

Marked supratherapeutic anticoagulation following S-1 therapy despite low-dose warfarin in a postgastrectomy Japanese patient: a case report highlighting sequential pharmacokinetic and pharmacodynamic risk factors

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Case Report

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Abstract

Background

The interaction between warfarin and fluoropyrimidines is well established; however, the clinical circumstances in which this interaction progresses to marked supratherapeutic anticoagulation, particularly in patients receiving low doses of warfarin, remain insufficiently characterized. We report a case illustrating how a low warfarin dose requirement and treatment-emergent clinical changes may converge to increase anticoagulant response during and after S-1 therapy.

Case presentation

A 69-year-old Japanese man with advanced gastric cancer had received warfarin for 5 years for a left ventricular thrombus. After distal gastrectomy, warfarin was maintained at 1.0 mg/day with long-term amiodarone 75 mg/day. At initiation of SOX therapy, the S-1 dose was reduced from the planned body-surface-area-based dose of 120 mg/day to 100 mg/day because of impaired renal function; estimated creatinine clearance was 46.5 mL/min. On day 13, estimated creatinine clearance transiently decreased to 41.1 mL/min, and fever, diarrhea, and anorexia developed. S-1 was completed on day 14, but diarrhea and anorexia persisted. The patient subsequently developed epistaxis and melena. On day 22, the prothrombin time-International Normalized Ratio (PT-INR) exceeded the institutional upper reportable limit (> 8.0), and the hemoglobin level decreased to 7.4 g/dL. Warfarin was discontinued, and menatetrenone was administered. Pharmacogenetic testing showed *CYP2C9* rs1057910 A/A (*CYP2C9**3 non-carrier), *VKORC1* rs9923231 A/A, *CYP4F2* rs2108622 C/C, and *GGCX* rs699664 G/G.

Conclusions

This case highlights that marked S-1-associated supratherapeutic anticoagulation can occur despite both a low warfarin dose and a reduced S-1 dose. A low warfarin dose requirement, impaired renal function during S-1 exposure, and persistent gastrointestinal symptoms may act as sequential clinical risk factors. PT-INR monitoring should be intensified when such changes occur and continued after S-1 discontinuation.

Background

Warfarin has a narrow therapeutic index and substantial interindividual variability in dose requirements. The more pharmacologically active S-enantiomer is metabolized predominantly by *CYP2C9*, whereas the pharmacodynamic effect of warfarin is mediated through inhibition of vitamin K epoxide reductase complex subunit 1 (*VKORC1*) [1]. Warfarin dose requirements are influenced by clinical factors, concomitant medications, and pharmacogenetic factors, particularly *CYP2C9* and *VKORC1* genotypes, with additional contributions from *CYP4F2* [1]. In Japanese patients, the *VKORC1* – 1639 A/A genotype is common, and maintenance warfarin doses of approximately 3 mg/day have been reported [2, 3]. Thus, a

low warfarin maintenance dose does not preclude clinically important enhancement of anticoagulation when additional risk factors are present.

Clinically significant interactions between warfarin and fluoropyrimidines, including 5-fluorouracil (5-FU), have long been recognized [4]. Pharmacokinetic and pharmacodynamic evidence supports this interaction. During capecitabine treatment, S-warfarin exposure increased by 57%, and its elimination half-life increased by 51%, accompanied by enhanced anticoagulant activity [5]. Repeated 5-FU exposure has also been shown to reduce CYP2C9 activity in patients with cancer [6]. These findings provide a pharmacological basis for enhanced warfarin activity during fluoropyrimidine treatment.

S-1 is an oral fluoropyrimidine comprising tegafur, a prodrug of 5-FU; gimeracil, an inhibitor of dihydropyrimidine dehydrogenase; and oteracil. It is widely used in the treatment of gastric cancer, either as monotherapy or as part of combination regimens [7]. Previous studies have reported prothrombin time-International Normalized Ratio (PT-INR) elevation during concomitant use of warfarin and S-1 and have characterized the occurrence, magnitude, and timing of this interaction [8–10]. However, the clinical circumstances in which this established interaction progresses to marked supratherapeutic anticoagulation, particularly in patients receiving low maintenance doses of warfarin, remain insufficiently characterized. We report the case of a Japanese patient receiving warfarin 1.0 mg/day who developed clinically significant bleeding with a PT-INR > 8.0 following S-1 treatment and examine the dynamic clinical factors that may have increased the risk of marked supratherapeutic anticoagulation during and after S-1 therapy.

Case presentation

A 69-year-old Japanese man with a history of myocardial infarction and atrial fibrillation had received warfarin for 5 years for a left ventricular thrombus. The target PT-INR had been set at 2.0–3.0. On day – 96 relative to the initiation of SOX therapy, his PT-INR was 2.51 while receiving warfarin 2.0 mg/day. He was subsequently diagnosed with stage IV gastric cancer (pT4aN3bCY1) and underwent distal gastrectomy with cholecystectomy on day – 92. After surgery, warfarin was maintained at 1.0 mg/day. Concomitant medications included long-term amiodarone 75 mg/day and aspirin 100 mg/day; other medications are listed in Table 1.

Table 1
Patient demographics and clinical characteristics

Characteristic	Details
Age, y	69
Sex	Male
Height, Weight, Body surface area	168.6 cm, 50.0 kg, 1.56 m ²
Primary Diagnosis	
Cancer Type	Advanced gastric cancer
Stage	Stage IV (pT4aN3bCY1)
Prior Surgery	Distal gastrectomy + cholecystectomy
Warfarin Therapy	
Indication	Left ventricular thrombus associated with prior myocardial infarction and atrial fibrillation
Duration of warfarin therapy, y	5
Target PT-INR	2.0–3.0
Postoperative maintenance warfarin dose	1.0 mg/day
Chemotherapy Regimen	
Protocol	SOX therapy
S-1 Dose	100 mg/day on days 1–14, followed by a 7-day rest
Oxaliplatin Dose	150 mg on day 1, every 3 weeks
Concomitant Medications, mg/day	
Aspirin	100
Amiodarone	75
Vonoprazan	10
Carvedilol	5
Enalapril	5
Furosemide	40
Abbreviations: CY1, positive peritoneal cytology; PT-INR, prothrombin time–international normalized ratio; SOX, S-1 plus oxaliplatin.	

Characteristic	Details
Dapagliflozin	10
Ferrous citrate Na	100
Abbreviations: CY1, positive peritoneal cytology; PT-INR, prothrombin time–international normalized ratio; SOX, S-1 plus oxaliplatin.	

Considering his cardiac comorbidity, postoperative chemotherapy was initiated with S-1 monotherapy 100 mg/day from day – 22 to day – 8. Based on his body surface area (approximately 1.56 m²), the planned S-1 dose was 120 mg/day; however, it was reduced to 100 mg/day because of impaired renal function. After the treatment-free interval, SOX therapy was initiated on day 1, consisting of S-1 100 mg/day on days 1–14 and oxaliplatin 150 mg on day 1. Warfarin 1.0 mg/day was continued concomitantly. The clinical course is shown in Fig. 1.

Estimated creatinine clearance (eCrCl) was calculated using the Cockcroft–Gault equation and actual body weight [11]. When body weight was not measured on the same day, the most recent preceding body weight was used. At SOX initiation, the patient’s body weight was 50.0 kg, serum creatinine level was 1.06 mg/dL, and eCrCl was 46.5 mL/min. On day 13, the patient developed a fever (> 37.5°C), diarrhea, and anorexia without upper respiratory symptoms, nausea, or abdominal tenderness. His serum creatinine level increased to 1.20 mg/dL, corresponding to an eCrCl of 41.1 mL/min. His serum albumin level decreased from 3.6 to 3.2 g/dL, whereas the C-reactive protein level increased from 1.1 to 83.4 mg/L. He was managed as an outpatient with 500 mL of intravenous lactated Ringer’s solution and symptomatic treatment. No definitive cause of the acute inflammatory response was documented. S-1 administration was completed as scheduled on day 14.

Diarrhea and anorexia persisted after S-1 discontinuation, and the patient’s body weight decreased from 50.0 kg on day 1 to 45.4 kg on day 21. On day 21, the patient developed epistaxis and melena and was subsequently hospitalized. On day 22, his PT-INR exceeded the institutional upper reportable limit (> 8.0), and warfarin was discontinued. Hemoglobin levels decreased from 14.0 g/dL on day 13 to 9.0 g/dL on day 21 and 7.4 g/dL on day 22, whereas the platelet count remained 184 × 10³/μL. Menatetrenone 10 mg/day was administered on days 22–24, and 2 units of irradiated leukocyte-reduced red blood cells were transfused on each of days 22 and 25. No endoscopic examination was performed, and the source of bleeding was not identified. Apart from menatetrenone administration and red blood cell transfusions, no additional hemostatic or anticoagulation-reversal treatment was given.

The PT-INR decreased to 1.59 on day 23, 1.25 on day 25, and 1.22 on day 27. The hemoglobin level reached a nadir of 6.6 g/dL on day 25, and the serum albumin level decreased to 1.9 g/dL. Renal function had already improved by day 22, with a serum creatinine level of 0.90 mg/dL and an eCrCl of 49.7 mL/min. No clinically meaningful elevations in alanine aminotransferase or total bilirubin were observed during the clinical course. Serial laboratory findings and body weight are summarized in Table 2.

Warfarin was restarted at 1.0 mg/day on day 28. The PT-INR was 1.56 on day 33, and the patient was discharged on day 34.

Table 2
Serial laboratory data and body weight during the clinical course

	Day relative to initiation of SOX therapy										
	-96	-22	1	13	19	21	22	23	25	27	33
PT-INR	2.51	-	-	-	-	-	> 8.00	1.59	1.25	1.22	1.56
Hb, g/dL	12.8	12.9	13.7	14.0	12.8	9.0	7.4	7.0	6.6	9.1	10.4
PLT, $\times 10^3/\mu\text{L}$	291	225	168	168	224	213	184	146	117	137	167
Alb, g/dL	3.9	3.8	3.6	3.2	2.7	2.3	2.2	2.2	1.9	2.1	2.3
CRP, mg/L	0.2	0.4	1.1	83.4	43.3	16.8	10.1	7.9	16.7	25.6	5.6
SCr, mg/dL	1.02	1.11	1.06	1.20	0.99	0.98	0.90	0.87	0.66	0.65	0.71
eCrCl, mL/min	48.7	44.4	46.5	41.1	49.8	45.7	49.7	51.5	67.8	72.7	66.5
ALT, IU/L	15	15	15	13	12	10	10	11	11	10	12
T-Bil, mg/dL	0.7	0.5	0.6	1.0	1.1	0.6	0.6	1.1	1.1	1.1	0.7
Body weight, kg	50.4	50.0	50.0	-	-	45.4	-	-	-	47.9	-
Days are relative to initiation of SOX therapy. eCrCl was estimated using the Cockcroft–Gault equation with actual body weight. When body weight was not measured on the same day, the most recent preceding body weight was used. A PT-INR value > 8.00 represents the upper reportable limit at our institution.											
Abbreviations: Alb, albumin; ALT, alanine aminotransferase; CRP, C-reactive protein; eCrCl, estimated creatinine clearance; Hb, hemoglobin; PLT, platelet count; PT-INR, prothrombin time–international normalized ratio; SCr, serum creatinine; SOX, S-1 plus oxaliplatin; T-Bil, total bilirubin.											

Pharmacogenetic testing was performed using residual whole-blood samples after verbal informed consent was obtained from the patient and documented in the medical record, in accordance with the recommendations of the Japanese Society of Clinical Pharmacology and Therapeutics [12]. No additional blood sampling was required.

Genomic DNA was extracted from the residual samples using a DNA extraction kit from QIAGEN (Hilden, Germany). Genotyping was performed using TaqMan SNP Genotyping Assays (Thermo Fisher Scientific, Waltham, MA, USA) with a CFX Connect Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA). *CYP2C9* rs1057910 was A/A (*CYP2C9*3 non-carrier), *VKORC1* rs9923231 was A/A, *CYP4F2* rs2108622 was C/C, and γ -glutamyl carboxylase (*GGCX*) rs699664 was G/G (Table 3).

Table 3
Patient pharmacogenetic characteristics

Gene / variant	Genotype	Pharmacological relevance
<i>CYP2C9</i> rs1057910	A/A (<i>CYP2C9</i> *3 non-carrier)	S-warfarin metabolism
<i>VKORC1</i> rs9923231	A/A	Warfarin target and vitamin K recycling
<i>CYP4F2</i> rs2108622	C/C	Vitamin K oxidation
<i>GGCX</i> rs699664	G/G	γ -Carboxylation of vitamin K-dependent clotting factors
Abbreviations: <i>CYP2C9</i> , cytochrome P450 family 2 subfamily C member 9; <i>CYP4F2</i> , cytochrome P450 family 4 subfamily F member 2; <i>GGCX</i> , γ -glutamyl carboxylase; <i>VKORC1</i> , vitamin K epoxide reductase complex subunit 1.		

Discussion and conclusions

The clinical significance of this case lies not in demonstrating the S-1–warfarin interaction itself, which is already established, but in illustrating a clinically recognizable setting in which a low warfarin dose requirement and treatment-emergent factors may increase the risk of marked supratherapeutic anticoagulation sequentially. The patient did not carry *CYP2C9**3, the major reduced-function *CYP2C9* allele relevant to S-warfarin metabolism in Japanese patients, whereas the *VKORC1* – 1639 A/A genotype is common in this population [2, 3]. The *CYP4F2* rs2108622 genotype was C/C, without the variant allele associated with higher warfarin dose requirements [1], whereas the clinical relevance of *GGCX* rs699664 is less well established. Thus, the marked supratherapeutic anticoagulation was not readily explained by a pharmacogenetic variant known to increase warfarin sensitivity markedly.

Previous reports have shown substantial variability in the magnitude of the S-1–warfarin interaction. PT-INR values of 6.84 and 5.82 have been reported in individual cases [13, 14], and increases to 3.79–4.92 were observed in patients receiving warfarin 1.5–3.5 mg/day [15]. PT-INR elevation to 3.49 has also been reported despite reduction of warfarin to 1.0 mg/day [16]. Importantly, Hata and colleagues demonstrated that PT-INR normalized to the current warfarin dose increased from 0.85 before fluoropyrimidine chemotherapy to a maximum of 1.41 despite warfarin dose reductions [10]. In the present patient, the PT-INR exceeded 8.0 with clinically significant bleeding while warfarin was maintained at only 1.0 mg/day. This dose was substantially lower than typical maintenance doses reported in Japanese cohorts [2, 3], suggesting a relatively low individual warfarin dose requirement.

Long-term amiodarone therapy, which is known to reduce warfarin dose requirements [17], may have contributed to this baseline setting; because it had been administered concomitantly with warfarin for approximately 5 years before the present event, it was unlikely to represent an acute trigger. Notably, S-1 had also been reduced from the planned 120 mg/day to 100 mg/day because of the patient's impaired renal function. Thus, marked supratherapeutic anticoagulation may occur even during low-dose warfarin therapy despite reduction of the S-1 dose, underscoring the need for careful PT-INR monitoring.

Renal dysfunction and gastrointestinal symptoms may have acted as temporally linked pharmacokinetic and pharmacodynamic risk factors. Renal function remained impaired at approximately 40–50 mL/min throughout and shortly after S-1 administration, with an eCrCl of 46.5 mL/min at SOX initiation, 41.1 mL/min on day 13, and 49.7 mL/min on day 22. Because gimeracil is eliminated predominantly by the kidneys and inhibits dihydropyrimidine dehydrogenase, persistent renal impairment may have reduced gimeracil clearance, thereby increasing gimeracil exposure and reducing 5-FU catabolism, with a consequent increase in systemic 5-FU exposure [18, 19]. Diarrhea and anorexia developed on day 13 and persisted after S-1 discontinuation. Although both are recognized adverse effects of S-1 [20], their etiology in this patient remained uncertain, because fever and a marked inflammatory response occurred simultaneously. Persistent diarrhea and anorexia may also have reduced intestinal vitamin K absorption and dietary vitamin K intake, respectively. Acute diarrhea is associated with supratherapeutic anticoagulation in patients receiving vitamin K antagonists [21], and lower dietary vitamin K intake has been associated with unstable warfarin anticoagulation [22]. This clinical setting may be particularly relevant in postgastrectomy patients with gastric cancer, in whom anorexia and diarrhea frequently necessitate S-1 dose reduction, lower creatinine clearance has been associated with a greater tendency to require dose modification, and postoperative body weight loss has been associated with poorer continuation of S-1 therapy [23, 24]. In the present patient, body weight decreased from 50.0 kg on day 1 to 45.4 kg on day 21, accompanied by a decline in the serum albumin level from 3.6 to 1.9 g/dL, findings consistent with substantial deterioration in nutritional and overall clinical status. Taken together, persistent renal impairment during S-1 treatment may have increased fluoropyrimidine exposure, whereas gastrointestinal symptoms and reduced oral intake extending beyond S-1 discontinuation may have increased warfarin sensitivity through reduced vitamin K availability.

Several limitations should be acknowledged. The PT-INR was not measured immediately before or during the second S-1 treatment period; therefore, although a PT-INR > 8.0 was documented on day 22, this represents the first documented severe elevation rather than the confirmed onset or peak of supratherapeutic anticoagulation. Plasma concentrations of R- and S-warfarin, gimeracil, and 5-FU were not measured, and vitamin K availability, including dietary intake and intestinal absorption, was not directly assessed. Consequently, the proposed pharmacokinetic and pharmacodynamic pathways cannot be directly confirmed, and the temporal sequence of these risk factors should be regarded as a clinically plausible interpretation rather than a demonstrated mechanism. Nevertheless, the timing remains clinically informative. Yamada et al. reported PT-INR elevation within 3 weeks of S-1 initiation in all nine patients studied [8], whereas Hata et al. reported a median time of 46.5 days to maximal PT-INR/dose in the S-1 group [10]. In the present patient, a PT-INR > 8.0 was detected approximately 44 days

after initiation of the first recorded S-1 treatment period and 8 days after completion of the second treatment period. These observations emphasize that clinically important supratherapeutic anticoagulation may become apparent after S-1 has already been discontinued.

In conclusion, this case demonstrates that marked supratherapeutic anticoagulation can occur during S-1 therapy, even with warfarin 1.0 mg/day and a reduced S-1 dose, in the absence of the major reduced-function *CYP2C9*3* allele. The clinical significance of this case lies in the convergence of a low individual warfarin dose requirement with persistent renal impairment during S-1 exposure and gastrointestinal symptoms extending beyond treatment, highlighting the importance of integrating dynamic clinical changes with baseline dose requirements and pharmacogenetic information when assessing anticoagulation risk. Close PT-INR monitoring is warranted when such dynamic clinical changes occur and should be continued after S-1 discontinuation.

Abbreviations

5-FU
5-fluorouracil
Alb
albumin
BSA
body surface area
CRP
C-reactive protein
eCrCl
estimated creatinine clearance
GGCX
γ-glutamyl carboxylase
Hb
hemoglobin
PLT
platelet count
PT-INR
prothrombin time–international normalized ratio
SCr
serum creatinine
SOX
S-1 plus oxaliplatin
VKORC1
vitamin K epoxide reductase complex subunit 1.

Declarations

Ethics approval and consent to participate:

Ethics approval was not required for this case report.

Consent for publication:

Written informed consent was obtained from the patient for publication of this case report, including the pharmacogenetic findings.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

S.Y. collected and analyzed the clinical data, interpreted the findings, and drafted the manuscript. T.M., E.Y., Y.M., K.H., and K.I. were involved in the clinical management of the patient and critically reviewed the manuscript. T.N. contributed to the interpretation of the findings and drafted and critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials:

All data relevant to this case are included in this article.

References

1. Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther. 2017;102:397–404. 10.1002/cpt.668.

2. Obayashi K, Nakamura K, Kawana J, Ogata H, Hanada K, Kurabayashi M, et al. VKORC1 gene variations are the major contributors of variation in warfarin dose in Japanese patients. *Clin Pharmacol Ther.* 2006;80:169–78. 10.1016/j.clpt.2006.04.010.
3. Tanaka T, Ihara M, Fukuma K, Yamamoto H, Washida K, Kimura S, et al. Influence of renal impairment and genetic subtypes on warfarin control in Japanese patients. *Genes (Basel).* 2021;12:1537. 10.3390/genes12101537.
4. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. *Clin Colorectal Cancer.* 2005;5:175–80. 10.3816/ccr.2005.n.028.
5. Camidge R, Reigner B, Cassidy J, Grange S, Abt M, Weidekamm E, et al. Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer. *J Clin Oncol.* 2005;23:4719–25. 10.1200/JCO.2005.09.129.
6. Gunes A, Coskun U, Boruban C, Gunel N, Babaoglu MO, Sencan O, et al. Inhibitory effect of 5-fluorouracil on cytochrome P450 2C9 activity in cancer patients. *Basic Clin Pharmacol Toxicol.* 2006;98:197–200. 10.1111/j.1742-7843.2006.pto_304.x.
7. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2025 (7th edition). *Gastric Cancer.* 2026;29(2):271–299. 10.1007/s10120-025-01698-4
8. Yamada T, Watanabe H, Yano T, Nonaka T, Takada A, Sonoda M, et al. Timing of expression of blood coagulation abnormality in patients treated with warfarin and S-1 concomitantly. *Yakugaku Zasshi.* 2010;130:955–60. 10.1248/yakushi.130.955. . [in Japanese].
9. Suzuki S, Ikegawa K, Yamamoto K, Saito S. Evaluation of the anticoagulant effect and timing of the concomitant use of S-1 and warfarin. *J Int Med Res.* 2016;44:1123–30. 10.1177/0300060516658162.
10. Hata T, Kudo T, Sakai D, Takahashi H, Haraguchi N, Nishimura J, et al. Impact of capecitabine and S-1 on anticoagulant activity of warfarin in patients with gastrointestinal cancer. *Cancer Chemother Pharmacol.* 2016;78:389–96. 10.1007/s00280-016-3080-0.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31–41. 10.1159/000180580.
12. Japanese Society of Clinical Pharmacology and Therapeutics Scientific Committee. Clinical use of pharmacogenetic tests: an official statement issued by the Japanese Society of Clinical Pharmacology and Therapeutics. *Jpn J Clin Pharmacol Ther.* 2022;53:155–7. 10.3999/jscpt.53.4_155. . [in Japanese].
13. Marutaka M, Kubota Y, Yoshida R, Orita Y. Difficult management of warfarin anticoagulant therapy due to S-1 administration for gastric cancer: report of a case. *Gan Kagaku Ryoho.* 2009;36:1561–3. [in Japanese].
14. Watanabe H, Itoh H, Tsuchiya Y, Miyagi N, Sugiyama T, Nakai Y, et al. Reinforcement of warfarin action in a patient administered S-1. *Gan Kagaku Ryoho.* 2015;42:131–3. [in Japanese].
15. Yamamuro F, Miki A, Kondo G, Maeda T, Satoh H, Hori S, et al. Individual differences in prothrombin time-international normalized ratio variation following coadministration of the anticancer agents S-1

- and warfarin: 3 case reports. *Int J Clin Pharmacol Ther*. 2011;49:700–4. 10.5414/CP201494.
16. Terui K, Takahata T, Sato J, Ishiguro A, Itoh J, Hayakari M, et al. Enhancement of warfarin anticoagulant activity by S-1. *Hirosaki Med J*. 2011;62:80–5. 10.32216/hirosakiigaku.62.1_80.
 17. Sanoski CA, Bauman JL. Clinical observations with the amiodarone/warfarin interaction: dosing relationships with long-term therapy. *Chest*. 2002;121:19–23. 10.1378/chest.121.1.19.
 18. Booka E, Imamura CK, Takeuchi H, Hamamoto Y, Gomi D, Mizukami T, et al. Development of an S-1 dosage formula based on renal function by a prospective pharmacokinetic study. *Gastric Cancer*. 2016;19:876–86. 10.1007/s10120-015-0536-6.
 19. Fujita K, Yamamoto W, Endo S, Endo H, Nagashima F, Ichikawa W, et al. CYP2A6 and the plasma level of 5-chloro-2,4-dihydroxypyridine are determinants of the pharmacokinetic variability of tegafur and 5-fluorouracil, respectively, in Japanese patients with cancer given S-1. *Cancer Sci*. 2008;99:1049–54. 10.1111/j.1349-7006.2008.00773.x.
 20. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357:1810–20. 10.1056/NEJMoa072252.
 21. Schweinfurth J, Bauer A, Bauer F, Seibert FS, Rohn B, Seidel M, et al. The impact of acute diarrhea on the coagulation status of patients with vitamin K antagonists. *Sci Rep*. 2021;11:11726. 10.1038/s41598-021-91316-x.
 22. Sconce E, Khan T, Mason J, Noble F, Wynne H, Kamali F. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. *Thromb Haemost*. 2005;93:872–5. 10.1160/TH04-12-0773.
 23. Iwasa S, Yamada Y, Fukagawa T, Nakajima TE, Kato K, Hamaguchi T, et al. Management of adjuvant S-1 therapy after curative resection of gastric cancer: dose reduction and treatment schedule modification. *Gastric Cancer*. 2011;14:28–34. 10.1007/s10120-011-0003-y.
 24. Aoyama T, Yoshikawa T, Shirai J, Hayashi T, Yamada T, Tsuchida K, et al. Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer. *Ann Surg Oncol*. 2013;20:2000–6. 10.1245/s10434-012-2776-6.
 25. Booka E, Imamura CK, Takeuchi H, Hamamoto Y, Gomi D, Mizukami T, et al. Development of an S-1 dosage formula based on renal function by a prospective pharmacokinetic study. *Gastric Cancer*. 2016;19:876–86. 10.1007/s10120-015-0536-6.

Figures

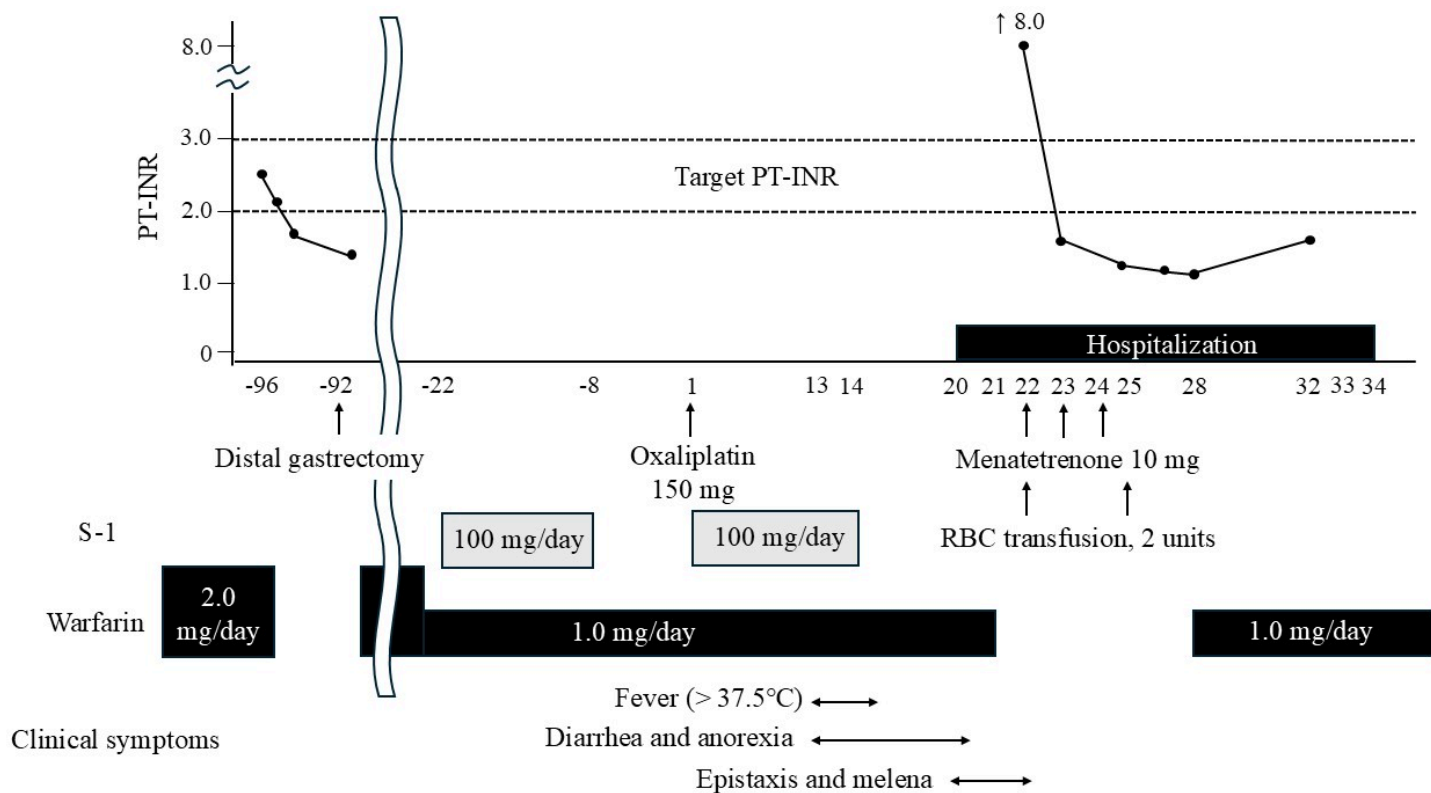


Figure 1

Clinical course of S-1 and warfarin therapy, clinical symptoms, and changes in the PT-INR.

Day 1 indicates the initiation of SOX therapy. S-1 was also administered from day -22 to day -8. The shaded area indicates the target PT-INR range of 2.0–3.0. A PT-INR > 8.0 represents the upper reportable limit at our institution. Warfarin was discontinued on day 22 and restarted at 1.0 mg/day on day 28. Menatetrenone 10 mg/day was administered on days 22–24. Two units of red blood cells were transfused on each of days 22 and 25.