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Survival Outcomes of Two Phase 2 Studies of Adjuvant Chemotherapy with S-1 Plus Oxaliplatin or Capecitabine Plus Oxaliplatin for Patients with Gastric Cancer After D2 Gastrectomy

Yoshiaki Nakamura, MD, PhD[1], Takeharu Yamanaka, PhD[2], Keisho Chin, MD[3], Haruhiko Cho, MD, PhD[4,5], Hitoshi Katai, MD, PhD[6], Masanori Terashima, MD, PhD[7], Kazunari Misawa, MD, PhD[8], Motohiro Hirao, MD, PhD[9], Kazuhiro Yoshida, MD, PhD[10], Eiji Oki, MD, PhD[11], Mitsuru Sasako, MD, PhD[12], Yasunori Emi, MD, PhD[13], Hideaki Bando, MD, PhD[1], Yoshiyuki Kawashima, MD, PhD[14], Tetsu Fukunaga, MD, PhD[15], Masahiro Gotoh, MD, PhD[16], Takako Ishibashi, BEd[17], and Kohei Shitara, MD[1]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; [2]Department of Biostatistics, Yokohama City University, Yokohama, Kanagawa, Japan; [3]Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan; [4]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Kanagawa, Japan; [5]Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku, Tokyo, Japan; [6]Division of Gastric Surgery, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan; [7]Division of Gastric Surgery, Shizuoka Cancer Center, Sunto-gun, Shizuoka, Japan; [8]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; [9]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Osaka, Japan; [10]Department of Surgical Oncology, Graduate School of Medicine, Gifu University, Gifu, Gifu, Japan; [11]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University Hospital, Fukuoka, Fukuoka, Japan; [12]Department of Surgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; [13]Department of Surgery, Saiseikai Fukuoka General Hospital, Fukuoka, Fukuoka, Japan; [14]Department of Gastroenterological Surgery, Saitama Cancer Center, Ina-machi, Saitama, Japan; [15]Department of Gastroenterological and General Surgery, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan; [16]Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, Osaka, Japan; [17]Center for Novel and Exploratory Clinical Trials, Yokohama City University Hospital, Yokohama, Kanagawa, Japan

ABSTRACT

Background. Two phase 2 trials of oxaliplatin-containing adjuvant therapy for patients with gastric cancer (GC) after D2 gastrectomy were conducted in Japan. The SOXaGC trial evaluated the tolerability and safety of adjuvant therapy with S-1 plus oxaliplatin (SOX), whereas the J-CLASSIC trial evaluated the feasibility of adjuvant therapy with capecitabine plus oxaliplatin (CAPOX). Because both were studies that did not evaluate survival results as study end points, the authors evaluated the survival outcomes for the patients in the two trials.

Methods. All 62 and 100 patients in the full analysis set of the SOXaGC and J-CLASSIC trials, respectively, were included in the current study. Their information about survival outcome was collected. The primary end point was relapse-free survival (RFS), and the secondary end point was overall survival (OS).

Results. For the pathologic stage (pStage 2) patients treated with CAPOX, the 3-year RFS rate was 87.8% and the 3-year OS rate was 92.7%. For the pStage 3 patients treated with SOX and CAPOX, the 3-year RFS rates were

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K. Shitara, MD
e-mail: kshitara@east.ncc.go.jp

respectively 70.9% and 67.8% (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.50–1.72), whereas the 3-year OS rates were respectively 75.7% and 79.3% (HR, 1.10; 95% CI, 0.54–2.26). Subgroup analysis showed significant interactions between the treatment (SOX vs. CAPOX) and both sex (male vs. female; $P = 0.024$) and histologic type (diffuse vs. other, $P = 0.069$).

Conclusions. This exploratory analysis demonstrated that SOX and CAPOX are suggested to have similar efficacy for pStage 3 GC patients after D2 gastrectomy. Differences in the treatment effect according to sex and histologic type warrant further evaluation.

According to two randomized phase 3 trials, adjuvant chemotherapy is recommended for pathologic stages (pS-tages) 2 and 3 gastric cancer (GC) patients after gastrectomy with D2 lymphadenectomy (D2 gastrectomy).[1,2] The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) showed that adjuvant S-1, an oral fluoropyrimidine composed of tegafur, gimeracil, and oteracil, significantly improved the overall survival (OS) compared with surgery alone for patients with pStage 2 or 3 GC.[1] Reduction of mortality risk was observed regardless of the histologic type, with a hazard ratio (HR) of 0.670 for the differentiated type of the disease and 0.673 for the undifferentiated type.[3]

The CLASSIC trial, conducted primarily in South Korea, demonstrated that treatment with adjuvant capecitabine plus oxaliplatin (CAPOX) significantly improved the 3-year disease-free survival compared with surgery alone for patients with pStage 2 or 3 disease.[2] Meanwhile, well or moderately differentiated types showed a trend toward greater reduction of mortality than tumors with poorly differentiated histology (HR in 5-year OS, 0.50 vs. 0.77).[4]

Because no randomized studies have directly compared S-1 monotherapy and CAPOX as adjuvant treatments, both regimens are recommended for pStage 3 disease in Japan. Meanwhile, S-1 plus oxaliplatin (SOX) is a widely used regimen in Japan in the metastatic setting based on the result from a randomized phase 3 trial suggesting that SOX seemed to be as effective as S-1 plus cisplatin (SP).[5] However, its efficacy in the adjuvant setting has not been evaluated in phase 3 trials.

Because the previous Japanese study of adjuvant SP showed that this doublet chemotherapy for patients immediately after gastrectomy is not as feasible as for metastatic patients, it is important to evaluate the feasibility of adjuvant SOX and CAPOX.[6] Therefore, we conducted two phase 2 trials to evaluate the safety of the oxaliplatin and oral fluoropyrimidine combination for patients with GC after D2 gastrectomy in Japan. The SOXaGC trial involved the use of SOX,[7] whereas the J-CLASSIC trial studied therapy with CAPOX.[8] The preliminary aims of the two studies were to evaluate safety and patient compliance, and the primary end points in this regard were met.[7,8] However, because no data on the efficacy of SOX and CAPOX existed for the Japanese population, we planned this observational follow-up study to investigate the survival outcomes in an attempt to outline the differences in efficacy between subgroups of patients to enable better choosing among treatment options for these patients.

PATIENTS AND METHODS

Study Design and Patients

This multicenter observational study aimed to evaluate the survival outcomes for patients enrolled in the SOXaGC and J-CLASSIC trials. As mentioned previously, because neither study included survival analysis, we planned this ad hoc observational study.

The study designs of the two trials have been described in previous studies.[7,8] In SOXaGC, the treatment completion rate was evaluated as the primary end point for 62 patients with pStage 3 GC who received SOX after D2 gastrectomy in 11 Japanese centers between July 2013 and February 2014. The SOX regimen consisted of S-1 alone (40–60 mg/m^2 twice daily on days 1–14 of a 3-week cycle) in the first cycle, followed by treatment using S-1 combined with oxaliplatin (100 mg/m^2 administered intravenously on day 1 of each cycle) from the second to the eighth cycle.

In the J-CLASSIC trial, the dose intensity was evaluated as the primary end point for 100 patients with pStage 2 or 3 GC who received CAPOX after D2 gastrectomy in 12 Japanese centers, including nine centers that also participated in the SOXaGC, between July 2012 and July 2013. The CAPOX regimen consisted of capecitabine (1000 mg/m^2 twice daily on days 1–14 of a 3-week cycle) and oxaliplatin (130 mg/m^2 administered intravenously on day 1 of each cycle) for eight cycles.

Disease stages were determined according to the 14th edition of the Japanese Classification of Gastric Carcinoma in both trials. After the completion of treatment, patients in each trial were followed up as recommended in version 4.0 of the Japanese Gastric Cancer Treatment Guidelines.[9]

In the current study, the information about survival outcome was collected. The cutoff date for the follow-up evaluation was April 2017, more than 3 years after the completion of enrollment in the original studies.

This study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol was approved by the institutional

review board of each participating institution. For patients and relatives, information concerning the research was disclosed on the website of the National Cancer Center, and opportunities to express their will were ensured.

Statistical Analysis

The primary end point of this analysis was relapse-free survival (RFS), defined as the interval between the date of enrollment in the original studies and the date that recurrence or mortality due to any cause, whichever occurred first, was confirmed. The secondary end point was OS, defined as the interval between the date of enrollment and the date of mortality due to any cause. The Kaplan–Meier method was used to estimate the survival rates.

As mentioned earlier, the two clinical trials were performed consecutively at almost the same hospitals, and patient heterogeneity between the studies was small except for pStages due to different inclusion criteria. Therefore, we also compared the efficacy of SOX and CAPOX in pStage 3 patients.

Both OS and RFS were compared using the log-rank test. For comparison of SOX and CAPOX, HR and 95% confidence interval (CI) were calculated using the Cox proportional hazards model. Planned subgroup analyses for RFS were performed according to age, sex, histologic type, and stage subcategories.

In terms of the histologic type, non-solid type poorly differentiated adenocarcinoma (por2), signet-ring cell carcinoma (sig), or both according to the Japanese Classification of Gastric Carcinoma were classified as diffuse-type disease, whereas other histologic subgroups were classified as other-type disease. Subgroup analysis was not performed according to the performance status (PS) because a different scoring system was used in each trial, namely the Eastern Cooperative Oncology Group (ECOG) PS in the SOXaGC trial and the Karnofsky PS in the J-CLASSIC trial.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Differences in baseline characteristics were compared by Fisher's exact test. All P values were reported as two-tailed. In accordance with ordinary practice, a P value lower than 0.10 was considered statistically significant for interaction tests. For tests used to compare the two groups, a P value lower than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

All 62 and 100 patients in the full analysis set of the SOXaGC and J-CLASSIC trials, respectively, were included in the current study. The median follow-up time was 39 months in the SOXaGC trial and 49 months in the J-CLASSIC trial. The patient characteristics in the two trials are shown in Table 1. The J-CLASSIC trial included 41 patients with pStage 2 disease and 59 patients with pStage 3 disease. The baseline characteristics of the pStage 3 patients did not differ significantly between the two trials.

Survival Outcome for the pStage 2 Patients Treated with CAPOX

Among 41 patients who had pStage 2 disease treated with CAPOX, 3 patients died after recurrence, 2 patients were alive with recurrence, and 36 patients were alive without recurrence at the time of the last follow-up evaluation. The pStage 2 patients had a 3-year RFS rate of 87.8% (95% CI, 73.2–94.7%; Fig. 1a) and a 3-year OS rate of 92.7% (95% CI, 79.0–97.6%; Fig. 1b). In addition, the 3-year RFS rate was 100% (95% CI, 100–100%) for the pStage 2A patients and 84.8% (95% CI, 67.4–93.4%) for the 2B patients. The 3-year OS rate was 100% (95% CI, 100–100%) for the pStage 2A patients and 90.6% (95% CI, 73.7–96.9%) for the 2B patients.

Survival Outcome for the pStage 3 Patients Treated with SOX and CAPOX

Among 62 and 59 patients with pStage 3 disease treated with SOX and CAPOX, respectively, 13 and 15 patients died after recurrence, 3 and 1 patients died due to causes unrelated to GC, 4 and 7 patients were alive with recurrence, and 42 and 36 patients were alive without recurrence at the last follow-up evaluation. The 3-year RFS rates for the pStage 3 patients were 70.9% (95% CI, 57.8–80.5%) for those treated with SOX and 67.8% (95% CI, 54.3–78.1%) for those treated with CAPOX. The 3-year OS rates for the pStage 3 patients were 75.7% (95% CI, 63.0–84.6%) for those treated with SOX and 79.3% (95% CI, 66.5–87.7%) for those treated with CAPOX (Fig. 1a, b). In addition, the HRs of SOX versus CAPOX treatment for pStage 3 patients were 0.93 (95% CI, 0.50–1.72; $P = 0.81$) for RFS and 1.10 (95% CI, 0.54–2.26; $P = 0.79$) for OS.

The results from the subgroup analysis of RFS for the pStage 3 patients are shown in Table 2. Significant interactions were observed between the treatment (SOX vs CAPOX) and sex (male vs female; $P = 0.024$) or histologic

TABLE 1 Patient characteristics

	SOX, pStage 3 (n = 62) n (%)	CAPOX, pStage 2 (n = 41) n (%)	CAPOX, pStage 3 (n = 59) n (%)	P value[a]
Age (years)				
< 65	31 (50)	25 (51)	32 (54)	0.72
≥ 65	31 (50)	20 (49)	27 (46)	
Sex				
Male	39 (63)	21 (51)	32 (54)	0.36
Female	23 (37)	20 (49)	27 (46)	
Karnofsky PS				
100	–	33 (80)	41 (69)	
90	–	7 (17)	17 (29)	
80	–	1 (2)	1 (2)	
ECOG PS				
0	56 (90)	–	–	
1	6 (10)	–	–	
Histologic type				
Diffuse	39 (63)	15 (37)	35 (59)	0.71
Other	23 (37)	26 (63)	24 (41)	
pStage				
2A	–	8 (20)	–	0.39
2B	–	33 (80)	–	
3A	17 (27)	–	23 (39)	
3B	22 (35)	–	16 (27)	
3C	23 (37)	–	20 (34)	
Surgical procedure				
Total gastrectomy	32 (52)	11 (27)	25 (42)	0.36
Distal gastrectomy	30 (48)	30 (73)	34 (58)	

SOX S-1 plus oxaliplatin, *CAPOX* capecitabine plus oxaliplatin, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *pStage* pathologic stage

[a]Fisher's exact test was used for comparison of SOX and CAPOX in pStage 3 patients

type (diffuse vs other; P = 0.069). According to the histologic type, the 3-year RFS rates for the patients with diffuse-type disease were 71.8% (95% CI, 57.7–85.9%) for those treated with SOX and 57.1% (95% CI, 40.6–73.6%) for those treated with CAPOX (HR, 0.60; 95% CI, 0.29–1.27; P = 0.18, log-rank; Fig. 2a). By contrast, the 3-year RFS rates for the patients who had other-type disease were 69.0% (95% CI, 49.8–88.2%) for those treated with SOX and 83.3% (95% CI, 68.4–98.2%) for those treated with CAPOX (HR, 2.30; 95% CI, 0.69–7.64; P = 0.16, log-rank; Fig. 2b). These trends were consistent in the subgroup of patients with an ECOG PS of 0 in the SOX group and a Karnofsky PS of 100 in the CAPOX group, showing that PS was not a confounding factor of the trends (data not shown).

The RFS for adjuvant SOX also was more favorable than that for CAPOX in the subgroups of patients younger than 65 years who had pStage 3B or 3C disease. The proportion of diffuse-type GC was higher than that of other-type GC in these subgroups, possibly explaining the reason behind the improved RFS for SOX compared with CAPOX (Table S1).

Site of First Recurrence and Subsequent Systemic Therapy After Recurrence

Among the 17 patients who presented with recurrence after SOX therapy, the peritoneum (n = 6, 35%), lymph node (n = 5, 29%), and liver (n = 4, 24%) were identified as the most common sites of first recurrence (Table 3). Of these patients, 13 (76%) received systemic chemotherapy after recurrence, including treatment with S-1 (n = 8, 62%), paclitaxel (n = 7, 54%), cisplatin (n = 5, 38%), oxaliplatin (n = 5, 38%), irinotecan (n = 5, 38%), and ramucirumab (n = 5, 38%) (Table S2).

On the other hand, among the 27 patients who exhibited recurrence after CAPOX treatment, the most common site of first recurrence was the peritoneum (n = 12; 44%),

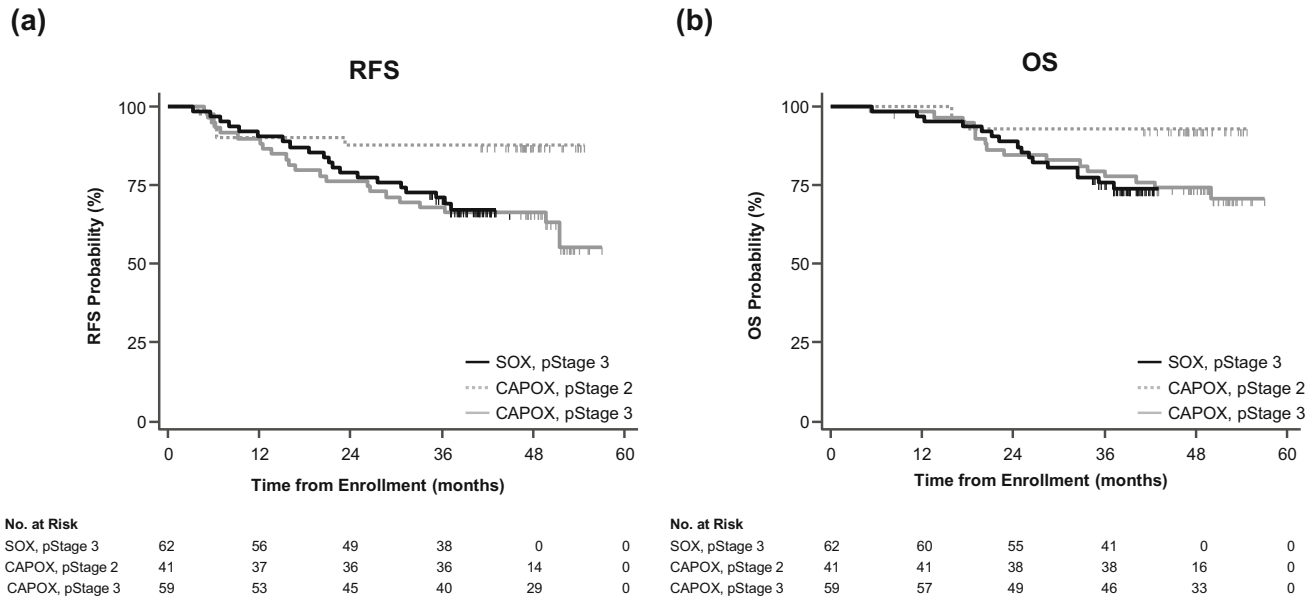

FIG. 1 **a** Relapse-free survival (RFS) and **b** overall survival (OS) for pStage 3 patients treated with SOX and pStages 2 and 3 patients treated with CAPOX. *SOX* S-1 plus oxaliplatin, *CAPOX* capecitabine plus oxaliplatin, *pStage* pathologic stage

TABLE 2 Relapse-free survival of pStage 3 patients according to different subgroups

	SOX		CAPOX		HR (95% CI)	*P* value for interaction
	3-year RFS % (95% CI)	Number (events/patients)	3-year RFS % (95% CI)	Number (events/patients)		
Sex						
Male	64.1 (47.0–76.9)	16/39	78.1 (59.5–88.9)	10/32	1.75 (0.75–4.09)	0.024
Female	82.6 (60.1–93.1)	4/23	55.6 (35.2–71.8)	13/27	0.33 (0.11–1.03)	
Age (years)						
< 65	74.2 (55.0–86.2)	9/31	65.0 (48.2–77.6)	15/40	0.78 (0.34–1.80)	0.821
≥ 65	67.6 (48.1–81.1)	11/31	73.7 (47.9–88.1)	8/19	1.17 (0.43–3.16)	
Histologic type						
Diffuse	71.8 (57.7–85.9)	12/39	57.1 (40.6–73.6)	18/35	0.60 (0.29–1.27)	0.069
Others	69.0 (49.8–88.2)	8/23	83.3 (68.4–98.2)	5/24	2.30 (0.69–7.64)	
pStage						
3A	81.9 (53.8–93.8)	4/17	87.0 (64.8–95.6)	4/23	2.01 (0.45–9.02)	0.478[a]
3B	72.7 (49.1–86.7)	6/22	68.8 (40.5–85.6)	6/16	0.87 (0.27–2.86)	0.234[b]
3C	60.9 (38.3–77.4)	10/23	45.0 (23.1–64.7)	13/20	0.60 (0.26–1.38)	

SOX S-1 plus oxaliplatin, *CAPOX* capecitabine plus oxaliplatin, *RFS* relapse-free survival, *HR* hazard ratio of SOX in reference to CAPOX, *CI* confidence interval, *pStage* pathologic stage

[a]Interaction *P* value for pStage (3A/3B) patients by regimen (SOX/CAPOX)

[b]Interaction *P* value for pStage (3A/3C) by regimen (SOX/CAPOX)

followed by the lymph nodes ($n = 4$; 15%) and liver ($n = 4$; 15%) (Table 3). Of these patients, 24 (89%) received systemic chemotherapy after the recurrence. The subsequent chemotherapies commonly used were S-1 ($n = 11$, 46%), cisplatin ($n = 12$, 50%), paclitaxel ($n = 13$, 54%), and irinotecan ($n = 10$, 42%) (Table S2). Oxaliplatin was administered to four patients.

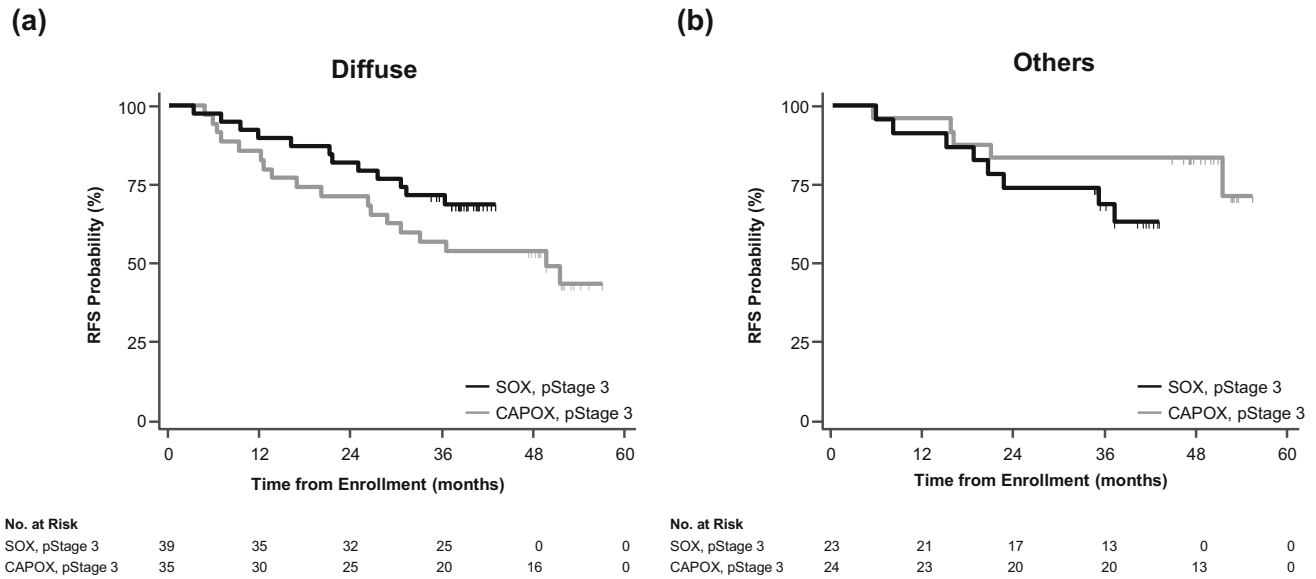

FIG. 2 Relapse-free survival (RFS) of pStage 3 patients treated with SOX and CAPOX for **a** diffuse-type and **b** other-type disease. *SOX* S-1 plus oxaliplatin, *CAPOX* capecitabine plus oxaliplatin, *pStage* pathologic stage

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the survival outcome of SOX and CAPOX used as adjuvant chemotherapy for Japanese patients with GC. The current study suggested that RFS and OS did not differ significantly between adjuvant SOX and CAPOX among the patients with pStage 3 GC who underwent D2 gastrectomy. This finding was consistent with the results of randomized trials showing similar survival outcomes of regimens containing S-1 and capecitabine for advanced GC.[10–12]

In the current study, the 3-year RFS rates of the pStages 2 and 3 patients treated with CAPOX and the pStage 3 patients treated with SOX were respectively 87.8%, 67.8% and 70.9%. This suggested a certain degree of improvement compared with the rates reported in the ACTS-GC trial, in which the 3-year RFS rates were 83.7% for pStage 2 patients and 62.3% for pStage 3 patients.[1]

In addition, the outcomes in the current study were comparable with those in the CLASSIC trial showing 3-year RFS rates of 85% for pStage 2, 66% for pStage 3a, and 61% for pStage 3b disease.[2] However, different stage classifications were used between the current study and previous trials, so the results should be interpreted cautiously.

Interestingly, outcomes were observed to be more favorable for the patients with diffuse-type disease after SOX treatment, whereas they were better for the patients with other-type disease after CAPOX treatment. Previous studies have suggested that the expression of dihydropyrimidine dehydrogenase (DPD), known to be inhibited by gimeracil in S-1, is associated with the efficacy of S-1 in the adjuvant setting,[13] and that diffuse-type GC has a higher expression of DPD than the intestinal type.[14] In accordance with these findings, retrospective analysis of a phase 3 trial, the First-Line Advanced Gastric Cancer Study (FLAGS), showed that S-1 plus cisplatin improved the OS for diffuse-type advanced GC compared with 5-fluorouracil plus cisplatin,[15] although this superiority was not confirmed in the subsequent the Diffuse Gastric and Esophagogastric Junction Cancer S-1 Trial (DIGEST) for diffuse-type advanced GC.[16] Furthermore, capecitabine is an oral fluoropyrimidine activated by thymidine phosphorylase (TP), and the expression of TP has been suggested to predict anti-tumor response to capecitabine in GC.[17]

TABLE 3 Site of first recurrence

Recurrence site	SOX, pStage 3 (n = 17)	CAPOX, pStage 2 (n = 5)	CAPOX, pStage 3 (n = 22)
Local recurrence	0	1	0
Peritoneum	6	1	11
Lymph node	5	0	4
Liver	4	3	1
Lung	0	0	1
Bone	2	0	1
Other	2	0	5

SOX S-1 plus oxaliplatin, *CAPOX* capecitabine plus oxaliplatin, *pStage* pathologic stage

Reports on the association between expression of TP and histologic type in GC have been contradictory.[18,19] In the current study, these associations between the expression levels of the potential biomarkers, DPD and TP, and the histologic type might have resulted in the different efficacy according to the histologic type. Actually, a randomized phase 2 trial, XParTS II, showed that S-1 plus cisplatin exhibited better progression-free survival than capecitabine plus cisplatin for diffuse-type advanced GC.[12] However, because the expression levels of biomarkers were not directly analyzed in the current study, this effect was not confirmed.

In addition to diffuse-type disease, female sex, age younger than 65 years, and pStages 3B and 3C disease seemed to be favorable factors for adjuvant SOX and vice versa. Interaction tests showed that the interaction between treatment and age or subcategory of stage was apparently weaker than between treatment and histologic type. Actually, diffuse-type disease is more common than other-type disease among patients younger than 65 years, and pStage 3B or 3C. Although the interaction between treatment and sex was strong, this might be explained by the fact that diffuse-type disease was more common among females than among males in this study, as previously reported.[20] These findings suggested that distribution of histologic type might influence the difference in the treatment efficacy in each subgroup.

Adjuvant CAPOX is one of the standard regimens based on the phase 3 CLASSIC trial, whereas adjuvant SOX has no survival results from phase 3 trials. Therefore, CAPOX still has clear priority based on evidence. However, our hypothesis-generating study interestingly suggested that SOX seems to show greater promise for patients with diffuse-type disease, warranting further evaluation in a prospective trial comparing the efficacies of adjuvant SOX and CAPOX stratified by histologic type.

The limitations of the current study must be noted. First, this study compared the outcomes of patients between two independently conducted clinical trials, in which different eligibility criteria were used. In addition, these trials were not phase 3 trials but single-arm phase 2 trials with small numbers of patients that aimed to evaluate feasibility as the initial end point. Most of the eligibility criteria overlapped between the two trials. In addition, these trials were sequentially conducted, and most of the participating centers were the same. Nevertheless, these survival results are based on exploratory analysis.

Second, the follow-up period differed between the two trials, which potentially affected the HR of these studies. Third, the two trials used different doses of oxaliplatin, which could have influenced the difference in survival outcomes according to some subgroups. Thus, this study did not directly compare S-1 and capecitabine. However, findings have shown each regimen to be effective as first-line chemotherapy for advanced gastric cancer.[5,21]

Finally, the number of patients was not sufficient for evaluation of the efficacy in each subgroup or its multiplicities, which should be confirmed in larger cohorts.

CONCLUSION

In conclusion, the treatments with SOX and CAPOX were suggested to have similar efficacy for patients with pStage 3 GC who underwent D2 gastrectomy. However, differences in the treatment effect with regard to sex and histologic type may be useful for selecting treatment among several options for these patients while waiting for more solid evidence by further evaluation.

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CONFLICT OF INTEREST There are no conflicts of interest.

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