Comparison of Sinusoidal Obstruction Syndrome in Gastric Cancer Patients Receiving S-1/oxaliplatin *Versus* Capecitabine/oxaliplatin

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Abstract. *Background/Aim: Oxaliplatin-based chemotherapy is associated with hepatic sinusoidal obstruction syndrome (SOS). Patients and Methods: We analyzed patients from two prospective trials, in which capecitabine/oxaliplatin (XELOX, 8 cycles; n=51) and S-1/oxaliplatin [SOX, continuous (SOX-C, n=50), or intermittent (discontinuation after cycle 6 and restart on progression, SOX-I, n=50)] were administered. We compared severity (splenomegaly, thrombocytopenia, liver enzyme levels, and hepatic parenchymal heterogeneity), clinical significance (delay or dose-reduction of chemotherapy), and reversibility of SOS (splenomegaly and thrombocytopenia after stopping chemotherapy) between SOX and XELOX in gastric cancer patients. Results: SOX was more likely to be associated with splenomegaly, thrombocytopenia, hyperbilirubinemia, and hepatic parenchymal heterogeneity than XELOX. Splenomegaly was partially reversible after stopping chemotherapy in both regimens, but recovery rate was lower in SOX. Proportion of delayed or dose-reduced chemotherapy cycles due to thrombocytopenia was significantly higher in SOX-C than in XELOX. Conclusion: S-1 combination is more likely to worsen oxaliplatin-induced hepatic sinusoidal injuries than capecitabine in gastric cancer patients.*

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Key Words: Gastric cancer, sinusoidal obstruction syndrome, oxaliplatin, S-1, capecitabine.

Various chemotherapeutic agents can cause liver injury by inflicting direct toxic effects on hepatocyte or biliary ducts, or by indirect mechanisms such as alterations in lipid metabolism or damage to the hepatic vascular network (1). Drug-induced injury to the hepatic sinusoidal endothelial cells may cause disruption of the sinusoidal wall, sinusoidal dilatation, peri-sinusoidal fibrosis, and obliteration of the hepatic venules, leading to sinusoidal obstruction syndrome (SOS) (2, 3). SOS was proposed as a more appropriate name than veno-occlusive disease since toxic injury to the hepatic sinusoids was the fundamental pathology (4). Oxaliplatin-based chemotherapy has been frequently associated with SOS, which is clinically characterized by portal hypertension, splenomegaly, subsequent thrombocytopenia, and liver dysfunction (5-11). The clinical implications of oxaliplatin-induced SOS have been demonstrated in up to 77% of colorectal cancer patients who underwent hepatectomy following oxaliplatin-based chemotherapy, in which surgical morbidity was significantly higher in patients with SOS (12, 13). Notably, the incidence and severity of

oxaliplatin-induced SOS correlated with the duration of oxaliplatin administration (14).

In clinical practice, oxaliplatin is commonly administered with fluoropyrimidines such as intravenous 5-fluorouracil (5-FU) or oral capecitabine or S-1, which are converted to 5-FU in the liver. Although fluoropyrimidines are associated with hepatotoxicity mainly in the form of hepatic steatosis, sinusoidal injury has also been reported (15-17). Kandutsch and colleagues reported that infusional 5-FU plus oxaliplatin (FOLFOX) and capecitabine plus oxaliplatin (XELOX) were similar in the incidence and extent of the hepatic sinusoidal damage (18). Unlike capecitabine, S-1 consists of 3 components including tegafur (a 5-FU prodrug) and 2 modulators, gimeracil [5-chloro-2,4-dihydroxypyridine, an inhibitor of 5-FU degrading enzyme dihydropyrimidine dehydrogenase (DPD)], and oteracil (potassium oxonate). Given that 5-FU is metabolized primarily in the liver by DPD and inhibition of DPD may potentiate hepatotoxicity of 5-FU, S-1 may enhance the hepatic sinusoidal injury by inhibiting DPD when combined with oxaliplatin (19, 20).

To evaluate this possibility, we compared the incidence, severity, and reversibility of hepatic SOS using surrogate clinical biomarkers such as splenomegaly, thrombocytopenia, and hepatic parenchymal heterogeneity on computed tomography (CT), and its clinical significance between S-1 and capecitabine administration groups when combined with oxaliplatin in gastric cancer patients (7, 21, 22).

Patients and Methods

Study population. This retrospective study included two patient populations that were enrolled in 2 separate prospective clinical trials: for adjuvant XELOX in curatively resected gastric cancer and for palliative first-line S-1 plus oxaliplatin (SOX) in recurrent/metastatic gastric cancer at the National Cancer Center, South Korea (23, 24).

Major eligibility criteria for the adjuvant XELOX study included curatively D2 resected stage II-III gastric adenocarcinoma (by the 6th edition of American Joint Committee on Cancer/ Union Internationale Contre le Cancer), adequate hepatic function [total bilirubin ≤1.5× the upper limit of normal (ULN), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5× ULN, alkaline phosphatase (ALP) ≤2.5× ULN], and hematologic function (absolute neutrophil count ≥1.5×10⁹/l or platelet count ≥100×10⁹/l) (23). Major eligibility criteria for the palliative SOX study included recurrent or metastatic gastric adenocarcinoma, adequate hepatic function [total bilirubin, ≤1.5× ULN; AST and ALT≤2.5× ULN (≤5× ULN if the liver metastases were present)], and hematologic function (same as above) (24). Exclusion criteria for the current study were prior splenectomy, known liver cirrhosis, acute or chronic hepatitis, and peribiliary or extensive liver metastasis, which could induce elevation of liver enzyme levels. Extensive liver metastasis was defined as more than 10 lesions, or the largest lesion greater than 5 cm.

Among 59 patients who received adjuvant XELOX from June 2006 to July 2011, we excluded 4 patients who underwent splenectomy, one with hyperbilirubinemia and 3 with chronic hepatitis B, leaving 51 for analysis in the XELOX group. Among 250 patients enrolled in the phase II study of first-line continuous *vs.* stop-and-go SOX for recurrent/ metastatic gastric cancer from July 2007 to December 2010, 121 patients who achieved disease control (complete or partial response or stable disease) after six cycles of SOX were randomized to the continuous SOX arm (n=59) or the stop-and-go (or intermittent) arm (n=62). In the continuous arm, SOX was continued until disease progression or unacceptable toxicity, whereas in the stop-and-go arm, SOX was stopped and reintroduced at disease progression (24). Among 59 patients in the continuous SOX arm, 9 were excluded because of extensive liver metastasis (n=6), prior splenectomy (n=1), liver cirrhosis (n=1), and elevated liver enzyme levels (n=1), leaving 50 patients for analysis in the SOX-continuous (SOX-C) group. Among 62 patients in the stop-and-go arm, 12 were excluded because of chronic hepatitis (n=7), elevated liver enzyme levels (n=3), and extensive liver metastases (n=2), leaving 50 patients for analysis in the SOX-intermittent (SOX-I) group.

This study was approved by the Institutional Review Board (IRB) at the National Cancer Center, Korea. All information was obtained with appropriate IRB waivers. The study was conducted according to the World Medical Association Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. All patients gave their written informed consent, conforming to institutional guidelines, indicating that they were aware of the investigational nature of the study.

Treatment and evaluation. Patients in the XELOX group received eight cycles of adjuvant XELOX, which consisted of oral administration of 1,000 mg/m² capecitabine twice daily on days 1-14 plus intravenous administration of 130 mg/m² oxaliplatin on day 1 in a 3-week cycle. Patients in the SOX group received oral administration of 40 mg/m² S-1 twice daily on days 1-14 plus intravenous administration of 130 mg/m² oxaliplatin on day 1 in a 3-week cycle. The doses of chemotherapy were modified for adverse events according to each study protocol.

Laboratory tests including complete cell count and chemistry were performed before starting chemotherapy, and every cycle in both study groups. Patients in the SOX-I group underwent laboratory tests every 6 weeks during the chemotherapy-free interval. The CT scans were conducted before starting chemotherapy, every 2 cycles of SOX, and every 6 weeks during the chemotherapy-free interval in the SOX group, whereas in the XELOX group, they were performed before starting chemotherapy, at the completion of 8 cycles of chemotherapy, and every 6 months thereafter.

The delay in chemotherapy was defined as a delay of ≥7 days from the scheduled date in any given cycle. The recovery rate of thrombocytopenia or splenomegaly was calculated by (value at the last chemotherapy – value after 24 weeks of being off chemotherapy)/ (value at the last chemotherapy – value at baseline) ×100 (%).

Assessment of surrogates for sinusoidal obstruction syndrome. Previous studies showed that splenomegaly correlated with the histologic grades of the hepatic sinusoidal injury and the occurrence of thrombocytopenia after oxaliplatin-based chemotherapy; the severity of hepatic parenchymal heterogeneity following oxaliplatin-based chemotherapy correlated with splenomegaly, thrombocytopenia, and elevated liver enzyme levels (7, 21, 22). Based on these, we selected the spleen size, hepatic parenchymal heterogeneity, thrombo-

Table I. *Baseline characteristics.*

	XELOX (n=51)	SOX (n=100)	*p*-Value
Median age (range)	56 (31-75)	60 (36-77)	0.11
Gender			0.28
Male (%)	37 (72.5%)	63 (63.0%)	
Female (%)	14 (27.5%)	37 (37.0%)	
ECOG PS			0.10
0-1 (%)	51 (100%)	94 (94.0%)	
2 (%)	0 (0%)	6 (6.0%)	
Treatment setting			<0.001
Adjuvant (%)	51 (100%)	0 (0%)	
Palliative (SOX-C/I, %)	0 (0%)	50 (50.0%)/50(50.0%)	
Median platelet count (×10^3/μl, range)	261.5 (142-530)	261.0 (140-621)	0.50
Median AST level (IU/l, range)	20.0 (12-40)	19.0 (10-40)	0.69
Median ALT level (IU/l, range)	14.5 (5-40)	15.0 (3-49)	0.53
Median bilirubin level (mg/dl, range)	0.5 (0.2-1.2)	0.4 (0.0-1.2)	0.004
Number of bilirubin ≥ULN (%)	3 (5.9%)	1 (1.0%)	0.11
Median spleen volume (cm^3, range)	139.6 (37.9-335.5)	141.3 (49.3-410.3)	0.45

Data are n (%) or median (range). XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; ECOG PS: Eastern Cooperative Oncology Group performance status; SOX-C: continuous SOX; SOX-I: intermittent SOX; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; ULN: upper limit of normal.

cytopenia, and liver enzyme levels as potential surrogate biomarkers for oxaliplatin-induced SOS.

All CT examinations were performed with one of the following four scanners: single-detector helical CT scanner (HiSpeed CT/i, GE Medical Systems, Milwaukee, WI; reconstruction, 5-mm section thickness; 120 kVp; and 130-250 mAs), 4-multidetector CT scanner (Mx 8000, Philips Medical System Highland Heights, Ohio; detector collimation, 4×1 mm; reconstruction, 3-5mm section thickness; 120 kVp; and 150-200 mAs), 16-multidetector CT scanner (LightSpeed Pro 16, GE Medical Systems, Milwaukee, WI; detector collimation, 16×0.625 mm; reconstruction, 3-mm section thickness; 120 kVp; and 100-350 mAs), and 64-multidetector CT scanner (Brilliance 64, Philips Medical Systems, Cleveland, Ohio; detector collimation, 64×0.625 mm; reconstruction, 3-mm section thickness; 120 kV; and 120-280 mAs). Nonionic contrast material containing 300-350 mg I/mL was injected at a rate of 2–3 ml/s in a total dose of 2 ml/kg of body weight. Portal venous phase imaging was started 60-80 seconds after starting the injection. All image data were reconstructed by using a body soft-tissue algorithm.

CT images were transferred to a workstation (Rapidia; INFINITT®, Seoul, Republic of Korea), which was equipped with software enabling automatic area measurements. Cross-sectional areas of spleen on each axial CT scan with 3-5 mm section thickness were calculated by tracing the contour of the spleen using an electronic free-curved line, which was drawn by a technologist experienced at computerized three-dimensional image processing. The splenic volumes were calculated automatically by summing the area measurements of consecutive CT scans. A change in the spleen volume was calculated by (measured volume – baseline volume)/baseline volume ×100 (%). Splenomegaly was defined as a ≥50% increase in spleen volume compared to the baseline.

The hepatic parenchymal heterogeneity on portal phase CT scan was classified into 4 grades of 0-3, which were modified from previous studies (21, 25); grade 0: homogeneous hepatic parenchymal attenuation without heterogeneity; grade 1: focal or segmental heterogeneous hypoattenuation on only a few sections; grade 2: patchy or segmental heterogeneous hypoattenuation on all sections; and grade 3: diffuse heterogeneous hypoattenuation on all sections. The images were reviewed by the radiologist blinded to clinical information.

Statistical analysis. Pearson's chi-square test and Fisher's exact test were used for comparison of discrete data, as required. *t*-tests and the Mann-Whitney *U*-test were used for comparison of parametric and non-parametric variables, respectively. Repeated-measure analysis of variance (ANOVA) was employed for paired and repeated measurements. The logistic regression test was used for predictive analysis. All tests were two-sided, and *p*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics. Totally, 151 patients (n=51 in the XELOX group, n=50 in the SOX-C group, and n=50 in the SOX-I group) were enrolled. The baseline characteristics are described in Table I. Except for the treatment setting and serum bilirubin levels, there were no significant differences between the two groups. Although the median bilirubin level was higher in the XELOX group than in the SOX group, it was not clinically significant because the proportion of patients with bilirubin levels ≥ULN was not different between the two groups.

Surrogate markers for the hepatic sinusoidal obstruction syndrome. The spleen size continuously increased during the course of chemotherapy with both XELOX and SOX, and the median spleen volume after 8 cycles of chemotherapy was significantly larger in the SOX-C group than in the
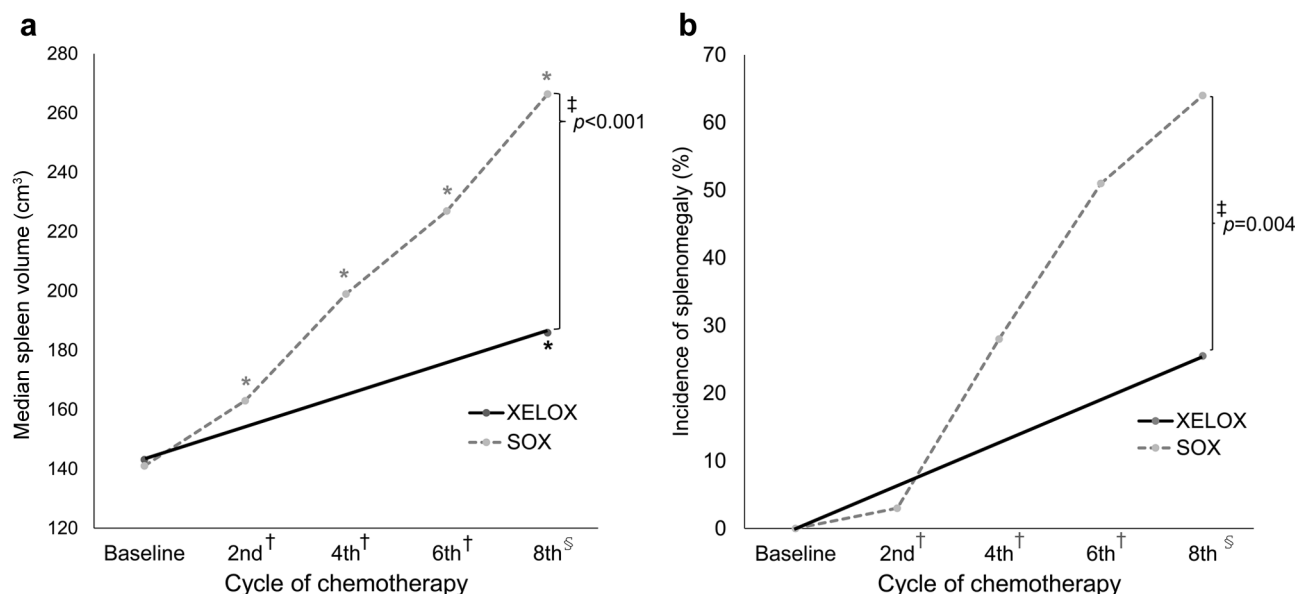
Figure 1. *Comparison of change in the (a) median spleen volume and (b) incidence of splenomegaly according to chemotherapy. †Computed tomography was not available in the XELOX group. §Spleen volume of the SOX group after the 8th cycle was obtained only in the SOX-C group. *p<0.05 compared to the baseline value, ‡p-value for SOX-C vs. XELOX. XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-C: continuous SOX.*

XELOX group (266.4 cm^3 *vs.* 185.9 cm^3, $p<0.001$) (Figure 1a). After 8 cycles of chemotherapy, the median increase in spleen volume compared to the baseline was 68.5% (range=7.6-183.0%) with SOX *vs.* 32.1% (range=0-151.5%) with XELOX ($p<0.001$), and the incidence of splenomegaly was about 2.5 times higher in the SOX-C group than in the XELOX group (64.0% *vs.* 25.5%; $p=0.004$, Figure 1b). The occurrence of splenomegaly was comparable between 4 cycles of SOX and 8 cycles of XELOX (28.0% *vs.* 25.5%).

In contrast, the platelet counts gradually decreased during the course of chemotherapy in both groups (Figure 2a). After six cycles of chemotherapy, the median platelet count was significantly lower in the SOX group than in the XELOX group (103.5×10^3/μl *vs.* 143.0×10^3/μl, $p<0.001$), and the median reduction of platelet count compared to the baseline was also larger in the SOX group (158.0×10^3/μl *vs.* 105.0×10^3/μl, $p<0.001$). The incidence of thrombocytopenia (≤100×10^3/μl) during chemotherapy was also significantly higher in the SOX group than that in the XELOX group (Table II).

The liver enzyme levels including AST, ALT, and ALP, and total bilirubin were significantly increased during the course of chemotherapy in both groups (Figure 2b-e). The total bilirubin level was significantly higher in the SOX group than that in the XELOX group after the 2nd, 4th, and 6th cycles ($p<0.05$ for all analyses). The levels of other liver enzymes did not show significant differences between the two groups.

The incidence and degree of the hepatic parenchymal heterogeneity after 8 cycles of chemotherapy were significantly higher in the SOX-C group than those in the XELOX group [All grades, 60.0% *vs.* 29.4%, $p=0.003$; high grades (grade≥2), 34.0% *vs.* 13.7%, $p=0.02$; Table II].

Splenomegaly was significantly associated with lower median platelet counts and higher AST, ALP, and bilirubin levels after 8 cycles of chemotherapy in patients of the XELOX or SOX-C groups: median platelet count, 136.0×10^3/μl in patients without splenomegaly *vs.* 98.5×10^3/μl in patients with splenomegaly, $p<0.001$; median AST, 34 IU/l *vs.* 40 IU/l, respectively, $p=0.008$; median ALP, 102 IU/l *vs.* 121 IU/l, respectively, $p=0.006$; and median bilirubin, 0.7 mg/dl *vs.* 1.0 mg/dl, respectively, $p=0.001$ (Table III). The hepatic parenchymal heterogeneity was significantly associated with elevated AST and ALT levels: median AST, 40.7 IU/l for patients with grade ≥2 *vs.* 36.2 IU/l for patients with grade <2, $p=0.046$; and median ALT, 23.5 IU/l *vs.* 20.7 IU/l, respectively, $p=0.024$ (Table III).

Chemotherapy delay or dose reduction because of the hepatic sinusoidal obstruction syndrome. Total number of delays or dose reductions of chemotherapy from any causes during 6 cycles of chemotherapy was 187 of 600 cycles in the SOX group (31.2%) and 100 of 306 cycles in the XELOX group (32.7%) (Table IV). The number of patients who experienced delay or dose reduction of chemotherapy from any causes during 6 cycles were 81 of 100 (81.0%) in the SOX group and 44 of 51 (86.3%) in the XELOX group.
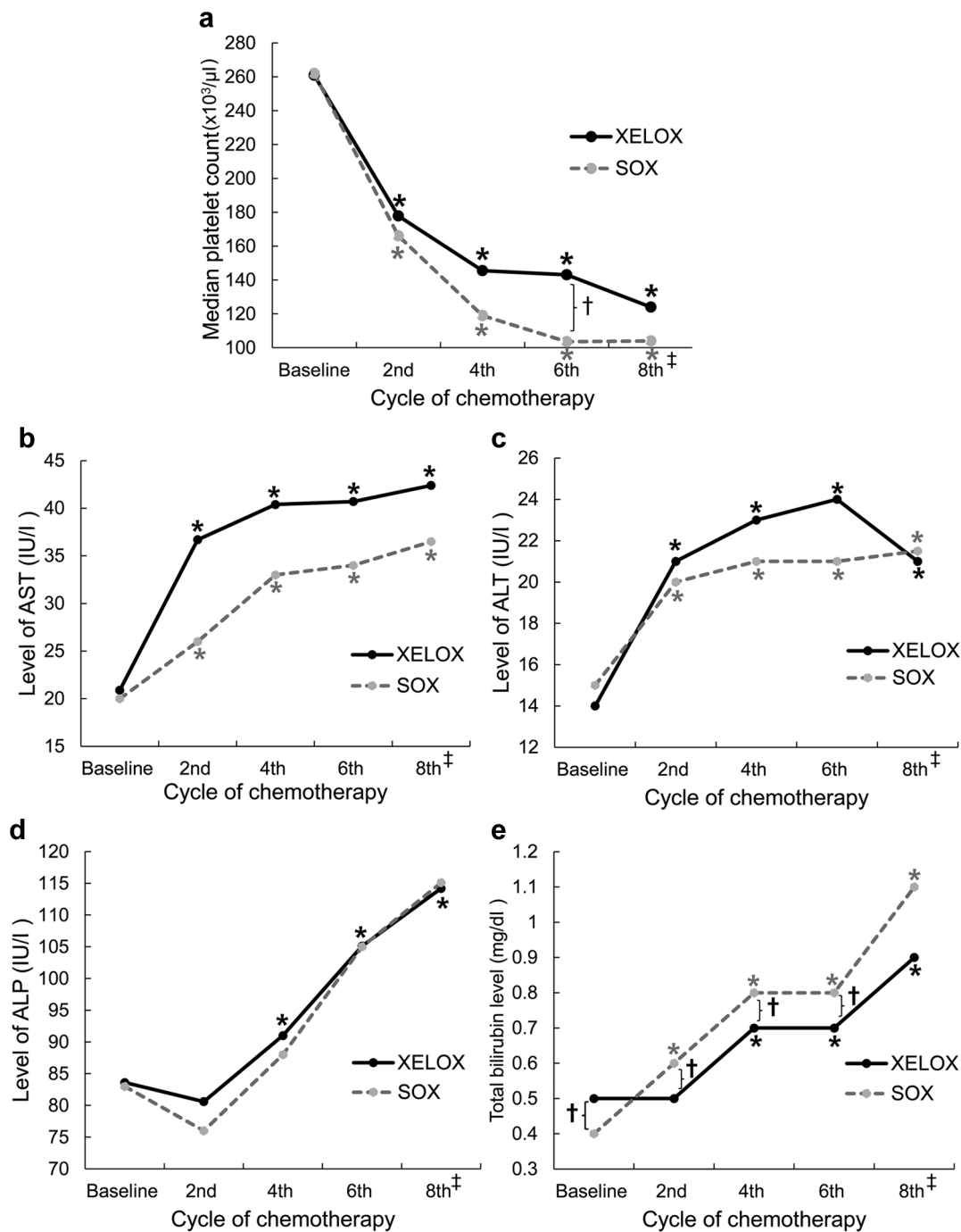
Figure 2. *Change in the levels of (a) platelet, (b) AST, (c) ALT, (d) ALP, and (e) bilirubin according to chemotherapy. *p<0.05 compared to the baseline value. †p<0.05 for SOX vs. XELOX. ‡Laboratory results after the 8th cycle in the SOX group included data of only the SOX-C group. AST: Aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase, XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-C: continuous SOX.*

The causes of delay or dose reduction of chemotherapy were various, which included not only elevated liver enzyme levels and thrombocytopenia, but also nausea, diarrhea, hand foot syndrome, hypersensitivity, and febrile neutropenia. The proportion of cycles of delayed or dose-reduced chemotherapy and that of patients with delayed or dose-reduced chemotherapy due to thrombocytopenia were both significantly higher in the SOX group than in the
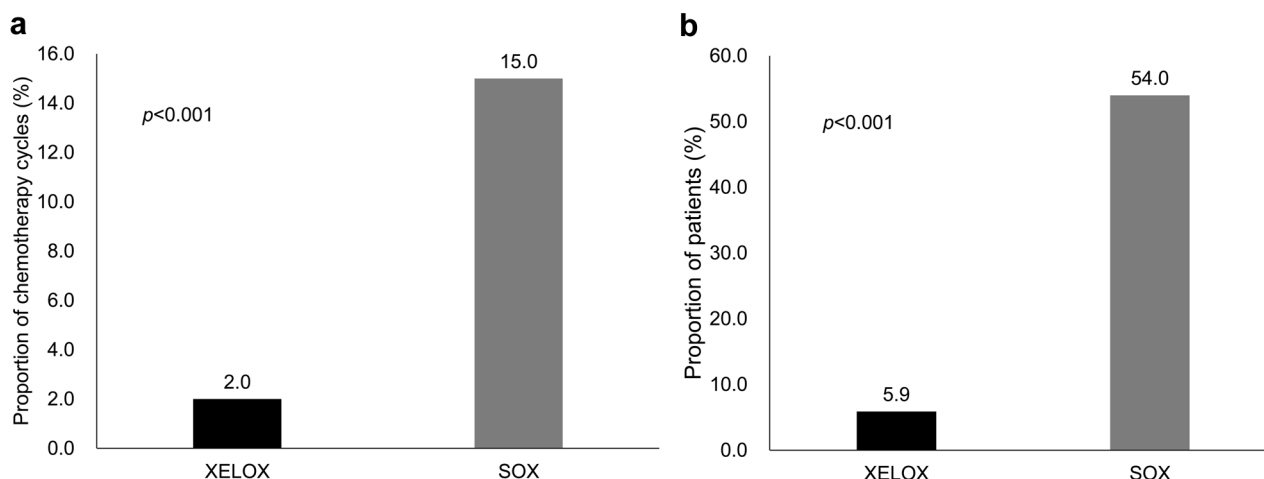
a

b

Figure 3. *Proportion of cycles of delayed or dose-reduced chemotherapy (a) and that of patients with delayed or dose-reduced chemotherapy due to thrombocytopenia (b). XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin.*

Table II. *Incidence rate of hepatic parenchymal heterogeneity on CT scan and thrombocytopenia related to chemotherapy.*

Hepatic parenchymal heterogeneity (after 8 cycles)	XELOX (n=51)	SOX-C (n=50)	*p*-Value
Grade 0 (%)	36 (70.6%)	20 (40.0%)	0.002
Grade 1 (%)	8 (15.7%)	13 (26.0%)	
Grade 2 (%)	6 (11.8%)	12 (24.0%)	
Grade 3 (%)	1 (2.0%)	5 (10.0%)	
All grades (Grade 1-3) (%)	15 (29.4%)	30 (60.0%)	0.003
High grades (Grade 2-3) (%)	7 (13.7%)	17 (34.0%)	0.02

Thrombocytopenia ($<100 \times 10^3/\mu l$)	XELOX (n=51)	SOX (n=100)	*p*-Value
Baseline (%)	0 (0%)	0 (0%)	
2nd cycle (%)	2 (3.8%)	20 (20.0%)	0.007
4th cycle (%)	11 (21.2%)	38 (38.0%)	0.045
6th cycle (%)	8 (15.7%)	42 (42.0%)	0.001
8th cycle (%)	15 (28.8%)	22 (44.0%)[a]	0.15

[a]Only SOX-C group was included in the analysis after the 8th cycle (n=50). CT: Computed tomography; XELOX: capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-C: continuous SOX.

XELOX group [90/600 cycles (15.0%) *vs*. 6/306 (2.0%); *p*<0.001, and 54/100 patients (54.0%) *vs*. 3/51 (5.9%); *p*<0.001, Figure 3].

Reversibility of the hepatic sinusoidal obstruction syndrome. Splenomegaly was partially reversible over time after completion of chemotherapy. In the XELOX group, the median spleen volume after 8 cycles was increased by 29.9% (185.9 cm^3) compared to that of the baseline (143.1 cm^3) (Figure 4a). Twenty-four weeks after stopping chemotherapy, the median volume was significantly decreased compared to

that of the last chemotherapy (159.7 cm^3, *p*<0.001), but it was still 11.6% larger than that of the baseline. A total of 12 patients in the SOX-I group who received 6 cycles of SOX and did not undergo further chemotherapy because of stable disease until after 24 weeks, also showed a peak in the spleen volume at stopping chemotherapy, and then a decreasing trend; 123.7 cm3 at baseline, +87.4% after 6th cycle, +85.5% after 6 weeks of discontinuing chemotherapy, +80.2% after 12 weeks, +78.4% after 18 weeks, and +56.5% after 24 weeks. The recovery rate of the spleen volume after 24 weeks of being off chemotherapy compared to the last chemotherapy

Table III. *Laboratory findings after the 8th cycle of chemotherapy according to spleen volume change and hepatic heterogeneity grades on CT scan with XELOX (n=51) or SOX-C (n=50) chemotherapy.*

Variable		Spleen volume <1.5 times (n=55)	Spleen volume ≥1.5 times (n=46)	*p*-Value
Platelet	Median (×10³/μl)	136.0	98.5	<0.001
AST	Median (IU/l)	34	40	0.008
ALT	Median (IU/l)	20	22	0.073
ALP	Median (IU/l)	102	121	0.006
Bilirubin	Median (mg/dl)	0.7	1.0	0.001
Hepatic heterogeneity	Number of Grade 0-1 (%)	46 (83.6%)	31 (67.4%)	0.064
	Number of Grade 2-3 (%)	9 (16.4%)	15 (32.6%)	

Variable		Hepatic heterogeneity, Grade 0-1 (n=77)	Hepatic heterogeneity, Grade 2-3 (n=24)	*p*-Value
Platelet	Median (×10³/μl)	112.3	113.5	0.735
AST	Median (IU/l)	36.2	40.7	0.046
ALT	Median (IU/l)	20.7	23.5	0.024
ALP	Median (IU/l)	111.3	117.0	0.458
Bilirubin	Median (mg/dl)	0.8	0.9	0.412

CT: Computed tomography; XELOX: capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-C: continuous SOX; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase.

Table IV. *Delay or dose-reduction of chemotherapy in SOX and XELOX groups during 6 cycles.*

	XELOX (N=51)	SOX (N=100)	*p*-Value
Total number of cycles	306	600	
Cycles with delayed schedule or dose reductions (%)	100 (32.7)	187 (31.2)	0.66
Due to thrombocytopenia (%)	6 (2.0)	90 (15.0)	<0.001
Cycles with delayed schedule (%)	69 (22.1)	140 (23.3)	0.99
Due to thrombocytopenia (%)	4 (1.3)	75 (12.5)	<0.001
Cycles with dose reductions (%)	44 (14.1)	98 (16.3)	0.56
Due to thrombocytopenia (%)	4 (1.3)	52 (8.7)	<0.001
Patients with delayed schedule or dose reduction (%)	44 (86.3)	81 (81.0)	0.28
Due to thrombocytopenia (%)	3 (5.9)	54 (54.0)	<0.001

XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin.

was significantly lower in the SOX group than that in the XELOX group (0.35 *vs*. 0.61 *p*<0.001).

Thrombocytopenia also showed reversibility. In the XELOX group, the median platelet count decreased by 52.5% (124×10³/μl) after 8 cycles compared to the baseline (261×10³/μl) (Figure 4b). Twenty-four weeks after stopping chemotherapy, the median platelet count significantly increased (202×10³/μl) compared to that of the last chemotherapy (*p*<0.001), which was still 77.4% of the baseline. In patients of the SOX-I group who received 6 cycles of SOX and did not undergo further chemotherapy, the median platelet count was 258.5×10³/μl at baseline, decreased to 28.8% of baseline after 6th cycle, and recovered significantly to 60.7% of baseline after 6 weeks of discontinuing chemotherapy, 63.1% of baseline after 12 weeks, 64.8% of baseline after 18 weeks, and 66.2% of baseline after 24 weeks. The median platelet count after 24 weeks of being off chemotherapy was still significantly lower in the SOX-I group than that in the XELOX group (169×10³/μl *vs*. 202×10³/μl, *p*=0.049). The recovery rate of the platelet count after 24 weeks of being off chemotherapy compared to that of the last chemotherapy was 0.52 *vs*. 0.53 in the XELOX *vs*. SOX group, respectively (*p*=0.99).

Additional analysis excluding patients with liver metastasis (not extensive). Although the patients with extensive liver metastasis or elevated liver enzyme levels were excluded in the primary analysis, there were still some patients with small liver metastasis. To overcome the different disease setting between palliative SOX and adjuvant XELOX groups, we conducted additional analysis with selected patients in the SOX group who did not have liver metastasis (n=46 in SOX-C group, n=38 in SOX-I group), and the results were equivalent (Figures 5 and 6).
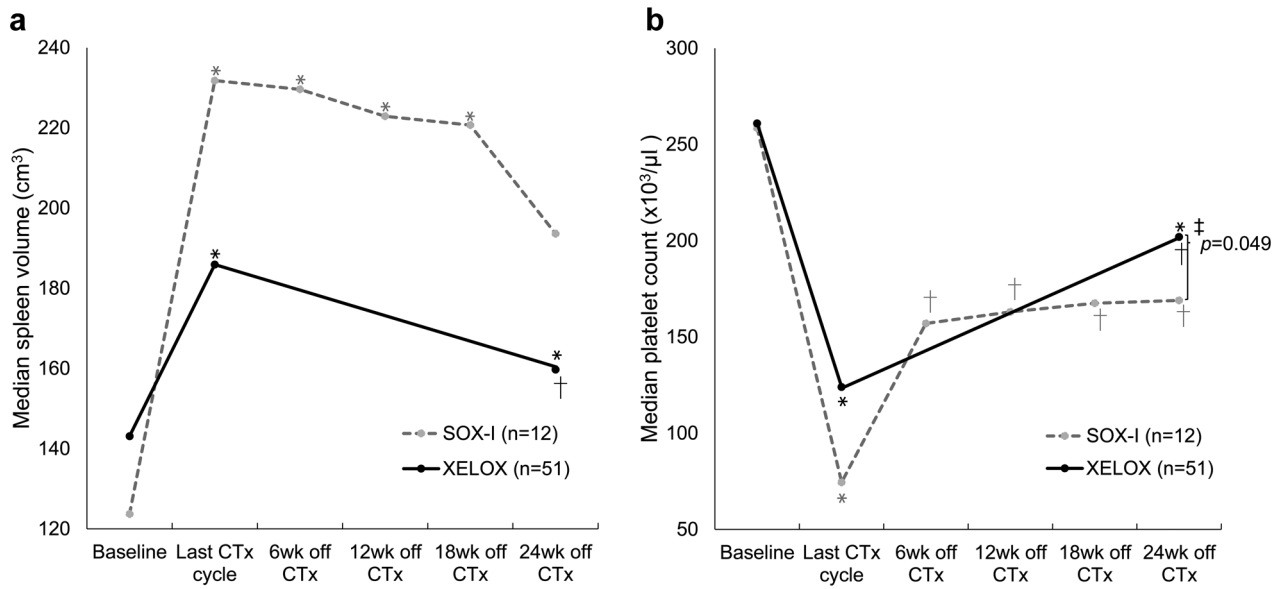
Figure 4. *Reversibility of (a) splenomegaly and (b) thrombocytopenia according to chemotherapy. *p<0.05 compared to the baseline value. †p<0.05 compared to the values after the last chemotherapy cycle (the 8th in XELOX, the 6th in SOX) in each chemotherapy group, respectively. ‡p-value for SOX-I vs. XELOX after 24 weeks of being off chemotherapy. XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-I: intermittent SOX; CTx: chemotherapy.*
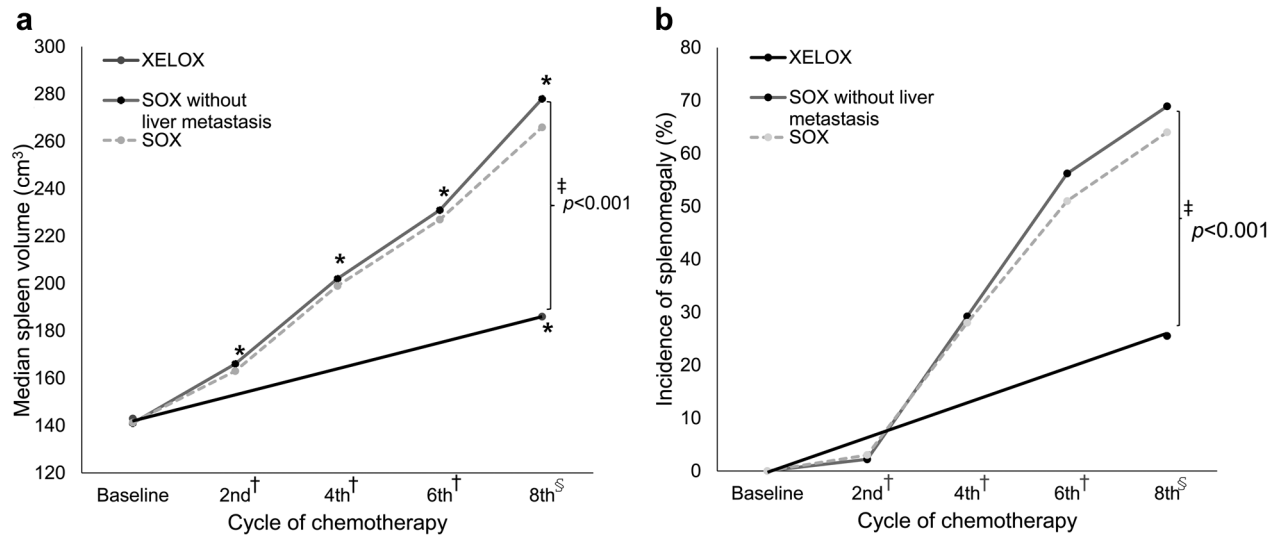

Figure 5. *Comparison of change in the (a) median spleen volume and (b) incidence of splenomegaly according to chemotherapy in patients without liver metastasis. [XELOX (n=51) vs. SOX without liver metastasis (SOX-C: n=46, SOX-I: n=38)]. *p<0.05 compared to the baseline value, ‡p-value for SOX-C without liver metastasis vs. XELOX. †Computed tomography was not available in the XELOX group. §Spleen volume in the SOX group after the 8th cycle was obtained only in the SOX-C group. XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-C: continuous SOX; SOX-I: intermittent SOX.*

Discussion

Oxaliplatin is one of the main chemotherapeutic agents that are currently used as neoadjuvant, adjuvant, and palliative therapy for gastrointestinal cancers, in combination with fluoropyrimidines. Oxaliplatin is well known to induce hepatic sinusoidal injury with incidence rates ranging from 18.9% to 77.4% when combined with 5-FU or capecitabine (2, 12, 26).
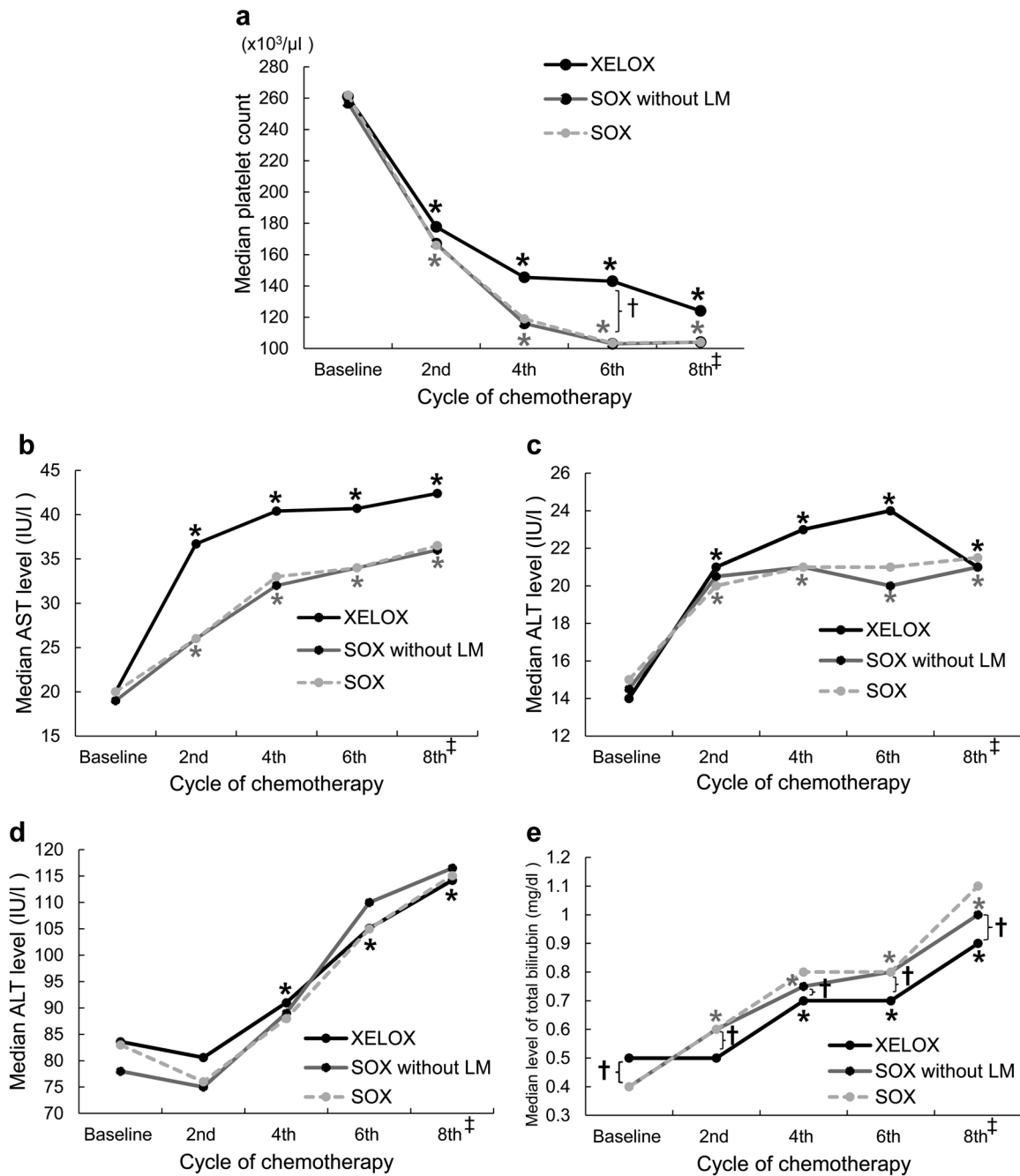
Figure 6. *Change in the levels of (a) platelet, (b) AST, (c) ALT, (d) ALP, and (e) bilirubin according to chemotherapy in patients without liver metastasis. [XELOX (n=51) vs. SOX without LM, SOX-C: n=46, SOX-I: n=38]. *p<0.05 compared to the baseline value. †p<0.05 for SOX without LM vs. XELOX. ‡Laboratory results after the 8th cycle in the SOX group included data of only the SOX-C group. LM: liver metastasis; AST: Aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase, XELOX: Capecitabine + oxaliplatin; SOX: S-1 + oxaliplatin; SOX-C: continuous SOX; SOX-I: intermittent SOX.*

Despite its clinical implications, little is known about the impact of different fluoropyrimidines combined with oxaliplatin on chemotherapy-induced SOS. To our knowledge, the present study is the first report evaluating and comparing the two oral fluoropyrimidines, capecitabine and S-1, combined with oxaliplatin in terms of chemotherapy-induced SOS and its clinical significance in gastric cancer patients. Surprisingly, SOX resulted in a higher incidence and greater extent of SOS than XELOX, as demonstrated by splenomegaly, thrombocytopenia, and hepatic parenchymal

heterogeneity. The incidence of splenomegaly increased during the course of chemotherapy. It was approximately 2.5 times higher in SOX-C than in XELOX after 8 cycles of chemotherapy. Although hepatic changes including elevated liver enzymes and parenchymal heterogeneity probably resulting from the pathologic findings of SOS and associated with SOS clinical severity were evident in both groups, the SOX-C group was likely associated with more severe parenchymal heterogeneity and more increased serum bilirubin level (27). More importantly, this chemotherapy-induced SOS was associated with thrombocytopenia, which was also significantly more severe in the SOX group throughout the chemotherapy cycles, and led to more frequent delays or dose reductions of chemotherapy in the SOX group. These results are in accordance with a previous randomized phase III study showing that SOX was more likely associated with thrombocytopenia and hyperbilirubinemia than XELOX in metastatic colorectal cancer (28). In addition, the reversibility of SOS after discontinuation of chemotherapy was also inferior in the SOX group than in the XELOX group, as demonstrated by slower recovery of the spleen size. Notably, the spleen size and platelet counts were not fully recovered to baseline even 6 months after discontinuation of SOX or XELOX, which was consistent with previous results with FOLFOX (7, 29).

Although single-agent fluoropyrimidines such as 5-FU, capecitabine, or S-1 may cause steatosis but seldom result in SOS, the current findings showing the increased occurrence of SOS by S-1 compared to capecitabine when combined with oxaliplatin suggest that S-1 might play a role in oxaliplatin-induced sinusoidal injury (30-32). The proposed underlying mechanisms by which oxaliplatin can cause sinusoidal damage are as follows: 1) oxaliplatin increases the porosity of the sinusoidal endothelium cellular fenestration, stimulating the release of free radicals that is followed by an increase in metalloproteinases, which favor migration of erythrocytes into the space of Dissé and formation of perisinusoidal fibrosis; 2) nodular regenerative hyperplasia is favored by chronic hypoxia in the centrilobular areas; 3) oxaliplatin can result in obliteration of the blood capillaries and areas of parenchymal extinction that may interrupt portal circulation and eventually elevate portal pressures (33). Treatment with 5-FU could induce hepatocellular inflammation by inducing oxidative stress through generation of reactive oxygen species and activation of c-Jun N-terminal kinase (JNK) and the expression of pro-inflammatory genes such as IL-8 and ICAM-1 (34). When 5-FU is combined with oxaliplatin, intrahepatic inflammation induced by 5-FU could enhance the pathophysiology of oxaliplatin-induced sinusoidal injury. By inhibiting 5-FU degradation through its component gimeracil, S-1 could potentiate this toxicity compared to 5-FU or capecitabine. However, this hypothesis needs to be further investigated.

As a clinical aspect of oxaliplatin-induced SOS, previous studies reported that preoperative FOLFOX-induced hepatic sinusoidal injury is associated with increased postoperative morbidity including hepatic dysfunction or blood transfusion requirements in patients with colorectal cancer liver metastasis (12, 13, 35, 36). As SOX is being increasingly used as a standard regimen based on non-inferior efficacy compared to XELOX or S-1/cisplatin, enhanced development of SOS by SOX should be considered and closely monitored in clinical practice and in research (28, 37). In particular, given that the incidence and degree of SOS are closely associated with the duration of exposure to oxaliplatin, strategies such as a limited number of chemotherapy cycles in the neoadjuvant setting or the stop-and-go strategy in the palliative setting should be considered (24).

The current study had some limitations. First, we compared two patient groups with different disease status, one in the adjuvant and the other in the palliative setting. Although the baseline characteristics were not different between the two groups, a different disease status might affect the laboratory and imaging results. To overcome this limitation, we also analyzed data only in the patients without liver metastases in the SOX group and confirmed that the trend of results did not change. Second, the CT scan was performed every 6 weeks in the SOX group, whereas it was performed every 6 months in the XELOX group, which made it difficult to compare imaging data between the two groups thoroughly. Because of the difference in the treatment setting and follow-up schedule between the two groups, the SOX-I group could not be included in the analyses after the 8th cycle, which might have compromised the consistency of the analysis. Third, the observation period after stopping chemotherapy was not sufficient to evaluate whether SOS was completely recovered. Moreover, the number of patients who stopped chemotherapy and continued providing the recovery data was small in the SOX-I group.

In conclusion, oxaliplatin-induced SOS is influenced by combined fluoropyrimidines. S-1 increases the incidence and severity of SOS when combined with oxaliplatin, compared with capecitabine. Further studies are needed to elucidate the underlying mechanisms involved in the S-1-mediated enhancement of hepatic sinusoidal injury when combined with oxaliplatin.

Conflicts of Interest

Authors' Contributions

References

1 Stine JG and Chalasani N: Chronic liver injury induced by drugs: a systematic review. Liver Int *35(11)*: 2343-2353, 2015. PMID: 26346512. DOI: 10.1111/liv.12958

2 Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, Brezault C, Soubrane O, Abdalla EK, Vauthey JN, Mentha G and Terris B: Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology *56(4)*: 430-439, 2010. PMID: 20459550. DOI: 10.1111/j.1365-2559.2010.03511.x

3 Shulman HM, Fisher LB, Schoch HG, Henne KW and McDonald GB: Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. Hepatology *19(5)*: 1171-1181, 1994. PMID: 8175139. DOI: 10.1002/hep.1840190515

4 DeLeve LD, Shulman HM and McDonald GB: Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis *22(1)*: 27-42, 2002. PMID: 11928077. DOI: 10.1055/s-2002-23204

5 Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G and Terris B: Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol *15(3)*: 460-466, 2004. PMID: 14998849. DOI: 10.1093/annonc/mdh095

6 Slade JH, Alattar ML, Fogelman DR, Overman MJ, Agarwal A, Maru DM, Coulson RL, Charnsangavej C, Vauthey JN, Wolff RA and Kopetz S: Portal hypertension associated with oxaliplatin administration: clinical manifestations of hepatic sinusoidal injury. Clin Colorectal Cancer *8(4)*: 225-230, 2009. PMID: 19822514. DOI: 10.3816/CCC.2009.n.038

7 Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, Eng C, Hoff PM, Vauthey JN, Wolff RA and Kopetz S: Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol *28(15)*: 2549-2555, 2010. PMID: 20406923. DOI: 10.1200/JCO.2009.27.5701

8 Angitapalli R, Litwin AM, Kumar PR, Nasser E, Lombardo J, Mashtare T, Wilding GE and Fakih MG: Adjuvant FOLFOX chemotherapy and splenomegaly in patients with stages II-III colorectal cancer. Oncology *76(5)*: 363-368, 2009. PMID: 19321964. DOI: 10.1159/000210025

9 Kim MJ, Han SW, Lee DW, Cha Y, Lee KH, Kim TY, Oh DY, Kim SH, Im SA, Bang YJ and Kim TY: Splenomegaly and its associations with genetic polymorphisms and treatment outcome

in colorectal cancer patients treated with adjuvant FOLFOX. Cancer Res Treat *48(3)*: 990-997, 2016. PMID: 26790967. DOI: 10.4143/crt.2015.296

10 Fan CQ and Crawford JM: Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol *4(4)*: 332-346, 2014. PMID: 25755580. DOI: 10.1016/j.jceh.2014.10.002

11 Duwe G, Knitter S, Pesthy S, Beierle AS, Bahra M, Schmelzle M, Schmuck RB, Lohneis P, Raschzok N, Öllinger R, Sinn M, Struecker B, Sauer IM, Pratschke J and Andreou A: Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. Eur J Surg Oncol *43(9)*: 1668-1681, 2017. PMID: 28599872. DOI: 10.1016/j.ejso.2017.05.008

12 Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, Bachellier P and Jaeck D: Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg *247(1)*: 118-124, 2008. PMID: 18156931. DOI: 10.1097/SLA.0b013e31815774de

13 Soubrane O, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, Goldwasser F and Scatton O: Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg *251(3)*: 454-460, 2010. PMID: 20160638. DOI: 10.1097/SLA.0b013e3181c79403

14 Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, Motta M, Ravarino N, Risio M, Curley SA, Abdalla EK, Capussotti L and Vauthey JN: Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol *17(11)*: 2870-2876, 2010. PMID: 20567921. DOI: 10.1245/s10434-010-1166-1

15 Peppercorn PD, Reznek RH, Wilson P, Slevin ML and Gupta RK: Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. Br J Cancer *77(11)*: 2008-2011, 1998. PMID: 9667683. DOI: 10.1038/bjc.1998.333

16 Miyake K, Hayakawa K, Nishino M, Morimoto T and Mukaihara S: Effects of oral 5-fluorouracil drugs on hepatic fat content in patients with colon cancer. Acad Radiol *12(6)*: 722-727, 2005. PMID: 15935970. DOI: 10.1016/j.acra.2005.02.010

17 Tsuji K and Doyama H: S-1 induced hepatic steatosis in patients with pancreatic cancer: retrospective analysis. World J Gastrointest Oncol *9(8)*: 314-318, 2017. PMID: 28868111. DOI: 10.4251/wjgo.v9.i8.314

18 Kandutsch S, Klinger M, Hacker S, Wrba F, Gruenberger B and Gruenberger T: Patterns of hepatotoxicity after chemotherapy for colorectal cancer liver metastases. Eur J Surg Oncol *34(11)*: 1231-1236, 2008. PMID: 18272318. DOI: 10.1016/j.ejso.2008.01.001

19 Diasio RB and Harris BE: Clinical pharmacology of 5-fluorouracil. Clin Pharmacokinet *16(4)*: 215-237, 1989. PMID: 2656050. DOI: 10.2165/00003088-198916040-00002

20 Yamada Y, Hamaguchi T, Goto M, Muro K, Matsumura Y, Shimada Y, Shirao K and Nagayama S: Plasma concentrations of 5-fluorouracil and F-beta-alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil. Br J Cancer *89(5)*: 816-820, 2003. PMID: 12942110. DOI: 10.1038/sj.bjc.6601224

21 Han NY, Park BJ, Kim MJ, Sung DJ and Cho SB: Hepatic parenchymal heterogeneity on contrast-enhanced CT scans following oxaliplatin-based chemotherapy: natural history and association with clinical evidence of sinusoidal obstruction syndrome. Radiology *276(3)*: 766-774, 2015. PMID: 25822471. DOI: 10.1148/radiol.2015141749

22 Han NY, Park BJ, Yang KS, Kim MJ, Sung DJ, Sim KC and Cho SB: Hepatic parenchymal heterogeneity as a marker for oxaliplatin-induced sinusoidal obstruction syndrome: correlation with treatment response of colorectal cancer liver metastases. AJR Am J Roentgenol *209(5)*: 1039-1045, 2017. PMID: 28813196. DOI: 10.2214/AJR.16.17528

23 Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzen F, Noh SH and for the CLASSIC trial investigators: Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet *379(9813)*: 315-321, 2012. PMID: 22226517. DOI: 10.1016/S0140-6736(11)61873-4

24 Park SR, Kim MJ, Nam BH, Kim CG, Lee JY, Cho SJ, Kong SY and Park YI: A randomised phase II study of continuous *versus* stop-and-go S-1 plus oxaliplatin following disease stabilisation in first-line chemotherapy in patients with metastatic gastric cancer. Eur J Cancer *83*: 32-42, 2017. PMID: 28711577. DOI: 10.1016/j.ejca.2017.06.008

25 Ward J, Guthrie JA, Sheridan MB, Boyes S, Smith JT, Wilson D, Wyatt JI, Treanor D and Robinson PJ: Sinusoidal obstructive syndrome diagnosed with superparamagnetic iron oxide-enhanced magnetic resonance imaging in patients with chemotherapy-treated colorectal liver metastases. J Clin Oncol *26(26)*: 4304-4310, 2008. PMID: 18779617. DOI: 10.1200/JCO.2008.16.1893

26 Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA and Abdalla EK: Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol *24(13)*: 2065-2072, 2006. PMID: 16648507. DOI: 10.1200/JCO.2005.05.3074

27 Cayet S, Pasco J, Dujardin F, Besson M, Orain I, De Muret A, Miquelestorena-Standley E, Thiery J, Genet T and Le Bayon AG: Diagnostic performance of contrast-enhanced CT-scan in sinusoidal obstruction syndrome induced by chemotherapy of colorectal liver metastases: Radio-pathological correlation. Eur J Radiol *94*: 180-190, 2017. PMID: 28712693. DOI: 10.1016/j.ejrad.2017.06.025

28 Hong YS, Park YS, Lim HY, Lee J, Kim TW, Kim K-p, Kim SY, Baek JY, Kim JH, Lee K-W, Chung I-J, Cho S-H, Lee KH, Shin SJ, Kang HJ, Shin DB, Jo SJ and Lee JW: S-1 plus oxaliplatin *versus* capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial. The Lancet Oncology *13(11)*: 1125-1132, 2012. PMID: 23062232. DOI: 10.1016/s1470-2045(12)70363-7

29 Iwai T, Yamada T, Koizumi M, Shinji S, Yokoyama Y, Takahashi G, Takeda K, Hara K, Ohta K and Uchida E: Oxaliplatin-induced increase in splenic volume; irreversible change after adjuvant FOLFOX. J Surg Oncol *116(7)*: 947-953, 2017. PMID: 28876454. DOI: 10.1002/jso.24756

30 Chun YS, Laurent A, Maru D and Vauthey JN: Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol *10*: 278-286, 2009. PMID: 19261256. DOI: 10.1016/S1470-2045(09)70064-6

31 Ryan P, Nanji S, Pollett A, Moore M, Moulton C-A, Gallinger S and Guindi M: Chemotherapy-induced liver injury in metastatic colorectal cancer: semiquantitative histologic analysis of 334 resected liver specimens shows that vascular injury but not steatohepatitis is associated with preoperative chemotherapy. Am J Surg Pathol *34(6)*: 784-791, 2010. PMID: 00000478-201006000-00004. DOI: 10.1097/PAS.0b013e3181dc242c

32 Pelegrina A, Marti J, Miquel R, Ferrer J, Hernandez-Gea V, Diaz A, Nadal C, Garcia-Valdecasas JC and Fuster J: Changes of liver hemodynamic and elastography parameters in patients with colorectal liver metastases receiving preoperative chemotherapy: "a note of caution". World J Surg Oncol *15(1)*: 224, 2017. PMID: 29246174. DOI: 10.1186/s12957-017-1290-5

33 Puente A, Fortea JI, Del Pozo C, Huelin P, Cagigal ML, Serrano M, Cabezas J, Arias Loste MT, Iruzubieta P, Cuadrado A, Llerena S, Lopez C, Fabrega E and Crespo J: Porto-sinusoidal vascular disease associated to oxaliplatin: An entity to think about it. Cells *8(12)*, 2019. PMID: 31771307. DOI: 10.3390/cells8121506

34 Sommer J, Mahli A, Freese K, Schiergens TS, Kuecuekoktay FS, Teufel A, Thasler WE, Müller M, Bosserhoff AK and Hellerbrand C: Analysis of molecular mechanisms of 5-fluorouracil-induced steatosis and inflammation *in vitro* and in mice. Oncotarget *8(8)*: 13059-13072, 2017. PMID: 28055957. DOI: 10.18632/oncotarget.14371

35 Aloia T, Sebagh M, Plasse M, Karam V, Levi F, Giacchetti S, Azoulay D, Bismuth H, Castaing D and Adam R: Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol *24(31)*: 4983-4990, 2006. PMID: 17075116. DOI: 10.1200/JCO.2006.05.8156

36 Hisaka T, Ishikawa H, Sakai H, Kawahara R, Goto Y, Nomura Y, Yasunaga M, Kinugasa T, Fujita F, Mizobe T, Fukahori M, Miwa K, Nakashima O, Tanigawa M, Naito Y, Akiba J, Yano H, Tanaka H, Akagi Y and Okuda K: Sinusoidal obstruction syndrome and postoperative complications resulting from preoperative chemotherapy for colorectal cancer liver metastasis. Anticancer Res *39(8)*: 4549-4554, 2019. PMID: 31366558. DOI: 10.21873/anticanres.13632

37 Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Tsuji A, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hironaka S, Shimada K, Miwa H, Hamada C and Hyodo I: Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol *26(1)*: 141-148, 2015. PMID: 25316259. DOI: 10.1093/annonc/mdu472