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Clinical Trial Results

Randomized, Open-Label Phase II Study Comparing Capecitabine-Cisplatin Every 3 Weeks with S-1-Cisplatin Every 5 Weeks in Chemotherapy-Naïve Patients with HER2-Negative Advanced Gastric Cancer: OGSG1105, HERBIS-4A Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Trial Information

- **ClinicalTrials.gov Identifier**: UMIN000006755
- **Sponsor(s):** Osaka Clinical Study Supporting Organization
- **Principal Investigator:** Hisato Kawakami
- **IRB Approved:** Yes

Lessons Learned

- Evidence has suggested that capecitabine-cisplatin is similar or possibly superior to S-1-cisplatin in terms of safety and efficacy for Japanese patients with advanced gastric cancer (AGC).
- As far as we are aware, our study is the first randomized trial of two regimens consisting of an oral fluoropyrimidine plus cisplatin in human epidermal growth receptor 2-negative AGC patients with measurable lesions.

Abstract

Background. We performed a phase II study to evaluate the safety and efficacy of capecitabine plus cisplatin in comparison with S-1 plus cisplatin for first-line treatment of human epidermal growth receptor 2 (HER2)-negative advanced gastric cancer in Japan.

Methods. Eligible patients were randomly assigned to receive either capecitabine at 1,000 mg/m^2 twice daily for 14 days plus cisplatin at 80 mg/m^2 on day 1 every 3 weeks (n = 43) or S-1 at 40–60 mg twice daily for 21 days plus cisplatin at 60 mg/m^2 on day 8 every 5 weeks (n = 41). The primary endpoint of the study was response rate.

Results. Response rate did not differ significantly between the capecitabine-cisplatin and S-1-cisplatin groups (53.5% vs. 51.2%, respectively, $p > .999$). S-1-cisplatin tended to confer a better progression-free survival (PFS; median of 5.9 vs. 4.1 months, $p = .284$), overall survival (OS; median of 13.5 vs. 10.0 months, $p = .290$), and time to treatment failure (TTF; median of 4.5 vs. 3.1 months, $p = .052$) compared with capecitabine-cisplatin. Common hematologic toxicities of grade 3 or 4 included anemia and neutropenia in both groups. However, anorexia, fatigue, and hyponatremia of grade 3 or 4 occurred more frequently in the capecitabine-cisplatin group.

Conclusion. Capecitabine-cisplatin failed to demonstrate superior efficacy compared with S-1-cisplatin. The higher incidence of severe adverse events with capecitabine-cisplatin suggests that S-1-cisplatin should remain the standard first-line chemotherapy for HER2-negative advanced gastric cancer in Japan. ***The Oncologist*** 2018;23:1411–e147

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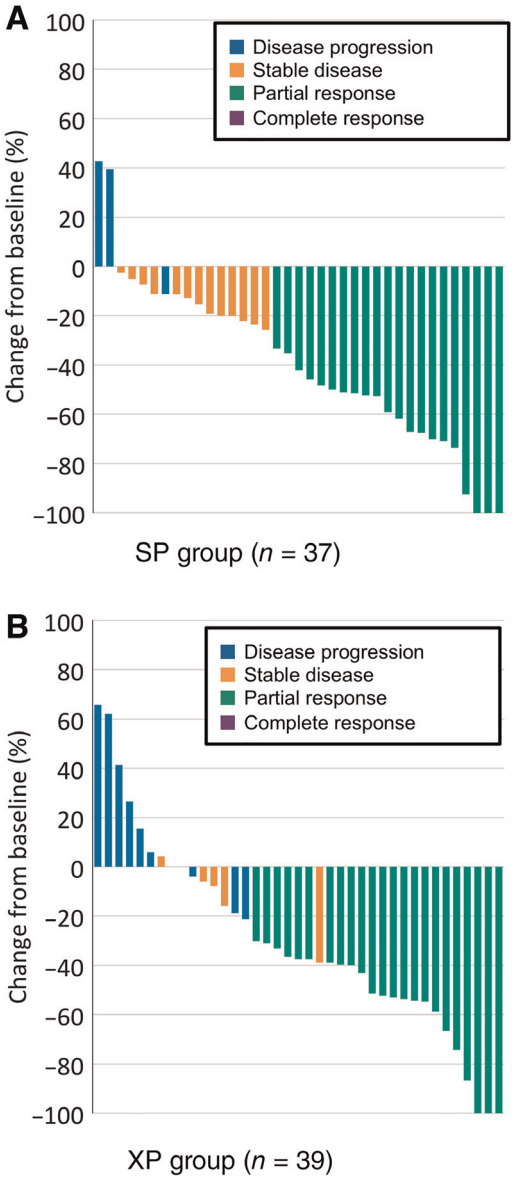

Figure 1. Waterfall plot of maximum percentage change in target lesion size according to RECIST. S-1–cisplatin **(A)** and capecitabine-cisplatin **(B)** groups, respectively.

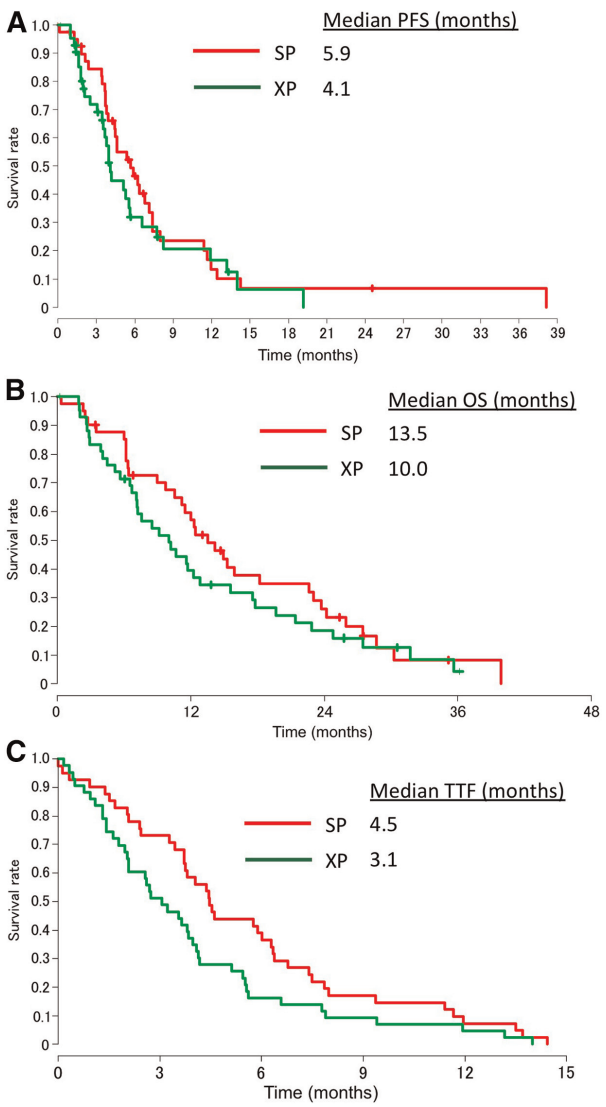

Figure 2. Kaplan-Meier estimates of survival. PFS **(A)**, OS **(B)**, and TTF **(C)**. Red and green lines indicate S-1–cisplatin (SP) and capecitabine-cisplatin (XP) groups, respectively.
Abbreviations: OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Discussion

The response rate was 51.2% (95% CI, 35.1%–67.1%) in the S-1–cisplatin group and 53.5% (95% CI, 37.7%–68.8%) in the capecitabine-cisplatin group ($p > .999$). The DCR for the FAS was higher in the S-1–cisplatin arm (82.9%) than in the capecitabine-cisplatin arm (67.4%). A waterfall plot analysis revealed that patients in the S-1–cisplatin arm showed greater tumor shrinkage and that a larger proportion of patients in this arm experienced tumor shrinkage from baseline compared with the capecitabine-cisplatin arm (Fig. 1).

For survival analysis, the median follow-up time was 11.3 months. The median PFS was 5.9 months in the S-1–cisplatin group and 4.1 months in the capecitabine-cisplatin group (HR, 0.763; 95% CI, 0.462–1.259; $p = .284$) (Fig. 2A), whereas the corresponding values for median OS were 13.5 and 10.0 months (HR, 0.776; 95% CI, 0.485–1.244; $p = .290$) (Fig. 2B) and those for median TTF were 4.5 and 3.1 months (HR, 0.651; 95% CI, 0.421–1.006; $p = .052$) (Fig. 2C).

The most common all-grade hematologic adverse events were anemia (79% in the S-1–cisplatin group, 74% in the capecitabine-cisplatin group) and neutropenia (54% and 60%), each of which occurred at a similar frequency in the two groups. In contrast, anemia and neutropenia of grade 3 or 4 were more common in the capecitabine-cisplatin group than in the S-1–cisplatin group. With regard to nonhematologic toxicities, anorexia (67% and 72%) and malaise (46% and 49%) were common all-grade adverse events in both treatment groups. Anorexia, fatigue, and hyponatremia of grade 3 or 4 were more frequent in the capecitabine-cisplatin group (23%, 14%, and 16%) than in the S-1–cisplatin group (13%, 0%, and 5%). Peripheral

neuropathy and hand-foot syndrome of grade 3 or 4 were apparent in the capecitabine-cisplatin arm (5% and 2%) but not in the S-1–cisplatin arm. One death in the capecitabine-cisplatin group (2%, 1 of 43) was due to brain infarction, which was considered to be treatment related by the investigators.

Trial Information	
Disease	Gastric cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Randomized
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Safety
Secondary Endpoint	Time to treatment failure

Additional Details of Endpoints or Study Design

The trial was based on a randomized phase II screening design with a primary endpoint of response rate (RR). On the basis of an assumed RR of 40% in the S-1-cisplatin arm, the study was designed to detect an improvement in RR of 15 percentage points (i.e., to 55%) in the capecitabine-cisplatin arm. For primary analysis, 100 patients were required to detect such an improvement in RR with ≥80% power, with a one-sided significance level of 0.20 in Fisher's exact test. However, as a result of slow accrual, the protocol was amended in December 2015 to reduce the planned sample size from 100 to 84 based on a one-sided significance level of 0.10 and power of 70%. Ultimately, enrollment was terminated after inclusion of 85 patients in April 2016.

The primary endpoint of the study was RR, with secondary end points including PFS, OS, TTF, and safety. Tumor response was assessed by investigators on the basis of RECIST version 1.1 at baseline and every 8 weeks after randomization until disease progression. The RR and disease control rate were defined as the proportion of patients who achieved a confirmed complete response (CR) or partial response (PR) or who achieved a confirmed CR, PR, or stable disease (SD), respectively. Tumor histology was based on the Japanese classification of gastric carcinoma, with differentiated-type tumors being defined as papillary or tubular adenocarcinoma and undifferentiated-type tumors as poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Investigator's Analysis

Inactive because results did not meet primary endpoint

Drug Information for Phase II S-1 + CDDP	
Drug 1	
Generic/Working Name	S-1
Trade Name	TS-1
Company Name	Taiho Pharmaceutical, Co, Ltd.
Dose	80–120 mg/m^2
Route	p.o.
Schedule of Administration	S-1 at 40–60 mg twice daily for 21 days every 5 weeks
Drug 2	
Generic/Working Name	Cisplatin (CDDP)
Drug Class	Platinum compound
Dose	60 mg/m^2
Route	IV
Schedule of Administration	Cisplatin at 60 mg/m^2 on day 8, every 5 weeks

Drug Information for Phase II Capecitabine + CDDP	
Drug 1	
Generic/Working Name	Capecitabine
Trade Name	Xeloda
Company Name	Chugai Pharmaceutical, Co, Ltd.

Dose	2,000 mg/m^2
Route	p.o.
Schedule of Administration	Capecitabine at 1,000 mg/m^2 twice daily for 14 days every 3 weeks
Drug 2	
Generic/Working Name	Cisplatin (CDDP)
Drug Class	Platinum compound
Dose	80 mg/m^2
Route	IV
Schedule of Administration	Cisplatin at 80 mg/m^2 on day 1 every 3 weeks

Patient Characteristics for Phase II S-1 + CDDP		
Number of Patients, Male	33	
Number of Patients, Female	8	
Stage	T factor	
	TX	1
	T1 (SM)	0
	T2 (MP)	6
	T3 (SS)	7
	T4a (SE)	21
	T4b (SI)	6
	N factor	
	NX	0
	N0	2
	N1	3
	N2	13
	N3a	17
	N3b	6
	M factor	
	MX/M0/M1	2/6/33
	Previous gastrectomy	
	Yes/No	6/35
Age	Median (range): 68 (38–77)	
Number of Prior Systemic Therapies	Median (range): 0	
Performance Status: ECOG	0 — 22	
	1 — 19	
	2 — 0	
	3 — 0	
	Unknown — 0	
Other	Metastatic/recurrent sites	
	Lymph node	33
	Peritoneum	8
	Liver	17
	Lung	5
	Bone	4
	Adrenal	1
	Portal vein tumor thrombus	1

Cancer Types or Histologic Subtypes	HER2 unknown, 0	
	HER2 negative 0/1+/2+ 23/14/4	
	Papillary adenocarcinoma 0	
	Tubular adenocarcinoma 23	
	Poorly differentiated adenocarcinoma 14	
	Signet ring cell carcinoma 3	
	Mucinous adenocarcinoma 0	
	Undetermined 1	

Patient Characteristics for Phase II Capecitabine + CDDP		
Number of Patients, Male	36	
Number of Patients, Female	7	
Stage	T factor	
	TX	1
	T1 (SM)	1
	T2 (MP)	1
	T3 (SS)	9
	T4a (SE)	21
	T4b (SI)	10
	N factor	
	NX	2
	N0	5
	N1	7
	N2	15
	N3a	9
	N3b	5
	M factor	
	MX/M0/M1	1/4/38
	Previous gastrectomy	
	Yes/No	2/41
Age	Median (range): 64 (34–79)	
Number of Prior Systemic Therapies	Median (range): 0	
Performance Status: ECOG	0 — 24	
	1 — 19	
	2 — 0	
	3 — 0	
	Unknown — 0	
Other	Metastatic/recurrent sites	
	Lymph node	37
	Peritoneum	13
	Liver	16
	Lung	4
	Bone	2
	Adrenal	0
	Portal vein tumor thrombus	0
Cancer Types or Histologic Subtypes	HER2 unknown 1	
	HER2 negative 0/1+/2+ 22/17/3	
	Papillary adenocarcinoma 2	
	Tubular adenocarcinoma 19	

Poorly differentiated adenocarcinoma 20
Signet ring cell carcinoma 0
Mucinous adenocarcinoma 1
Undetermined 1

Primary Assessment Method for Phase II S-1 + CDDP	
Title	Total patient population
Number of Patients Screened	41
Number of Patients Enrolled	39
Number of Patients Evaluable for Toxicity	39
Number of Patients Evaluated for Efficacy	41
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 21 (51%)
Response Assessment SD	*n* = 13 (32%)
Response Assessment PD	*n* = 3 (7%)
Response Assessment OTHER	*n* = 4 (10%)
(Median) Duration Assessments PFS	179 days, confidence interval (CI): 136–225
(Median) Duration Assessments OS	412 days, CI: 340–701

Secondary Assessment Method for Phase II S-1 + CDDP	
Title	Total patient population
(Median) Duration Assessments PFS	179 days, CI: 136–225
(Median) Duration Assessments OS	412 days, CI: 340–701

Primary Assessment Method for Phase II Capecitabine + CDDP	
Title	Total patient population
Number of Patients Screened	43
Number of Patients Enrolled	43
Number of Patients Evaluable for Toxicity	43
Number of Patients Evaluated for Efficacy	43
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 23 (53%)
Response Assessment SD	*n* = 6 (14%)
Response Assessment PD	*n* = 10 (3%)
Response Assessment OTHER	*n* = 4 (10%)
(Median) Duration Assessments PFS	124 days, CI: 108–200
(Median) Duration Assessments OS	305 days, CI: 218–474

Secondary Assessment Method for Phase II Capecitabine + CDDP	
Title	Total patient population
(Median) Duration Assessments PFS	124 days, CI: 108–200
(Median) Duration Assessments OS	305 days, CI: 218–474

Phase II S-1 + CDDP Adverse Events							
All Cycles							
Name	NC/NA	1	2	3	4	5	All grades
Neutrophil count decreased	46%	5%	26%	8%	15%	0%	54%
Platelet count decreased	46%	21%	15%	15%	3%	0%	54%
Aspartate aminotransferase increased	79%	18%	0%	3%	0%	0%	21%
Hypokalemia	79%	13%	3%	5%	0%	0%	21%
Hypoalbuminemia	48%	23%	26%	3%	0%	0%	52%
Febrile neutropenia	95%	0%	0%	5%	0%	0%	5%
Anemia	21%	28%	28%	23%	0%	0%	79%
Hyponatremia	64%	28%	3%	5%	0%	0%	36%
Peripheral sensory neuropathy	97%	0%	3%	0%	0%	0%	3%
Fatigue	54%	28%	18%	0%	0%	0%	46%
Creatinine increased	61%	33%	3%	3%	0%	0%	39%
Anorexia	33%	26%	28%	13%	0%	0%	67%
White blood cell decreased	49%	18%	15%	18%	0%	0%	51%
Abdominal pain	77%	18%	5%	0%	0%	0%	23%
Nausea	67%	28%	5%	0%	0%	0%	33%
Diarrhea	82%	10%	8%	0%	0%	0%	18%
Hyperkalemia	80%	15%	0%	5%	0%	0%	20%
Palmar-plantar erythrodysesthesia syndrome	95%	5%	0%	0%	0%	0%	5%
Mucositis oral	87%	3%	5%	5%	0%	0%	13%

Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events		
Name	Grade	Attribution
Sepsis	4	Unlikely
Syncope	3	Unlikely

Phase II Capecitabine + CDDP Adverse Events							
All Cycles							
Name	NC/NA	1	2	3	4	5	All grades
Neutrophil count decreased	40%	2%	23%	21%	14%	0%	60%
Platelet count decreased	46%	21%	15%	15%	3%	0%	54%
Aspartate aminotransferase increased	87%	9%	2%	2%	0%	0%	13%
Hypokalemia	79%	12%	0%	7%	2%	0%	21%
Hypoalbuminemia	56%	21%	23%	0%	0%	0%	44%
Febrile neutropenia	93%	0%	0%	7%	0%	0%	7%
Anemia	25%	19%	28%	28%	0%	0%	75%
Hyponatremia	63%	21%	0%	14%	2%	0%	37%
Peripheral sensory neuropathy	85%	5%	5%	5%	0%	0%	15%
Fatigue	51%	19%	30%	0%	0%	0%	49%
Vomiting	95%	5%	0%	0%	0%	0%	5%
White blood cell decreased	47%	7%	28%	16%	2%	0%	53%
Creatinine increased	72%	9%	14%	5%	0%	0%	28%
Anorexia	28%	19%	30%	23%	0%	0%	72%
Abdominal pain	98%	0%	0%	2%	0%	0%	2%

Nausea	54%	23%	14%	9%	0%	0%	46%
Diarrhea	86%	5%	9%	0%	0%	0%	14%
Alanine aminotransferase increased	82%	16%	2%	0%	0%	0%	18%

Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Brain infarction	5	Probable
Stomach perforation	4	Unlikely
Gastric hemorrhage	3	Unlikely

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Gastric cancer is the fifth most common malignant disease and the second leading cause of cancer deaths worldwide [1], with an especially high incidence in East Asia. Individuals newly diagnosed with gastric cancer often present with unresectable or metastatic disease, known as advanced gastric cancer (AGC). Trastuzumab in combination with chemotherapy has been found to confer a significantly better overall survival (OS) compared with chemotherapy alone in patients with AGC positive for human epidermal growth receptor 2 (HER2) [2]. On the other hand, for individuals with HER2-negative disease, who account for most cases of AGC, treatment options are largely restricted to conventional therapy such as doublet or triplet combination chemotherapy. The outcome for such patients thus remains poor, with a global standard regimen for treatment of HER2-negative AGC remaining to be established.

In East Asia, including Japan and Korea, the combination of a fluoropyrimidine plus a platinum agent has been adopted as standard therapy for HER2-negative AGC [3,4]. S-1 is a fluoropyrimidine preparation that includes tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1 and was designed to minimize gastrointestinal toxicity and maximize antitumor activity [5]. The SPIRITS phase III trial showed that S-1 in combination with cisplatin conferred a significant survival benefit (median survival time of 13.1 months) compared with S-1 alone, resulting in this combination being accepted as a standard first-line regimen for AGC in East Asia [3]. In Western countries, regimens containing a fluoropyrimidine plus a platinum compound and either docetaxel [6] or epirubicin [7] have improved survival in patients with AGC. However, the combination of a fluoropyrimidine plus a platinum agent has been widely accepted as a standard treatment option for such patients in practice, given that the addition of docetaxel or epirubicin was associated with a limited improvement in survival but substantial hematologic toxicity [6,7].

Capecitabine is an oral fluoropyrimidine prodrug that manifests high antitumor activity in association with low toxicity, given that it is converted to 5-fluorouracil (5-FU) by thymidine phosphorylase, which is present at much higher concentrations in tumor cells than in normal cells [8]. As capecitabine plus cisplatin was found to be noninferior to 5-FU plus cisplatin in terms of progression-free survival (PFS) for the first-line treatment of AGC, the former combination is now considered an effective alternative to the latter [4]. Moreover, capecitabine-cisplatin has been adopted as a standard backbone chemotherapy for combination with trastuzumab [2] or other molecularly targeted agents such as bevacizumab [9] or cetuximab [10] in global phase III trials for AGC.

In Japan, capecitabine was approved for AGC in 2011, and the safety and efficacy of capecitabine-cisplatin in the Japanese population have been demonstrated in two global phase III trials—the AVAGAST [9] and ToGA [2] studies—in which 94 Japanese AGC patients of unknown HER2 status and 50 Japanese patients with HER2-positive AGC, respectively, received this combination alone [11]. In these two studies, the median OS, median PFS, and overall response rate (RR) were 14.2–17.7 months, 5.6–5.7 months, and 49.2%–58.5%, respectively. Adverse events were generally mild, with the most common events of grade 3 or 4 being neutropenia, anemia, anorexia, and nausea. Similar efficacy and safety profiles for capecitabine-cisplatin in Japanese AGC patients were also apparent in a retrospective study [12]. These data have suggested that capecitabine-cisplatin is similar or possibly superior to S-1-cisplatin in terms of safety and efficacy for Japanese patients with AGC. However, capecitabine-cisplatin has not been prospectively compared with S-1-cisplatin in patients with HER2-negative AGC to date. We have therefore now conducted a phase II study to assess the efficacy and safety of capecitabine-cisplatin versus S-1-cisplatin in Japanese patients with HER2-negative AGC.

In our trial, however, capecitabine-cisplatin failed to show a superior efficacy relative to S-1-cisplatin. Although RR, the primary endpoint of our trial, did not differ significantly between the two treatment groups, disease control rate (DCR) was higher in the S-1-cisplatin arm, with this benefit being confirmed by waterfall analysis. The benefit of S-1-cisplatin with regard to its high DCR likely reflects the observed trend toward a better PFS and OS in the S-1-cisplatin arm than in the capecitabine-cisplatin arm.

With respect to adverse events, both regimens in the present study showed similar hematologic toxicity profiles, with anemia and neutropenia being most frequently observed. In contrast, the overall incidence of nonhematologic toxicities of grade 3 or 4 was higher in the capecitabine-cisplatin group than in the S-1-cisplatin group. A meta-analysis comparing S-1 with capecitabine in AGC found no overall difference in terms of serious adverse events [13]. In the present study, however, anorexia, fatigue, and hyponatremia of grade 3 or 4 occurred more frequently in the capecitabine-cisplatin arm than in the S-1-cisplatin arm. Moreover, brain infarction of grade 5 occurred in one patient of the capecitabine-cisplatin group, possibly as a result of the high dose intensity of cisplatin, which is known to be associated with venous thromboembolism [14]. Indeed, most of the differences in nonhematologic toxicity between the two groups were likely due to the higher dose of cisplatin administered in the capecitabine-cisplatin arm, which was also associated with a shorter time to treatment failure. Together, our findings suggest that, at least in the setting of the present trial, administration of cisplatin at 80 mg/m^2 every 3 weeks in combination with capecitabine did not increase efficacy but was more toxic compared with that at 60 mg/m^2 every 5 weeks in combination with S-1.

In conclusion, although our study was a phase II trial and our results thus need confirmation, capecitabine-cisplatin failed to demonstrate superior efficacy over S-1-cisplatin. The higher incidence of severe nonhematologic adverse events observed with capecitabine-cisplatin suggests that S-1-cisplatin should remain the standard first-line chemotherapy for HER2-negative AGC with measurable lesions, at least in Japan.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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