International Journal of Clinical Oncology (2023) 28:1176–1182
https://doi.org/10.1007/s10147-023-02376-0

ORIGINAL ARTICLE

Phase I dose-escalation study on irinotecan, cisplatin, and S-1 combination in chemotherapy-naïve patients with HER2-negative advanced gastric cancer (HERBIS-4B, OGSG 1106)

Hiroki Yukami[1] · Hisato Kawakami[2] · Toshifumi Yamaguchi[1] · Daisuke Sakai[3,6] · Toshio Shimokawa[3,5] · Yukinori Kurokawa[4] · Masahiro Goto[1] · Taroh Satoh[3]

Received: 15 April 2023 / Accepted: 20 June 2023 / Published online: 7 July 2023

Abstract

Background The development of triplet regimens for advanced gastric cancer is challenging. The aim of this phase I dose-escalation study was to determine the maximum tolerated dose and recommended dose of the combination of irinotecan, cisplatin, and S-1 in chemotherapy-naïve patients with HER2-negative advanced gastric cancer.

Methods The 3 + 3 design was adopted. Every 4 weeks, patients received an escalating dose of intravenous irinotecan (100–150 mg/m^2) on day 1 and fixed doses of intravenous cisplatin (60 mg/m^2) on day 1 and oral S-1 (80 mg/m^2) on days 1 to 14.

Results Twelve patients were enrolled in two dose level cohorts. In the level 1 cohort (irinotecan 100 mg/m^2, cisplatin 60 mg/m^2, and S-1 80 mg/m^2), dose-limiting toxicity including grade 4 neutropenia and febrile neutropenia occurred in one of six patients, whereas in the level 2 cohort (irinotecan 125 mg/m^2, cisplatin 60 mg/m^2, and S-1 80 mg/m^2), dose-limiting toxicities including grade 4 neutropenia developed in two of six patients. Thus, the level 1 and 2 doses were determined to be the recommended and maximum tolerated doses, respectively. Common grade 3 or higher adverse events were neutropenia (75%; n = 9), anemia (25%; n = 3), anorexia (8%; n = 1), and febrile neutropenia (17%; n = 2). Irinotecan, cisplatin, and S-1 combination therapy achieved an overall response rate of 67% with a median progression-free survival and overall survival of 19.3 and 22.4 months, respectively.

Conclusions The potential treatment efficacy of this triplet regimen in HER2-negative advanced gastric cancer warrants further evaluation, especially in patients requiring intensive chemotherapy.

Keywords Gastric cancer · Phase I · Irinotecan · S-1 · Cisplatin

✉ Hisato Kawakami
kawakami_h@med.kindai.ac.jp

[1] Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Osaka, Japan

[2] Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2, Ohno-higashi, Osakasayama, Osaka 589-8511, Japan

[3] Center for Cancer Genomics and Precision Medicine, Osaka University Hospital, Suita, Osaka, Japan

[4] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

[5] Department of Medical Data Science, Graduate School of Medicine, Wakayama Medical University, Wakayama, Wakayama, Japan

[6] Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan

Introduction

Gastric cancer is the fifth most common cancer worldwide and the third most common cause of death from cancer [1]. Most patients with gastric cancer are diagnosed with advanced or metastatic disease, and the prognosis is poor. A combination of fluoropyrimidine and platinum agent is globally recognized as the gold standard for the treatment of HER2-negative advanced metastatic disease. According to the phase III SPIRITS trial conducted in Japan, the combination therapy of S-1 (80 mg/m^2, days 1–21, q5w) and cisplatin (60 mg/m^2, q5w) (SP) significantly improved overall survival (OS) compared with S-1 monotherapy in advanced gastric cancer (AGC); therefore, this combination is considered a standard first-line treatment for HER2-negative AGC [2].

Combination therapies involving three cytotoxic chemotherapeutic agents have been examined to identify therapies that achieve more potent therapeutic effects in patients with HER2-negative AGC. The triplet combination therapy of docetaxel (75 mg/m^2, q3w), cisplatin (75 mg/m^2, q3w), and fluorouracil (750 mg/m^2, days 1–5, q3w) (DCF) was shown to improve progression-free survival (PFS), OS, and overall response rate (ORR) compared with doublet combination therapy of cisplatin (100 mg/m^2, q4w) and fluorouracil (1000 mg/m^2, days 1–5, q4w) (CF) in patients with AGC during the phase III V325 trial [3]. The median PFS was 5.6 months for DCF versus 3.7 months for CF (P < 0.001), the median OS was 9.2 months for DCF versus 8.6 months for CF (P = 0.02), and the ORR was 37% for DCF versus 25% for CF (P = 0.01). However, DCF is not currently considered a standard therapy for AGC because of its high toxicity, as shown by the occurrence of grade 3 or higher neutropenia, anemia, anorexia, and febrile neutropenia in 82%, 65%, 10%, and 29%, respectively, of all cases of adverse events. In the phase III JCOG1013 trial, the triplet combination regimen of docetaxel (40 mg/m^2, q4w), cisplatin (60 mg/m^2, q4w), and S-1 (80 mg/m^2, days 1–14, q4w) (DCS) failed to demonstrate prolonged OS compared with SP in HER2-negative AGC as a first-line treatment [4]. The adverse events of DCS were mild but did not demonstrate the same efficacy as DCF did in the V325 trial, possibly because the investigated dose of docetaxel was lower because of concerns about toxicity. These findings suggest that a triplet regimen with docetaxel for AGC treatment is a double-edged sword, as it is challenging to balance efficacy and safety.

In addition to cisplatin, irinotecan is another anticancer drug that has shown good results when used in combination with S-1. In the phase III TOP-002 trial, the combination of S-1 (80 mg/m^2, days 1–21, q5w) and irinotecan (80 mg/m^2, days 1 and 15, q5w) demonstrated significantly higher ORR compared to S-1 monotherapy (42% vs. 27%, P = 0.035) with acceptable toxicity [5]. The S-1 and irinotecan combination therapy further showed longer but not significant OS compared to S-1 monotherapy with a median OS of 12.8 versus 10.5 months. Based on these findings, we thought it appropriate to add irinotecan to SP as a new triplet regimen for HER2-negative AGC. We thus conducted a phase I dose-finding study with the intention of developing the irinotecan, cisplatin, and S-1 (IPS) combination therapy. The aim of this study was to determine the maximum tolerated dose (MTD) and recommended dose (RD) of the IPS combination therapy in chemotherapy-naïve patients with HER2-negative AGC.

Patients and methods

Patients

The patients were enrolled if they met the following eligibility criteria: histologically confirmed gastric adenocarcinoma, unresectable recurrent or metastatic disease, age between 20 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, HER2-negative or unknown, leukocyte count ≥ 3500/mm^3, neutrophil count ≥ 2000/mm^3, platelet count ≥ 100,000/mm^3, serum aspartate aminotransferase < 100 IU/l (<200 IU/l in cases of liver metastasis), serum bilirubin < 1.5 mg/dl, serum creatinine ≤ 1.5 mg/dl, creatinine clearance ≥ 60 ml/min, possible oral intake, and life expectancy of at least 3 months. The exclusion criteria were previous chemotherapy or radiotherapy for AGC, brain metastasis, massive ascites, massive pleural effusion retention, and severe comorbidity. All the patients provided written informed consent prior to initiating chemotherapy. The study protocol was approved by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) Steering Committee and the Institutional Review Boards of all participating hospitals. The current study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Study design

The OGSG 1106 (HERBIS-4B) study was a phase I trial of IPS in patients with AGC. This dose-escalation study followed the traditional 3 + 3 design. Three patients were enrolled at each level. If dose-limiting toxicity (DLT) occurred in one of the three patients, three additional patients were enrolled. The dosage schedules are shown in Fig. 1, and the dosages at each level are shown in Table 1. The fixed dose of S-1 was 80 mg/day for body surface area (BSA) < 1.25 m^2, 100 mg/day for BSA ≥ 1.25 and < 1.5 m^2,

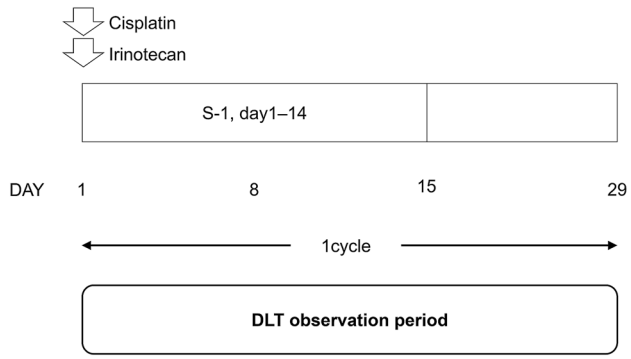

Fig. 1 Dosage schedule

Table 1 Dose level

Level	S-1 (mg/m^2)	Cisplatin (mg/m^2)	Irinotecan (mg/m^2)
Level 1	80	60	100
Level 2	80	60	125
Level 3	80	60	150

and 120 mg/day for BSA ≥ 1.5 m^2, administered orally twice daily for the first 2 weeks of a 4-week cycle. The fixed dose of cisplatin 60 mg/m^2 was administered intravenously on day 1 of each cycle. Irinotecan was also administered intravenously on day 1 of each cycle at three dose levels of 100, 125, and 150 mg/m^2 (levels 1, 2, and 3, respectively) based on the BSA. Cisplatin was administered for a maximum of five cycles. Treatment was continued until disease progression or development of intolerable toxicity.

Each cycle was started if all the following criteria were met: neutrophil count ≥ 1500/mm^3; platelet count ≥ 100,000/mm^3; serum aspartate aminotransferase < 100 IU/l; serum bilirubin < 1.5 mg/dl; serum creatinine ≤ 1.2 mg/dl; absence of active infection; and presence of grade 1 or less non-hematological toxicity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Irinotecan, cisplatin, and S-1 doses were all reduced if the following criteria were met: leukocyte count < 1000/mm^3, neutrophil count < 500/mm^3, platelet count < 50,000/mm^3, presence of febrile neutropenia, serum creatinine ≥ 1.2 mg/dl, or presence of grade 3 non-hematological toxicity. DLT was defined as grade 4 leukopenia or neutropenia, febrile neutropenia, grade 4 thrombocytopenia, need for platelet transfusion, grade 3 and higher non-hematological toxicity except for nausea and vomiting, or treatment delay of 14 days or more due to unresolved toxic effects during the first cycle.

The MTD was defined as the dose level at which at least two of three patients or at least two of six patients experienced DLT. In principle, the RD was defined as the dose level immediately below the estimated MTD.

Assessment

We assessed the ORR, PFS, and OS. Tumor measurements were obtained through computed tomography at baseline and every 6 weeks thereafter. Tumor response was assessed in patients with measurable lesions according to the guidelines of the Response Criteria in Solid Tumors version 1.1. The ORR was defined as the proportion of patients with the best overall response in terms of complete response or partial response within the study period. PFS was defined as the time from enrollment until the date of disease progression or death from any cause. OS was defined as the time from enrollment until the date of death from any cause. We estimated PFS and OS using the Kaplan–Meier method.

Table 2 Baseline characteristics

	n = 12
Age	65 (53–74)
Sex	
Male	9 (75%)
Female	3 (25%)
ECOG PS	
0	7 (58.3%)
1	5 (41.7%)
Primary tumor	
Upper	4 (33.3%)
Middle	6 (50%)
Lower	2 (16.7%)
Borrmann	
Type 1	1 (8.3%)
Type 2	2 (16.7%)
Type 3	8 (66.7%)
Type 5	1 (8.3%)
Histology	
Intestinal	4 (33.3%)
Diffuse	8 (66.7%)
Disease status	
Unresectable	10 (83.3%)
Recurrent	2 (16.7%)
Metastatic site	
Lymph node	8 (66.7%)
Peritoneum	5 (41.7%)
Liver	2 (16.7%)

ECOG Eastern Cooperative Oncology Group, *PS* performance status

Results

Characteristics of enrolled patients

A total of 12 patients with untreated AGC were enrolled in the current study between June 2013 and February 2017 and followed up until February 2018. Among the 12 patients, six patients received the level 1 dose and the other six received the level 2 dose. The median age was 65 years (range 53–74). There were nine males and three females. An ECOG PS of 0 and 1 were found in seven and five patients, respectively. The patient characteristics are summarized in Table 2.

Tolerability and adverse events

Although one of the first three patients in the level 1 cohort experienced grade 4 neutropenia and febrile neutropenia, the three additional patients did not exhibit any DLT. In the level 2 cohort, one of the three patients experienced grade 4 neutropenia. Furthermore, one of the three additional patients experienced grade 4 leukopenia and neutropenia. We thus determined that the level 1 and level 2 doses were the RD and MTD of the IPS regimen, respectively.

Adverse events were observed in all patients during the protocol treatment as shown in Table 3. The most common adverse events of all grades were neutropenia (92%; n = 11), anemia (83%; n = 10), anorexia (83%; n = 10), diarrhea (83%; n = 10), and alopecia (83%; n = 10). The common grade 3 or higher adverse events were neutropenia (75%; n = 9), leukopenia (42%; n = 5), anemia (25%; n = 3), febrile neutropenia (17%; n = 2), and anorexia (8%; n = 1). In the level 1 cohort, common all grade adverse events were neutropenia (83%; n = 5), anemia (100%; n = 6), anorexia (100%; n = 6), diarrhea (83%; n = 5), and alopecia (83%; n = 5), and common grade 3 or higher adverse events were neutropenia (67%; n = 4), anemia (50%; n = 3), anorexia (17%; n = 1), and febrile neutropenia (33%; n = 2). In the level 2 cohort, common all grade adverse events were leukopenia (67%; n = 4), neutropenia (100%; n = 6), anemia (67%; n = 4), anorexia (67%; n = 4), fatigue (67%; n = 4), diarrhea (83%; n = 5), and alopecia (83%; n = 5), and common grade 3 or higher adverse events were neutropenia (83%; n = 5) and leukopenia (50%; n = 3). Treatment-related death was not observed in any patient.

Efficacy

Of 12 patients, six had target lesions. We found that 4 (67%) patients showed a response to IPS. Two patients underwent radical resection after chemotherapy. Of these two patients, one achieved a pathological response of grade 2, while the other achieved a grade 3 response. The median PFS and OS were 19.3 months and 22.4 months, respectively, in all 12 patients. In the level 1 cohort, the median PFS and OS were 9.3 months and 16.3 months, respectively. In the level 2 cohort, the median PFS and OS were not reached. The Kaplan–Meier survival curves are shown in Fig. 2.

Discussion

Recently, the addition of an immune checkpoint inhibitor to the combination chemotherapy of fluoropyrimidine and oxaliplatin further prolonged overall survival in chemotherapy-naïve HER2-negative AGC as demonstrated in phase III CheckMate649 and KEYNOTE-859 trials [6, 7]. However, the survival benefit of immune checkpoint inhibitors is limited in AGC patients with lower combined positive scores, suggesting that intensive cytotoxic chemotherapies remain the mainstay of treatment for such "immune-poor" subjects. Unfortunately, however, the development of triplet regimens for AGC has remained challenging.

The current phase I study is the first to evaluate the safety and tolerability of the IPS regimen in patients with untreated AGC. We determined the RD to be irinotecan 100 mg/m^2, cisplatin 60 mg/m^2, and S-1 80 mg/m^2 for the subsequent phase II study. IPS showed a similar trend of toxicity as seen in DCF during the V325 trial in grade 3 or higher neutropenia (75%; n = 9) and anorexia (8%; n = 1) but a lower

Table 3 Adverse events during the protocol treatment

	All patients (*N* = 12)				Level 1 (*N* = 6)				Level 2 (*N* = 6)			
	All grade *N*, (%)		Grade 3 or 4 *N*, (%)		All grade *N*, (%)		Grade 3 or 4 *N*, (%)		All grade *N*, (%)		Grade 3 or 4 *N*, (%)	
Leukopenia	8	(67)	5	(42)	4	(67)	2	(33)	4	(67)	3	(50)
Neutropenia	11	(92)	9	(75)	5	(83	4	(67)	6	(100)	5	(83)
Anemia	10	(83)	3	(25)	6	(100)	3	(50)	4	(67)	0	(0)
Thrombocytopenia	5	(42)	0	(0)	3	(50)	0	(0)	2	(33)	0	(0)
Febrile neutropenia	2	(17)	2	(17)	2	(33)	2	(33)	0	(0)	0	(0)
Diarrhea	10	(83)	0	(0)	5	(83)	0	(0)	5	(83)	0	(0)
Stomatitis	6	(50)	0	(0)	3	(50)	0	(0)	3	(50)	0	(0)
Nausea	8	(67)	0	(0)	5	(83)	0	(0)	3	(50)	0	(0)
Vomiting	2	(17)	0	(0)	2	(33)	0	(0)	0	(0)	0	(0)
Anorexia	10	(83)	1	(8)	6	(100)	1	(17)	4	(67)	0	(0)
Fatigue	6	(50)	0	(0)	2	(33)	0	(0)	4	(67)	0	(0)
Alopecia	10	(83)	0	(0)	5	(83)	0	(0)	5	(83)	0	(0)

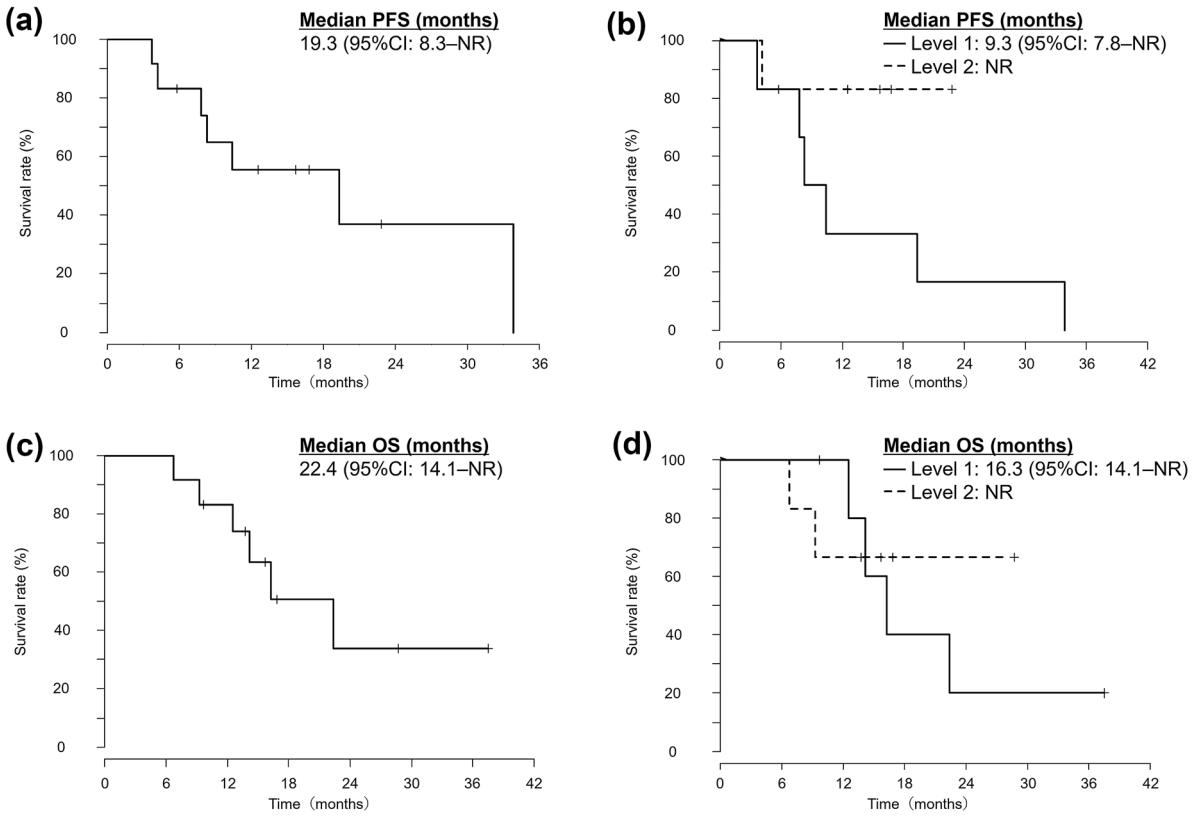

Fig. 2 Kaplan–Meier survival curves for progression-free survival (PFS) and overall survival (OS). **a**, **b** Kaplan–Meier curve of PFS; **a** in all patients and **b** according to each dose level. **c**, **d** Kaplan–Meier curve of OS; **c** in all patients and **d** according to each dose level. Note for (**b**) and (**d**): solid line: level 1, dashed line: level 2

incidence of anemia (25%; n = 3) and febrile neutropenia (17%; n = 2). Therefore, the IPS regimen seems manageable with the use of prophylactic administration of G-CSF and an antiemetic agent, such as the newly developed aprepitant, which was not available when this phase I study was conducted. Further study on this aspect is warranted.

Although the data in the current study was preliminary and the patients were in good condition because of the phase I design of this study, the IPS regimen achieved an ORR of 67% with a median PFS and OS of 19.3 and 22.4 months, respectively, for untreated AGC. Furthermore, two patients were able to undergo radical resection owing to significant tumor shrinkage.

Triplet regimens involving docetaxel have shown efficacy as preoperative treatments; for example, FLOT (fluorouracil 2600 mg/m^2, day 1, q2w; oxaliplatin 85 mg/m^2, day 1, q2w; docetaxel 50 mg/m^2, day 1, q2w) [8] and DOS (docetaxel 50 mg/m^2, day 1, q3w; oxaliplatin 100 mg/m^2, day 1, q3w; S-1 80 mg/m^2, days 1–14, q3w) [9]. These regimens do not raise the concerns seen with DCF and DCS for AGC treatment, possibly due to the difference in the settings of these studies (i.e., preoperative versus metastatic settings), and the relatively good general condition of the patients enrolled in the former study. Another possibility includes the use of oxaliplatin instead of cisplatin. Consequently, the IPS regimen may become even more useful in the future when utilizing oxaliplatin, which was not available when this trial was conducted, in place of cisplatin.

Besides S-1 and cisplatin in the three-drug combination, we adopted irinotecan instead of taxane, which we believe is reasonable considering the current second or later line treatment for AGC. Initially, irinotecan proved to be superior to best supportive care as a second-line treatment for AGC [10]. Later, paclitaxel was found to be more suitable than irinotecan in patients who were refractory to first-line treatment with the fluoropyrimidine and platinum doublet regimen in a phase III WJOG4007G study [11]. Currently, the standard second-line treatment established for AGC is paclitaxel plus ramucirumab based on the results of the phase III RAINBOW trial, which demonstrated the efficacy of ramucirumab added to paclitaxel [12]. Therefore, irinotecan is currently administered as third-line or later treatment. Although it has proved to be effective, irinotecan is often challenging to use in later lines of treatment due to the poor systemic status of patients with AGC, such as peritoneal metastases, severe ascites, or gastrointestinal obstruction. Furthermore,

considering the robustness of paclitaxel plus ramucirumab as the second-line treatment, the use of taxane-containing regimens as the first-line treatment may not be appropriate. The phase II RAMIRIS trial results did not demonstrate the clinical benefit of second-line paclitaxel plus ramucirumab over experimental FOLFIRI plus ramucirumab in a group of patients who had previously received docetaxel therapy, implying the importance of avoiding cross-resistance [13]. We, therefore, consider it reasonable to use the irinotecan-containing regimen, IPS, as the first-line treatment for AGC. Although further evaluation is needed, our data suggest that IPS can be a promising option for HER2-negative AGC in first-line settings, similar to the FOLFOXIRI regimen in colorectal cancer [14] and the FOLFIRINOX regimen in pancreatic cancer [15].

In conclusion, we determined the RD of IPS to be irinotecan 100 mg/m^2, cisplatin 60 mg/m^2, and S-1 80 mg/m^2. Although this is a preliminary study, the results indicate that IPS regimen is tolerable with a favorable efficacy, potentially providing a new therapeutic option for "immune-poor" patients with HER2-negative AGC. Further studies are needed to improve the IPS regimen; the possibility of using oxaliplatin instead of cisplatin can be considered in these studies.

Acknowledgements We thank the patients and their families as well as the nurses and investigators who participated in the current study.

Author contributions Conceptualization: Goto Masahiro and Taroh Satoh; methodology: Goto Masahiro; formal analysis and investigation: Toshio Shimokawa and Yukinori Kurokawa; writing—original draft preparation: Hiroki Yukami and Hisato Kawakami; writing—review and editing: all authors; supervision: Hisato Kawakami.

Funding No funding was received for conducting this study.

Data availability The data generated in this study are available upon request from the corresponding authors.

Declarations

Conflict of interest HY has no competing interests to disclose. HK has received consulting fees from Daiichi-Sankyo Co. Ltd.; honoraria from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Merck Biopharma Co., Ltd., Takeda Pharmaceutical Co. Ltd., Yakult Pharmaceutical Industry, Teijin Pharma Ltd., Incyte Biosciences Japan, and Taiho Pharmaceutical Co. Ltd.; lecture fees from Glaxo Smith Kline K.K. and Otsuka Pharmaceutical Co., Ltd.; and research funding from Bristol-Myers Squibb Co. Ltd., Taiho Pharmaceutical Co. Ltd., Kobayashi Pharmaceutical. Co., Ltd., and Eisai Co. Ltd. TY has no competing interests to disclose. DS has received honoraria from Daiichi Sankyo Co. Ltd., and Chugai Pharmaceutical Co., Ltd.; and research funding from Daiichi Sankyo Co. Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Eisai Co., Ltd., Taiho Pharmaceutical Co. Ltd., and Ono Pharmaceutical Co. Ltd. TS has no competing interests to disclose. YK has received honoraria from Taiho Pharmaceutical Co. Ltd. and research funding from Taiho Pharmaceutical Co. Ltd. and Yakult Pharmaceutical Industry. MG has no competing interests to disclose. TS has received honoraria from Daiichi Sankyo Co. Ltd., Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., Lilly Japan K.K., Taiho Pharmaceutical Co. Ltd., and Yakult Pharmaceutical Industry; research funding from Daiichi Sankyo Co. Ltd., Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., Lilly Japan K.K., Taiho Pharmaceutical Co. Ltd., and Yakult Pharmaceutical Industry.; scholarship donations from Taiho Pharmaceutical Co. Ltd.; and endowed chairs from Ono Pharmaceutical Co. Ltd., Yakult Pharmaceutical Industry, and Chugai Pharmaceutical Co.

Ethical approval and informed consent The study protocol was approved by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) Steering Committee and the Institutional Review Boards of all participating hospitals. The current study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All the patients provided written informed consent prior to initiating chemotherapy.

References

1. Erratum: global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries (2020) CA Cancer J Clin 70: 313. https://doi.org/10.3322/caac.21609
2. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221. https://doi.org/10.1016/S1470-2045(08)70035-4
3. Van Cutsem E, Moiseyenko VM, Tjulandin S et al (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 24:4991–4997. https://doi.org/10.1200/JCO.2006.06.8429
4. Yamada Y, Boku N, Mizusawa J et al (2019) Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 4:501–510. https://doi.org/10.1016/S2468-1253(19)30083-4
5. Narahara H, Iishi H, Imamura H et al (2011) Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer 14:72–80. https://doi.org/10.1007/s10120-011-0009-5
6. Janjigian YY, Shitara K, Moehler M et al (2021) First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 398:27–40. https://doi.org/10.1016/S0140-6736(21)00797-2
7. Rha SY, Wyrwicz LS, Weber PEY et al (2023) VP1-2023: pembrolizumab (pembro) plus chemotherapy (chemo) as first-line therapy for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: phase III KEYNOTE-859 study. Ann Oncol 34:319–320. https://doi.org/10.1016/j.annonc.2023.01.006
8. Al-Batran SE, Homann N, Pauligk C et al (2019) Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 393:1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1
9. Kang YK, Yook JH, Park YK et al (2021) PRODIGY: a phase III study of neoadjuvant docetaxel, oxaliplatin, and S-1 plus surgery and adjuvant S-1 versus surgery and adjuvant S-1 for resectable

advanced gastric cancer. J Clin Oncol 39:2903–2913. https://doi.org/10.1200/JCO.20.02914
10. Thuss-Patience P, Albrecht K, Dmitry B et al (2011) Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 15:2306–2314. https://doi.org/10.1016/j.ejca.2011.06.002
11. Hironaka S, Ueda S, Yasui H et al (2013) Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 31:4438–4444. https://doi.org/10.1200/JCO.2012.48.5805
12. Wilke H, Muro K, Van Cutsem E et al (2014) Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 15:1224–1235. https://doi.org/10.1016/S1470-2045(14)70420-6
13. Lorenzen S, Thuss-Patience P, Pauligk C et al (2022) FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel—results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO. Eur J Cancer 165:48–57. https://doi.org/10.1016/j.ejca.2022.01.015
14. Falcone A, Ricci S, Brunetti I et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 25:1670–1676. https://doi.org/10.1200/JCO.2006.09.0928
15. Conroy T, Desseigne F, Ychou M et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825. https://doi.org/10.1056/NEJMoa1011923