Master of Medicine

Comparison of oxaliplatin-related hepatic sinusoidal injuries in patients with gastric cancer who received S-1 or capecitabine as a combination chemotherapy

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Comparison of oxaliplatin-related hepatic sinusoidal injuries in patients with gastric cancer who received S-1 or capecitabine as a combination chemotherapy

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Abstract

Comparison of oxaliplatin-related hepatic sinusoidal injuries in patients with gastric cancer who received S-1 or capecitabine as a combination chemotherapy

Background: Oxaliplatin-based chemotherapy causes hepatic sinusoidal obstruction syndrome (SOS), resulting in portal hypertension with splenomegaly (SM). We herein aimed to compare the severity of hepatic SOS, and its impact on chemotherapy dose reduction or delay between two of the most commonly used oral fluoropyrimidines, S-1 and capecitabine, when combined with oxaliplatin in patients with gastric cancer.

Methods: We analyzed patients from two prospective trials for gastric cancer, adjuvant XELOX (capecitabine 1000 mg/m^2 bid on D1–14 + oxaliplatin 130 mg/m^2 on D1 q3w, eight cycles; n = 52) and palliative SOX (S-1 40 mg/m^2 bid on D1–14 + oxaliplatin 130 mg/m^2 on D1 q3w, continuous [SOX-C, n = 52] vs. intermittent [SOX-I, discontinuing after 6th and restarting on progression, n = 53]). Spleen volume was measured using the Rapidia software.

Results: Baseline sex, age, Eastern Cooperative Oncology Group Performance Status, platelet/liver enzyme/bilirubin levels, and spleen volume did not significantly differ between the XELOX and SOX-C groups. After the eight cycles, the SOX-C group showed more SM and hepatic parenchymal heterogeneity on CT scan and more severe hyperbilirubinemia and thrombocytopenia than the XELOX group. SM was significantly more associated with S-1 combination therapy (63.5% after eight cycles of SOX vs. 26.9% after the eight cycles XELOX; p < 0.001). The

incidence of thrombocytopenia (≤ 100 × 10^3/μL) was significantly higher in SOX-C than in XELOX after six cycles (*n* = 20, 38.5% vs. *n* = 8, 15.4%; *p* = 0.008). In the SOX-C group, 209 of 1288 cycle treatments (16.2%) were delayed or reduced among 23 of 52 patients (44.2%) due to the thrombocytopenia and liver function test abnormalities, whereas in the XELOX group, only 28 of 832 cycles (3.3%) among four of 52 patients (7.6%) were delayed or reduced with same causes (*p* = 0.001).

Conclusion: S-1 apparently worsens oxaliplatin-induced hepatic sinusoidal injuries more than capecitabine in gastric cancer patients. This could increase the incidences of splenomegaly, thrombocytopenia, bilirubin increase, and dose reduction or delay of chemotherapy.

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1. Introduction

Oxaliplatin-based chemotherapy has been associated with hepatic sinusoidal obstruction syndrome (SOS), which is clinically characterized by portal hypertension, splenomegaly, and subsequent thrombocytopenia and liver dysfunction; this syndrome is caused by toxic injury to sinusoidal endothelial cells [1-4]. In patients with colorectal metastasis undergoing hepatic resection after oxaliplatin-based chemotherapy, higher biliary complications, longer hospital stays, and a need for blood transfusions have been reported [5,6]. These changes could have a negative clinical impact, such as discontinuing chemotherapy or reducing the dose of anticancer drugs.

Although oxaliplatin is particularly incriminated in hepatic sinusoidal obstruction syndrome, fluoropyrimidines, including 5-fluorouracil (5-FU), capecitabine, and S-1, have also been suggested to cause sinusoidal dilatation or hepatic sinusoidal obstruction syndrome, albeit to a lesser extent [7]. Robinson et al. experimentally reproduced FOLFOX-induced model of SOS in mice [8].

Given that 5-FU is primarily metabolized in the liver by dihydropyrimidine dehydrogenase (DPD) and that inhibition of DPD may potentiate hepatotoxicity, S-1 containing 5-chloro-2,4-dihydroxypyridine (CDHP; gimeracil), a DPD inhibitor, may potentiate hepatic SOS when combined with oxaliplatin [9]. S-1 consists of tegafur (a 5-FU prodrug) and two modulators, gimeracil (CHDP) and oteracil (potassium oxonate). Gimeracil inhibits DPD and prolongs the half-life of 5-FU and its active metabolites. These properties of gimeracil reduce the production of toxic 5-FU metabolites and lower the tegafur content in S-1 [10]. Capecitabine is an oral prodrug that is converted to FU, its only active metabolite, by thymidine phosphorylase. The enzyme is found at higher levels in tumor cells than in healthy tissues. The predominant route of elimination for capecitabine is kidney [11].

In the current study, we aimed to compare the severity and reversibility of hepatic SOS, and its clinical significance in the aspect of chemotherapy dose intensity

between the two most commonly used oral fluoropyrimidines—S-1 and capecitabine—when combined with oxaliplatin in patients with gastric cancer.

2. Patients and methods

2.1. Patients

We analyzed two different prospective registries; patients treated with adjuvant capecitabine plus oxaliplatin regimen (XELOX) for resectable advanced gastric cancer and those treated with first-line palliative S-1 plus oxaliplatin regimen (SOX) for metastatic or recurrent gastric cancer at the National Cancer Center, South Korea, from June 2006 to July 2011.

The exclusion criteria were prior splenectomy, known cirrhosis, acute or chronic hepatitis, and peribiliary or extensive liver metastasis that may elevate liver enzyme levels. A total of 59 patients enrolled in the CLASSIC study and received adjuvant XELOX [12]. Among them, 52 patients were included in current analysis, whereas seven patients were excluded (prior splenectomy, 4; chronic hepatitis B, 3). We evaluated 250 patients who were enrolled in the phase Ⅱ study of first-line continuous versus stop-and-go SOX for metastatic gastric cancer (Clinical Trials.gov identifier NCT00515190) [13]. According to the study protocol, 126 patients who could not achieve objective response or disease control even with six cycles of SOX were excluded. Of the remaining 124 patients, 62 received continuous SOX chemotherapy till progression (continuous SOX group; the SOX-C group), whereas the other 62 patients were treated with stop-and-go SOX chemotherapy (intermittent SOX group; the SOX-I group); when the patients achieved objective response or disease control, SOX therapy was stopped and chemotherapy was restarted at confirmed disease progression. A total of 52 patients in the SOX-C group met the inclusion criteria; one patient each with prior splenectomy and liver cirrhosis and eight patients with extensive metastasis were excluded. After the exclusion of seven patients with chronic hepatitis and two patients with extensive

metastases, 53 patients were finally included in current analysis as the SOX-I group.

2.2. Study design

Patients assigned to the XELOX group completed eight cycles of adjuvant XELOX chemotherapy after D2 gastrectomy for AJCC 6th stage Ⅱ–Ⅲ gastric cancer. Patients assigned to the adjuvant XELOX group received 1000 mg/m^2 oral capecitabine twice daily on days 1–14 of each cycle plus 130 mg/m^2 oxaliplatin intravenously on day 1 of each cycle every three weeks.

The patients who had confirmed recurrent or metastatic gastric adenocarcinoma without previous palliative chemotherapy were included in the phase Ⅱ of first-line continuous versus stop-and-go SOX study. Patients who achieved complete response (CR)/partial response (PR) or stable disease (SD) after six cycles of SOX were randomly assigned in a 1:1 ratio to either receive maintenance SOX or have a chemotherapy-free interval. Patients in SOX-C were maintained on SOX until disease progression to unacceptable toxicity levels. Patients in SOX-I were observed without any treatment until disease progression, and at disease progression, SOX was reintroduced unless they had residual sensory neuropathy grade >1. SOX was given as follows: 40 mg/m^2 S-1 administered orally twice daily on days 1–14 of each cycle plus 130 mg/m^2 oxaliplatin administered intravenously on the day of each cycle every three weeks.

In both studies, the toxicity experienced by the patients was assessed according to National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) v.4.0 at every visit. When any ≥grade 2 toxicity occurred, chemotherapy was delayed or dose was reduced according to the respective study protocols.

Baseline computed tomographic (CT) scans and laboratory tests were performed in both XELOX and SOX groups. The XELOX group underwent a laboratory test after every two cycles of chemotherapy, followed by a CT scan and laboratory tests after all eight cycles completed. In addition, CT scan and laboratory tests were performed at 24 weeks after the end of treatment. In patients with SOX, CT scans

and laboratory tests were performed after every two cycles up to six cycles of palliative induction chemotherapy, and the same tests were performed every two cycles after completion of the six induction cycles. Among the patients without disease progression after six SOX induction cycles, 13 could be followed up after 24 weeks of induction chemotherapy without additional cycles.

2.3. Study assessments

Spleen volume was measured using the Rapidia software (INFINITT, Seoul, Republic of Korea). Cross-sectional areas of spleen on CT data were processed to obtain a three-dimensional image, and the spleen volume was calculated. Spleen volume change was calculated by (measured volume − baseline volume)/baseline volume × 100. Splenomegaly was defined as having a spleen volume 50% greater than baseline volume.

Hepatic parenchymal heterogeneity on contrast-enhanced CT scan was classified into four grades (0–3) by the radiologist's reading: 0: homogeneous hepatic parenchymal attenuation without heterogeneity; 1: focal or segmental heterogeneous hypoattenuation on only a few sections; 2: patchy or segmental heterogeneous hypoattenuation on all sections; and 3: diffuse heterogeneous hypoattenuation on all sections [14,15].

2.4. Statistical analysis

The primary end-points were splenomegaly occurrence rate and frequency and severity of thrombocytopenia after SOX and XELOX treatments. The secondary end-points were treatment delay or dose reduction, experiencing hepatotoxicity, and spleen volume recovery after discontinuing chemotherapy.

Data analysis was performed using the IBM Statistical Package for the Social Sciences (IBM, NY, USA) version 22. We compared categorical variables with the χ^2 test, Fisher exact test, Mann–Whitney U test, repeated ANOVA test and logistic regression analysis. All tests were two sided, and our level of statistical significance

was $p < 0.05$.

3. Results

The baseline characteristics are described in Table 1. The median ages of the XELOX group ($n = 52$) and SOX group ($n = 105$) were 56 and 60, respectively. The baseline median platelet count and spleen volume were comparable (261.5 vs. 261.0 × 10^3/μL and 139.55 vs. 141.25 cm^3, respectively).

Figure 1 shows the changes in spleen volume following chemotherapy. After eight cycles of chemotherapy, the mean spleen volume was increased in both XELOX and SOX-C groups. The mean spleen volume after eight cycles was significantly greater in the SOX-C group (279.7 cm^3) than in the XELOX group (197.5 cm^3; $p = 0.004$). Splenomegaly developed in both chemotherapy groups. The occurrence of splenomegaly showed higher association with S-1 combination therapy (63.5% after eight cycles of SOX vs. 26.9% after eight cycles of XELOX; $p < 0.001$; Fig. 2).

On observing CT scans, the incidence of hepatic parenchymal heterogeneity was found to be different between the SOX and XELOX groups (Table 2). After eight cycles of SOX ($n = 52$ in SOX-C) and XELOX ($n = 52$), high–grade hepatic parenchymal heterogeneity on CT scan was frequently observed in the SOX-C group ($p = 0.004$). Total bilirubin, as well as liver enzymes, including aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP), showed increasing tendency during the course of chemotherapy in both groups (Fig. 3B). In particular, total bilirubin was significantly higher in the SOX-C group than in the XELOX group on assessing after every two cycles ($p < 0.05$, respectively, Fig. 3B). Platelet count was also decreased gradually as the cycle of chemotherapy in both groups (Fig. 3A). Mean platelet counts were 114.7 × 10^3/μL and 148.2 × 10^3/μL in the SOX-C and XELOX groups, respectively, after eight cycles of treatment. The platelet count was reduced significantly more ($p < 0.05$) in the SOX-C group than in the XELOX group after 6^{th} and 8^{th} cycles

Table 1. Baseline characteristics

	XELOX (*n* = 52)	SOX (*n* = 105)	*P* value
Age (years)	56 (31–75)	60 (36–77)	0.09
Sex			0.20
Male	38 (73.1%)	66 (62.9%)	
Female	14 (26.9%)	39 (37.1%)	
ECOG PS			0.08
0–1	52 (100%)	99 (94.3%)	
≥2	0 (0)	6 (5.7%)	
Treatment setting			<0.01
Adjuvant	52 (100%)	0 (0%)	
Palliative (SOX-C/I)	0 (0%)	52(49.5%)/53(50.5%)	
Platelet ($\times 10^3$/μL)	261.5 (142–530)	261.0 (140–621)	0.12
AST (IU/L)	20.0 (12–40)	20.0 (10–484)	0.36
ALT (IU/L)	14.5 (5–40)	15.0 (3–586)	0.38
Bilirubin (mg/dL)	0.5 (0.2–2.1)	0.4 (0.1–2.0)	<0.01
Bilirubin > UNL	1 (1.9%)	1 (1.0%)	0.55
Spleen volume ($\times 10^3$ cm^3)	139.55 (37.86–335.50)	141.25 (49.29–410.27)	0.17

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; UNL, upper normal limit.

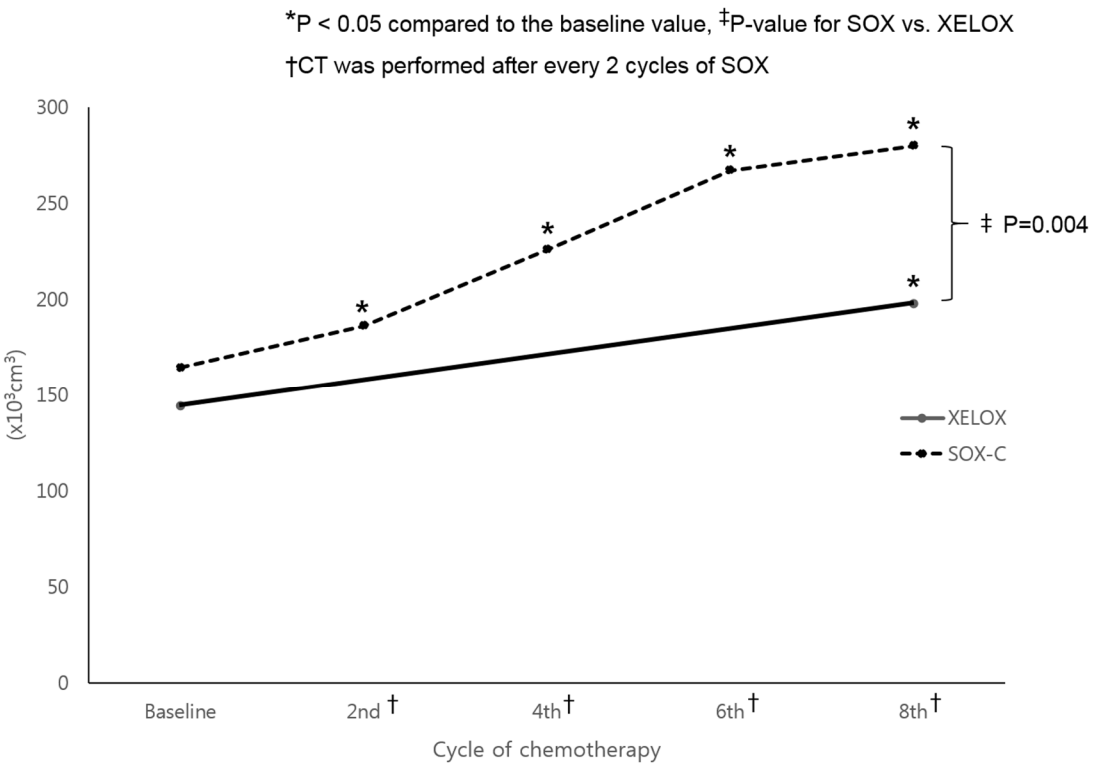


Fig. 1. Change in spleen volume (mean) due to both chemotherapy regimens.

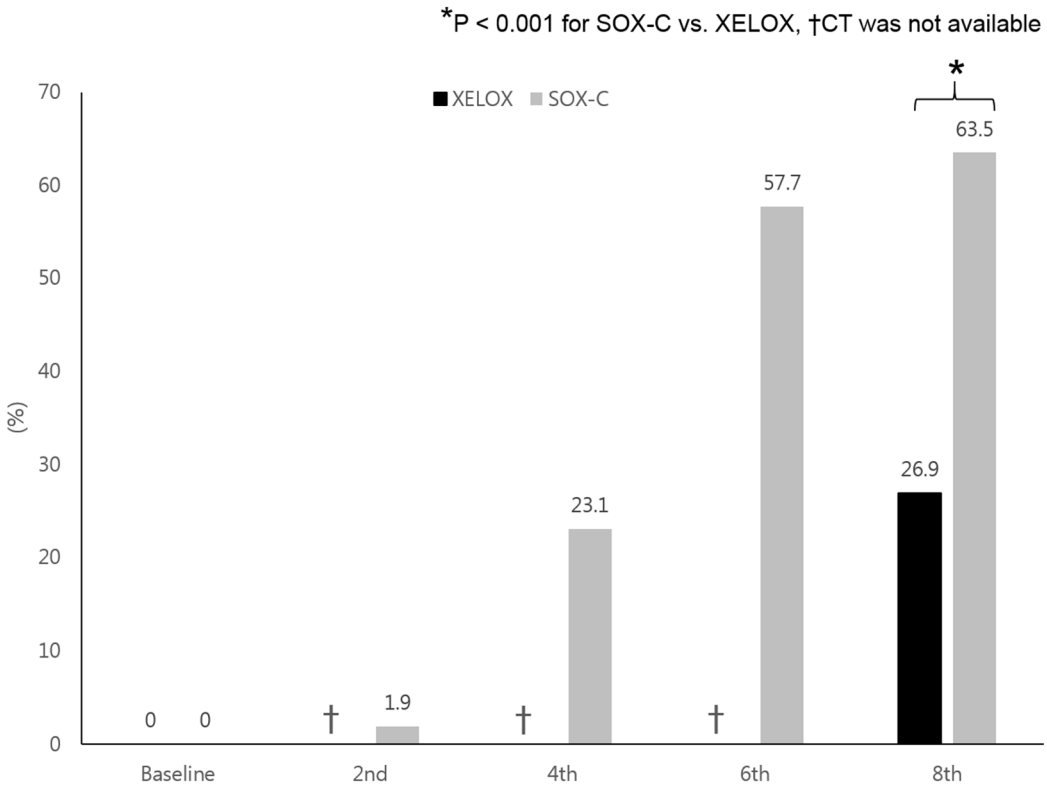


Fig. 2. Comparison of the incidence of splenomegaly due to both chemotherapy regimens.

Table 2. Hepatic parenchymal heterogeneity on CT scan after eight cycles of chemotherapy

	G0	G1	G2	G3	*p*-value
XELOX (*n* = 52)	37 (71.2%)	8 (15.4%)	6 (11.5%)	1 (1.9%)	0.004
SOX-C (*n* = 52)	20 (38.5%)	13 (25.0%)	12 (23.1%)	7 (13.5%)	

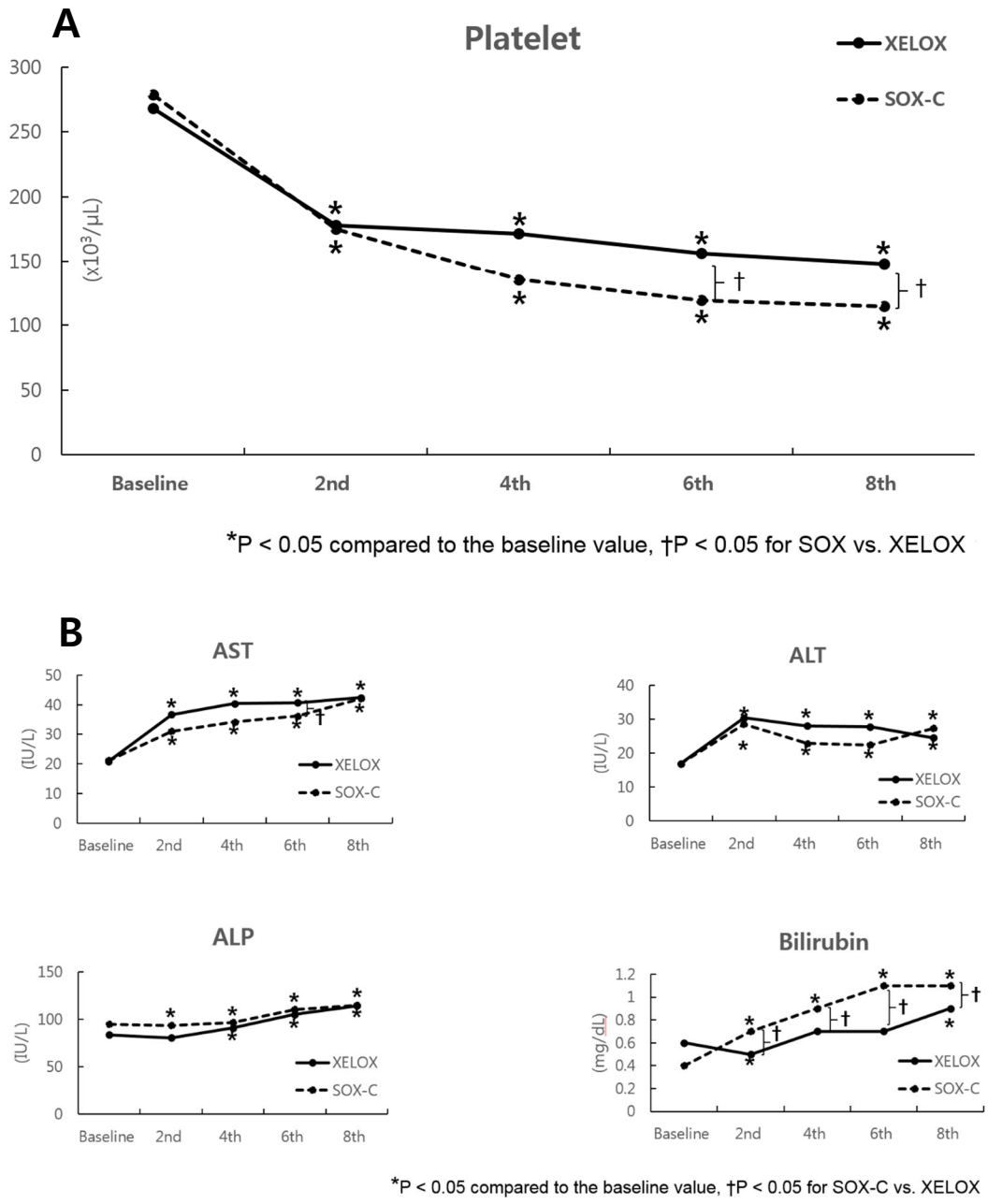


Fig. 3. Change in the levels in platelet and liver enzymes. (A) Platelet count and (B) liver enzymes, including aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), as well as total bilirubin

The frequency of thrombocytopenia (≤ 100 × 10^3/μL) was also increased with chemotherapy administration. The incidence of thrombocytopenia was significantly higher in the SOX-C group than in the XELOX group after six cycles (n = 20, 38.5% vs. n = 8, 15.4%; p = 0.008) (Fig. 4).

During chemotherapy, dose reduction or delay occurred for various reasons. The total number of chemotherapy delays or dose reduction events were 411 of 1288 cycles in the SOX-C group (31.9%) and 273 of 832 cycles in the XELOX group (32.8%); they occurred because of several reasons, including nausea, diarrhea, hand–foot syndrome, hypersensitivity reaction, febrile neutropenia, liver function test (LFT) abnormalities, and thrombocytopenia. Moreover, the patients experiencing treatment delays or dose–reductions from any abovementioned cause were 36 of 52 (69.2%) in the SOX-C group and 37 of 52 (71.2%) in the XELOX group.

In the SOX-C group, 209 of 1288 cycle treatments (16.2%) were delayed or reduced in 23 of 52 patients (44.2%) due to thrombocytopenia or LFT abnormalities, whereas in the XELOX group, only 28 of 832 cycle treatments (3.3%) were delayed among four of 52 patients for similar reasons (7.6%; p < 0.001, Fig. 5).

Both mean and median platelet counts were significantly lower in patients with splenomegaly than in those without (p < 0.001). Furthermore, median AST, ALT, ALP, and total bilirubin were also significantly higher in patients with splenomegaly than in those without (Table 3A). However, CT scan showed no significant difference in hepatic parenchymal heterogeneity between grade 0–1 and 2–3 (Table 3B).

Splenomegaly and thrombocytopenia were reversible over time after chemotherapy completion. In the XELOX group, after eight cycles, the mean spleen volume increased by 37.4% (197.49 cm^3) compared to the baseline volume. Twenty-four weeks after chemotherapy, the mean volume decreased (159.88 cm^3), which rendered the volume larger by 11.2% compared to the baseline volume (p

= 0.001). A total of 13 patients in the SOX-I group who received six cycles of SOX induction and were followed up without further chemotherapy because of stable disease until after 24 weeks also showed this trend of significant decreasing volume: +56% (193.69 cm^3), +45.8% (180.73 cm^3), +34.5% (166.73 cm^3), +27.0% (157.56 cm^3), and +20.7% (149.67 cm^3), respectively after six cycles, off six weeks, twelve weeks, eighteen weeks and twenty-four weeks (Fig. 6A).

Thrombocytopenia also showed reversible tendency in 13 patients of the SOX-I group; the mean platelet count was 104.4 × 10^3/μL (64.7% lower than baseline) after six cycles, and the mean platelet count recovered to 205.5 × 10^3/μL (30.5% lower than baseline) after 24 weeks from discontinuing SOX treatment (Fig. 6B).

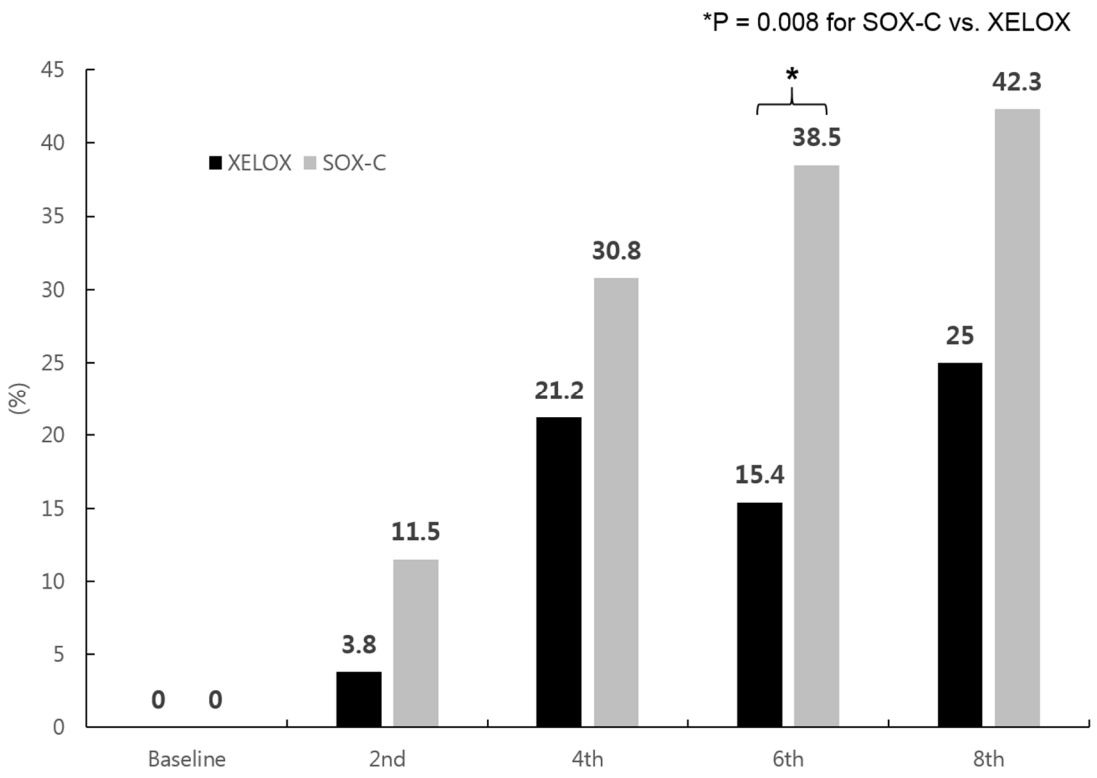


Fig. 4. Comparison of the incidence of thrombocytopenia (<100 × 10^3/μL) due to both chemotherapy regimens.

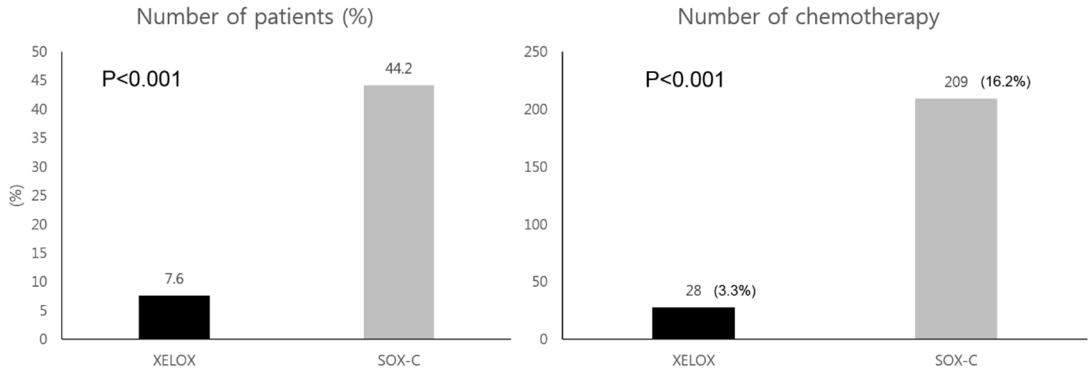


Fig. 5. Frequency of dose reduction or delay of chemotherapy due to thrombocytopenia or liver function test abnormalities.

Table 3. Laboratory findings after 8th chemotherapy according to spleen volume change (A), and hepatic heterogeneity on CT scan grades (B) in XELOX (*n* = 52) and SOX-C (*n* = 52) groups

A		Spleen volume, <1.5 times	Spleen volume, ≥1.5 times	*p*-value
Platelet	Median	137.0	99.0	<0.001
AST	Median	34.4	40.7	0.006
ALT	Median	19.8	22.2	0.030
ALP	Median	102.0	122.0	0.008
Bilirubin	Median	0.7	1.0	0.001
Hepatic heterogeneity	G 0–1 (%)	46 (80.7)	32 (68.1)	0.139
	G 2–3 (%)	11 (19.3)	15 (31.9)	

B		Hepatic heterogeneity, G 0–1	Hepatic heterogeneity, G 2–3	*p*-value
Platelet	Median	112.3	113.5	0.967
AST	Median	36.2	40.7	0.065
ALT	Median	20.7	23.5	0.100
ALP	Median	111.3	117.0	0.516
Bilirubin	Median	0.8	0.9	0.472
Spleen volume	<1.5 times (%)	46 (59.0)	11 (42.3)	0.139
	≥1.5 times (%)	32 (41.0)	15 (57.7)	

4. Discussion

We assessed the effect on oxaliplatin-induced spleen injury when oxaliplatin was administered in combination with either capecitabine or S-1 in gastric cancer patients. The patients with gastric cancer seemed to experience more splenomegaly and thrombocytopenia with the S-1 combination than with the capecitabine combination. We assume that the former enhances the oxaliplatin-induced hepatic SOS. Moreover, we confirmed the reversibility of SOX- or XELOX-induced splenomegaly after discontinuation of therapy. To our knowledge, this is the first report about synergistic impact of S-1 on oxaliplatin adverse events and the first study to compare the effects of S-1 and capecitabine in terms of hepatic SOS.

The disease status was different between the two groups—adjuvant vs. palliative setting. For overcoming this limitation, we conducted additional analysis with selected patients in the SOX-C group who did not have liver metastasis (n = 45), and the results were equivalent (Supplementary Table 2 and Supplementary Fig. 1, 2, 3A, 3B, 4, 5).

Despite the widely accepted use of oxaliplatin as a combination partner in both adjuvant and palliative chemotherapy of colorectal and gastric cancer, thrombocytopenia and splenomegaly have been frequently reported [16-18]. These adverse events are considered to have resulted from oxaliplatin-induced hepatic SOS [19-21]. Histologic evidences of SOS have been reported to be present in up to 78% of patients receiving neoadjuvant oxaliplatin-based chemotherapy before hepatectomy of colorectal liver metastasis [16,22].

Pathogenesis of this condition because of chemotherapy is correlated with obstruction at the level of hepatic sinusoids, followed by obliteration of the terminal hepatic veins [23]. Toxic effects on sinusoidal endothelial cells result in the disruption of the sinusoids, thus obstructing sinusoidal blood flow. Later, SOS was proposed as a more appropriate name for a veno-occlusive disease wherein toxic

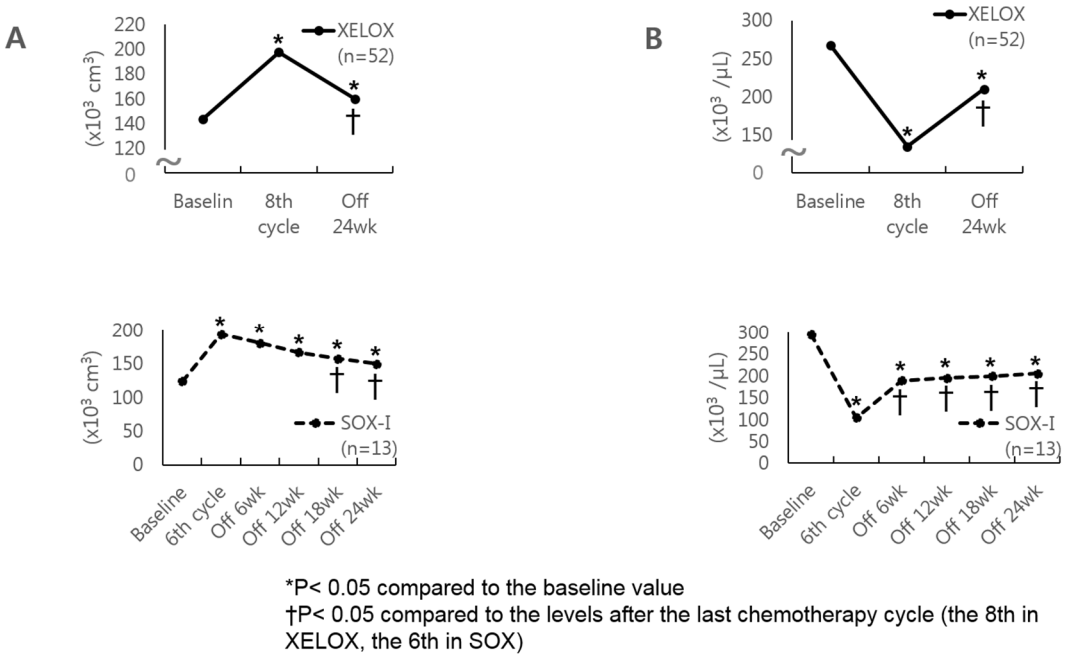


Fig. 6. Reversibility of splenomegaly (A) and thrombocytopenia (B) in XELOX (*n* = 52) and SOX-I (*n* = 13) groups.

injury to the hepatic sinusoids was the fundamental reason behind the condition [24].

At the beginning of this study, we hypothesized that splenomegaly was a surrogate marker to predict oxaliplatin-induced sinusoidal injury and that S-1 and oxaliplatin combination can promote the use of splenomegaly as an indicator by causing SOS [1].

5-FU has traditionally been used to treat gastric cancer, and several prodrugs of 5-FU have been developed to improve efficacy, tolerability, and convenience. Capecitabine, tegafur uracil (UFT), and S-1 are representative oral prodrugs. The REAL-2 study demonstrated that capecitabine could replace 5-FU continuous infusion and that oxaliplatin was not inferior to cisplatin [25].

Subsequently, a multinational phase Ⅲ study reported that S-1 plus cisplatin does not provide inferior overall survival than conventional 5-FU plus cisplatin does [26]. Currently, S-1 is approved for use in combination with cisplatin as a therapeutic agent for advanced gastric cancer in Asian and European countries. Thus, S-1 and capecitabine are actively used in advanced gastric cancer when administered in combination with oxaliplatin [27].

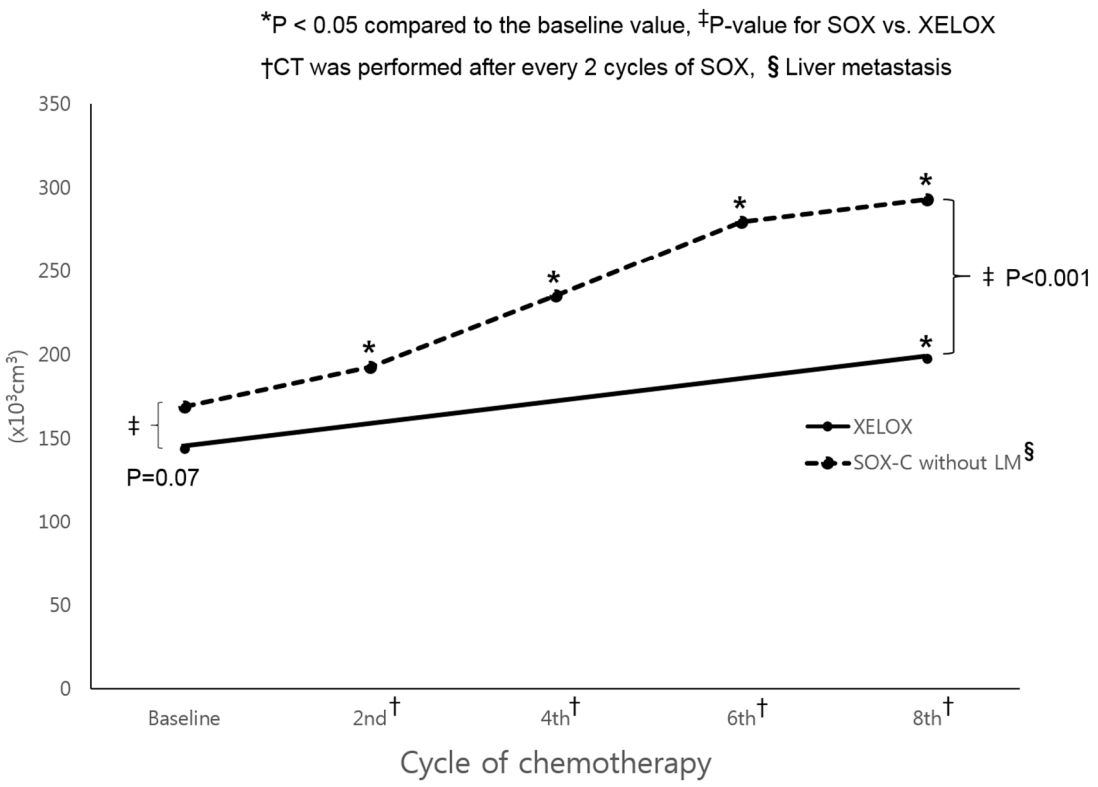
The most common adverse effects of S-1 and capecitabine are hyperbilirubinemia, diarrhea, and hand–foot syndrome. In addition, there is higher incidence of hand–foot syndrome with capecitabine than with S-1. However, capecitabine- or S-1-related SOS has not been previously investigated. There is only one case report about SOS occurring in advanced gastric cancer patients treated using S-1 plus cisplatin [7]. There have been many studies about oxaliplatin use, most of which pertain to colorectal cancer with liver metastasis. We consider it significant that we could observe such results in stomach cancer.

There have been several studies on the reversibility of chemotherapy-associated liver injury. Rubbia-Brandt et al. reported cases of SOS regression without interval chemotherapy after several months [16]. Vigano et al. recently reported that chemotherapy-associated liver injury regressed after nine months of

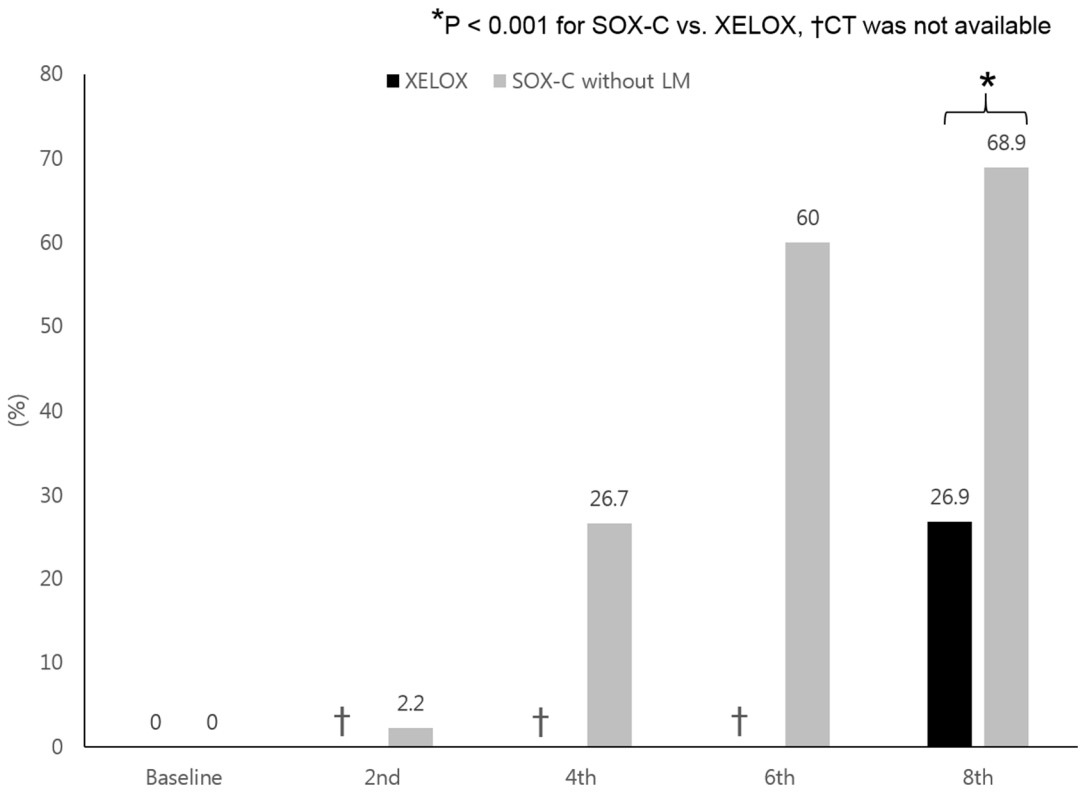
discontinuation of chemotherapy [28].

The current study has some limitations. First, we reviewed two prospective trials. There are some aspects of retrospective nature, whereas the study subjects' data were prospective. Second, as we mentioned above, the disease status was different between the two groups. Third, even though we confirmed regression of chemotherapy-induced splenomegaly and thrombocytopenia, the observation period was not sufficient to observe till complete recovery.

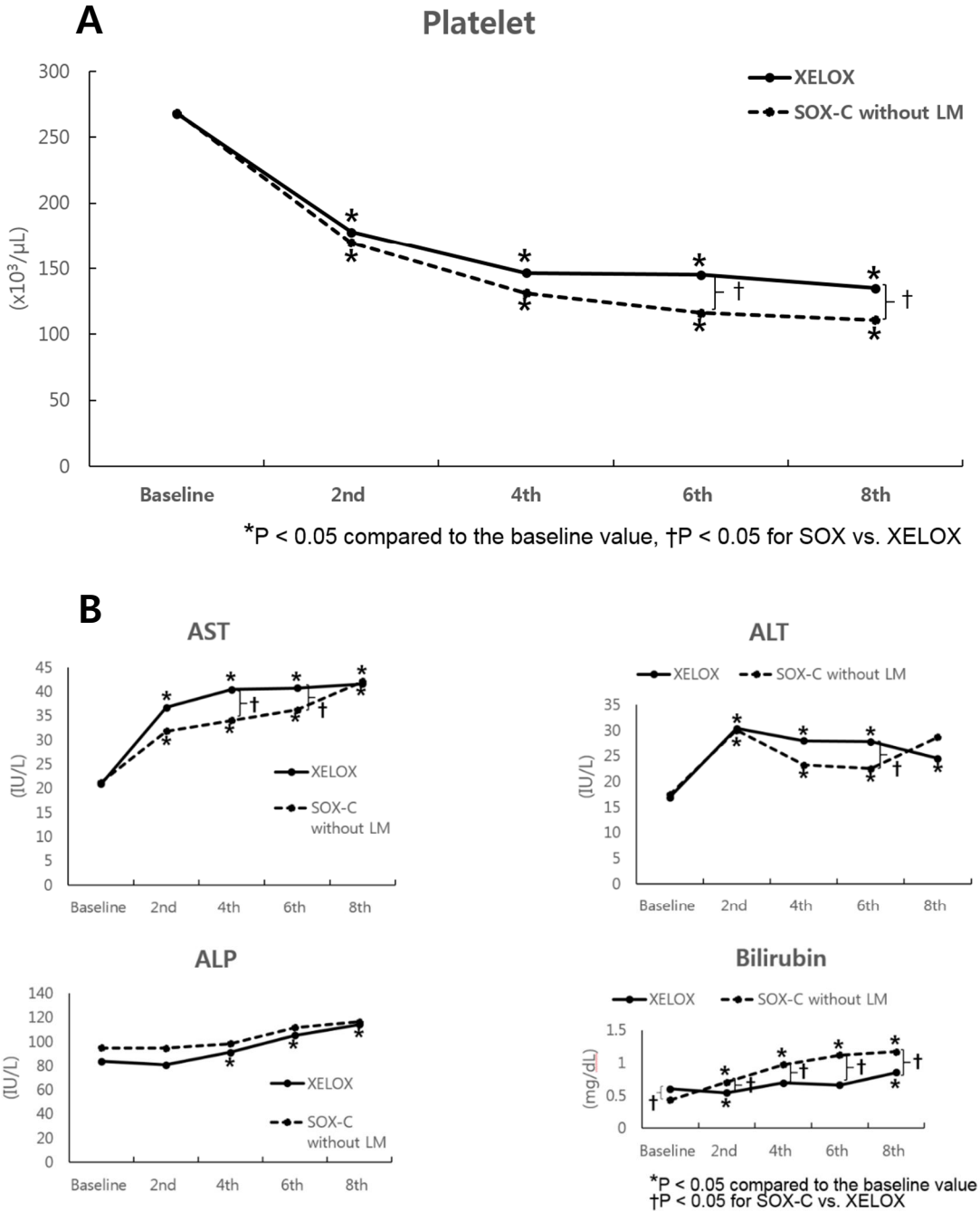
In conclusion, S-1 apparently worsens oxaliplatin-induced hepatic sinusoidal injuries more than capecitabine in gastric cancer patients. This could increase the incidences of splenomegaly, thrombocytopenia, bilirubin increase, and dose reduction or delay of chemotherapy. Given that that hepatic sinusoidal injuries induced by either S-1 or capecitabine plus oxaliplatin are reversible after discontinuation of chemotherapy, a better treatment strategy such as a stop-and-go chemotherapy approach needs to be pursued in the palliative setting. Further studies are needed to elucidate the underlying mechanisms for this phenomenon.



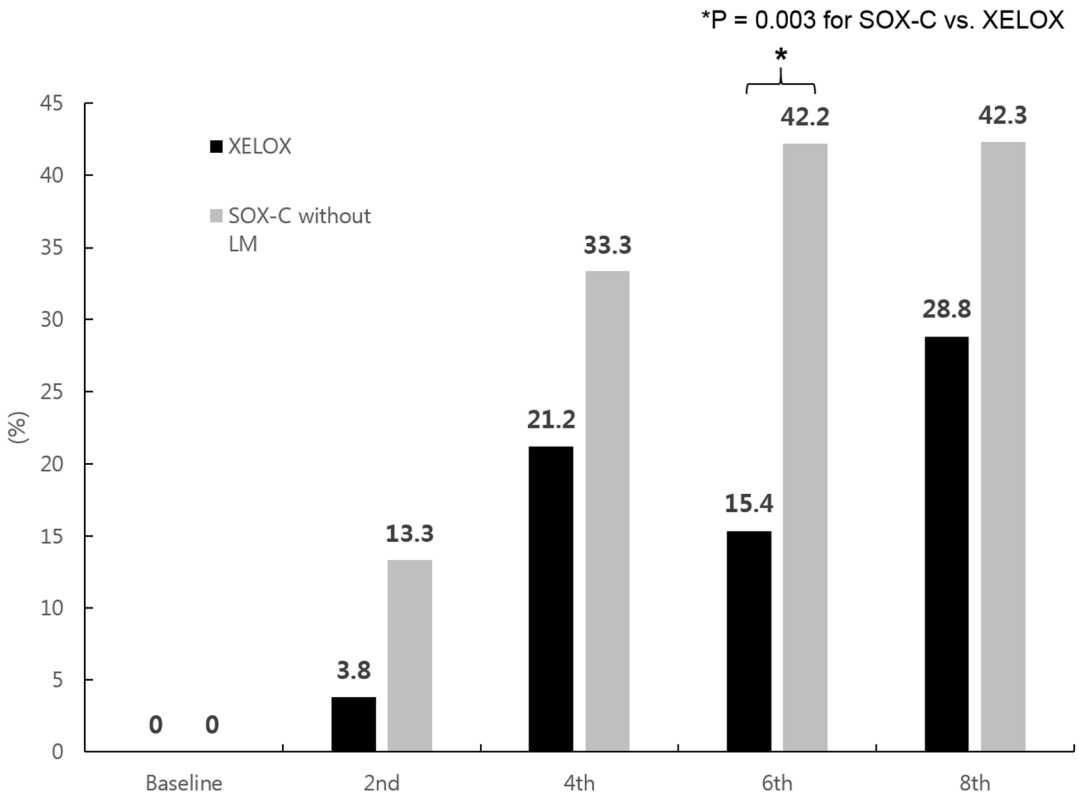
Supplementary Fig. 1. Change in spleen volume (mean) due to both chemotherapy regimens (XELOX; *n* = 52, SOX-C without LM; *n* = 45).



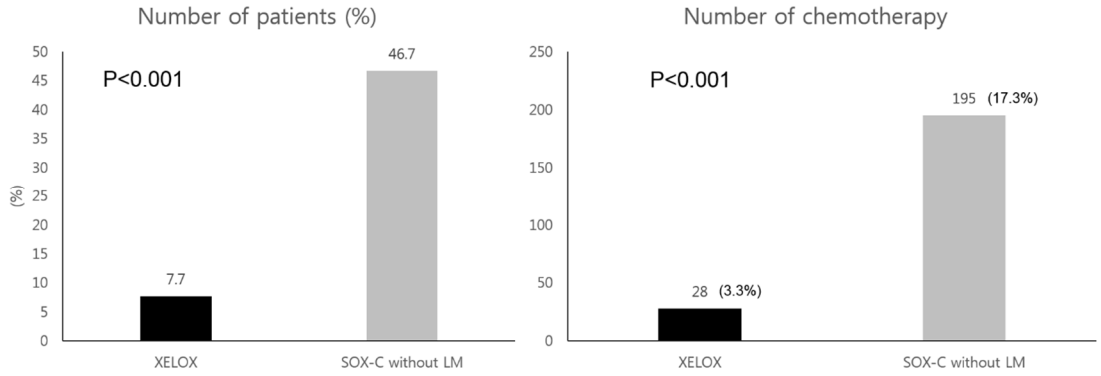
Supplementary Fig. 2. Comparison of the incidence of splenomegaly due to both chemotherapy regimens.



Supplementary Fig. 3. Change in the levels in platelet and liver enzymes.



Supplementary Fig. 4. Comparison of the incidence of thrombocytopenia (<100 × 10^3/μL) due to both chemotherapy regimens.



Supplementary Fig. 5. Frequency of dose reduction or delay of chemotherapy due to thrombocytopenia or LFT abnormalities.

Supplementary Table 1. Hepatic parenchymal heterogeneity on CT scan after eight cycles of chemotherapy

	G0	G1	G2	G3	*p*-value
XELOX (*n* = 52)	37 (71.2%)	8 (15.4%)	6 (11.5%)	1 (1.9%)	0.002
SOX-C without LM* (*n* = 45)	18 (40%)	12 (26.7%)	10 (22.2%)	5 (11.1%)	

* liver metastasis.

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국문 요약

Oxaliplatin을 S-1 또는 Capecitabine과 병합하여 치료한 위암 환자에서 Oxaliplatin-related hepatic sinusoidal injury 발생의 비교

Oxaliplatin 기반 항암치료는 문맥고혈압, 비장비대 등으로 발현되는 hepatic sinusoidal injury를 유발한한다. 본 연구는 위암에서 Oxaliplatin에 S-1과 Capecitabine을 각각 각각 병합하여 항암치료제의 감량 및 치료 연기 횟수 등을 조사하여 hepatic sinusoidal injury의 정도를 비교해 보고자 하였다.

두 개의 전향적 위암 연구에 등록된 환자들을 대상으로 분석하였다. Adjuvant XELOX (Capecitabine + Oxaliplatin, 8주기, n = 52) 군과 palliative SOX (S-1 + Oxaliplatin) 군을 비교하였다. Palliative SOX 군은 임상시험 설계에 따라 continuous SOX [SOX-C, n = 52, 6주기 진행 이후 Progressive disease가 될 때까지 계속 항암치료를 시행한 군]와 intermittent SOX [SOX-I, n = 53, 6주기 진행 이후 반응 평가하여 progressive disease이면 다시 SOX 치료를 시작) 군으로 구분하였다. 비장비대는 Rapidia 소프트웨어를 이용하여 평가하였다.

항암치료 8주기 시행 후, SOX-C 군에서 XELOX 군보다 비장비대, hepatic parenchymal heterogeneity, 고빌리루빈혈증, 혈소판감소증 (≤ 100 × 10^3/μL) 이 더 많이 발생하였다. 비장비대의 발생 빈도는 SOX 군에서 현저히 많았고 (63.5%, SOX 8주기 이후 vs. 26.9%, XELOX 8주기 이후; p < 0.001), 혈소판감소증의 빈도도 SOX-C 군에서 XELOX 군보다 유의하게 높았다 (n = 20, 38.5% vs. n = 8, 15.4%; p = 0.008). 혈소판감소증이나 간기능검사 이상으로 인한 항암치료제의 감량 또는 치료 연기가 필요했던 항암주기는 SOX-C 군에서 16.2% (총 1288 주기 중 209 주기), XELOX 군에서 3.3% (총 832 주기 중 28 주기)로 SOX-C에서 더 많았다 (p = 0.001). 환자 수 측면에서는 SOX-C 군에서 44.2% (총 52명 중 23명), XELOX 군에서 7.6% (총 52명 중 4명) 이었다 (P = 0.001).

결론적으로, S-1이 위암에서 Capecitabine을 병용했을 때보다 Oxaliplatin-related hepatic sinusoidal injury를 확연하게 악화시켰다. 이러한 hepatic sinusoidal injury는 비장비대, 혈소판감소증, 고빌리루빈혈증, 그리고 항암제 감량 또는 치료

연기 등으로 이어져 임상적 악영향을 미쳤다.

중심단어 : 위암, Hepatic sinusoidal injury, 비장비대, Capecitabine, Oxaliplatin, S-1