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Effect of Liver Dysfunction on S-1 Therapy Induced Adverse Effects: A Retrospective Cohort Study

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Abstract. *Background/Aim: Renal dysfunction necessitates S-1 dose reduction. However, decreased dihydropyrimidine dehydrogenase (DPD) activity may lead to adverse events due to 5-FU. The guidelines provided by pharmaceutical companies state that total bilirubin (T-Bil) should be ≤upper limit of normal (ULN)×1.5 as a reference value for safely taking S-1. Nevertheless, the relationship between the degree of liver dysfunction and S-1 dose reduction has not been clearly established. Patients and Methods: This study focused on patients who received S-1 monotherapy for various types of cancer. The primary outcome was defined as the variation between blood sampling results on the test day and the subsequent test. The variation data were categorized based on the difference in T-Bil: Low T-Bil group (≤2.25) and High T-Bil group (>2.25). Results: The number of patients that underwent S-1 monotherapy was 883 and the running number was 7,511; Low T-Bil group included 7,245 and High T-Bil group included 266. Examination of the effect of the T-Bil Group on clinical outcomes revealed a correlation with red blood cell (RBC) count, platelet (PLT) count, and T-Bil level. When the impact of the interaction between the T-Bil Group and any of the clinical outcomes, such as the RBC count, PLT count, and T-Bil level, was determined, each outcome showed a significant decrease in the High T-Bil group compared with the Low T-Bil group. Conclusion: S-1 administration in patients with liver dysfunction accompanied by elevated T-Bil levels may cause thrombocytopenia.*

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Key Words: S-1, liver dysfunction, bilirubin, thrombocytopenia, side effects.

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S-1 is an anticancer preparation administered for various types of cancer in Japan, including gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, and biliary tract cancer (1-8). S-1 consists of tegafur, gimeracil, and oteracil potassium. The results of a post-marketing survey for S-1 administered to patients with advanced gastric cancer showed that those with a creatinine clearance of ≤49 ml/min had a higher incidence of developing Grade 3 or higher adverse events (9). Based on this result, the recommended dose of S-1 was determined based on the renal function and was included in the guide for proper use issued by the pharmaceutical company. In terms of liver function, the guide provides the following reference values for the safe administration of S-1: total bilirubin (T-Bil), ≤ULN×1.5; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), ≤ULN×2.5. However, as the basis for these values were from various clinical studies with different selection criteria for the participants, the incidence rate for adverse events when S-1 is administered to patients with impaired liver function was not considered. Aside from S-1, there are several anticancer drugs that can cause adverse events when administered to patients with liver dysfunction.

Raymond *et al*. reported that irinotecan administration to patients whose T-Bil at the start of therapy was 3.6-5.8 times that of the ULN caused further deterioration in liver function and exacerbation of hepatic tumors as well as decreased performance status (10). John *et al*. reported that gemcitabine administration to a group of patients with a median T-Bil of 2.7 mg/dl (range=1.7-5.7 mg/dl) caused a significant deterioration in liver function (11).

S-1 is an oral combined form of 1M tegafur [FT, a prodrug of 5-fluorouracil (5-FU)], 0.4M 5-chloro-2,4-dihydroxypyridine (CDHP, a reversible inhibitor of DPD), and 1M potassium oxonate [Oxo, an inhibitor of orotate phosphoribosyl transferase (OPRT)]. The antitumor activity of S-1 can be attributed to 5-fluoronucleotides, such as 5-Fluoro-2'-deoxyuridine-5'-phosphoric acid, which is an active metabolite of 5-FU that is converted from FT mainly by CYP2A6. CDHP increases the concentration of 5-FU derived from FT by selectively inhibiting DPD, a catabolic enzyme of 5-FU that is predominantly distributed in the liver. With the increased concentration of 5-FU in the body, 5-fluoronucleotide, which is an active metabolite of 5-FU, is maintained at a high concentration in the tumor, which enhances the antitumor effect. After administration, Oxo is mainly distributed in gastrointestinal tissue and selectively inhibits OPRT and suppresses the conversion of 5-FU to uridine fluoride 1 phosphate. As a result, gastrointestinal disorders are alleviated without compromising the strong antitumor effect of 5-FU (12, 13).

In terms of the relationship between the pharmacokinetics of the medicinal components constituting S-1 and renal function, CDHP has the strongest correlation owing to its high renal excretion rate. CDHP has a 52.8% renal excretion rate up to 72 hours after administration (14). Therefore, CDHP clearance will decrease because of the decreased renal function, leading to an increase in 5-FU concentration. However, considering the relationship between the pharmacokinetics of the medicinal components constituting S-1 and liver function, it is necessary to also consider its effects on 5-FU concentration. As FT is converted to 5-FU by the hepatic metabolizing enzyme CYP2A6, which is then metabolized by DPD that is widely distributed in the liver, 5-FU concentration is low in patients with decreased liver function in whom the effect of S-1 is expected to be lower than that in normal patients. Previous reports have shown that CYP2A6 mRNA levels and CYP2A6 activity are correlated (15, 16). However, the results of a study in which S-1 was administered to Japanese patients states that even if the activity level of CYP2A6 decreases, the pharmacokinetics of 5-FU are not affected, and 5-FU activity is not decreased (17). Furthermore, it has been reported that when liver function declines, the DPD mRNA expression level decreases, and DPD activity also decreases, resulting in a possible increase in the incidence rate of adverse events caused by 5-FU (16). Based on the above, it is possible that decreased liver function increases the incidence of adverse events; however, it has not been clarified how decreased liver function during treatment affects the incidence of adverse events.

Table I. *Patient background (prior to chemotherapy).*

Patients receiving S-1 monotherapy (n=883).	
Age (years)	70.0 (62.0-76.0)
Sex (male)	579 (65.6%)
BMI (kg/m^2)	20.6 (18.4-23.0)
BSA (m^2)	1.5 (1.4-1.7)
Metastatic liver tumor	74 (8.4%)
T-Bil (mg/dl)	0.70 (0.6-1.0)
AST (IU/l)	22.0 (17.0-30.0)
ALT (IU/l)	16.0(11.0-26.0)
WBC (×10^3/μl)	5.3 (4.1-6.7)
ANC (×10^3/μl)	3.2 (2.4-4.4)
RBC (×10^6/μl)	3.8 (3.4-4.2)
Hb (g/dl)	11.6 (10.4-12.6)
PLT (×10^4/μl)	20.3 (15.6-25.8)
sCr (mg/dl)	0.8 (0.60-0.90)
eGFRcreat (ml/min/1.73 m^2)	71.6 (60.3-85.6)

BMI: Body mass index; BSA: body surface area; T-Bil: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cells; ANC: absolute neutrophil count; RBC: red blood cells; Hb: hemoglobin, PLT: platelets; sCr: serum creatinine; eGFRcreat: estimated glomerular filtration rate using serum creatinine; eGFRcreat: estimated glomerular filtration rate using serum creatinine.

As S-1 can be a key drug for treating many types of cancer, some cancer patients who require S-1 therapy develop liver dysfunction during treatment. Therefore, it is necessary to predict the occurrence of adverse events that can be caused by S-1 therapy when administered to patients with liver dysfunction. Furthermore, it is crucial to determine how the severity of the impairment can affect the incidence rate of adverse events when selecting anticancer therapy for cancer patients with liver dysfunction. At this stage, the safety of S-1 in patients with liver dysfunction has not been established, and it is ethically unacceptable to verify it in prospective clinical trials. Therefore, we retrospectively investigated how liver function affects the incidence rate of adverse reactions caused by S-1 using the records of patients who have been previously treated with S-1.

Patients and Methods

Participants. The participants were patients who underwent S-1 monotherapy at the Fujita Medical University Hospital from January 2012 to December 2018 for gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, and biliary tract cancer.

Investigations. This is a retrospective observational cohort study in which information on target patients was collected using electronic medical records at the Fujita Medical University Hospital. Patient data were collected by accessing electronic medical records in

Table II. *Effect of liver function*.

	Variable	Coefficient	95%CI	*p*-Value	*p*-Value for interaction
ΔWBC	T-Bil	–0.277	–0.930-0.376	0.134	0.083
	Days (32–185.5)	–0.216	–0.324-(–0.108)	<0.001	
ΔANC	T-Bil	–0.476	–1.809-0.875	0.387	0.371
	Days (32–185.5)	–0.243	–0.404-(–0.082)	0.029	
ΔRBC	T-Bil	0.004	–0.058-0.066	0.008	0.039
	Days (32–185.5)	0.075	0.060-0.091	<0.001	
ΔHb	T-Bil	–0.065	–0.246-0.116	0.013	0.186
	Days (32–185.5)	0.085	0.041-0.129	<0.001	
ΔPLT	T-Bil	0.239	–0.542-1.020	0.02	0.01
	Days (32–185.5)	–0.101	–0.333-0.131	<0.001	
ΔT-Bil	T-Bil	–0.601	–1.023-(–0.179)	<0.001	0.012
	Days (32–185.5)	–0.047	–0.071-(–0.023)	<0.001	
ΔAST	T-Bil	4.326	–23.666-32.318	0.09	0.097
	Days (32–185.5)	0.635	–2.019-3.289	0.268	
ΔALT	T-Bil	0.79	–13.546-15.126	0.292	0.433
	Days (32–185.5)	–0.044	–2.097-2.009	0.357	

August 2019. Some authors had access to identifiable information about individual participants during or after data collection. The study period for each patient was 365 days from initiation of S-1 therapy or seven days after the end of S-1 therapy, depending on which duration was shorter.

Data aggregation was performed by test value and not by patient. Data were classified into two groups for comparison: The primary outcome was defined as the variation between blood sampling results of the test day and the subsequent test. The variation data were divided based on the difference in T-Bil: Low T-Bil group (≤2.25) and High T-Bil group (>2.25). The cutoff value of 2.25 mg/dl was computed from the upper limit of the T-Bil level recommended in the guideline issued by the pharmaceutical company and the upper limit of the T-Bil level in Japan (1.5 mg/dl) (18), which corresponds to 2.25 mg/dl. In terms of patient background, we analyzed age, sex, body mass index, body surface area, and the presence or absence of metastatic liver tumors at the initiation of S-1 therapy. T-Bil level, white blood cell (WBC) count, RBC count, platelet (PLT) count, hemoglobin (Hb), absolute neutrophil count (ANC), serum creatinine level, and estimated glomerular filtration rate were analyzed as blood biochemical test values during the survey period. The primary outcome was defined as the difference in clinical parameters between blood sampling results of the test day and the subsequent test day, confirmed using the multivariable linear regression model with robust covariance.

Statistical analysis. Demographic and clinical variables were summarized using median and interquartile range. Categorical variables were summarized using frequencies and percentages.

The effect of the T-Bil Group on the variation in clinical outcomes until the next measurement (ΔWBC, ΔANC, ΔRBC, ΔHb, ΔPLT, ΔT-Bil, ΔAST, and ΔALT) was confirmed using the multivariable linear regression model with robust covariance. The explanatory variables in the multivariable regression model included the T-Bil Group at each measurement several days after S-1 administration, and covariates for adjustment of confounding variables. Each model was adjusted for pre-defined covariates, including age, sex, and the baseline value of each outcome. An interaction term (T-Bil Group×days) was also included in the model to confirm the modifying effect of T-Bil on days and outcomes. As there were multiple measurements for each patient, the Huber-White robust sandwich estimator (19) was used to calculate the variance estimator of the regression coefficients. Nonlinear associations between each outcome and days after administration of S-1 were assessed by including nonlinear cubic splines with three knots in the regression model. We also performed regression analysis by replacing the T-Bil Group with a continuous variable before binarization. We concluded that there was a significant relationship when the *p*-value of the global test for the regression coefficient of the T-Bil Group for each outcome was <0.05. The modifying effect of T-Bil was deemed significant when the *p*-value of the global test for the interaction term was <0.05. Statistical analyses were performed using R version 4.0.3. (The R Project for Statistical Computing, www.r-project.org).

Ethics. This study was approved by the Ethical Review Board of the Fujita Health University. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and

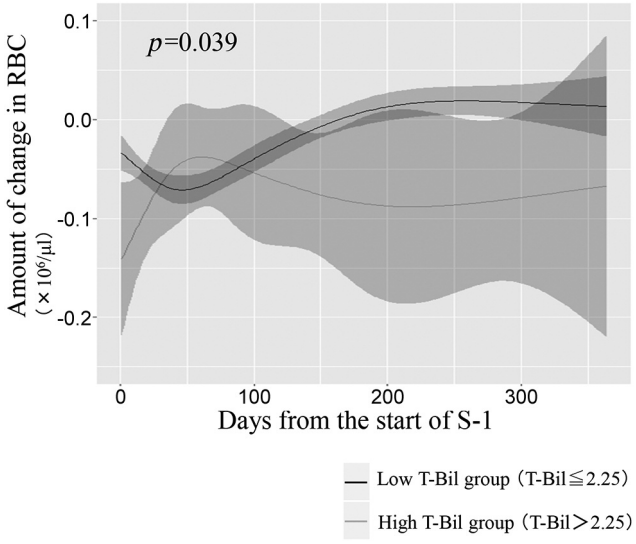

Figure 1. *Amount of change in red blood cells (RBC).*

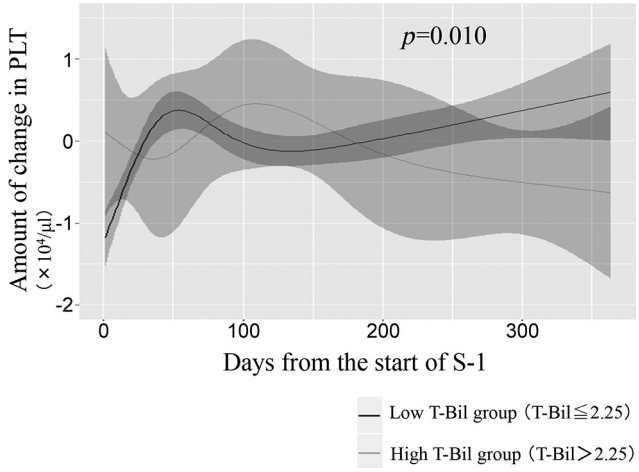

Figure 2. *Amount of change in platelet (PLT) count.*

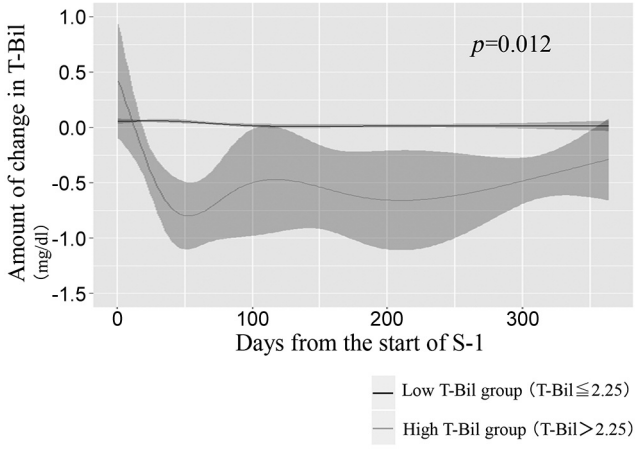

Figure 3. *Amount of change in total bilirubin (T-Bil).*

with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The requirement for obtaining patients' informed consent was waived by the ethics review board of Fujita Health University due to the retrospective nature of the study.

Results

Patients. The number of cases treated with S-1 monotherapy during the target period was 883, and the number of test values was 7,245 in Low T-Bil group and 266 in High T-Bil group. The median age of all patients was 70 years. The median liver function parameters of all patients at the start of S-1 therapy were as follows: T-Bil, 0.7 mg/dl; AST, 22 IU/l; and ALT, 16 IU/l, all of which were within their respective reference ranges (20) (Table I).

Safety. We examined the correlation between various test values and the T-Bil level and number of days (Table II). The results showed a clear correlation with the RBC count, PLT count, and T-Bil level, but there was no correlation with the WBC count, ANC, Hb level, and AST and ALT levels. The resulting data were then divided into two groups (Low T-Bil group and High T-Bil group) and investigated how differences in liver function affected the temporal fluctuation of the RBC count, PLT count, and T-Bil level during S-1 therapy. A significant decrease in the High T-Bil group compared to the Low T-Bil group was observed in the RBC and PLT counts after approximately 90 days (Figure 1) and approximately 180 days (Figure 2) after the initiation of therapy, respectively. The T-Bil level significantly decreased 10 days following the commencement of S-1 therapy in the High T-Bil group and reached a steady state (Figure 3). To confirm the influence of T-Bil on changes in RBC count, PLT count, and T-Bil level, we created and evaluated prediction models for changes in test values by further dividing the outcomes based on the T-Bil level as follows: 0.8 mg/dl, 2.25 mg/dl, 4 mg/dl, 7 mg/dl, and 10 mg/dl. The difference in RBC count was not affected by the value of the T-Bil level (p=0.703). The difference in PLT count tended to be inversely related to the T-Bil level (p=0.084) (Figure 4). The difference in the T-Bil was affected by the T-Bil level, and a significant decrease was observed in the difference as the T-Bil level increased (p<0.001) (Figure 5).

Discussion

S-1 plays an important role in cancer chemotherapy in Japan. Since S-1 is a drug that is mainly excreted through

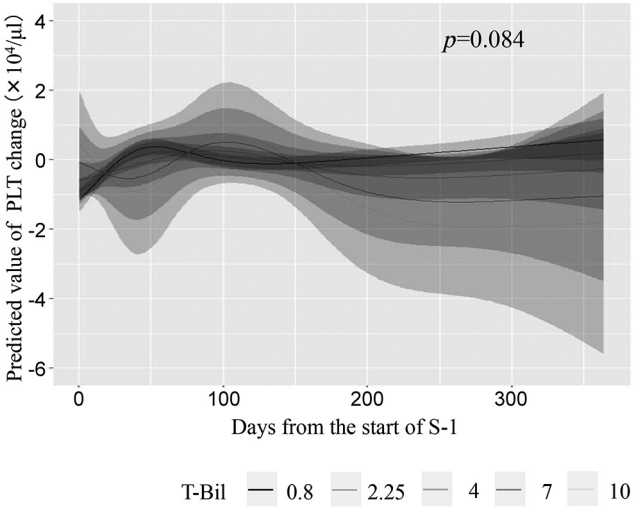

Figure 4. *Predicted value of platelet (PLT) count change.*

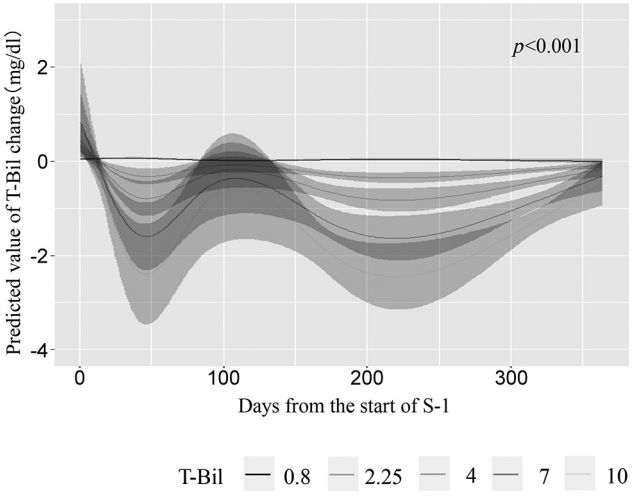

Figure 5. *Predicted value of total bilirubin (T-Bil) change.*

the kidneys, dose adjustment according to renal function is necessary to avoid adverse events. However, the relationship between liver function and the occurrence of adverse events has not been clarified. As the proportion of elderly people grows and the need for cancer treatment increases, it is important to gather data that can form the basis for dose adjustment of S-1 after clarifying the relationship between the values that indicate renal and/or liver function and adverse events. In this study, we retrospectively compared the occurrence of adverse events in patients with decreased liver function, which may possibly affect the pharmacokinetics of S-1. The median age of the patients included in this study was 70 years, which was not greatly different from the participant groups of other clinical trials involving cancer patients. Furthermore, the fact that liver and renal functions prior to the initiation of S-1 treatment and the median test values in the patients' backgrounds were all within their respective normal ranges meant that the results of this study can be regarded as being more accurate.

The amount of change in the RBC and PLT counts was larger when S-1 was administered in the High T-Bil group (T-Bil >2.25 mg/dl) than when it was administered in the Low T-Bil group (T-Bil ≤2.25 mg/dl). The RBC and PLT counts decreased significantly after approximately 90 days and 180 days, respectively. Since 5-FU is metabolized in the liver, it is recommended to refrain S-1 administration if the T-Bil level is 5 mg/dl or higher (21). The results also showed that the higher the T-Bil level, the lower the PLT count tended to be, and when the T-Bil level exceeded 7 mg/dl, PLT count decreased by approximately 20,000. Furthermore, when the T-Bil level was >2.25 mg/dl during administration, it decreased during S-1 therapy. The analysis also showed that a higher T-Bil level correlated with a higher rate of decrease in PLT count. These results suggest that when S-1 therapy is used for patients with T-Bil level of >2.25 mg/dl, T-Bil level and PLT decrease further. In addition, this phenomenon suggests that a higher T-Bil level can lead to severe thrombocytopenia, due to the higher rate of decrease in PLT; this should be noted as it may lead to severe thrombocytopenia. The results of this study showed that even during cytopenia, the PLT count showed a strong correlation with the deterioration in liver function. Similar to carboplatin-induced thrombocytopenia being closely related to a decrease in renal function (22), S-1-induced thrombocytopenia may have a strong impact on liver dysfunction. In this study, 8.4% of target patients had liver metastases. One of the reasons the rate of decrease in the T-Bil level was high in patients with high T-Bil levels may be attributed to hepatic metastasis causing impaired excretion of bile into the small intestine, resulting in extrahepatic cholestasis and hyperbilirubinemia, and that the addition of S-1 may have caused the decrease in the T-Bil level. Although it is appropriate to use T-Bil as an indicator for liver dysfunction aside from the AST and ALT levels and Child-Pugh scores, we believe that it is necessary to include such markers in future considerations of overall liver function and their influence on the occurrence of adverse events due to S-1. Regarding the adjustment of the S-1 dose according to renal function, the attending physician was advised during clinical practice that the standard dose would need to be reduced by one step when 40 ≤CLcr (ml/min) <60, two steps when 30 ≤CLcr (ml/min) <40 and discontinued when CLcr (ml/min) <30. Thus, the S-1 dose was administered as determined by the attending physician based on the patient's parameters (*i.e.*, performance status,

age, and renal function). While this may introduce a potential bias in the evaluation of the results, we consider the results of this study are valuable in demonstrating the S-1 treatment course at a T-Bil level that prohibits its use. Additionally, it is important to note that the same patient may fall into both the Low T-Bil group and High T-Bil group during the grouping in this study, thus caution should be exercised in evaluating the results. Moreover, the cancer types of the enrolled patients are not indicated, as it is unlikely that the expression of hematotoxicity by S-1 would differ based on cancer type.

Yoshisue *et al*. (23) found that administration of S-1 to rats with nitrosamine-induced liver dysfunction reduced the conversion of FT to 5-FU without altering the activity of DPD, which metabolizes 5-FU. In their study, the decline in CYP activity may have been reflected in the decrease in conversion to 5-FU, and as a result, a decrease in Cmax and the area under the curve for 5-FU were observed. Their results suggested that S-1 administration at the time of onset of liver dysfunction may have led to a reduction in adverse events, which are different from the results revealed in our study. There is a possibility that liver dysfunction, indicated by the T-Bil value, strongly reflects the increase in 5-FU serum concentration caused by a decline in DPD activity, rather than an induced decline in CYP2A6 activity associated with the conversion of FT to 5-FU.

In Japan, chemotherapy regimens containing S-1 are used to treat various types of cancer. In terms of chemotherapy for advanced recurrent gastric cancer, S-1 + cisplatin has been the first-line therapy following the results of the SPIRITS trial (24). Currently, the combination of oxaliplatin and S-1 therapy (SOX) is being used as first-line treatment based on the results of the G-SOX study (25). In terms of postoperative adjuvant chemotherapy for pancreatic cancer, S-1 monotherapy showed good results, with a median overall survival of 46.5 months in the JASPAC study (6). For advanced recurrent colorectal cancer, SOX + bevacizumab therapy, which is a combination of S-1, oxaliplatin, and bevacizumab, is recommended as first-line treatment based on the results of the SOFT study (26). Based on the above studies, S-1 plays an important role in cancer chemotherapy in Japan. Since the enrollment criteria for these clinical trials excluded patients with T-Bil levels greater than 1.5 of ULN, we believe that data regarding the administration of S-1 to patients with high T-Bil levels is invaluable. The results of this study provide important insights into the assessment of the safety of regimens containing S-1 for patients with high T-Bil levels.

Conclusion

S-1 administration in patients with liver dysfunction accompanied by elevated T-Bil levels may cause thrombocytopenia. However, our results suggest that by administering S-1 when the T-Bil level is high, there is a tendency for the T-Bil value to improve.

Conflicts of Interest

The Authors have no conflicts of interest to declare that are relevant to the content of this article.

Authors' Contributions

YA and YS designed the study. YA, YS, SN-T, NM-H contributed to data acquisition. IT, YA, TH, YI analyzed and interpreted the data. YS and YA drafted the manuscript. K I, KK, K I, S Y substantively revised the manuscript. All Authors read and approved the final manuscript.

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