Results Between April 2002 and July 2003, 45 eligible patients were registered and analyzed. Among the 45 patients, 40 (89%) had previously received chemotherapy for metastasis and 24 (53%) had a performance status (PS) of 0. Thirteen partial responses were obtained among the 45 patients, resulting in an overall RR of 29% (95% CI, 16–42%). The median time to progression was 4.1 months, and the median survival time was 10 months, with a 1-year survival rate of 36%. Grade 4 neutropenia was observed in 29% of the patients, whereas febrile neutropenia occurred in 9%. The incidence rates of grade 3 nausea and diarrhea were 13 and 2%, respectively.

Conclusions Although this study did not achieve the per-protocol definition of activity, the progression-free survival and overall survival appeared to be promising, with acceptable tolerability. Thus, MMC/CPT-11 therapy as second-line chemotherapy for fluoropyrimidine-resistant advanced gastric cancer presents a potential treatment option in patients with a good PS.

Keywords Gastric cancer · Mitomycin-C · Irinotecan · Fluoropyrimidine-resistant · Second-line chemotherapy

Introduction

Gastric cancer is the most common malignancy in Asian countries, with approximately 50,000 deaths in Japan annually [1]. The treatment of choice for this malignancy is primary tumor resection. In patients with curatively resected stage I–III gastric cancer, the 5-year survival proportion is >50%; however, this proportion remains at <10% in stage IV or recurrent disease. Randomized trials have demonstrated that fluorouracil-based regimens improve survival proportions in patients with advanced gastric cancer (AGC) compared with best supportive care (BSC) alone as first-line chemotherapy [2–4]. Moreover, combination chemotherapy results in superior outcomes compared with monotherapy. In Japan, the efficacy and toxicity of the combination of an oral fluoropyrimidine (S-1) and platinum was previously evaluated in the phase III SPIRITS (S-1 plus cisplatin vs. S-1 alone for first-line treatment of AGC) trial. S-1 plus cisplatin resulted in superior overall survival (OS) compared with S-1 alone [hazard ratio (HR), 0.77; 95% confidence interval (CI), 0.61–0.98%; $P = 0.04$], with an impressive median OS of 13.0 months [5]. The Japan Clinical Oncology Group (JCOG) 9912 trial (5-fluorouracil [FU] alone vs. S-1 alone vs. irinotecan [CPT-11] plus cisplatin [CDDP] combination for the first-line treatment of AGC) was also conducted in Japan. S-1 showed significant noninferiority for progression-free survival (PFS) and OS compared with 5-FU alone; however, CPT-11 plus CDDP showed no significant superior effects on PFS and OS compared with 5-FU alone [6]. In Japan, S-1 plus CDDP combination therapy is considered the standard first-line treatment for AGC.

Thuss-Patience et al. [7] reported at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) that CPT-11 monotherapy significantly prolonged OS compared with BSC as second-line chemotherapy. Although that report was the first randomized phase III study investigating second-line chemotherapy for AGC, no objective responses were observed. Thus, a consensus regarding the standard regimen for second-line chemotherapy has not yet been obtained.

Many AGC patients who failed to respond to first-line chemotherapy showed symptoms of pain, weight loss, or nausea due to their progressive disease. Thus, the induction of a tumor response is as important as delaying tumor progression for as long as possible. Patients who received combination chemotherapy showed higher response rates than those who received single-agent chemotherapy alone. Therefore, combination chemotherapy is preferable to single-agent chemotherapy for palliation. Moreover, combination chemotherapy may prolong OS compared with single-agent chemotherapy alone.

CPT-11 is a potent topoisomerase I inhibitor and is effective against AGC. In a phase II trial, the response rate (RR) to CPT-11 alone was 16% in previously treated AGC patients [8]. The administration of a CDDP and CPT-11 combination in AGC patients resulted in a higher RR and longer time to progression (TTP) [9–11]. As mentioned above, CDDP/CPT-11 did not significantly prolong OS over 5-FU, but induced a significantly higher RR than 5-FU in the JCOG9912 trial [6]. A 5-FU, leucovorin (LV), and CPT-11 combination produced a higher RR and longer TTP than CDDP/CPT-11 in AGC patients [12]. In another randomized phase III trial, 5-FU/LV/CPT-11 showed a trend to have superiority in TTP over CDDP/5-FU (5.0 vs. 4.2 months, respectively; HR, 1.23; 95% CI, 0.97–1.57%; $P = 0.088$), and a better safety profile [13]. These results support the finding that CPT-11 is active against AGC.

Mitomycin C (MMC) is also effective against AGC. Preclinical studies have shown that a MMC and CPT-11 combination synergistically inhibits tumor growth in vitro [14]. This is due to the possible induction of topoisomerase I gene expression by MMC, thereby increasing tumor cell sensitivity to CPT-11. A phase I/II study of this combination recommended an MMC dose of 5 mg/m^2 and a CPT-11 dose of 150 mg/m^2 administered biweekly [15]. The dose-limiting toxicities of this combination regimen when administered at 10 mg/m^2 for MMC and 150 mg/m^2 for CPT-11 were grade 4 neutropenia with or without febrile neutropenia and grade 3 diarrhea. The overall RR was 50% (15/30 patients), and 5 of 14 patients (36%) with prior chemotherapy showed a partial response (PR). We

previously showed that MMC and CPT-11 combination chemotherapy was effective and well tolerated in patients with fluoropyrimidine-resistant metastatic colorectal cancer; the RR, median TTP, and median survival time (MST) were 34% (95% CI, 20–49%), 4.2 months, and 11.9 months [16], respectively.

These results led us to conduct the present phase II clinical trial to investigate the efficacy and toxicity of MMC/CPT-11 therapy in patients with AGC resistant to a fluoropyrimidine-containing regimen in the JCOG0109-DI study.

Patients and methods

Eligibility

A patient was considered eligible if there was evidence of a refractory response to one prior chemotherapy containing fluoropyrimidine, which was any of the following types of history of chemotherapy:

1. In the case of unresectable gastric cancer, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine, or confirmed immediately after the discontinuation for any reason other than disease progression.
2. In the case of recurrent gastric cancer, recurrence detected within 24 weeks from the last dose of postoperative adjuvant chemotherapy containing fluoropyrimidine, and further chemotherapy was not administered after recurrence.
3. In the case of recurrent gastric cancer detected 25 weeks after the last dose of postoperative adjuvant chemotherapy, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after the discontinuation for any reason other than progression.
4. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the effect of neoadjuvant chemotherapy containing fluoropyrimidine was stable disease, progressive disease, or not evaluated, and recurrence was identified after curative resection. Chemotherapy was not performed following recurrence.
5. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the chemotherapy effect was a complete response or PR, and progression was detected during one chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after discontinuation for any reason other than progression.

Disease progression and the nonefficacy of neoadjuvant chemotherapy were believed to represent clinical failure by treating physicians. Elevation of the level of a tumor marker, such as carcinoembryonic antigen (CEA), was not accepted as adequate evidence for treatment failure. Documentation of evidence of a refractory response by computed tomography (CT) and magnetic resonance imaging was required.

For the other eligibility criteria, patients must be between 20 and 75 years of age, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate baseline bone marrow function [white blood cell (WBC) and platelet counts $\geq$4,000 and 100,000/mm^3, respectively], adequate hepatic function (serum bilirubin level $\leq$1.5 mg/dl and both serum aspartate aminotransferase and alanine aminotransferase levels $\leq$100 U/l), adequate renal function (serum creatinine level $\leq$1.5 mg/dl), adequate respiratory function (arterial partial pressure of oxygen $\geq$70 mmHg), and have received no blood transfusion within 14 days before enrollment. All patients were required to have $\geq$1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Patients were excluded if they had symptomatic brain metastasis, symptomatic ascites and/or pleural effusion, previous history of MMC or CPT-11 chemotherapy, pre-existing diarrhea of >4 times/day, suspicion of existing active bleeding which needed blood transfusion at 14 days prior to registration in this study, or a high risk of a poor outcome due to concomitant nonmalignant disease (i.e., cardiac, pulmonary, renal, or hepatic disease; poorly controlled diabetes; or uncontrolled infection), or severe psychiatric disease. Pregnant or lactating women were excluded.

The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating hospital. All patients gave their written informed consent.

Treatment plan

The treatment schedule consisted of one MMC dose (5 mg/m^2, bolus injection), then CPT-11 (150 mg/m^2, 90-min i.v. infusion) repeated every 2 weeks, as described previously [16]. All patients were treated on an outpatient basis and were recommended to receive both a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone to prevent emesis. Subsequent treatment cycles were withheld until the WBC and platelet counts were $\geq$3,000 and 100,000/mm^3, respectively; diarrhea was $\leq$grade 1; and there were no infection symptoms such as pyrexia ($\geq$38°C). When the treatment course was delayed within 8 days from the planned schedule, the same dosage levels as those used previously were administered. When the treatment course was delayed beyond 8 days and within 21 days from the planned schedule, one lower dose level (CPT-11 level -1,

125 mg/m^2; level -2, 100 mg/m^2) than the previous level was administered, while the MMC dose was maintained at 5 mg/m^2. The treatment course was discontinued if it could not be started within 21 days from the planned schedule. When grade 4 leukopenia or thrombocytopenia occurred in a previous treatment course causing a delay within 8 days, the same dosage levels as those used previously were administered. When grade 2 diarrhea or higher was observed in a preceding course, dosages 1 level lower than the previous dosages were administered.

Treatment was repeated until disease progression or when severe toxicity was observed. The total MMC dose was limited to 50 mg/m^2, to prevent cumulative toxicity (e.g., interstitial pneumonia and hemolytic uremic syndrome), and thereafter CPT-11 alone was administered. This indicates that the maximum number of total treatment cycles of MMC/CPT-11 therapy is 10 cycles.

Evaluation of response and toxicity

During protocol treatment, the patient's signs and symptoms, as well as laboratory data (i.e., WBC with differential counts, liver function tests, urea nitrogen, creatinine, electrolytes, and urinalysis) were examined biweekly. Adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria version 2.0. Tumor response was assessed by CT every 4 weeks. The response of measurable and evaluable disease sites was assessed by each investigator in accordance with RECIST, and then reviewed by central review at the group meeting.

Statistical analysis

For this study, the primary endpoint was the RR and the secondary endpoints were OS and toxicity. Here, we used the standard design (attained design) of the Southwest Oncology Group [17]. Based on reports of RRs of 22% with paclitaxel alone [18] and 16% with CPT-11 alone [8] in the second-line setting and an RR of 36% in phase I/II studies of MMC/CPT-11 therapy [15], the RR in this study was expected to be within 30–40% for a future phase III trial. Here, the required sample size was calculated to be 45 patients, with the following parameters: $\alpha = 0.05$, $\beta = 0.10$, threshold response rate $(p_0) = 20\%$, and expected response rate $(p_a) = 40\%$. Interim analysis was performed when the number of enrolled subjects reached 25. The significance level for the interim analysis was set as $P < 0.02$. Furthermore, when the number of patients who reached RR was <5 at the interim analysis, the study was prematurely discontinued because it would have been difficult to exceed the expected RR despite further patient accumulation, or because it would not be worth advancing this regimen to an ensuing clinical study. When the study was not completed after the interim analysis, the number of patients was increased to 45 in order to allow the null hypothesis (threshold RR) to be tested. When α was <0.05, or when the lower boundary of the 95% CI of the RR exceeded 20% of the threshold RR, this therapy was considered to be efficacious as chemotherapy for gastric cancer patients who had received pretreatment. That is, when ≥16 of 45 patients had a PR, this study was judged to be positive. Here, patient enrollment was not temporarily discontinued.

OS was defined as the time from the registration date to death as a result of any cause. PFS was defined as the time from the registration date to the first documentation of objective tumor progression. Time-to-event and OS data were summarized using the Kaplan–Meier method.

Results

Patient population and study treatment

Between April 2002 and July 2003, 45 patients (33 men, 12 women) from 12 hospitals were enrolled and analyzed. Table 1 shows the demographic data, baseline disease, and regimens of prior chemotherapy. The median age was 64 years (range 36–75), and all patients had a good PS of 0 or 1. Eighteen patients (40%) had diffuse-type gastric cancer. As for prior chemotherapy, 40 (89%) had previously received chemotherapy for metastasis, whereas 5 had received adjuvant chemotherapy. In the first-line chemotherapy, 33 patients (73%) had received 5-FU or S-1 alone.

In all 45 patients, MMC/CPT-11 therapy was administered 281 times, and the median number of doses was 6 (range 1–10). Of the 45 patients, 10 (22%) completed the planned 10 chemotherapy cycles. In the remaining 35 patients, the reasons for treatment discontinuation were disease progression in 25, toxicity in 6, patient's refusal in 3, and death in 1. Regarding CPT-11 administration, 11 patients (24%) required -1 level dose reduction and 8 (18%) required -2 level reduction because of leukopenia and thrombocytopenia.

Efficacy

Of the 45 patients, 13 showed a PR (RR: 28.9%; 95% CI, 15.6–42.1%) (Table 2). The median PFS was 4.1 months (Fig. 1). The median OS time was 10.1 months (95% CI, 7.3–12.6 months), and the 1-year survival rate was 38% (Fig. 2).

Because the lower boundary of the 95% CI of the RR (15.6%) did not exceed the threshold RR (20%), the

Table 1 Patient characteristics ($n = 45$)

Age (years)	
Median	64
Range	36–75
Gender	
Male	33
Female	12
ECOG performance status	
0	24
1	21
2	0
Borrmann macroscopic type of primary cancer	
0	1
1	1
2	17
3	18
4	5
Unknown	3
Histological type	
Intestinal	25
Diffuse	18
Unclassified	2
Prior chemotherapy	
5-FU alone	18
S-1 alone	15
S-1 + CDDP	6
MTX + 5-FU	2
Others	4

ECOG Eastern Cooperative Oncology Group, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *MTX* methotrexate

Table 2 Evaluation of response ($n = 45$)

Tumor response	Patients	
	n	% (95% CI)
Complete response	0	0
Partial response	13	28.9 (15.6–42.1)
Stable disease	17	37.7 (23.6–51.9)
Progressive disease	14	31.1 (17.6–44.6)
Not evaluated	1	4.4 (0–6.5)
Survival	Months (95% CI)	
PFS	4.1 M (2.5–5.7)	
OS	10.1 M (7.3–12.6)	

CI confidence interval, *PFS* progression-free survival, *OS* overall survival

MMC/CPT-11 combination as second-line chemotherapy could not be definitively concluded as efficacious for further investigation.

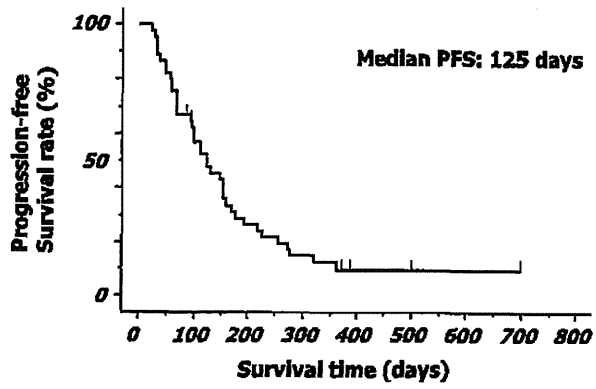

Fig. 1 Kaplan–Meier estimates of progression-free survival (*PFS*) rates

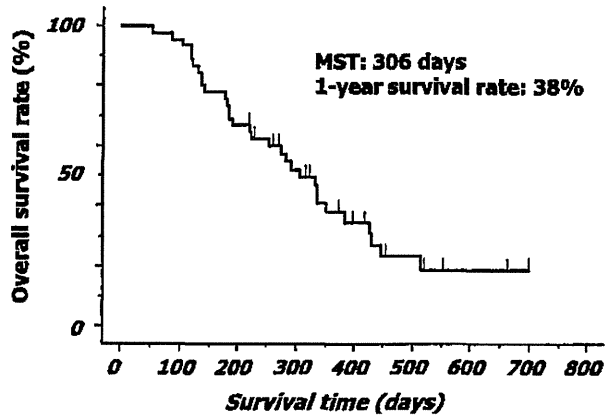

Fig. 2 Kaplan–Meier estimates of overall survival. *MST* Median survival time

Toxicity

The toxicities of the MMC/CPT-11 therapy are summarized in Table 3, with myelosuppression and gastrointestinal toxicity as major toxicities. Grade 3 and 4 neutropenia occurred in 24 and 29% of the patients, respectively, whereas grade 3 and 4 thrombocytopenia developed in only 7%. As for the nonhematological toxicities, the incidence rate of grade 3 diarrhea was 2%, and nausea and vomiting were mild. Early death due to interstitial pneumonitis within 30 days from the last chemotherapy occurred in 1 patient, which was considered by the JCOG Data and Safety Monitoring Committee to have been possibly related to the treatment.

Discussion

In second-line chemotherapy for AGC, the potential benefits remain unclear because of the few prospective studies that have been conducted thus far. These trials demonstrated that

Table 3 Grade 2–4 adverse events according to NCI-CTC ver. 2.0 ($n = 45$)

	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Hematological WBC	24	8	5	29
Neutrophils	10	11	13	53
Hb	25	3	3	13
Platelets	1	2	1	7
Febrile neutropenia	0	4	0	9
Non-hematological Anorexia	13	11	0	24
Nausea	11	6	0	13
Diarrhea	4	1	0	2
Infection with grade 3/4 neutropenia	0	2	0	4
Infection without neutropenia	4	2	0	4

NCI-CTC National Cancer Institute-Common Toxicity Criteria, *Hb* hemoglobin

the RRs to second-line chemotherapy in phase II trials for gastric cancer were similar to those observed for other cancers which are more commonly treated after the failure of first-line chemotherapy. Furthermore, 2 Japanese randomized trials (i.e., SPIRITS [5] and JCOG9912 [6]) achieved a median OS of 13.0 months despite the relatively short median PFS of about 4–6 months. Although both JCOG9912 and our previous phase III study (JCOG9205 [19]) utilized 5-FU continuous infusion (c.i.) and 5-FU/CDDP, the obtained median PFS was 2 months and the OS in JCOG9912 was much longer than that in JCOG9205. In the present study, the proportion of patients who received second-line chemotherapy was >70%, which is higher than that obtained in our previous study (53%). The results of previous phase II trials consistently suggest that patients treated with second-line chemotherapy may survive longer than those provided with BSC, although the survival benefit of the second-line chemotherapy has not yet been clarified.

According to the 26 prospective phase II studies reported in the literature, obtained using the search expressions "gastric cancer" and "second-line chemotherapy" in PubMed, the average and median RRs were 18.8 and 20.0% (0–34.6%), respectively [18, 20–44]. Although the present study did not disprove the null hypothesis about RR, it is suggested that MMC/CPT-11 therapy with an RR of 28.9% may possess some antitumor activity as second-line chemotherapy.

As for survival, the present study showed a median survival time of 10.1 months (95% CI, 7.3–12.9 months), and a 1-year survival proportion of 38%. These data are similar to those obtained in the first-line chemotherapy setting and appeared to be better than those obtained using several other regimens, showing a survival period of 3.5–13 months compared with the reported median survival period of 7–10 months in untreated patients. However, it is very difficult to compare phase II studies due to differences in patient background and subsequent therapy. One reason for improved survival may be good clinical selection of a patient. At the baseline evaluation, the median age of the patients in the present study was 64 years (range, 36–75), and all the patients had a good PS of 0 or 1. Another reason for the improved survival was the high proportion of tumor stabilization (66.7%) after the administration of the MMC/CPT-11 regimen. Therefore, it is considered that MMC/CPT-11 therapy may provide some survival benefit.

The toxicity of the MMC/CPT-11 regimen can be considered tolerable and manageable. Hematological toxicity was within the expected range, including grade 4 neutropenia, observed in 13 patients (29%) and grade 3 febrile neutropenia in 4 patients (9%). According to a Japanese prospective pharmacogenomic study of CPT-11, homozygotes and double heterozygotes of *6 and *28 (*6/*6, *28/*28 and *6/*28) were significantly associated with severe neutropenia. The UGT1A1 gene test prior to receiving this regimen may be useful to decide the starting dose of CPT-11 or to decide whether the patient should receive CPT-11 and MMC combination chemotherapy or CPT-11 monotherapy [45]. Although treatment-related death was observed in 1 patient (2%) in the present study, the occurrence of adverse events was similar to that in JCOG9911-DI, a phase II study of the same regimen for colon cancer; thus, MMC/CPT-11 therapy was considered tolerable. In the present study, the proportion of patients with toxicity was similar to that of patients where MMC/CPT-11 therapy was used as second-line treatment against colorectal cancer [16].

From the above results, the present phase II study of MMC/CPT-11 therapy for FU-based chemotherapy-refractory gastric cancer is judged to be negative on the basis of the decision rule defined in the protocol. This may be due to the threshold RR being set very high owing to the lack of data as the basis for setting the threshold level and expected RR, because of the small number of phase II studies of second-line treatment when this protocol was developed. In fact, the RR cannot be considered poor compared with that in phase II studies performed in other treated patients (as shown in Table 2), with a favorable

survival time of 10 months. In conclusion, the MMC/CPT-11 regimen might be one treatment option for pretreated AGC in patients with good PS.

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Conflict of interest None.

Appendix

Investigators in participating institutions: Yamagata Prefectural Central Hospital, H. Saito; Tochigi Cancer Center, H. Fuji; Saitama Cancer Center, K. Yamaguchi; National Cancer Center Hospital East, T. Doi; Chiba Cancer Center Hospital, T. Denda; National Cancer Center Hospital Tokyo, Y. Shimada; Kitasato University East Hospital, W. Koizumi; Aichi Cancer Center Hospital, Y. Inaba; Nagoya Medical Center, H. Iwase; Osaka Medical College, H. Takiuchi; National Hospital Organization Shikoku Cancer Center, J. Nasu; Kumamoto Regional Medical Center Hospital, M. Yoshida.

References

1. Statistics of Cancer, Center for Information Services, National Cancer Center, Japan. http://ganjoho.ncc.go.jp/public/statistics/pub/update.html.
2. Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoden PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol. 1994;5:189–90.
3. Murad A, Santiago F, Petroianou A. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer. 1993;72:37–41.
4. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer. 1995;71:587–91.
5. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
6. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063–9.
7. Thuss-Patience PC, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B, et al. Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol. 2009;27:abstr 4540.
8. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, et al. Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. Gan To Kagaku Ryoho. 1994;21:1033–8.
9. Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol. 1999;17:319–23.
10. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. Cancer. 2002;94:641–6.
11. Ilson DH, Saltz L, Enzinger P, Huang Y, Kornblith A, Gollub M, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol. 1999;17:3270–5.
12. Pozzo C, Barone C, Szanto J, Padi E, Peschel C, Bukki J, et al. Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. Ann Oncol. 2004;15:1773–81.
13. Dank M, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol. 2008;19:1450–7.
14. Kano Y, Suzuki K, Akutsu M, Suda K, Inoue Y, Yoshida M, et al. Effects of CPT-11 in combination with other anti-cancer agents in culture. Int J Cancer. 1992;50:604–10.
15. Yamao T, Shirao K, Matsumura Y, Muro K, Yamada Y, Goto M, et al. Phase I-II study of irinotecan combined with mitomycin-C in patients with advanced gastric cancer. Ann Oncol. 2001;12:1729–35.
16. Yamada Y, Shirao K, Hyodo I, Arai Y, Denda T, Ambo T, et al. Phase II study of biweekly irinotecan and mitomycin C combination therapy in patients with fluoropyrimidine-resistant advanced colorectal cancer. Cancer Chemother Pharmacol. 2003;52:125–30.
17. Green S, Benedetti J, Crowley J. Clinical trials in oncology (interdisciplinary statistics). 2nd ed. Boca Raton: Chapman & Hall/CRC; 2002.
18. Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET, et al. Phase II study of paclitaxel in pretreated advanced gastric cancer. Anticancer Drugs. 1998;9:307–10.
19. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol. 2003;21:54–9.
20. Schmitz SH, Voliotis DL, Schimke J, Diehl V. Continuous 5-fluorouracil and leucovorin as a second-line therapy for advanced gastric carcinoma. Oncology. 1994;51:502–6.
21. Vanhoefer U, Wilke H, Weh HJ, Clemens M, Harstrick A, Stahl M, et al. Weekly high-dose 5-fluorouracil and folinic acid as salvage treatment in advanced gastric cancer. Ann Oncol. 1994;5:850–1.
22. Hartmann JT, Kanz L, Bokemeyer C. Phase II study of continuous 120-hour-infusion of mitomycin C as salvage chemotherapy in patients with progressive or rapidly recurrent gastrointestinal adenocarcinoma. Anticancer Res. 2000;20:1177–82.
23. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. Irinotecan/cisplatin in advanced, treated gastric or gastroesophageal junction carcinoma. Oncology (Huntingt). 2002;16:16–8.
24. Kim DY, Kim JH, Lee SH, Kim TY, Heo DS, Bang YJ, et al. Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol. 2003;14:383–7.

25. Chun JH, Kim HK, Lee JS, Choi JY, Lee HG, Yoon SM, et al. Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. Jpn J Clin Oncol. 2004;34:8–13.
26. Park SH, Kang WK, Lee HR, Park J, Lee KE, Lee SH, et al. Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen. Am J Clin Oncol. 2004;27:477–80.
27. Giuliani F, Molica S, Maiello E, Battaglia C, Gebbia V, Di Bisceglie M, et al. Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). Am J Clin Oncol. 2005;28:581–5.
28. Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, et al. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. Br J Cancer. 2005;92:1850–4.
29. Kunisaki C, Imada T, Yamada R, Hatori S, Ono H, Otsuka Y, et al. Phase II study of docetaxel plus cisplatin as a second-line combined therapy in patients with advanced gastric carcinoma. Anticancer Res. 2005;25:2973–7.
30. Park SH, Choi EY, Bang SM, Cho EK, Lee JH, Shin DB, et al. Salvage chemotherapy with irinotecan and cisplatin in patients with metastatic gastric cancer failing both 5-fluorouracil and taxanes. Anticancer Drugs. 2005;16:621–5.
31. Nguyen S, Rebischung C, Van Ongeval J, Flesch M, Bennamoun M, Andre T, et al. Epirubicin–docetaxel in advanced gastric cancer: two phase II studies as second and first line treatment. Bull Cancer. 2006;93:E1–6.
32. Barone C, Basso M, Schinzari G, Pozzo C, Trigila N, D'Argento E, et al. Docetaxel and oxaliplatin combination in second-line treatment of patients with advanced gastric cancer. Gastric Cancer. 2007;10:104–11.
33. Hartmann JT, Pintoffl JP, Al-Batran SE, Quietzsch D, Meisinger I, Horger M, et al. Mitomycin C plus infusional 5-fluorouracil in platinum-refractory gastric adenocarcinoma: an extended multicenter phase II study. Onkologie. 2007;30:235–40.
34. Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, et al. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). Anticancer Res. 2007;27:2667–71.
35. Jeong J, Jeung HC, Rha SY, Im CK, Shin SJ, Ahn JB, et al. Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. Ann Oncol. 2008;19:1135–40.
36. Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, et al. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. Cancer Chemother Pharmacol. 2008;61:631–7.
37. Park SH, Kim YS, Hong J, Park J, Nam E, Cho EK, et al. Mitomycin C plus S-1 as second-line therapy in patients with advanced gastric cancer: a noncomparative phase II study. Anticancer Drugs. 2008;19:303–7.
38. Shin SJ, Jeung HC, Ahn JB, Choi HJ, Cho BC, Rha SY, et al. Capecitabine and doxorubicin combination chemotherapy as salvage therapy in pretreated advanced gastric cancer. Cancer Chemother Pharmacol. 2008;61:157–65.
39. Sym SJ, Chang HM, Kang HJ, Lee SS, Ryu MH, Lee JL, et al. A phase II study of irinotecan and docetaxel combination chemotherapy for patients with previously treated metastatic or recurrent advanced gastric cancer. Cancer Chemother Pharmacol. 2008;63:1–8.
40. Takiuchi H, Goto M, Imamura H, Furukawa H, Imano M, Imamoto H, et al. Multi-center phase II study for combination therapy with paclitaxel/doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). Jpn J Clin Oncol. 2008;38:176–81.
41. Zhong H, Zhang Y, Ma S, Ying JE, Yang Y, Yong D, et al. Docetaxel plus oxaliplatin (DOCOX) as a second-line treatment after failure of fluoropyrimidine and platinum in Chinese patients with advanced gastric cancer. Anticancer Drugs. 2008;19:1013–8.
42. Baize N, Abakar-Mahamat A, Mounier N, Berthier F, Caroli-Bosc FX. Phase II study of paclitaxel combined with capecitabine as second-line treatment for advanced gastric carcinoma after failure of cisplatin-based regimens. Cancer Chemother Pharmacol. 2009;64:549–55.
43. Leary A, Assersohn L, Cunningham D, Norman AR, Chong G, Brown G, et al. A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophagogastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. Cancer Chemother Pharmacol. 2009;64:455–62.
44. Lorizzo K, Fazio N, Radice D, Boselli S, Ariu L, Zampino MG, et al. Simplified FOLFIRI in pre-treated patients with metastatic gastric cancer. Cancer Chemother Pharmacol. 2009;64:301–6.
45. Minami H, Sai K, Saeki M, Saito Y, Ozawa S, Suzuki K, et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics. 2007;17:497–504.

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Phase II trial of preoperative S-1 plus cisplatin followed by surgery for initially unresectable locally advanced gastric cancer

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Abstract

Background: The aim of this study was to evaluate the efficacy and feasibility of preoperative chemotherapy with S-1 plus cisplatin in patients with initially unresectable locally advanced gastric cancer.
Methods: We enrolled patients with initially unresectable locally advanced gastric cancer because of severe lymph node metastases or invasion of adjacent structures. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8, repeated every 35 days. If a tumor decreased in size, patients received 1 or 2 more courses. Surgery involved radical resection with D2 lymphadenectomy.
Results: Between December 2000 and December 2007, 27 patients were enrolled on the study. No CR was obtained, but PR was seen in 17 cases, and the response rate was 63.0%. Thirteen patients (48.1%) had R0 resections. There were no treatment related deaths. The median overall survival time (MST) and the 3-year overall survival (OS) of all patients were 31.4 months and 31.0%, respectively. Among the 13 patients who underwent curative resection, the median disease-free survival (DFS) and the 3-year DFS were 17.4 months and 23.1%, respectively. The MST and the 3-year OS were 50.1 months and 53.8%, respectively. The most common site of initial recurrence after the R0 resection was the para-aortic lymph nodes.
Conclusions: Preoperative S-1 plus cisplatin can be safely delivered to patients undergoing radical gastrectomy. This regimen is promising as neoadjuvant chemotherapy for resectable gastric cancer. For initially unresectable locally advanced gastric cancer, new trials using more effective regimens along with extended lymph node dissection are necessary.

Keywords: Neoadjuvant chemotherapy; Lymph node dissection; Bulky lymph node; TS-1; Cisplatin; Para-aortic lymph node

Introduction

Gastric cancer is still one of the most common cancers in the world; 876,000 new cases were anticipated worldwide in the year 2000.[1] In Japan, 110,323 new cases were anticipated in the year 2003 and the 5-year survival rate of gastric cancer diagnosed from 1993 to 1996 was 54.4%.[2,3]

Currently, surgery remains the mainstay of curative treatment. However, only an R0 resection is associated with significant cure rates. Patients having microscopic (R1) or macroscopic (R2) residual tumor have an extremely poor prognosis.[4]

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Preoperative and neoadjuvant chemotherapy represent investigational options. The rationale of preoperative chemotherapy is based on the difficulty of performing an R0 resection in patients with initially unresectable locally advanced tumors and the high risk of micrometastatic disease in these patients. Neoadjuvant chemotherapy has potential for resectable gastric cancer for the purpose of treating micrometastases.

Intensive chemotherapy is necessary for the improvement of the R0 resection rate and complete elimination of the micrometastases. However, it is difficult for patients who undergo gastrectomy to tolerate intensive chemotherapy. Because weight decreases by gastrectomy, it is necessary to reduce the dose of chemotherapy. The tolerance to chemotherapeutic agents with digestive organ toxicity was often reduced by gastrectomy-related gastrointestinal effects.

S-1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) at a molar ratio of 1:0.4:1. The response rate of S-1 alone exceeded 40% in two phase 2 trials involving patients with metastatic gastric cancer.[5,6] The combination chemotherapy of S-1 plus cisplatin (CDDP) achieved a high response rate (74%, 95%CI: 54.9–90.6) in a previous phase I/II study of patients with metastatic gastric cancer.[7]

These factors led us to perform the current phase II trial to investigate the use of an active preoperative chemotherapy regimen. The primary objectives of the trial were to investigate tolerance to the preoperative regimen, its effects on operative morbidity and mortality, and the response rate. Secondary objectives included evaluation of the R0 resection rate, disease-free and overall survival, and failure pattern.

Patients and methods

Patients

The study was conducted as a prospective multi-institutional phase II trial by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) in Japan. All patients had histologically confirmed adenocarcinoma of the stomach. They also had to have initially unresectable locally advanced tumors because of invasion to adjacent structures or severe lymph node metastases, staged by contrast-enhanced CT as T2-3N2-3M0 or T4NanyM0, according to the Japanese Classification of Gastric Carcinoma (2nd English Edition).[8] They also had to have lymph node metastases that were measurable according to the RECIST[1.0] guidelines.[9] We did not require laparoscopic staging as an entry criterion for this study. Any sites of suspected M1 disease had to be ruled out prior to entrance into the study. No prior chemotherapy or radiation was allowed. The age range was 20–75 years. The performance status (ECOG) was 0 from 1.

Because of the worse prognosis of type IV gastric cancer, also known as scirrhous or linitis plastica, we excluded such cases.[10] Acceptable hematologic profile (WBC $\geqq$ 4000 cells/mm^3, hemoglobin $\geqq$ 8.0 g/dl, platelets $\geqq$ 100,000 cells/mm^3), and renal (BUN $\leqq$ 25 mg/dl, creatinine $\leqq$ 1.2 mg/dl and/or creatinine clearance $>$ 60 ml/min) and hepatic function (total serum bilirubin $<$ 1.5 mg/dl) were required. In addition, certain respiratory function test results (ratio of the forced expiratory volume in one second $\geqq$ 50%, PaO2 in room air $\geqq$ 70 mmHg) were required criteria. No clinically significant auditory impairment was allowed. Patients with prior cancer diagnosed during the previous 5-year period (except for colon carcinoma *in situ*) were excluded. Other exclusion criteria included significant cardiac disease, pregnancy or serious infections. The protocol was reviewed and approved by the Institutional Review Board of each institution. All patients gave written informed consent.

Preoperative chemotherapy

Patients found to have locally advanced gastric cancer as defined above, received two cycles of S-1 plus cisplatin every 35 days. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8. Physical examination, abdominal CT scan and assessment of toxicity were performed prior to each cycle. The response measurement of the preoperative chemotherapy was carried out according to the RECIST[1.0] guidelines. Because it was preoperative chemotherapy, response was not confirmed at least 4 weeks apart. Toxicity was recorded and graded according to the National Cancer Institution Common Toxicity Criteria (NCI-CTC) version 2.0 scale. Operative complication was graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). If a tumor decreased in size, according to protocol criteria, we added 1 or 2 more courses. If curative resection was considered possible after planned chemotherapy, the patient had surgery. If curative resection was considered difficult, a further course of chemotherapy was added. The doses of both agents were attenuated for grade $\geqq$3 toxicities, using standard reduction criteria.

Surgery

The surgery was planned for 3–6 weeks from the day of last administration of chemotherapy. Surgery involved a radical resection, the extent of which (total or distal gastrectomy) depended on the site of the primary tumor, with a D2 lymphadenectomy. We performed D2 or more dissection in patients with metastasis to N3 lymph nodes before chemotherapy. Spleen preservation in total gastrectomy procedure was entrusted to the decision of each clinician.

Patients in whom curative resection was impossible underwent palliative operation. The postoperative treatment was left to the decision of each physician.

Biostatistical considerations

The 3 primary end points of the study were as follows; 1) tolerance to preoperative chemotherapy, 2) operative morbidity and mortality, and 3) objective response rate (ORR). Secondary end points were R0 resection rate, failure pattern, and disease-free and overall survival. One of the primary end points was ORR. The number of patients to be enrolled was calculated at 24, which was required given the assumption that the 95% confidence interval (CI) would be ±20%, assuming an expected response rate of 60%. Finally, we set the number as 30 patients in consideration of disqualified patients. The early stopping criterion of the trial was 3 treatment related deaths. Analogous samples were used to estimate the response rate, R0 resection rate, operative morbidity and mortality, and incidence of treatment related grade 3–4 toxicity. Overall survival (OS) of all patients was calculated from the day of registration in the trial. OS and disease-free survival (DFS) of the patients who underwent R0 resections were calculated from the day of surgery. Survival distributions were estimated using the Kaplan–Meier method.

Follow-up

Following completion of chemotherapy and surgery, patients were followed at 3- monthly intervals until year 3. Thereafter, 6-month follow-up visits were performed. CT scans and appropriate blood studies were performed on the occasion of each evaluation.

Results

Patient population

Between December 2000 and December 2007, 27 patients with initially unresectable local advanced gastric cancer were enrolled into the study from 9 institutions. As shown in Table 1, the male to female ratio was 20:7. The median age was 63 years. As for the histologic type, 15 cases were undifferentiated (including signet ring cell carcinoma) and 11 cases were differentiated type. One case was classified as mucinous carcinoma. There were 3 cStage IIIa (11.1%) preoperatively, 8 cStage IIIb (29.6%), and 16 cStage IV (59.3%).

Preoperative chemotherapy

The median number of preoperative chemotherapy regimens was 3 courses. Grade 3–4 toxicities associated with preoperative S-1/CDDP are described in Table 2. Hematologic toxicity (Grade 3/4) was 7.4% and non-hematologic toxicity (Grade 3/4) was 3.7%. Treatment was generally well tolerated and no chemotherapy-related deaths were observed. While there was no CR, there were 17 cases of PR and the response rate was 63.0% [95%CI: 42.4–80.6] (Table 2).

Table 1
Patient characteristics ($n = 27$).

		Number	%
Age, years	Median (range)	63	(48–75)
Gender	Male	20	74.1
	Female	7	25.9
Histology	Differentiated	11	40.7
	Undifferentiated	15	55.6
	Other	1	3.7
Pretreatment cStage	T2N2M0 (IIIA)	3	11.1
	T3N2M0 (IIIB)	7	25.9
	T4N1M0 (IIIB)	1	3.7
	T2N3M0 (IV)	5	18.5
	T3N3M0 (IV)	6	22.2
	T4N2M0 (IV)	3	11.1
	T4N3M0 (IV)	2	7.4

Operative outcome

All patients who were entered into this trial had initially unresectable tumors. Nine patients were diagnosed as being unresectable when chemotherapy was completed and did not undergo surgery. Eighteen patients (66.7%) underwent laparotomy (Table 3). Thirteen patients (48.1%) had R0 resections. Three patients (11.1%) underwent R1 surgery, because of positive results of peritoneal washing cytology. Two patients underwent simple laparotomy because of peritoneal metastases or unresectable local extension of metastatic lymph nodes. Postoperative complications are described in Table 3. The incidence of complications was 22.2%. One patient underwent operative intervention because of pancreatic leakage; however, there were no surgery-related deaths.

Table 2
Courses, responses and toxicities of preoperative chemotherapy.

				n	%
Courses	Median (range)			3	(1–9)
Response	CR			0	0.0
	PR			17	63.0
	SD			6	22.2
	PD			4	14.8
Toxicities		Grade1/2		Grade3/4	
		n	%	*n*	%
	Neutropenia	10	37.0	2	7.4
	Thrombocytopenia	3	11.1	1	3.7
	Hemoglobin	21	77.8	1	3.7
	Vomiting	7	25.9	1	3.7
	Nausea	13	48.1	1	3.7
	Diarrhea	4	14.8	1	3.7
	Anorexia	17	63.0	1	3.7
	Cerebral infarction	0	0	1	3.7
Treatment related death				0	0.0

Table 3
Operative outcome ($n = 27$).

		Number	%
No operation		9	33.3
Operation		18	66.7
	R0 resection	13	48.1
	R1 resection	3	11.1
	R2 resection	0	0
	Simple Laparotomy	2	22.2
Complications			
	None	14	77.8
	Pancreatic leak	3 (Grade 1: 2, Grade 4: 1)	16.7
	Lymphorrhea	1 (Grade 1)	5.6
	Anastomotic leak	0	0.0
Re-operation		1	5.6
Mortality		0	0.0

Seven of 9 patients who did not undergo surgery received 2nd-line chemotherapy (S-1: 3 patients, S-1/CPT-11: 2 patients, CPT-11/CDDP: 1 patient, Paclitaxel: 1 patient). Four of 5 patients who underwent R1-2 surgery received further chemotherapy (S-1/Paclitaxel: 2 patients, S-1: 1 patient, CPT-11/CDDP: 1 patient).

Overall survival of all patients

Only one patient was lost to follow-up at 8 months from the first day of preoperative chemotherapy, but all other patients were followed more than three years. The median overall survival time and the 3-year overall survival rate of all patients were 31.4 months and 31.0% [95%CI: 17.5–55.1], respectively.

DFS, OS, and first relapse site of patients who underwent R0 resection

Thirteen patients underwent R0 resection. The details of these patients are shown in Table 4. Twelve of these 13 patients (92.3%) achieved PR after preoperative chemotherapy. The median number of course of chemotherapy of these patients was 3 (2–5). Of these patients, only 2 patients (15.4%) underwent D2 plus para-aortic lymph node dissection (D3). Downstaging was observed in 11 patients (84.6%). Seven of 13 patients received postoperative adjuvant chemotherapy (S-1: 4 patients, S-1 plus CDDP: 1 patient, CPT-11: 1 patient, CPT-11/CDDP: 1 patient). To date, recurrence has been diagnosed in 10 patients. First relapse site of five of ten patients was para-aortic lymph nodes. The median disease-free survival time and the 3-year disease-free survival rate of the 13 patients were 17.4 months and 23.1% [95%CI: 8.6–62.3], respectively (Fig. 1A). The median overall survival time and the 3-year overall survival rate of the 13 patients were 50.1 months and 53.8% [95% CI: 32.6–89.1], respectively (Fig. 1B).

Discussion

The combination chemotherapy of S-1 plus cisplatin was chosen because it had achieved a high response rate of 74% (95%CI: 54.9–90.6) in previous phase I/II study of patients with metastatic gastric cancer. The incidences of severe (Grade 3/4) hematological and non-hematological toxicities were 15.8 and 26.3%, respectively.[7] A randomized controlled trial in Japan showed the superiority of S-1/cisplatin compared with S-1 monotherapy according to the response rate and survival for metastatic gastric cancer.[11] Therefore, S-1/cisplatin therapy is now the standard treatment for metastatic gastric cancer in Japan.

This multi-institutional phase II prospective trial of preoperative chemotherapy in initially unresectable locally advanced gastric cancer showed that preoperative chemotherapy using S-1/cisplatin was not only feasible but also achieved a high response rate. The overall response rate was 63.0% [95%CI: 42.4–80.6]. The incidence of grade 3/4 toxicities was less than 10% and treatment related

Table 4
Patients who underwent R0 resection.

No.	cStage	Course	Response	Gastrectomy	D	Combined resection	fStage	Nodes	First relapse
1	T3N2M0 (IIIB)	2	PR	Distal	D3	Liver, Gallbladder	T2N2M0 (IIIA)	4	None
2	T3N3M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail) Gallbladder	T2N2M0 (IIIA)	6	Brain
3	T3N2M0 (IIIB)	2	PR	Total	D2	Spleen	T2N2M0 (IIIA)	10	Lymph (para AO)
4	T3N2M0 (IIIB)	2	PR	Distal	D3	None	T2N2M0 (IIIA)	3	None
5	T3N2M0 (IIIB)	3	PR	Total	D1*	Liver	T2N0M0 (IB)	0	None
6	T2N2M0 (IIIA)	2	SD	Distal	D2	Panc. (head)	T4N3M0 (IV)	7	Peritoneum
7	T4N2M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail)	T3N2M0 (IIIB)	10	Lymph (para AO)
8	T2N3M0 (IV)	4	PR	Distal	D2	Gallbladder	T2N2M0 (IIIA)	1	Bone
9	T4N3M0 (IV)	3	PR	Distal	D2	None	T1N0M0 (IA)	0	Lung
10	T4N1M0 (IIIB)	3	PR	Total	D2	Spleen	T2N2M0 (IIIA)	4	Lymph (hepatic)
11	T2N3M0 (IV)	5	PR	Total	D1*	None	T2N3M0 (IV)	2	Lymph (para AO)
12	T2N2M0 (IIIA)	3	PR	Total	D1*	None	T2N0M0 (IB)	0	Lymph (para AO)
13	T3N2M0 (IIIB)	3	PR	Total	D1*	None	T2N2M0 (IIIA)	13	Lymph (para AO)

D1*: we performed almost D2 dissection, but it classified D1 dissection according to the Japanese classification of gastric carcinoma (2nd English edition), because of preserving spleen.

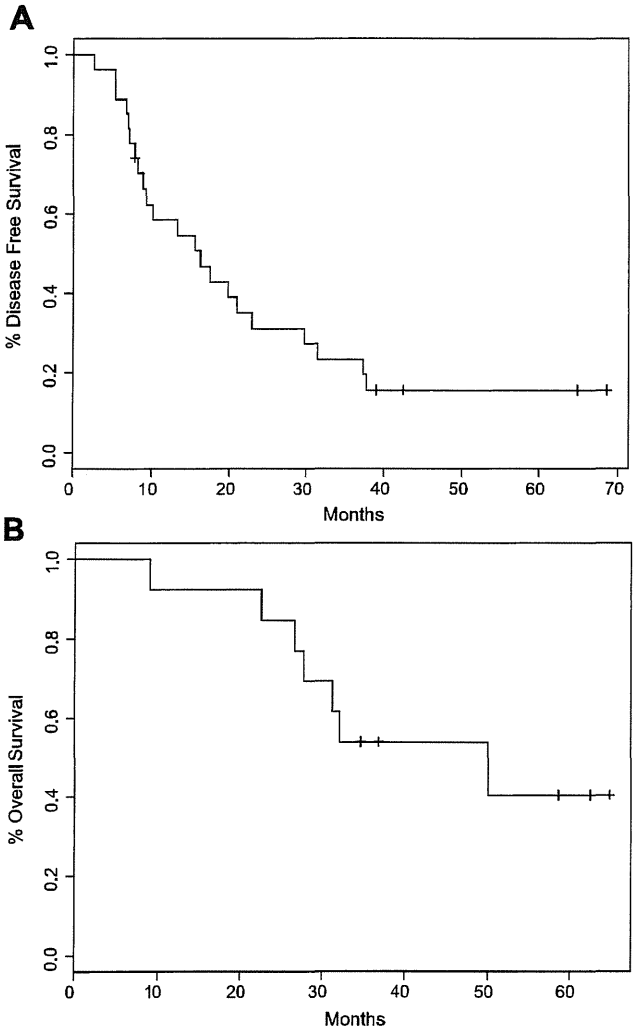

Figure 1. Disease-free and overall survival of the patients who underwent R0 surgery ($n = 13$).

mortality was 0.0%. Similar results were reported in other studies.[12,13] These results encourage the use of S-1/cisplatin combination chemotherapy as neoadjuvant treatment for patients who have resectable gastric cancer. Such trials are currently under way in Japan.[14,15]

The recently completed MAGIC trial constitutes a larger study regarding neoadjuvant chemotherapy in gastric cancer. In this study, 503 patients were randomized to three cycles of pre- and three cycles of postoperative epirubicin/cisplatin/5-FU (ECF) chemotherapy or surgery alone. Neoadjuvant chemotherapy was tolerable and was completed in 88% of patients. Significant downsizing (5.0 versus 3.1 cm median tumor size, $P < 0.001$), downstaging (54% versus 36% T1–T2 tumors, $P = 0.01$) and enhanced resectability (79% versus 69%, $P = 0.02$) were noted. Improved progression-free survival and survival were demonstrated, with an overall 5-year survival of 36% versus 23% for those undergoing surgery alone.[16] We should conduct phase III clinical trials of the neoadjuvant chemotherapy of S-1/cisplatin therapy for resectable gastric cancer.

In Japan, the ACTS-GC trail demonstrated a survival advantage of postoperative adjuvant chemotherapy after R0 resection. R0 patients were randomized to adjuvant chemotherapy using S-1 (529 patients) versus surgery alone (530 patients); improved survival (3-year overall survival rates of 80.1% versus 70.1%, $P = 0.003$) was noted.[17] Adjuvant chemotherapy, as reported by the ACTS-GC Group, is now considered a standard treatment for R0 patients. However, of the 283 patients who had stage III disease and received S-1 adjuvant chemotherapy, 73 patients died. The hazard ratio of the adjuvant chemotherapy group worsened with an increasingly advanced stage. These results suggest that S-1 monotherapy is insufficient for patients who have stage III or more. However, for patients who have initially unresectable gastric cancer like the patients enrolled in this trial, S-1/cisplatin chemotherapy is insufficient because of the high relapse rate of patients who underwent R0 resection.

For the patients immediately after gastrectomy, highly toxic chemotherapy is difficult because of overlaps between chemotherapy-induced gastrointestinal toxicity and digestive symptoms due to gastrectomy.[18] Therefore, further improvements in preoperative therapy will require development of more effective chemotherapeutic regimens. During the last decade, several new agents with promising activity against gastric cancer were identified. These include paclitaxel, docetaxel, irinotecan and trastuzumab. These agents are now undergoing phase II and III trials, as part of combination regimens.[19–22] If improved outcome is seen in metastatic disease, these agents will undergo extensive testing in the preoperative setting.

The absence of laparoscopic staging might have allowed inclusion of patients with positive peritoneal cytology or small peritoneal implants that could have disappeared with the chemotherapy; these patients have a worse prognosis, which could have impacted on the final results. Actually, there were 3 cases of positive cytology at exploration after chemotherapy. Laparoscopic staging should be mandatorily included in future similar projects.

An interesting point is that there were many para-aortic lymph node recurrences in the patients who underwent R0 resection. Among 13 patients who underwent curative resection, initial recurrence in 5 patients was in a para-aortic lymph node. These patients had not undergone para-aortic lymph node dissection. The prognostic improvement effect of the para-aortic lymph node dissection was refuted by two clinical trials.[23,24] In the JCOG 9501 trial, 523 patients with resectable gastric cancer were enrolled, and 263 were assigned to D2 group and 260 were assigned to D2 plus para-aortic nodal dissection. The 5-year overall survival rate was 69.2% for D2 lymphadenectomy group and 70.3% for the D2 lymphadenectomy plus para-aortic nodal dissection group; the hazard ratio for death was 1.03 (95%CI, 0.77 to 1.37; $P = 0.85$). There were also no significant differences in recurrence-free

survival and the pattern of recurrence between the two groups.[23] In the East Asian Surgical Oncology Group trial, 269 patients with resectable gastric cancer were enrolled, and 135 were assigned to the D2 group and 134 were assigned to the D2 plus para-aortic nodal dissection. The 5-year overall survival rates were 52.6% for the D2 lymphadenectomy group and 55.0% for the D2 lymphadenectomy plus para-aortic nodal dissection group. There was no significant difference in survival between the two groups ($P = 0.801$).[24] It was concluded that the D2 lymphadenectomy plus para-aortic nodal dissection did not improve prognosis regarding D2 lymph node dissection in the resectable gastric cancer.

However, in these trials, patients who had gross metastases to the para-aortic nodes were excluded. The incidence of metastases in the para-aortic nodes was lower than expected in 8.5% and 9.7%, respectively. The median number of metastatic nodes was only 2 nodes among the patients who underwent D2 plus para-aortic nodal dissection in the JCOG 9501. In the East Asian Surgical Oncology Group trial, the mean number of metastatic nodes was 5.9 in the para-aortic lymph node dissection group.

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were published. 711 patients underwent randomly assigned treatment with curative intent (380 in the D1 group and 331 in the D2 group). Overall 15-year survival was 21% for the D1 group and 29% for the D2 group. Gastric cancer-related death rate was significantly higher in the D1 group (48%, 182 patients) than that in the D2 group (37%, 123 patients). Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2. After a median follow-up of 15 years, D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related death rates than D1 surgery.[25] This difference was greater in the patients with lymph node metastases from 7 to 15.[26]

The observation period was shorter in the clinical trials of JCOG and East Asian Surgical Oncology Group than in the Dutch trail, and fewer mortality events occurred and also fewer metastases to lymph nodes. Therefore, para-aortic lymph node dissection might have better prognosis in patients with severe lymph node metastases like the patients enrolled in our trial.

In summary, preoperative S-1/cisplatin can be safely delivered to patients undergoing radical gastrectomy. The response rate was high, with no increase in operative morbidity and mortality compared with those upon surgery without preoperative chemotherapy.[27] Controlled trials of neoadjuvant chemotherapy using this regimen with the postoperative S-1 monotherapy for resectable gastric cancer are necessary. For initially unresectable locally advanced gastric cancer, the rate of recurrence was high, and the most common initial recurrent site was para-aortic lymph node. New trials, using a more effective regimen along with extended lymph node dissection are necessary.

Conflict of interest statement

The authors declare no conflict of interest.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001;**94**(2):153–6.
2. Matsuda T, Marugame T, Kamo K, et al. Japan Cancer Surveillance Research. Cancer incidence and incidence rates in Japan in 2003: based on data from 13 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2009;**39**(12):850–8.
3. Tsukuma H, Ajiki W, Ioka A, et al. Research Group of Population-Based Cancer Registries of Japan. Survival of cancer patients diagnosed between 1993 and 1996: a collaborative study of population-based cancer registries in Japan. *Jpn J Clin Oncol* 2006;**36**(9):602–7.
4. Inoue K, Nakane Y, Michiura T, et al. Trends in long-term survival following surgery for gastric cancer: a single institution experience. *Oncol Rep* 2004;**11**(2):459–64.
5. Sakata Y, Ohtu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1M tegaful-0.4M gimestat- 1M otastat potassium) in advanced gastric cancer patients. *Eur. J Cancer* 1998;**34**(11):1715–20.
6. Sugimachi K, Maehara Y, Horikoshi N, et al. An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. The S-1 Gastrointestinal Cancer Study Group. *Oncology* 1999;**57**(3):202–10.
7. Koizumi W, Tanabe S, Saigenji K, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2003;**89**(12):2207–12.
8. Association, Japanese Gastric Cancer. Japanese classification of gastric carcinoma – 2nd English Edition. *Gastric Cancer* 1998;**1**(1): 10–24.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**(3):205–16.
10. Takahashi S, Kinoshita T, Konishi M, et al. Phase II study of sequential high-dose methotrexate and fluorouracil combined with doxorubicin as a neoadjuvant chemotherapy for scirrhous gastric cancer. *Gastric Cancer* 2001;**4**:192–7.
11. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;**9**(3):215–21.
12. Yoshikawa T, Omura K, Kobayashi O, et al. A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). *Eur J Surg Oncol* 2010;**36**(6):546–51.
13. Nakata B, Tsuji A, Mitachi Y, et al. Phase II trial of S-1 plus low-dose cisplatin for unresectable and recurrent gastric cancer (JFMC27-9902 Step2). *Oncology* 2010;**79**(5–6):337–42.

14. Yoshikawa T, Tsuburaya A, Morita S, et al. A comparison of multimodality treatment: two or four courses of paclitaxel plus cisplatin or S-1 plus cisplatin followed by surgery for locally advanced gastric cancer, a randomized Phase II trial (COMPASS). *Jpn J Clin Oncol* 2010; **40**(4):369–72.
15. Japan Clinical Oncology Group. Randomized phase III trial of surgery plus neoadjuvant TS-1 and cisplatin compared with surgery alone for type 4 and large type 3 gastric cancer: Japan Clinical Oncology Group Study (JCOG 0501). Clinical Trials. gov NCT00252161. http://clinicaltrials.gov/show/NCT00252161.
16. Cunningham D, Allum WH, Stenning SP, et al. MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;**335**(1):11–20.
17. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;**357**(18):1810–20.
18. Takahari D, Hamaguchi T, Yoshimura K, et al. Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. *Cancer Chemother Pharmacol* 2010;**67**(6):1423–8.
19. Iwase H, Shimada M, Tsuzuki T, et al. A phase II multi-center study of triple therapy with paclitaxel, S-1 and cisplatin in patients with advanced gastric cancer. *Oncology* 2011;**80**(1–2):76–83.
20. Sato Y, Takayama T, Sagawa T, et al. Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. *Cancer Chemother Pharmacol* 2010;**66**(4):721–8.
21. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as firstline treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011;**14**(1):72–80.
22. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;**376**(9742):687–97.
23. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;**359**(5):453–62.
24. Yonemura Y, Wu CC, Fukushima N, et al. Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. *Int J Clin Oncol* 2008;**13**(2):132–7.
25. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;**11**(5):439–49.
26. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004;**22**(11):2069–77.
27. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy – Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;**22**(14):2767–73.

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ORIGINAL ARTICLE

Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study

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Abstract
Background The Trastuzumab for Gastric Cancer (ToGA) study is the first international trial to include Japanese patients with human epidermal growth factor 2 (HER2) positive advanced/metastatic gastric or gastroesophageal junction cancer. ToGA showed that trastuzumab plus chemotherapy (capecitabine/cisplatin or 5-fluorouracil/cisplatin) improved overall survival in the overall population (hazard ratio 0.74). Regional differences in outcome in favor of Japanese populations were observed in other studies; therefore, subgroup analyses of ToGA may contribute to the evaluation of the potential benefits of this regimen in Japanese patients.
Methods We performed subgroup analyses on 101 Japanese patients enrolled into ToGA (trastuzumab plus chemotherapy, $n = 51$; chemotherapy, $n = 50$).
Results Median overall survival in the Japanese subgroup was 15.9 months (95% confidence interval 12–25) for trastuzumab plus chemotherapy and 17.7 months (95% confidence interval 12–24) for chemotherapy (hazard ratio 1.00; 95% confidence interval 0.59–1.69). After adjusting

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for prespecified covariates, the estimated hazard ratio for overall survival was 0.68 (95% confidence interval 0.36–1.27). Further post hoc and exploratory examinations supported the robustness of the adjusted hazard ratios.
Conclusions After adjusting for imbalanced patient backgrounds between arms, overall survival of Japanese patients with human epidermal growth factor 2 positive advanced/metastatic gastric or gastroesophageal junction cancer who received trastuzumab plus chemotherapy was improved compared with patients who received chemotherapy alone.

Keywords Trastuzumab · Drug therapy · Stomach neoplasms · Randomized controlled trial

Background

Approximately 110,000 people in Japan develop gastric cancer each year [1], with 65,000 estimated deaths (which is second only to lung cancer among cancer-related deaths [1]). For advanced disease, the oral fluoropyrimidine S-1, in combination with cisplatin, has become the standard treatment for gastric cancer in Japan, based on the results of the SPIRITS trial [2]. However, the prognosis still remains poor, and therefore new therapies such as molecular-targeted drugs are needed. Trastuzumab is a recombinant monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2). Trastuzumab derives its anticancer effects from inducing antibody-dependent cytotoxicity, inhibiting HER2-mediated signaling, and preventing cleavage of the extracellular domain of HER2 [3].

Trastuzumab has been approved for use in HER2-positive metastatic breast cancer and as a postoperative adjuvant therapy for HER2-positive breast cancer, and is now the standard of care worldwide for these indications, including in Japan. The Trastuzumab for Gastric Cancer (ToGA) study was the first international randomized controlled phase III trial to include Japanese patients with HER2-positive advanced/metastatic gastric or gastroesophageal junction (GEJ) cancer. The percentage of patients with HER2-positive gastric cancer, as assessed by immunohistochemistry (IHC; 3+ on a scale of 0 to 3+) or fluorescence in situ hybridization (FISH; *HER2*:CEP17 ratio ≥2.0) was 22.1% in the overall ToGA population. The proportion of patients with HER2-positive disease was similar for Europe (23.6%), Asia (23.5%), and Japan (27.6%) [4], and similar to that seen in patients with breast cancer in other trial populations (25–30%) [5]. ToGA showed that patients who received combination treatment with trastuzumab and chemotherapy [capecitabine plus cisplatin (XP) or fluorouracil plus cisplatin (FP)] had significantly improved survival compared with those who received chemotherapy alone: the median overall survival (OS) in the intent-to-treat (ITT) population was 13.8 months in the trastuzumab plus chemotherapy arm and 11.1 months in the chemotherapy-only arm [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.60–0.91; $P = 0.0046$] [6].

There were substantial differences in OS reported from recent phase III trials of chemotherapy for gastric cancer, and these are especially evident between Japan and other countries. Recent trials in Japan have demonstrated that combination therapy resulted in longer survival than was seen in studies outside of Japan, with a median survival exceeding 1 year [7, 8], as compared with around 10 months in Western trials [9, 10]. There are considered to be two reasons for the longer survival observed in Japanese trials. Firstly, up to 70% of Japanese patients receive subsequent chemotherapy following failure of first-line therapy [11–13]. Secondary, there may be differences in the eligibility criteria and baseline patient characteristics between the Japanese and non-Japanese trials; the studies in Japan included patients with and without measurable metastatic disease, whereas non-Japanese trials usually included patients with measurable metastatic disease only [11]. Since the primary endpoint of the ToGA study was OS, there is a possibility that the impact of trastuzumab on survival might be reduced in Japanese patients due to inherently longer survival in this population. To evaluate the efficacy of trastuzumab in combination with chemotherapy specifically in the Japanese population of ToGA, we conducted preplanned and post hoc subgroup analyses.

Patients and methods

The details of the ToGA trial design and methods have been reported elsewhere [6].

Japanese patient subgroup

To evaluate the efficacy and safety of the combination treatment (trastuzumab plus XP) in the Japanese population

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of the ToGA study, we performed subgroup analyses using data from patients who were enrolled from institutions in Japan.

Preplanned sample size for Japanese patients

In the ToGA study, the HR for OS was expected to be 0.77, the expected number of events was 460, and the target sample size was set at 584 patients [6]. Before starting the ToGA study, we set the sample size of Japanese patients to allow us to evaluate similarities between the overall ToGA results and our subgroup analysis in an exploratory manner. Assuming a 70% probability that the HR for OS in the Japanese subgroup would be less than 0.88 (the midpoint between 0.77 and 1.00), the expected number of events was 70. To reach this expected number of events within the study period, the minimum sample size was determined to be 89 patients to allow us to conduct four analyses: preplanned (unadjusted and adjusted), post hoc, and exploratory analyses of the HR.

Unadjusted analyses

We calculated the unadjusted OS and progression-free survival (PFS) of the Japanese sub-group using the same methods as those used for the overall ToGA study [6]. Objective response rate of the Japanese sub-group was analysed with a χ^2 test in patients with measurable disease ($n = 45$ in the trastuzumab plus XP arm and 41 in the XP arm).

Preplanned analyses

Prior to carrying out the Japanese subgroup analysis, we predicted an imbalance in the baseline patient characteristics. Therefore, we planned to calculate an adjusted HR and 95% CI in the Japanese subgroup using a multivariate Cox regression analysis with 15 factors: extent of disease, primary tumor site, measurability of disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS), chemotherapy regimen (stratification factors), sex, age, number of lesions, number of metastatic sites, type of gastric cancer, visceral metastasis, prior gastrectomy, prior chemotherapy, HER2 status, and region of origin (other prespecified covariates). All factors were prespecified in the ToGA study protocol. Each covariate was also evaluated using a univariate Cox regression analysis.

Post hoc analyses

During the preplanned multivariate Cox regression analysis, we excluded patients for whom HER2 status was reported as IHC 3+/FISH unknown (no result). In addition, estimates of effects were extremely unstable for covariates that contained a category which included only one patient. Therefore, to target all of the enrolled patients and ensure the stability of the model, a post hoc analysis was conducted using a multivariate Cox analysis. Among covariates, HER2 status was divided into two categories: high expression (IHC 2+ and FISH-positive or IHC 3+) and low expression (IHC0 and FISH-positive or IHC 1+ and FISH-positive). Covariates that contained a category with only one patient (extent of disease and previous chemotherapy) were excluded from the model to ensure its stability.

Exploratory analyses to evaluate deviation of patient prognosis

To identify factors that affect prognosis specifically in the Japanese subgroup, and to confirm the robustness of our preplanned and post hoc analyses, an exploratory multivariate Cox regression analysis on the HR for OS with various combinations of covariates was carried out. We created a series of models that included the treatment group as a base covariate with 3–6 other covariates, and selected the top four models ranked by value following a chi-square test. The procedure was repeated for the models with three, four, five, and six covariates, and a total of 16 models were selected. From the well-fitting model that was obtained, we compared the HR for OS with the results of preplanned and post hoc analyses. To ensure that HER2 status was not a confounding variable, we carried out a multivariate Cox regression analysis with HER2 expression (high or low) as the stratification factor, and determined the HR for OS in which selected covariates were included in the model.

Furthermore, scoring of the prognosis of each patient in both study arms using the Cox regression model and estimation of the risk for each patient were carried out with the selected covariates. The risk was shown by the estimated value of logarithm HR for each patient. To eliminate the influence of treatment on the mortality risk, we set the treatment group as the stratification factor and produced a histogram plot according to the distribution of patient risk to evaluate potential bias between the treatment arms.

Safety

Adverse events and serious adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 and the International Conference on Harmonization guidelines, respectively.

Results

Patients

Between September 2005 and December 2008, 594 patients were enrolled in the primary ToGA study at 122

Table 1 HER2 testing results in the Japanese population of ToGA

FISH result	IHC score				
	IHC 0	IHC 1+	IHC 2+	IHC 3+	Total
FISH-positive, *n*	14	19	36	37	106
FISH-negative, *n*	155	57	14	1	227
NE, *n*	48	12	8	8	83
Total, *n*	217	88	58	46	409

FISH fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *NE* not evaluable

centers in 24 countries, of whom 584 were included in the primary analysis. Four hundred twenty-one tumor samples were provided for HER2 testing from 16 centers in Japan. Twelve samples were not evaluated due to a lack of tumor tissue in the sample ($n = 7$), shipment failure ($n = 4$), or disease progression before shipment ($n = 1$). Of the 409 samples successfully screened, 115 (28.1%) were scored as HER2-positive (IHC 3+ or FISH-positive; Table 1) and 102 patients were registered into the study. After excluding one patient who did not receive the study drug, 101 Japanese patients (trastuzumab plus chemotherapy, $n = 51$; chemotherapy alone, $n = 50$) were included in this subgroup analysis. All patients received capecitabine as the chemotherapy partner of cisplatin.

Table 2 shows the baseline characteristics of the Japanese patients included in this subgroup analysis ($n = 101$) and the non-Japanese patients ($n = 483$). There is similarity in the baseline characteristics of patients from other countries between the study arms. On the other hand, number of metastatic sites, histologic type, and prior gastrectomy were imbalanced by approximately 10% between the study arms in the Japanese subgroup, and were considered to be prognostic factors. Median follow-up times were 18.6 months [interquartile range (IQR) 11–25] in the trastuzumab plus XP arm and 17.1 months (IQR 1–49) in the XP arm. The median number of cycles of trastuzumab therapy was eight (range 1–24). Forty-one patients in the trastuzumab plus XP arm (80.4%) and 41 patients in the XP arm (82.0%) received second-line treatment (at least one chemotherapy treatment after disease progression despite the study treatments).

Efficacy

Unadjusted analyses

Twenty-eight patients (54.9%) in the trastuzumab plus XP arm and 27 patients (54.0%) in the XP arm had died by the data cutoff point. As shown in Table 3, unadjusted median OS was 15.9 months (95% CI 12–25 months) in the trastuzumab plus XP arm and 17.7 months (95% CI 12–24 months) in the XP arm (HR 1.00, 95% CI 0.59–1.69). The number of PFS events (defined as disease progression or death) was 43 (84.3%) in the trastuzumab plus XP arm and 40 (80.0%) in the XP arm. Unadjusted median PFS was 6.2 months (95% CI 5–7 months) in the trastuzumab plus XP arm and 5.6 months (95% CI 5–7 months) in the XP arm (HR 0.92, 95% CI 0.60–1.43). The objective response rate was 64.4% (95% CI 48.8–78.1%) in the trastuzumab plus XP arm and 58.5% (95% CI 42.1–73.7%) in the XP arm.

Preplanned analyses

In the multivariate analysis, the HR for OS, adjusted by the 15 prespecified covariates above, was 0.68 (95% CI 0.36–1.27, $P = 0.2251$, Table 4). The adjusted HR for PFS was 0.66 (95% CI 0.40–1.09%), which was slightly improved compared with the results for the overall population. Among the covariates in the preplanned analysis, the univariate analysis showed that prior gastrectomy was the covariate most strongly associated with longer OS (HR 0.39, 95% CI 0.16–0.91). There were more patients with prior gastrectomy in the XP arm (26%) than in the trastuzumab arm (16%). After adjusting for gastrectomy only, the HR for OS between the treatment arms was 0.85 (95% CI 0.49–1.45).

Post hoc analyses

For the post hoc exploratory multivariate Cox regression analysis, the adjusted HRs for OS and PFS were 0.82 (95% CI 0.45–1.50) and 0.81 (95% CI 0.50–1.30), respectively (Fig. 1).

Exploratory analyses to evaluate deviation of patient prognosis

We evaluated the HR for OS with different combinations of covariates in the model. In the well-fitting models with high chi-square values, the HRs using three, four, five, and six covariates ranged between 0.79 (95% CI 0.49–1.38) and 0.89 (95% CI 0.52–1.54), 0.77 (95% CI 0.44–1.33) and 0.88 (95% CI 0.51–1.53), 0.68 (95% CI 0.39–1.20) and 0.80 (95% CI 0.45–1.42), and 0.68 (95% CI 0.38–1.20) and 0.76 (95% CI 0.44–1.33), respectively. In choosing the well-fitting models, the covariates sex, HER2 status, type of gastric cancer, prior gastrectomy, prior chemotherapy, and number of lesions tended to be chosen. The sets of covariates were similar to those used as prespecified covariates (15 factors). A similar analysis was carried out

Table 2 Baseline patient characteristics of the Japanese population and the non-Japanese population of ToGA

Characteristic	Japanese		Non-Japanese	
	Trastuzumab plus XP ($n = 51$)	XP/FP ($n = 50$)	Trastuzumab plus XP ($n = 243$)	XP/FP ($n = 240$)
Sex				
Male, *n*	40 (78.4%)	40 (80.0%)	186 (76.5%)	178 (74.2%)
Median age, years (range)	63.0 (29–76)	63.5 (45–81)	60.0 (23–83)	59.0 (21–82)
Extent of disease				
Locally advanced, *n*	0 (0.0%)	1 (2.0%)	10 (4.1%)	9 (3.8%)
Metastatic, *n*	51 (100.0%)	49 (98.0%)	233 (95.9%)	231 (96.3%)
Primary tumor site				
Stomach, *n*	49 (96.1%)	44 (88.0%)	187 (77.0%)	198 (82.5%)
Gastroesophageal junction, *n*	2 (3.9%)	6 (12.0%)	56 (23.0%)	42 (17.5%)
Measurability of disease				
Measurable, *n*	45 (88.2%)	41 (82.0%)	224 (92.2%)	216 (90.0%)
Nonmeasurable, *n*	6 (11.8%)	9 (18.0%)	19 (7.8%)	24 (10%)
ECOG performance status				
0–1, *n*	51 (100.0%)	50 (100.0%)	213 (87.7%)	213 (88.7%)
2, *n*	0 (0.0%)	0 (0.0%)	30 (12.3%)	27 (11.3%)
Chemotherapy regimen				
XP, *n*	51 (100%)	50 (100%)	205 (84.4%)	205 (85.4%)
FP, *n*	0 (0.0%)	0 (0.0%)	38 (15.6%)	35 (14.6%)
Number of lesions			($n = 242$)	
1–4, *n*	16 (31.4%)	18 (36.0%)	112 (46.3%)	98 (40.8%)
>4, *n*	35 (68.6%)	32 (64.0%)	130 (53.7%)	142 (59.2%)
Median value (range)	6 (1–15)	6 (1–15)	5 (1–20)	5 (1–16)
Number of metastatic sites			($n = 242$)	
1–2, *n*	28 (54.9%)	32 (64.0%)	124 (51.2%)	114 (47.5%)
>2, *n*	23 (45.1%)	18 (36.0%)	118 (48.8%)	126 (52.5%)
Median value (range)	2 (1–5)	2 (1–5)	2 (1–7)	3 (1–8)
Type of gastric cancer (central review)[a]			($n = 242$)	($n = 237$)
Intestinal type, *n*	37 (72.5%)	42 (84.0%)	188 (77.7%)	171 (72.2%)
Diffuse type, *n*	5 (9.8%)	4 (8.0%)	21 (8.7%)	21 (8.9%)
Mixed type, *n*	9 (17.6%)	4 (8.0%)	33 (13.6%)	45 (19.0%)
Visceral metastasis (liver or lung)				
Yes, *n*	35 (68.6%)	33 (66.0%)	134 (55.1%)	139 (57.9%)
No, *n*	16 (31.4%)	17 (34.0%)	109 (44.9%)	101 (42.1%)
History of treatment for gastric cancer				
Prior gastrectomy, *n*	8 (15.7%)	13 (26.0%)	62 (25.5%)	49 (20.4%)
Prior chemotherapy, *n*	1 (2.0%)	0 (0.0%)	26 (10.7%)	12 (5.0%)
HER2 status				
IHC 0/FISH-positive, *n*	3 (5.9%)	9 (18.0%)	20 (8.2%)	29 (12.2%)
IHC 1+/FISH-positive, *n*	10 (19.6%)	7 (14.0%)	28 (11.5%)	25 (10.4%)
IHC 2+/FISH-positive, *n*	18 (35.3%)	13 (26.0%)	62 (25.5%)	66 (27.5%)
IHC 3+/FISH-positive, *n*	16 (31.4%)	17 (34.0%)	115 (47.3%)	108 (45.0%)
IHC 3+/FISH-negative, *n*	1 (2.0%)	0 (0.0%)	8 (3.3%)	6 (2.5%)
IHC unknown/FISH-positive, *n*	0 (0.0%)	0 (0.0%)	5 (2.1%)	2 (0.8%)
IHC 3+/FISH unknown, *n*	3 (5.9%)	4 (8.0%)	5 (2.1%)	4 (1.7%)
Region of origin				
Japanese, *n*	51 (100%)	50 (100%)	0 (0.0%)	0 (0.0%)
Non-Japanese, *n*	0 (0.0%)	0 (0.0%)	243 (100%)	240 (100%)

ECOG Eastern Cooperative Oncology Group, *FISH* fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *XP* capecitabine plus cisplatin

[a] Type of gastric cancer was described by the Lauren Classification

using HER2 expression (high or low) as the stratification factor. The HR was approximately 0.7, and the HRs using three, four, five, and six covariates were between 0.67 (95% CI 0.38–1.18) and 0.79 (95% CI 0.46–1.39), 0.70 (95% CI 0.40–1.24) and 0.82 (95% CI 0.47–1.42), 0.68 (95% CI 0.39–1.22) and 0.76 (95% CI 0.43–1.34), and 0.67 (95% CI 0.37–1.22) and 0.78 (95% CI 0.44–1.36), respectively. Influential covariates chosen in the well-fitting models included sex, prior gastrectomy, and number of lesions. Table 5 shows the covariate combinations that resulted in a good fit based on these analyses. Figure 2 shows the distribution of patient risk with these three models. The risk distribution is broad in each arm; however, the XP arm shows a somewhat greater distribution toward the left, indicating that this arm included a greater number of patients with better prognosis.

Table 3 Overall survival in the Japanese population of ToGA (unadjusted Cox regression analysis)

	Trastuzumab plus XP ($n = 51$)	XP ($n = 50$)
Number of events (%)	28 (54.9)	27 (54)
Median OS, months (95% CI)	15.9 (12–25)	17.7 (12–24)
Survival rate (%)		
6 months	92	92
12 months	68	64
18 months	48	49
24 months	41	35
Hazard ratio (95% CI)	1.00 (0.59–1.69)	

CI confidence interval, *OS* overall survival, *XP* capecitabine plus cisplatin

Safety

Table 6 shows the adverse events in the Japanese population of ToGA, and indicates that all patients experienced at least one adverse event in each arm. Grade 3/4 adverse events occurred in 43 patients (84%) in the trastuzumab

Table 4 Preplanned multivariate Cox regression analysis of overall survival by extent of disease, primary tumor site, measurability of disease, ECOG status, chemotherapy regimen, and other prespecified covariates: sex, age, number of lesions, number of metastatic sites, type of gastric cancer, visceral metastasis, prior gastrectomy, prior chemotherapy, HER2 status, and region of origin

	Hazard ratio (95% CI)		*P* value
Trastuzumab plus XP versus XP	0.68	(0.36–1.27)	0.2251
Sex (male vs. female)	0.16	(0.07–0.41)	<0.0001
Age (<60 vs. ≥60)	1.07	(0.54–2.13)	0.8382
Extent of disease (locally advanced vs. metastatic)	0.00	(0.00–.)	0.9902
Primary tumor site (stomach vs. gastroesophageal junction)	0.68	(0.25–1.87)	0.4559
Measurability of disease (measurable vs. nonmeasurable)	0.95	(0.29–3.05)	0.9268
ECOG performance status	–	–	–
Chemotherapy regimen	–	–	–
Number of lesions (1–4 vs. >4)	0.49	(0.22–1.09)	0.0818
Number of metastatic sites (1–2 vs. >2)	0.79	(0.41–1.50)	0.4695
Type of gastric cancer			
Diffuse type versus intestinal type	3.24	(1.08–9.70)	0.0356
Mixed type versus intestinal type	0.91	(0.30–2.71)	0.8644
Visceral metastasis (yes vs. no)	1.15	(0.48–2.74)	0.7510
Prior gastrectomy (yes vs. no)	0.22	(0.06–0.75)	0.0159
Prior chemotherapy (yes vs. no)	27.72	(1.11–694.38)	0.0432
HER2 status			
IHC 0/FISH-positive versus IHC 3+/FISH-positive	5.31	(1.29–21.86)	0.0208
IHC 1+/FISH-positive versus IHC 3+/FISH-positive	4.87	(1.73–13.70)	0.0027
IHC 2+/FISH-positive versus IHC 3+/FISH-positive	1.53	(0.73–3.18)	0.2578
IHC 3+/FISH-negative versus IHC 3+/FISH-positive	25.66	(1.72–382.49)	0.0186
Region of origin	–	–	–

Among 15 prespecified factors, chemotherapy regimen, performance status, and region of origin were not calculated in this table because all Japanese patients received capecitabine as the chemotherapy partner of cisplatin, had Karnofsky performance status of 0–1, and were from Asia (Japan)

CI confidence interval, *ECOG* Eastern Cooperative Oncology Group, *FISH* fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *XP* capecitabine plus cisplatin