Since his warfarin-related genetic polymorphisms resulted in high sensitivity to the warfarin dose, his PT-INR needed to be measured more than weekly after starting S-1. However, such frequent visits would have increased his burden in terms of both time and money. It was reported that point-of-care testing of PT-INR of patients on warfarin using the CoaguChek® device in Japanese outpatient clinics has improved TTR.4) We therefore developed a pharmacological treatment support system where outpatients obtain a home-measured PT-INR value using the CoaguChek® (Roche Diagnostics) system and submit it along with details of any side effects to us via the Internet using their mobile phone. This study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

The procedure for sending and receiving data via our website is explained below.

1. The patient sends via email his/her data to the pharmacist.
2. The pharmacist evaluates the data based on a protocol developed jointly with physicians. In case of abnormalities, the pharmacist discusses the data with the physician to determine a new warfarin dose.
3. An email is sent to the patient to notify him/her of the new dose.

Our patient has sent his data to the hospital pharmacist every two days since starting S-1 therapy. When the PT-INR was outside the target range of 1.5–2.7, the pharmacist, after consulting the physician, instructed the patient to change his warfarin dose by 0.5 mg. On day 24 after starting S-1, PT-INR had increased from 1.6 to 2.8, so the dose was
decreased by 0.5 mg. Thereafter, the dose was adjusted by 0.5–1.0 mg during the observation period undergoing warfarin therapy (Figure), maintaining TTR at approximately 90%. No bleeding or embolism occurred, and warfarin and S-1 therapy could be safely combined. The benefit of our internet-based system is being able to instruct patients on the warfarin dose based on current PT-INR values prior to their next outpatient visit.

This system enabled the patient to spend more time with his family while safely undergoing cancer treatment and concurrent warfarin therapy with a once monthly hospital visit during the approximately 300 day period before his death. We anticipate the system can be applied to S-1 that interact with warfarin, thereby enabling safer anticoagulation therapy.

Acknowledgements

We thank all staff who were involved in this study.

Funding for the professional translation and editing of this case report was provided by Aichi Gakuin University.

Contributors

K. Yamamura supervised the anticoagulation control and compiled the manuscript in cooperation with Y. Hirooka, A. Hirashiki, and T. Murohara.

K. Yano and K. Yamada collated the patient’s data and participated in pharmaceutical care discussions.

Y. Hirooka managed the patient’s digestive tract condition.

A. Hirashiki and T. Murohara provided clinical care for the patient after coronary graft surgery and managed the patient during anticancer therapy.
Conflicts of interest

The authors declare no conflict of interest.
REFERENCES


Figure 1. Changes in warfarin dose, and prothrombin time and international normalized ratio.
Figure 1