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Evaluation of the anticoagulant effect and timing of the concomitant use of S-1 and warfarin

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Abstract

Objectives: To evaluate the effects of the timing of warfarin (WF) administration in patients with gastric cancer who received S-1 oral chemotherapy.

Methods: This retrospective chart review collected patient data including the prothrombin time international normalized ratio (PT-INR). Patients were categorized into three groups based on the timing of WF administration in relation to S-1 oral chemotherapy: group A patients received WF before S-1 chemotherapy; group B patients started WF during S-1 chemotherapy; and group C patients started WF after completing S-1 chemotherapy.

Results: A total of 21 patients with gastric cancer were included in the study; group A ($n = 8$), group B ($n = 10$) and group C ($n = 3$). Seven patients (88%) in group A, seven (70%) in group B and all of the patients (100%) in group C had >2.5 PT-INR. There was no significant difference in the time-to-exceed 2.5 PT-INR between groups A and B.

Conclusions: These findings suggest that the timing of WF use in relation to S-1 chemotherapy might not be an important factor for PT-INR, although the low patient numbers included in the study should be taken into consideration.

Keywords

S-1, warfarin, prothrombin time international normalized ratio (PT-INR), drug interaction

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Introduction

Cancer and its treatment with chemotherapy are known to be important risk factors for the development of a thromboembolism, such as a venous thromboembolism, due to an enhancement of blood clotting.[1] Cancer is defined as a risk factor for thromboembolism in the guidelines for the diagnosis,

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treatment and prevention of pulmonary thromboembolism and deep vein thrombosis.[2] Warfarin (WF) is one of the major anticoagulants used for the treatment of thromboembolism.[3] The American Society of Clinical Oncology clinical practice guideline for venous thromboembolism prophylaxis and treatment in patients with cancer recommends WF for long-term treatment, while also recommending at least 6 months of WF.[4]

The S-1 combination of oral anticancer agents, which is comprised of a molar ratio of 1:0.4:1 of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate,[5] is indicated for various cancer types in Japan; for example, gastric cancer, colorectal cancer, non-small cell lung cancer, head and neck cancer, breast cancer, pancreatic cancer and biliary tract cancer.[6] The cytochrome P-450 isoenzymes, CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP1A2 and CYP3A4, metabolize WF.[7] CYP2C9 plays the main role in WF metabolism and 5-fluorouracil (5-FU) inhibits the hepatic metabolism of WF by inhibiting the synthesis of CYP2C9.[7] The effects of drug interactions have been reported for 5-FU, capecitabine and S-1.[8] A prolonged prothrombin time was observed in patients taking WF with a fluoropyrimidine, such as S-1, due to drug–drug interactions via CYP2C9.[9] Therefore, close monitoring of the prothrombin time international normalized ratio (PT-INR) is required to adjust the WF dose.[10,11] Several studies have reported a drug–drug interaction between fluoropyrimidines and WF based on the effects on PT-INR.[12–15] The drug–drug interaction between S-1 and WF has proven to be an especially difficult issue for clinical practitioners in Japan due to the broad range of indications for WF.[16–18]

A previous report from Japan demonstrated that most of the patients using WF who then started using S-1 oral chemotherapy exceeded the upper limit of PT-INR, with the period of the maximum PT-INR being approximately 1 month.[19] These data were obtained only in patients who had used WF before they commenced S-1 chemotherapy, and no clinical data were available on the timing of WF administration in relation to starting S-1 oral chemotherapy and the effect that timing had on PT-INR.[19] Moreover, the previous study evaluated patients with any type of cancer who had already used WF and then started S-1 oral chemotherapy, because the study only wanted to evaluate the effects of S-1 oral chemotherapy administration on WF therapy.[19] To eliminate the bias possibly associated with evaluating different cancer types and their various chemotherapy regimens, this present study focused solely on patients with gastric cancer, who form the majority of cancer patients in Japan,[6] who used both WF and S-1. This study was designed to evaluate the effects of the timing of WF administration in relation to S-1 oral chemotherapy in patients with gastric cancer.

Patients and methods

Participants and study design

This study was conducted as a retrospective chart review of patients with gastric cancer who received WF and S-1. Patients were identified from a computer-generated list produced by the pharmacy database, which is managed by the Division of Pharmacy, National Cancer Center Hospital East, Kashiwa, Japan, of patients treated for gastric cancer between 1 January 2009 and 31 December 2013. Although all of the patients had gastric cancer, the specific reason for WF use and the S-1 chemotherapy regimen used varied between patients. According to clinical guidelines for deep vein thrombosis,[2] the baseline of INR is defined as 2.5. The majority of patients used WF for deep vein thrombosis, but there is no standard baseline for WF PT-INR in cancer patients, therefore, >2.5 PT-INR was defined as a drug interaction event

between S-1 and WF in this study. This present study defined 2.5 PT-INR as the upper limit of the laboratory data for an adequate anticoagulant effect. Subject-specific information, such as age, sex, chemotherapy regimen, initial PT-INR, purpose of WF use and initial WF dose was collected from electronic medical databases. The adverse events due to WF were evaluated by oncologists according to the Common Terminology Criteria for Adverse Events version 4.0.[20]

The study endpoints were: (i) the incidence of excess 2.5 PT-INR; (ii) the time-to-exceed 2.5 PT-INR; (iii) the time-to-maximum PT-INR; and (iv) adverse drug reactions to WF. To analyse the differences due to the timing of WF administration for S-1 oral chemotherapy, the patients were categorized into three groups based on the WF administration timing in relation to S-1 oral chemotherapy; group A comprised of patients who had already received WF before S-1 chemotherapy; group B comprised of patients who started WF during S-1 chemotherapy; and group C comprised of patients who started WF after finishing S-1 chemotherapy.

The study was approved by the Institutional Review Board of the National Cancer Center Hospital East (approval number: 2013-313). As this was a retrospective chart review study, the need to obtain informed patient consent was waived.

Chemotherapy regimens

All patients received a chemotherapy regimen that was registered with the Division of Pharmacy, National Cancer Center Hospital East and generated by a computerized provider order entry (CPOE) system. The validity of the chemotherapy regimen that was selected by the CPOE system was evaluated by the Division of Pharmacy. After the review process, the Division of Pharmacy built the protocol into the order template in the CPOE system. After the template was approved, the oncologist only needed to choose the name of the regimen to order the chemotherapy on each patient's electronic medical record. The CPOE utilized weight and height to calculate the dose of the components of the chemotherapy regimen and the template provided the administration sequence for the anticancer agents, along with any supportive medicines and hydration that the oncologist had authorized for the specific protocol. Therefore, all patients who had a given chemotherapy regimen had essentially the same treatment. This study evaluated patients who received any one of the following three chemotherapy regimens: S-1 monotherapy,[21] S-1+cisplatin (CDDP) chemotherapy[22] and docetaxel (DOC)+CDDP + S-1 chemotherapy.[23]

PT-INR measurements

Due to the retrospective nature of this analysis, it was not possible to control the frequency and timing of the blood sampling. The PT-INR testing frequency was based on the chemotherapy cycle that was used. S-1 monotherapy was normally performed in an outpatient setting, so the PT-INR test was performed at each outpatient clinic visit. The outpatient examination was performed once weekly at first, and after the establishment of a stable PT-INR, the examination changed to either biweekly or monthly. The S-1 + CDDP chemotherapy and DOC + CDDP + S-1 chemotherapy regimens were performed in an inpatient setting, but after discharge from hospital, oncologists closely monitored the patients and examined the PT-INR on a weekly or biweekly basis. To evaluate and compare any potential drug–drug interactions between S-1 and WF, the mean PT-INR for the time-to-exceed 2.5 PT-INR for the first time and the mean PT-INR for the time-to-maximum PT-INR were determined.

Routine venous blood samples were taken in order to determine haematological

parameters such as white and red blood cell counts. PT-INR was measured using a Thromborel® S Kit (Siemens Healthcare Diagnostics, Marburg, Germany) and a Sysmex CA-1500® System (Siemens Healthcare Diagnostics) following the manufacturer's instructions. PT-INR was measured within 24 h of blood collection. In brief, venous blood (9 parts) was carefully mixed with 1 part sodium citrate solution (0.11 mol/l), avoiding the formation of a foam. The blood specimen was centrifuged at 1500 ***g*** for ≥15 min at room temperature and then stored at room temperature to prevent cold activation of Factor VII. The citrated plasma (100 µl) was incubated for 1 min at 37°C in a test tube prewarmed to 37°C. Then 200 µl of Thromborel® S Reagent prewarmed to 37°C was added to the plasma and the Sysmex CA-1500® System was used to determine the coagulation time.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Bivariate analysis, Mann–Whitney *U*-test or log-rank test were used to examine the time-to-events due to a drug–drug interaction between S-1 and WF. Fisher's exact probability test was used for categorical variables. A P-value < 0.05 was considered statistically significant.

Results

This retrospective chart review identified 21 patients with gastric cancer who were administered WF and S-1. There were eight patients in group A, 10 in group B and three in group C. Table 1 presents the demographic and clinical characteristics of the study participants. There were no significant differences in the median age, sex distribution or initial PT-INR between the three groups (Mann–Whitney *U*-test and Fisher's exact probability test). The most common chemotherapy regimen was S-1 monotherapy, while group B had five patients who had the S-1 + CDDP regimen. Patients used WF for a variety of indications, but the most frequent reasons were to prevent deep vein thrombosis or pulmonary embolism due to cancer and chemotherapy treatment. There were no significant differences in the initial WF dose used between the three groups (Mann–Whitney *U*-test).

Seven of eight patients (88%) in group A, seven of 10 patients (70%) in group B and all of the patients (100%) in group C had >2.5 PT-INR (Table 2). There was no significant difference in the mean time-to-exceed 2.5 PT-INR between groups A and group B (log-rank test). The median time-to-exceed 2.5 PT-INR was also not significantly different between groups A and group B (log-rank test) (Figure 1). In group C, all three patients exceeded 2.5 PT-INR after using WF, even though they had already finished their S-1 chemotherapy. The times from the last S-1 administration to WF administration were 21, 24 and 26 days, respectively.

There was no significant difference in the mean time-to-maximum PT-INR between groups A and group B (log-rank test) (Table 2).

In terms of drug reactions to WF, there were two patients who experienced bleeding in group A; and the time-to-bleeding was 41 days and 119 days, respectively. In group B, five patients underwent heparinization before switching to oral WF. No patients experienced bleeding in groups B or C.

Discussion

From the PT-INR results obtained in this present study, the timing of WF administration appeared not to be a significant factor in the drug–drug interactions between WF and S-1, a fluoropyrimidine-based combination of oral chemotherapy agents.

Table 1. Demographic and clinical characteristics of the patients ($n = 21$) with gastric cancer who received warfarin in addition to a chemotherapy regimen and who participated in this study to evaluate drug–drug interactions with warfarin.

	Overall	Group A	Group B	Group C
Characteristics	$n = 21$	$n = 8$	$n = 10$	$n = 3$
Sex				
Male	14	8	5	1
Female	7	0	5	2
Age				
Median	62	69	61	52
Range	28–81	50–81	28–75	50–68
Initial PT-INR				
Median	1.25	1.70	1.15	1.99
Range	0.99–2.49	0.99–2.49	1.00–2.21	1.22–1.30
Chemotherapy				
S-1	13	6	4	3
S-1 + CDDP	6	1	5	0
DOC+ CDDP+ S-1	2	1	1	0
Initial WF dose, mg				
Median	2.0	2.5	1.0	1.0
Range	0.5–4.0	1.0–4.0	0.5–4.0	1.0–3.0
Purpose of WF use[a]				
Renal vein thrombosis	1	0	1	0
Deep vein thrombosis	10	2	6	2
Atrial fibrillation	5	4	0	1
Internal carotid artery stenosis	1	1	0	0
Pulmonary embolism	8	1	6	1
Portal vein thrombosis	1	1	0	0
Iliac vein thrombosis	2	1	1	0

Data presented as median (range) or *n* of patients.

[a]There could be more than one reason for using WF.

No significant between-group differences ($P \geq 0.05$); Mann–Whitney U-test for continuous variables; Fisher's exact probability test for categorical variables.

PT-INR, prothrombin time international normalized ratio; S-1, tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate; CDDP, cisplatin; DOC, docetaxel; WF, warfarin.

However, it should be noted that the patient numbers in this present study were low and should be taken into consideration when drawing any conclusions. There have been several reports that have examined the incidence of drug interactions between S-1 and WF and the time-to-exceed the therapeutic range of PT-INR due to an S-1 drug interaction.[16–18] The mean time-to-exceed the upper limit of PT-INR was approximately 1 month.[16–18] The results in this present study, as well as those of other studies,[16–18] show that neither the initial PT-INR nor the initial dose of WF were important factors in the drug–drug interaction between S-1 and WF. A metabolite of S-1, 5-FU, diminishes CYP2C9, so the concurrent use of S-1 and WF results in a delay of WF metabolism.[7]

The adverse drug reaction of bleeding due to WF use was observed in two patients in group A. It was difficult to manage this drug–drug interaction. None of the patients

Table 2. Time-to-event data for patients ($n = 21$) with gastric cancer who received warfarin in addition to a chemotherapy regimen and who participated in this study to evaluate drug–drug interactions with warfarin.

	Group A	Group B	Group C
Time-to-event	$n = 8$	$n = 10$	$n = 3$
Time-to-exceed 2.5 PT-INR			
Number of patients	7	7	3
Days	40.2 ± 37.0	65.5 ± 42.1	33.6 ± 36.1
PT-INR	3.78 ± 1.26	4.25 ± 2.75	4.14 ± 2.32
Time-to-maximum PT-INR			
Number of patients	8	10	3
Days	73.8 ± 75.4	77.8 ± 59.9	35.0 ± 35.6
PT-INR	3.98 ± 1.31	4.23 ± 2.62	4.17 ± 2.30

Data presented as mean ± SD.
No significant between-group differences ($P \geq 0.05$); Mann–Whitney *U*-test for continuous variables; log-rank test for time-to-event data.
PT-INR, prothrombin time international normalized ratio.

in group B experienced bleeding, but half of them had undergone heparinization before WF oral anticoagulation therapy. The heparin and WF treatments were carefully administered, so bleeding did not occur in group B. It was noted in the two patients in group A that the time-to-bleeding was not similar, occurring on days 41 and 119, which suggests that it will be extremely difficult to predict this type of adverse drug reaction. In group C, all three patients exceeded 2.5 PT-INR after they started WF following completion of their S-1 chemotherapy. The times from the last S-1 administration to WF administration were 21, 24 and 26 days, respectively. The half-life of WF ranges from 55 to 133 h and its pharmacological mechanism of action is via the inhibition of vitamin K epoxide reductase and suppression of the blood clotting factors II, VII, IX and X.[7] Even though there was almost a 1-month wash-out period for S-1, the drug interactive effect appeared to persist in group C.

This retrospective chart review study had a number of limitations. First, it was limited to a specific chemotherapeutic regimen and only included Japanese patients with gastric cancer. Secondly, even though most of the patients had the PT-INR test weekly or biweekly after the concurrent use of WF and S-1, the PT-INR test was not measured within the same period due to the retrospective nature of the study. Thirdly, the study only evaluated 21 patients with gastric cancer who concomitantly used WF and S-1 for the period of the study. The patient numbers were limited because, in an attempt to eliminate bias, the study focused on patients with gastric cancer and their treatment with S-1-based chemotherapy regimens. Gastric cancer was selected because it is the most prevalent cancer in Japan. Even though the number of patients was limited, it was worthwhile evaluating this study population because of its rarity. However, the number of patients might have been insufficient to evaluate the differences due to the timing of WF administration in relation to S-1 chemotherapy use. Further studies to evaluate the effects of the timing of WF and S-1 use in patients with cancer are needed.

In conclusion, to the best of our knowledge, this retrospective chart review study is the first report to show that the timing of WF administration does not appear to be a significant factor in the drug–drug interaction that takes place between S-1, a fluoropyrimidine-based oral combination, and WF, although the low patient numbers included in the study should be taken into consideration. There were two cases of bleeding in group A, but these did not occur in the initial phase of WF administration. Therefore, the potential for an adverse drug reaction remains a concern during the whole period of the concomitant use of WF and S-1.

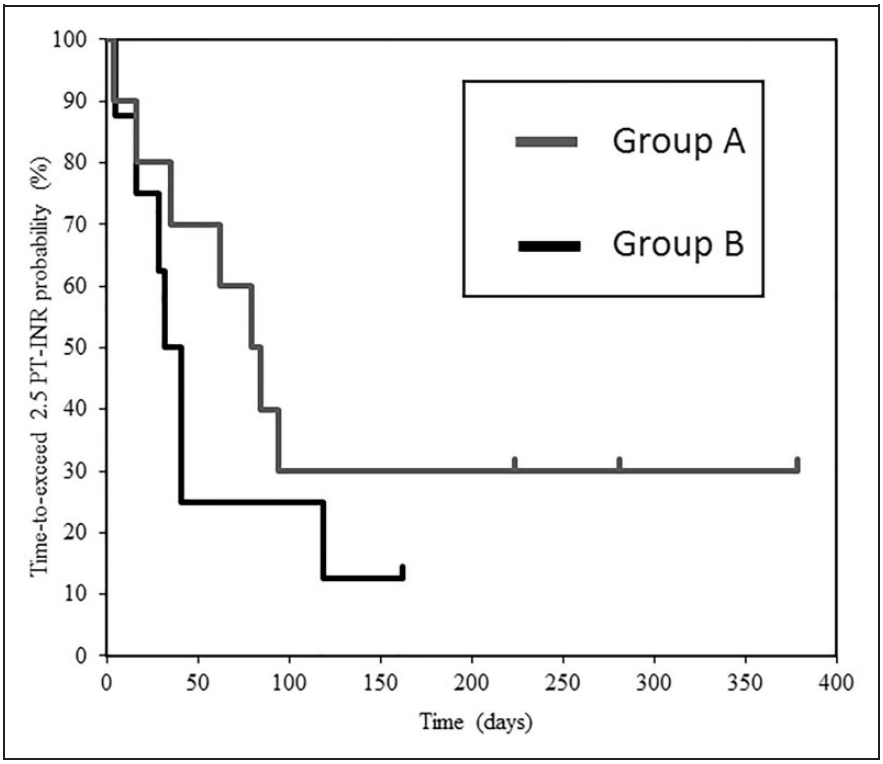

Figure 1. Time-to-exceed 2.5 prothrombin time international normalized ratio (PT-INR) in patients ($n = 18$) with gastric cancer who received warfarin either before their chemotherapy regimen (group A, $n = 8$) or during their chemotherapy regimen (group B, $n = 10$). Group A median of 32 days versus group B median of 79 days. Hazard ratio 1.71; 95% confidence interval, 0.59, 5.51; $P = 0.29$. There was no significant between-group difference ($P \geq 0.05$); log-rank test.

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Declaration of Conflicting Interests

The authors declare that there are no conflicts of interest.

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