Conclusions

In this minireview, we have described how Cohen's discovery of the 'tooth-lid factor' led to the identification of the genetic causes of certain types of human cancers, and to the genetic classification of a variety of tumors of apparently the same phenotype that has significant therapeutic implications.

References

1 Gschwind A, Fischer OM & Ullrich A (2004) The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev* **4**, 361–370.

2 Burgess AW, Cho H-S, Elgenblot C, Ferguson KM, Garrett TPJ, Leahy DJ, Lemmon MA, Siwkowski MX, Ward CW & Yokoyama S (2003) An open-and -shut case? Recent insights into the activation of EGF/ErbB receptors *Mol Cell* **12**, 541–552.

3 Hynes NE & Lane HA (2005) ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev* **5**, 341–354.

4 Schneider MR & Wolf E (2009) The epidermal growth factor receptor ligands at a glance. *J Cell Physiol* **218**, 460–466.

5 Zhang X, Gureasko J, Shen K, Cole PA & Kuriyan J (2006) An allosteric mechanism for activation of the kinase domain of epidermal growth factor receptor. *Cell* **125**, 1137–1149.

6 Voldborg BR, Damstrup L, Spang-Thomsen M & Poulsen HS (1997) Epidermal growth factor receptor (EGFR) and EGFR mutations, function and possible role in clinical trials. *Ann Oncol* **8**, 1197–1206.

7 Ji H, Zhao X, Yuza Y, Shimamura T, Li D, Protopopov A, Jung BL, McNamara K, Xia H, Glatt KA *et al.* (2006) Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. *Proc Natl Acad Sci USA* **103**, 7817–7822.

8 Lee JC, Vivanco I, Beroukhim R, Huang JH, Feng WL, DeBiasi RM, Yoshimoto K, King JC, Nghiemphu P, Yuza Y *et al.* (2006) Epidermal growth factor receptor activation in glioblastoma through novel missense mutations in the extracellular domain. *PLoS Med* **3**, e485.

9 Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG *et al.* (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* **350**, 2129–2139.

10 Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ *et al.* (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science (New York, NY)* **304**, 1497–1500.

11 Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L *et al.* (2004) EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* **101**, 13306–13311.

12 Mitsudomi T & Yatabe Y (2007) Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. *Cancer Sci* **98**, 1817–1824.

13 Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T & Mitsudomi T (2004) Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* **64**, 8919–8923.

14 Matsuo K, Ito H, Yatabe Y, Hiraki A, Hirose K, Wakai K, Kosaka T, Suzuki T, Tajima K & Mitsudomi T (2006) Risk factors differ for non-small-cell lung cancers with and without EGFR mutation: assessment of smoking and sex by a case-control study in Japanese. *Cancer Sci* **98**, 96–101.

15 Miller VA, Kris MG, Shah N, Patel J, Azzoli C, Gomez J, Krug LM, Pao W, Rizvi N, Pizzo B *et al.* (2004) Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* **22**, 1103–1109.

16 Yatabe Y, Mitsudomi T & Takahashi T (2002) TTF-1 expression in pulmonary adenocarcinomas. *Am J Surg Pathol* **26**, 767–773.

17 Yatabe Y, Kosaka T, Takahashi T & Mitsudomi T (2005) EGFR mutation is specific for terminal respiratory unit type adenocarcinoma. *Am J Surg Pathol* **29**, 633–639.

18 Sordella R, Bell DW, Haber DA & Settleman J (2004) Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science (New York, NY)* **305**, 1163–1167.

19 Greulich H, Chen T-H, Feng W, Janne PA, Alvarez JV, Bulmer SE, Zappaterra M, Frank DA, Hahn WC, Sellers WR *et al.* (2005) Oncogenic transformation by inhibitor-sensitive and resistant EGFR mutations. *PLoS Med* **2**, e313.

20 Carey KD, Garton AJ, Romero MS, Kahler J, Thomson S, Ross S, Park F, Haley JD, Gibson N & Sliwkowski MX (2006) Kinetic analysis of epidermal growth factor receptor somatic mutant proteins shows increased sensitivity to the epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib. *Cancer Res* **66**, 8163–8171.

21 Mulloy R, Ferrand A, Kim Y, Sordella R, Bell DW, Haber DA, Anderson KS & Settleman J (2007) Epidermal growth factor receptor mutants from human lung cancers exhibit enhanced catalytic activity and increased sensitivity to gefitinib. *Cancer Res* **67**, 2325–2330.

22 Ji H, Li D, Chen L, Shimamura T, Kobayashi S, McNamara K, Mahmood U, Mitchell A, Sun Y, Al-Hashem R *et al.* (2006) The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. *Cancer Cell* **9**, 485–495.
23 Politi K, Zakowski MF, Fan PD, Schonfeld EA, Pao W & Varmus HE (2006) Lung adenocarcinomas induced in mice by mutant EGF receptors found in human lung cancers respond to a tyrosine kinase inhibitor or to down-regulation of the receptors. *Genes Dev* **20**, 1496–1510.
24 Yatabe Y, Takahashi T & Mitsudomi T (2008) Epidermal growth factor receptor gene amplification is acquired in association with tumor progression of EGFR-mutated lung cancer. *Cancer Res* **68**, 2106–2111.
25 Slebos RJ, Kibbelaar RE, Dalesio O, Kooistra A, Stam J, Meijer CJ, Wagenaar SS, Vanderschueren RG, van Zandwijk N, Mooi WJ *et al.* (1990) K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med* **323**, 561–565.
26 Shigematsu H, Takahashi T, Nomura M, Majmudar K, Suzuki M, Lee H, Wistuba II, Fong KM, Toyooka S, Shimizu N *et al.* (2005) Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res* **65**, 1642–1646.
27 Han SW, Kim TY, Jeon YK, Hwang PG, Im SA, Lee KH, Kim JH, Kim DW, Heo DS, Kim NK *et al.* (2006) Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. *Clin Cancer Res* **12**, 2538–2544.
28 Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara SI, Watanabe H, Kurashina K, Hatanaka H *et al.* (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* **448**, 561–566.
29 Inamura K, Takeuchi K, Togashi Y, Hatano S, Ninomiya H, Motoi N, Mun MY, Sakao Y, Okumura S, Nakagawa K *et al.* (2009) EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. *Mod Pathol* **22**, 508–515.

Annals of Oncology Advance Access published October 29, 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdp464

Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study)

W. Koizumi[1]*, H. Takiuchi[2], Y. Yamada[3], N. Boku[4], N. Fuse[5], K. Muro[6], Y. Komatsu[7] & A. Tsuburaya[8]

[1]*Department of Gastroenterology/Gastrointestinal Oncology, Kitasato University School of Medicine, Sagamihara;* [2]*Department of Gastroenterology, Osaka Medical College, Takatsuki;* [3]*Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo;* [4]*Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun;* [5]*Division of Gastrointestinal Oncology and Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa;* [6]*Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya;* [7]*Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo and* [8]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan*

Received 8 August 2009; accepted 17 August 2009

Background: The efficacy and safety of oxaliplatin combined with S-1 (SOX regimen) for unresectable advanced or recurrent gastric cancer were investigated.
Patients and methods: Oxaliplatin was administered i.v. (100 mg/m^2) on day 1, while S-1 was administered orally (80 mg/m^2/day, b.i.d.) for 14 days followed by a 7-day rest. This schedule was repeated every 3 weeks.
Results: Among 55 patients enrolled, one patient received oxaliplatin for the other study, and three patients were considered unsuitable against the inclusion criteria. Accordingly, 51 patients were assessable for efficacy. The response rate was 59%, and the disease control rate was 84%. The median progression-free survival time was 6.5 months, the 1-year survival rate was 71%, and the median survival time was 16.5 months. In 54 patients assessed for safety, the major grade 3/4 toxic effects were neutropenia (22%), thrombocytopenia (13%), anemia (9%), anorexia (6%), fatigue (6%), and sensory neuropathy (4%).
Conclusion: These findings indicate that SOX regimen with oxaliplatin at a dose of 100 mg/m^2 is feasible and shows promising efficacy against advanced gastric cancer.
Key words: advanced gastric cancer, oxaliplatin, phase II, S-1, SOX

introduction

Chemotherapy for advanced gastric cancer was proven to be superior to best supportive care in terms of survival and quality of life [1–3]. Phase III studies have been carried out to compare epirubicin/cisplatin/5-fluorouracil (5-FU) with 5-FU/doxorubicin/methotrexate, cisplatin/5-FU with docetaxel/cisplatin/5-FU, and 5-FU/cisplatin with capecitabine/cisplatin [4–6]. On the basis of the results of these studies, advanced gastric cancer is mainly treated with combination chemotherapy that includes fluoropyrimidine derivatives and platinum compounds.

Oxaliplatin is a third-generation platinum compound that was developed to improve tolerability and ease of administration compared with cisplatin [7]. The non-inferiority of oxaliplatin-based regimens to cisplatin-based regimens was demonstrated in the Revised European-American Lymphoma (REAL)-2 phase III study [8]. In addition, the result of phase III study comparing 5-FU/leucovorin/cisplatin with 5-FU/leucovorin/oxaliplatin showed that oxaliplatin was at least as effective as cisplatin [9].

S-1 is an orally active prodrug of 5-FU that contains tegafur (which is continuously metabolized to 5-FU) blended with two modulators, gimeracil and potassium oxonate [10]. In Japan, advanced gastric cancer is mainly treated with S-1 alone or S-1 combined with other drugs. The SPIRITS phase III study demonstrated the superiority of S-1 plus cisplatin to S-1 alone [11]. The S-1 plus cisplatin regimen was also investigated by the FLAGS phase III study carried out in Western countries, which demonstrated that S-1 plus cisplatin was at least as effective as 5-FU plus cisplatin and less toxic [12].

We conducted a multicenter phase II study to evaluate the efficacy and safety of the combination regimen of S-1 and oxaliplatin (SOX regimen) in advanced gastric cancer as first-line therapy.

patients and methods

patients' eligibility

The following criteria were used to enroll patients for the present study. All patients had unresectable advanced or recurrent gastric cancer excluding the esophagus and gastroesophageal junction, confirmed by histological or

Correspondence to: Dr W. Koizumi, Department of Gastroenterology/Gastrointestinal Oncology, Kitasato University School of Medicine, 2-1-1 Asamizodai, Sagamihara, Kanagawa 228-8520, Japan. Tel: +81-42-748-9111; Fax: +81-42-748-5120; E-mail: koizumi@med.kitasato-u.ac.jp

cytological examination. They had survived at least 4 weeks if extended or standard surgery had been carried out (or at least 2 weeks after minor surgery) and were able to take oral drugs. They were aged ≥20 years, had an Eastern Cooperative Oncology Group performance status (PS) of zero to two, and were expected to survive for at least 2 months. In general, they had not received prior chemotherapy, but those who had completed postoperative adjuvant therapy at least 180 days before enrollment were eligible. They had at least one measurable lesion according to RECIST guidelines [13]. They also had adequate bone marrow function (hemoglobin level ≥ 80 g/l, white blood cell count of 3–12 × 10^9/l, neutrophil count ≥ 1.5 × 10^9/l, and platelet count ≥ 100 × 10^9/l), liver function (total bilirubin ≤ 1.5 × the institutional upper limit of normal, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × the institutional upper limit of normal, and alkaline phosphatase ≤ 2.5 × the institutional upper limit of normal), and renal function (serum creatinine level ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min). All patients provided written informed consent.

This study was carried out in accordance with the Helsinki declaration and Good Clinical Practice guidelines and was approved by the institutional review boards of all participating medical institutions.

treatment plan

Oxaliplatin was administered i.v. at a dose of 100 mg/m^2 on day 1. S-1 was administered orally at a dose of 80 mg/m^2/day b.i.d. for 14 days (from the evening on day 1 until the morning on day 15), followed by a 7-day rest period in the 3-weekly schedule. Treatment was repeated until there was disease progression, unacceptable toxicity, or withdrawal of consent.

In the event of grade 4 neutropenia or febrile neutropenia or grade 3 diarrhea or stomatitis, the doses of oxaliplatin and S-1 were reduced by one dose level from the next cycle. If grade 2 sensory neuropathy not recovering by the end of the cycle or grade 3 sensory neuropathy occurred, the dose of oxaliplatin was reduced by one dose level from the next cycle after recovering to grade 2 or less. If grade 2 thrombocytopenia continued ≥8 days after the scheduled day for starting the next cycle or if platelet transfusion was required, oxaliplatin was reduced by one dose level from the next cycle. Oxaliplatin and S-1 could be reduced by two dose levels, but treatment was discontinued if subsequent reduction was indicated. The doses of oxaliplatin and S-1 could be reduced by 25 mg/m^2 and 10–30 mg/day, respectively, for each level. Treatment was discontinued if grade 4 diarrhea, stomatitis, or sensory neuropathy occurred, if grade 3 sensory neuropathy failed to recover by the time when the next cycle was scheduled, if grade 2 thrombocytopenia continued ≥15 days after the scheduled day for starting the next cycle, or if the rest period of S-1 was over 21 days.

evaluation

The data on the patients' characteristics, a 12-lead electrocardiogram, computed tomography (CT) scans, and tumor marker levels (CA19-9 and carcinoembryonic antigen) were obtained within 14 days of enrollment, while hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out within 7 days before enrollment. During the study, hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out every week until the end of the fourth cycle and subsequently every 3 weeks. CT scans were carried out and tumor markers were measured every 6 weeks (every 2 months after the best overall response was achieved).

Responses were evaluated according to the RECIST guidelines. To confirm partial response (PR) (30% or greater decrease in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions) or complete response (CR) (disappearance of all target and nontarget lesions together with normalization of tumor marker levels), tumor measurements were repeated no <4 weeks after objective response was firstly obtained. Responses were assessed by the independent review committee. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Progression-free survival (PFS) was the time from treatment initiation to first documentation of disease progression detected by the review committee or death from any cause (censored at second-line chemotherapy). Time-to-treatment failure (TTF) was the time from treatment initiation to discontinuation of treatment, first documentation of disease progression by the review committee, or death from any cause. Toxic effects were evaluated according to the Common Terminology Criteria for Adverse Events V3.0.

statistical analysis

The primary end point was the response rate (RR), while the secondary end points were OS, PFS, TTF, and safety. The required sample size was calculated to be at least 49 patients on the null hypothesis of the RR of ≤40% versus the alternative hypothesis of the RR of >60%, power 80%, and α 2.5% (one sided). The 95% confidence interval (CI) was calculated for the RR, PFS, and TTF. OS, PFS, and TTF were calculated by the Kaplan–Meier method. Safety was analyzed in all patients who received at least one dose of study medication.

The cut-off date for RR, PFS, TTF, and safety was 27 May 2008, while that for OS was 13 July 2009.

results

patients' characteristics

Fifty-five patients were enrolled from April to December in 2007. Among them, one patient who received oxaliplatin for the other study by mistake was excluded from all analyses. Three other patients were excluded from efficacy analysis because of prior chemotherapy (methotrexate), severe interstitial pneumonia, or absence of measurable lesions (one patient each). Accordingly, 51 patients formed the efficacy analysis set (Table 1), while 54 patients were analyzed for safety. The median age of the 51 patients was 63 years (range 30–77 years) and the PS was zero or one in 50 patients. Prior adjuvant chemotherapy with S-1 had been carried out in one patient, while 50 patients had received no prior chemotherapy.

treatment

At the data cut-off date, treatment was ongoing in eight patients. The major reasons for discontinuation of treatment in 46 patients were disease progression (63%), adverse events (28%), and withdrawal of consent (2%).

The median number of treatment cycles was 6.0 (range 1–16+). The median dose intensity was 88 mg/m^2/3 weeks for oxaliplatin and 867 mg/m^2/3 weeks for S-1, and the median relative dose intensity was 87.5% and 85.7%, respectively. The median total dose was 600 mg/m^2 for oxaliplatin and 5966 mg/m^2 for S-1.

efficacy

The response was assessed as PR, stable disease (SD) (less than a 30% reduction and less than a 20% increase in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions), and progressive disease (PD) in 30, 13, and 5, respectively, of the 51

Table 1. Patients' profile (n = 51)

Characteristic	No. of patients	%
Median age, years (range)	63 (30–77)	
Sex		
Male	34	67
Female	17	33
ECOG PS		
0	32	63
1	18	35
2	1	2
Disease status		
Advanced	47	92
Recurrent	4	8
Primary tumor		
No	12	24
Yes	39	77
Prior adjuvant chemotherapy		
No	50	98
Yes	1	2
Histology		
Diffuse	35	69
Intestinal	16	31
Sites of metastasis		
Lymph nodes	41	80
Liver	23	45
Lung	9	18
Peritoneum	7	14
Other	9	18
No. of metastases		
1	22	43
≥2	29	57

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Objective response to treatment (n = 51)

Response	No. of patients	% (95% CI)
CR	0	0
PR	30	59
SD	13	26
PD	5	10
Not evaluable	3	6
Overall response rate	30	59 (44.2–72.4)
Disease control rate (CR + PR + SD)	43	84 (71.4–93.0)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients in the efficacy analysis set (three were not assessable). The RR was 59% (95% CI 44.2% to 72.4%) and the disease control rate (CR + PR + SD) was 84% (95% CI 71.4% to 93.0%) (Table 2).

The median follow-up period was 16.5 months as of 13 July 2009. The median survival time (MST) was 16.5 months (95% CI 13.2–22.3 months) (Figure 1), median PFS was 6.5 months (95% CI 4.8–11.2 months) (Figure 2), and median TTF was 4.8 months (95% CI 4.0–5.6 months). The patients who received

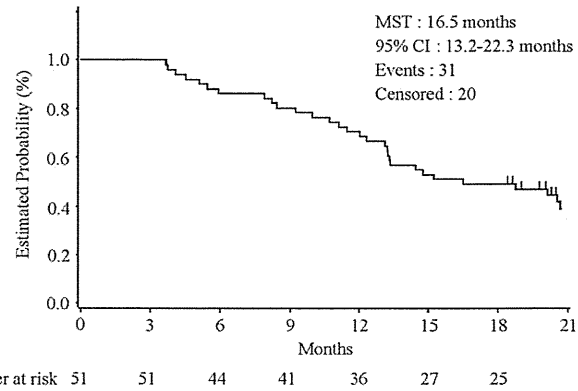

Figure 1. Kaplan–Meier estimates of overall survival (n = 51).

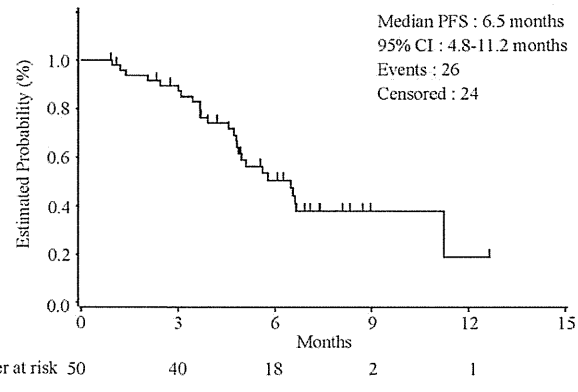

Figure 2. Kaplan–Meier estimates of progression-free survival (n = 50).

the second-line chemotherapy without PD were censored at the date of image examination immediately before the second-line chemotherapy in PFS analysis. The 1-year survival rate was 70.6% (95% CI 58.1% to 83.1%).

Forty-one of the 46 patients (89%) who discontinued treatment received second-line chemotherapy. One patient (2%) with PR underwent surgery and pathological CR was observed.

safety assessment

Grade 3/4 toxicity occurred in 33 of the 54 patients (61%) in the safety analysis set. Grade 3/4 leukopenia, neutropenia, thrombocytopenia, anemia, anorexia, and fatigue were noted in 2 (4%), 12 (22%), 7 (13%), 5 (9%), 3 (6%), and 3 patients (6%), respectively (Table 3). The median onset of thrombocytopenia in all grades was after 42 days and the nadir platelet count was seen at 113 days. The median time from the nadir to grade 0 or platelet count of treatment initiation was 15 days and the duration of thrombocytopenia in all grades was 21 days. Sensory neuropathy was observed in 48 patients (89%), but grade 3/4 neuropathy occurred only in two patients (4%). The median cumulative dose of oxaliplatin associated with sensory neuropathy of any grade was 150 mg/m^2 (grade 1: 150 mg/m^2, grade 2: 900 mg/m^2). There were no treatment-related deaths.

Table 3. Toxicity of therapy ($n = 54$)

Toxicity (CTCAE)	No. of patients (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 3/4
Hematological						
Leukopenia	15 (28)	16 (30)	2 (4)	0	33 (61)	2 (4)
Neutropenia	3 (6)	15 (28)	12 (22)	0	30 (56)	12 (22)
Thrombocytopenia	25 (46)	9 (17)	7 (13)	0	41 (76)	7 (13)
Anemia	14 (26)	14 (26)	4 (7)	1 (2)	33 (61)	5 (9)
Non-hematological						
Nausea	27 (50)	10 (19)	1 (2)	0	38 (70)	1 (2)
Vomiting	15 (28)	4 (7)	0	0	19 (35)	0
Diarrhea	17 (32)	4 (7)	1 (2)	0	22 (41)	1 (2)
Anorexia	21 (39)	16 (30)	2 (4)	1 (2)	40 (74)	3 (6)
Fatigue	24 (44)	14 (26)	2 (4)	1 (2)	41 (76)	3 (6)
Rash	13 (24)	2 (4)	0	0	15 (28)	0
Pigmentation	20 (37)	2 (4)	0	0	22 (41)	0
Hand–foot syndrome	12 (22)	2 (4)	0	0	14 (26)	0
Stomatitis	20 (37)	1 (2)	0	0	21 (39)	0
Increased creatinine	3 (6)	0	0	0	3 (6)	0
Febrile neutropenia	0	0	1 (2)	0	1 (2)	1 (2)
Sensory neuropathy	35 (65)	11 (20)	2 (4)	0	48 (89)	2 (4)

CTCAE, Common Terminology Criteria for Adverse Events V3.0.

discussion

Advanced gastric cancer is usually treated by combination chemotherapy with fluoropyrimidine derivatives and platinum compounds. Several recent large-scale phase III studies have shown that the RR ranges from 25% to 54%, median PFS from 2.9 to 7 months, and MST from 8.6 to 13 months [5, 6, 8, 9, 11, 14]. Unfortunately, these results are not satisfactory. In Japan, S-1 plus cisplatin is considered to be the standard treatment for advanced gastric cancer on the basis of the results of two phase III studies: the JCOG9912 study demonstrated non-inferiority of S-1 to i.v. infusion of 5-FU [14] and the SPIRITS study showed that S-1 plus cisplatin was superior to S-1 alone [11]. In the SPIRITS study, the RR, median PFS, and MST achieved with S-1 plus cisplatin were 54%, 6.0 months, and 13 months, respectively. However, more frequent incidences of grade 3/4 adverse events were reported as compared with S-1-alone group, and the combination regimens with improved safety are expected.

With the present SOX regimen, the RR was 59%, median PFS was 6.5 months, 1-year survival was 70.6%, and MST was 16.5 months, indicating similar efficacy to that of S-1 plus cisplatin. The excellent result of our SOX regimen in MST may be explicable by good PFS and feasible safety profile, which enabled patients to receive the second-line chemotherapy in the high proportion (89%). The efficacy of SOX regimen was also comparable with epirubicin and oxaliplatin plus capecitabine in the REAL-2 study (1-year survival rate of 47% and MST of 11.2 months) [8], which demonstrated that oxaliplatin was as effective as cisplatin combined with epirubicin and 5-FU or capecitabine.

Comparison of safety between the present SOX regimen and S-1 plus cisplatin that were reported previously [11] indicates a lower incidence of grade 3/4 toxicity with SOX regimen than S-1 plus cisplatin for leucopenia (4% versus 11%), neutropenia (22% versus 40%), anemia (9% versus 26%), anorexia (6% versus 30%), and nausea (2% versus 11%). The incidence of grade 3/4 thrombocytopenia was higher with SOX regimen (13% versus 5%). Sensory neuropathy is a characteristic toxicity of oxaliplatin, and 89% of the patients receiving SOX regimen had neuropathy, but only 4% had severe (grade 3/4) neuropathy. These results indicate that SOX regimen is more tolerable and tends to be superior to S-1 plus cisplatin in terms of safety.

Yamada et al. [15] reported that the treatment was discontinued at high frequency (28%) due to prolonged thrombocytopenia when metastatic colorectal cancer patients were treated with S-1 plus 130 mg/m^2 of oxaliplatin. This discontinuation was supposed to be caused by the geniality of dose reduction criteria which allowed the reduction of oxaliplatin only in case of occurrence of grade 3 or more toxicity in terms of thrombocytopenia. The incidence of thrombocytopenia was 93% in all grades and 28% in grade 3/4, resulting in low median relative dose intensity of S-1 74.6% and that of oxaliplatin 82.8%. Zang et al. [16] also reported the study of SOX regimen with 130 mg/m^2 of oxaliplatin in patients with metastatic colorectal cancer. In their study, the treatment was interrupted in cases of grade 2 or higher toxicity until the recovery to grade 0 or 1, and the doses of oxaliplatin and S-1 were reduced after a second occurrence of grade 2 toxicity. As a result, the incidence of thrombocytopenia was 13% in grade 3/4, and the median relative dose intensity of oxaliplatin and S-1 was 82% and 82%, respectively. In this study, we used 100 mg/m^2 dose of oxaliplatin as SOX regimen for advanced gastric cancer to decrease the incidence of thrombocytopenia considering the possible bleeding from the primary tumor and to maintain the dose intensity of S-1, which have been demonstrated to a key drug against advanced gastric cancer as a single agent. In this new regimen, the incidence of

thrombocytopenia was 13% in grade 3/4 without reducing the antitumor activity. The median relative dose intensity of oxaliplatin and S-1 was 87.5% and 85.7%, respectively, indicating that the treatment was carried out as scheduled in most of patients in this study.

In conclusion, SOX regimen with oxaliplatin at a dose of 100 mg/m^2 was effective and well tolerated in patients with advanced gastric cancer. SOX regimen has the potential to replace current regimens such as S-1 plus cisplatin or 5-FU plus cisplatin because of similar efficacy with less toxicity and more convenient treatment. Further investigation of this SOX regimen is expected.

funding

Yakult Honsha Co., Ltd.

acknowledgements

We are grateful to I. Hyodo, Y. Sakata, N. Masuda, and F. Nagamura for their kind advice and to A. Sato, K. Yoshikawa, and K. Miyagawa who carried out the independent review committee. We also thank S. Sugiura and S. Takahashi for their helpful advice. This study has been presented at the Annual Conference of the American Society of Clinical Oncology, Orlando, FL, 2009. This study was registered with Japan Pharmaceutical Information Center Clinical Trials Information (no. 070374).

disclosure

All authors declared no conflicts of interest.

references

1. Murad AM, Santiago FF, Petroianu A et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993; 72: 37–41.
2. Glimelius B, Hoffman K, Haglund U et al. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 1994; 5: 189–190.
3. Pyrhönen 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: 587–591.
4. Waters JS, Norman A, Cunningham D et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 1999; 80: 269–272.
5. Van Cutsem E, Moiseyenko VM, Tjulandin S et al. 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 2006; 24: 4991–4997.
6. Kang YK, Kang WK, Shin DK et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. Ann Oncol 2009; 20: 666–673.
7. Kidani Y, Inagaki K, Tsukagoshi S. Examination of antitumor activities of platinum complexes of 1,2-diaminocyclohexane isomers and their related complexes. Gann 1976; 67: 921–922.
8. Cunningham D, Starling N, Rao S et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358: 36–46.
9. Al-Batran SE, Hartmann JT, Probst S et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008; 26: 1435–1442.
10. Kato T, Shimamoto Y, Uchida J et al. Possible regulation of 5-fluorouracil-induced neuro- and oral toxicities by two biochemical modulators consisting of S-1, a new oral formulation of 5-fluorouracil. Anticancer Res 2001; 21: 1705–1712.
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: 215–221.
12. Ajani JA, Rodriguez W, Bodoky G et al. Multicenter phase III comparison of cisplatin/S-1 (CS) with cisplatin/5-FU (CF) as first-line therapy in patients with advanced gastric cancer (FLAGS). Gastrointestinal Cancers Symposium. 2009 Abstr 8.
13. 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: 205–216.
14. Boku N, Yamamoto S, Shirao K et al. Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG9912). J Clin Oncol *(Meeting Abstracts)* 2007; 25: (Abstr LBA4513).
15. Yamada Y, Tahara M, Miya T et al. Phase I/II study of oxaliplatin with oral S-1 as first-line therapy for patients with metastatic colorectal cancer. Br J Cancer 2008; 98: 1034–1038.
16. Zang DY, Lee BH, Park HC et al. Phase II study with oxaliplatin and S-1 for patients with metastatic colorectal cancer. Ann Oncol 2009; 20: 892–896.

Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study

Narikazu Boku, Seiichiro Yamamoto, Haruhiko Fukuda, Kuniaki Shirao, Toshihiko Doi, Akira Sawaki, Wasaburo Koizumi, Hiroshi Saito, Kensei Yamaguchi, Hiroya Takiuchi, Junichiro Nasu, Atsushi Ohtsu, for the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group

Summary

Background The best chemotherapy regimen for metastatic gastric cancer is uncertain, but promising findings have been reported with irinotecan plus cisplatin and S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate). We aimed to investigate the superiority of irinotecan plus cisplatin and non-inferiority of S-1 compared with fluorouracil, with respect to overall survival, in patients with metastatic gastric cancer.

Methods We undertook a phase 3 open label randomised trial in 34 institutions in Japan. We enrolled patients aged 20–75 years or younger, who had histologically proven gastric adenocarcinoma, and randomly assigned them by minimisation to receive either: a continuous infusion of fluorouracil (800 mg/m² per day, on days 1–5) every 4 weeks (n=234); intravenous irinotecan (70 mg/m², on days 1 and 15) and cisplatin (80 mg/m², on day 1) every 4 weeks (n=236); or oral S-1 (40 mg/m², twice a day, on days 1–28) every 6 weeks (n=234). The primary endpoint was overall survival. Analyses were done by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00142350, and with UMIN-CTR, number C000000062.

Findings All randomised patients were included in the primary analysis. Median overall survival was 10·8 months (IQR 5·7–17·8) for individuals assigned fluorouracil, 12·3 months (8·1–19·5) for those allocated irinotecan plus cisplatin (hazard ratio 0·85 [95% CI 0·70–1·04]; p=0·0552), and 11·4 months (6·4–21·3) for those assigned S-1 (0·83 [0·68–1·01]; p=0·0005 for non-inferiority). Three treatment-related deaths occurred in the irinotecan plus cisplatin group and one was recorded in the S-1 group.

Interpretation S-1 is non-inferior to fluorouracil and, in view of the convenience of an oral administration, could replace intravenous fluorouracil for treatment of unresectable or recurrent gastric cancer, at least in Asia. Irinotecan plus cisplatin is not superior to fluorouracil in this setting.

Funding Ministry of Health, Labour, and Welfare of Japan; Taiho Pharmaceutical; Yakult Honsha.

Lancet Oncol 2009; 10: 1063–69
Published Online October 8, 2009
DOI:10.1016/S1470-2045(09)70259-1

See Reflection and Reaction page 1027

Shizuoka Cancer Centre, Shizuoka, Japan (N Boku MD); Japan Clinical Oncology Group Data Centre, Centre for Cancer Control and Information Services, National Cancer Centre, Tokyo, Japan (S Yamamoto PhD, H Fukuda MD); National Cancer Centre Hospital, Tokyo, Japan (Prof K Shirao MD); National Cancer Centre Hospital East, Chiba, Japan (T Doi MD, A Ohtsu MD); Aichi Cancer Centre Hospital, Aichi, Japan (A Sawaki MD); Kitasato University East Hospital, Kanagawa, Japan (W Koizumi MD); Yamagata Prefectural Central Hospital, Yamagata, Japan (Saito MD); Saitama Cancer Centre, Saitama, Japan (K Yamaguchi MD); Osaka Medical College, Osaka, Japan (H Takiuchi MD); and Shikoku Cancer Centre, Ehime, Japan (J Nasu MD)

Correspondence to:
Dr Narikazu Boku, Division of Gastrointestinal Oncology, Shizuoka Cancer Centre, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777 Japan
n.boku@scchr.jp

Introduction

Gastric cancer is the second leading cause of death from malignant disease worldwide.[1] The prognosis of unresectable or recurrent tumours is dismal: with best supportive care, median survival is about 4 months, and with chemotherapy it is around 8 months.[2–4]

During the early 1990s, several randomised trials for gastric cancer were undertaken of anthracyclines, mitomycin C, fluorouracil, methotrexate, and cisplatin.[5–13] At that time, the standard treatment for this malignant disease had not been established. When planning our current trial, no meta-analysis had been published of chemotherapy for advanced gastric cancer. Data from three phase 3 trials did not show a survival benefit of fluorouracil plus cisplatin over fluorouracil alone.[11–13] We reported previously that fluorouracil plus cisplatin caused more toxic effects and did not extend survival compared with continuous infusion of fluorouracil alone, despite a higher response rate and longer progression-free survival.[13] We concluded that continuous infusion of fluorouracil would be a standard arm in any subsequent phase 3 study.

In the late 1990s, new antitumour agents were developed for gastric cancer. In a phase 2 trial, combination chemotherapy with irinotecan plus cisplatin showed a response rate of 59% and median survival time of 322 days with grade 4 neutropenia (57%) and grade 3 or 4 diarrhoea (20%).[14] These efficacy measures were the best compared with those of other phase 2 trials. Although this regimen showed substantial toxic effects, they were deemed manageable, with dose reduction in some patients.

S-1 is a new oral fluoropyrimidine, consisting of tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate. Data of two phase 2 studies of S-1 alone[15,16] showed a response rate of 45% and 2-year survival of 17%, in association with 5% or lower frequencies of grade 3 or 4 toxic effects. Furthermore, treatment could be administered on an outpatient basis.

With these findings in mind, we planned a three-arm phase 3 study of two pair-comparisons. On behalf of the gastrointestinal oncology study group of Japan Clinical Oncology Group (GIOSG/JCOG), we aimed to investigate

superiority of irinotecan plus cisplatin, and non-inferiority of S-1, compared with continuous infusion of fluorouracil for metastatic gastric cancer.

Methods

Patients

We undertook a three-arm, phase 3, randomised trial in 34 institutions in Japan. We used the following eligibility criteria to screen patients for inclusion: histologically proven gastric adenocarcinoma; unresectable or recurrent disease; adequate self-supported nutritional intake; age-range 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; no history of chemotherapy, radiation therapy, or both (however, adjuvant chemotherapy with an oral fluoropyrimidine other than S-1, not exceeding 1-year duration, completed more than 6 months before entry, was allowed); preserved organ functions; white-blood-cell count of $3{\cdot}0$–$12{\cdot}0\times10^9$/L; number of platelets 100×10^9/L or more; aspartate aminotransferase and alanine aminotransferase concentrations of 99 U/L or less; total bilirubin $25{\cdot}65$ μmol/L or lower; creatinine concentration $132{\cdot}6$ μmol/L or less; and creatinine clearance of 50 mL/min or faster. Having a target lesion or lesions according to response evaluation criteria in solid tumours was not mandatory. We excluded patients with severe peritoneal metastasis such as ileus or sub-ileus, ascites beyond the pelvic cavity, or narrowing of the colon detected by barium enema.

All eligible patients provided written informed consent to participate. The study was approved by the institutional review board of every participating institution. The JCOG data and safety monitoring committee (standing committee) monitored patients' safety, adverse events, and progress of the trial.

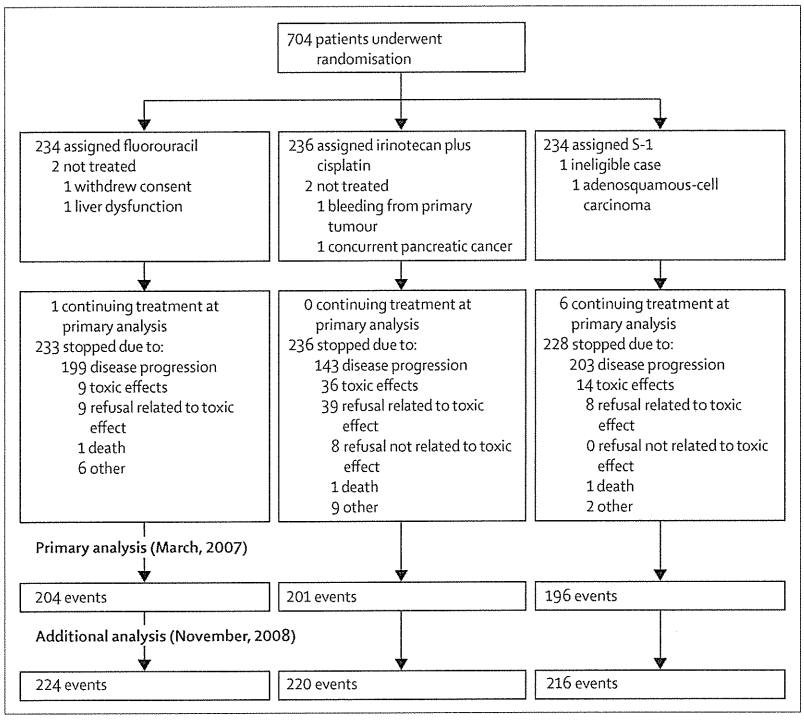

Figure 1: Trial profile

Randomisation and masking

We communicated patient's details to the data centre by fax or telephone. Staff in data centre entered these details into the computer to check eligibility, complete registration if appropriate, and randomly allocate the patient to a treatment group. Staff at the JCOG data centre randomly assigned every patient to either continuous infusion of fluorouracil, irinotecan plus cisplatin, or S-1, using the minimisation method,[17] with an algorithm (concealed to the investigators) that balanced institution, ECOG performance status (0, 1, or 2), and previous treatment (none, curative surgery alone, curative surgery and adjuvant chemotherapy). The treatment allocation was then communicated to the appropriate investigator by fax or telephone. The investigators participating in this trial treated their patients and took care of them all through the clinical course. Because the three treatment methods studied were quite different, the treatment allocation could not be masked from the investigators or patients. All data in case-report forms were sent to the JCOG data centre and checked by central data managers.

Procedures

Patients assigned fluorouracil received 800 mg/m² daily as a continuous infusion for 5 days, repeated every 4 weeks. Those assigned irinotecan plus cisplatin received an infusion of 70 mg/m² irinotecan on days 1 and 15 and 80 mg/m² cisplatin as a drip infusion on day 1 with adequate hydration, repeated every 4 weeks. After six cycles, the same dose of irinotecan alone was continued every 2 weeks. Individuals assigned S-1 received 40 mg/m² twice a day orally for 4 weeks, followed by a 2-week rest.

We delayed every treatment cycle until non-haematological toxic effects had recovered to grade 1 or lower, body temperature was 38°C or less, white-blood-cell count was $3{\cdot}0$–$12{\cdot}0\times10^9$/L, platelets were 100×10^9/L or more, aspartate aminotransferase and alanine aminotransferase concentrations were 99 U/L or less, total bilirubin was $25{\cdot}65$ μmol/L or lower, and creatinine concentration was $132{\cdot}6$ μmol/L or less. We reduced the treatment dose if, during the previous cycle, one of the following events had arisen: grade 4 leucopenia (less than $1{\cdot}0\times10^9$/L); thrombocytopenia (less than $10{\cdot}0\times10^9$/L); haemoglobin (less than 65g/L); grade 3 or higher non-haematological toxic effect; irinotecan not given on day 15; or S-1 or fluorouracil administration was suspended. The dose of cisplatin was reduced if the amount of creatinine was $106{\cdot}1$–$132{\cdot}6$ μmol/L. We discontinued treatment if disease progression was diagnosed clinically or by imaging, if a serious adverse

event arose, if a treatment cycle was delayed due to an adverse event continuing for longer than 2 weeks, if an adverse event meant a subsequent dose reduction was needed after the first reduction, if the patient refused treatment, or if judged necessary by the treating doctor for other reasons.

We did physical examinations and laboratory tests at least once every 2 weeks, and we assessed all adverse events according to the National Cancer Institute's common toxicity criteria (version 2.0). The JCOG data and safety monitoring committee reviewed serious adverse events and judged whether an adverse event was attributable to treatment. We assessed tumour response every 2 months according to RECIST (version 1.0). CT and endoscopic images of responders taken every 2 months independently of the treatment schedule were reviewed centrally at a trial group meeting; reviewers were unaware of treatment allocations at this time. We calculated response rates without interval confirmation.

The primary endpoint was overall survival. Secondary endpoints were time to treatment failure, non-hospitalised survival, adverse events, and response rate in patients with target lesions. We measured overall survival from the date of randomisation to the date of death and censored at the date of last contact for a surviving patient. We calculated progression-free survival to the date disease progression was detected, or death, and censored at the date on which progression-free status was verified. We deemed time to treatment failure to be the date when the doctor decided to discontinue treatment for any reason, and we censored at the date of last contact. We calculated non-hospitalised survival by subtracting the sum of all days in hospital from overall survival.

Statistical analysis

We estimated 6-month and 1-year survival with a continuous infusion of fluorouracil as 50% and 30%. The initial sample size was 450 in total, which allowed detection of a 10% increase in overall survival for irinotecan plus cisplatin and a 5% margin of non-inferiority for S-1, with a study-wide one-sided α level of 0·05 and a power of 70% for each pair comparison. Non-inferiority with a 5% margin corresponds to a hazard ratio of 1·16. We adjusted for multiplicity due to two pair-comparisons with the Bonferroni method, with a one-sided α level of 0·025 for each comparison keeping a study-wide α error of 0·05. We planned an interim analysis when 300 patients had been accrued, using the O'Brien and Fleming type α spending function.

We calculated 1-year survival for all randomised patients when initial accrual was almost complete and it was much higher than anticipated. Therefore, in March, 2005, we recalculated the sample size along with an increase of power from 70% to 80%, and the final sample size was 690. To raise statistical efficiency, we amended the method for adjustment of multiplicity in February, 2007, to that of Holm.[18] According to Holm's method, the pair with the largest difference is compared at first with an α of 0·025 and, if significant, then the other is compared with an α of 0·05. If non-inferiority of S-1 is confirmed, superiority is tested with the same significance level. We planned these amendments in a masked way and they were approved by the data and safety monitoring committee before the primary analysis.

We did the primary analysis in March, 2007, of all randomised patients, based on data up to 1 year after the last patient was enrolled. We analysed overall survival with the stratified log-rank test, and we estimated every hazard ratio (HR) with stratified Cox's proportional-hazards model. We did these stratified analyses with the balancing factors used for randomisation, except for institution. For analyses of progression-free survival, time to treatment failure, and non-hospitalised survival, and for subgroup analyses, we used the log-rank test and estimated the hazard ratio with the Cox model, assuming a common baseline hazard without balancing factors. All subgroup analyses were exploratory and details were not prespecified in the protocol. We revised the protocol to undertake additional analyses of overall survival, progression-free survival, and non-hospitalised survival after 2 years of follow-up, in November, 2008.

	Fluorouracil (n=234)	Irinotecan plus cisplatin (n=236)	S-1 (n=234)
Age (years)	63·5 (57–69)	63 (59–68)	64 (58–69)
Sex (male)	176	180	175
ECOG performance status			
0	152	151	151
1	79*	81	80
2	3	4	3
Surgery			
Unresectable	189	190	188
Recurrent	45	46	46
Previous adjuvant chemotherapy	1	1	1
Macroscopic type†			
0	5	5	5
1, 2	63	73	68
3, 4, 5	164	155	161
Histological type‡			
Intestinal	111	102	110
Diffuse	121	134	124
Target lesions§	175	181	175
Metastatic sites			
0, 1	103	100	102
≥2	131	136	132
Peritoneal metastasis	87	76	69

Data are median (range) or number of patients, with the exception of age (median; IQR). *Includes one patient who underwent random allocation as ECOG performance status 1, but was later found to be 0. This patient was treated as performance status 1 in all analyses. †Japanese classification of gastric carcinoma; no data available for two patients assigned fluorouracil and three assigned irinotecan plus cisplatin. ‡Assessed with Lauren classification; no data available for two patients assigned fluorouracil and for one in the S-1 arm with adenosquamous-type cancer. §Assessed with the RECIST; target lesions larger than double the size of a CT slice.

Table 1: **Baseline characteristics**

We did all analyses by intention to treat using SAS version 9.1. Unless otherwise specified, we present one-sided p values for superiority. This study is registered with ClinicalTrials.gov, number NCT00142350, and UMIN-CTR, number C000000062.

For UMIN-CTR see http://www.umin.ac.jp/ctr

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 13, 2000, and Jan 20, 2006, 704 patients underwent randomisation: 234 were allocated continuous infusion of fluorouracil, 236 irinotecan plus cisplatin, and 234 S-1 (figure 1). Baseline characteristics were well balanced between the three treatment groups (table 1). Nearly all individuals had an ECOG performance status of 0 or 1. Only one patient in every group had received previous adjuvant chemotherapy. About 75% (531/704) of participants had a target lesion or lesions.

Table 2 shows adverse events recorded within 6 months. For patients assigned continuous infusion of fluorouracil, grade 3 or 4 adverse events with frequencies greater than 10% were haemoglobin (<80 g/L) and anorexia. For individuals assigned irinotecan plus cisplatin, grade 3 or 4 leucopenia and neutropenia had the highest frequencies and were associated with febrile neutropenia and infection with neutropenia. Frequencies of grade 3 or 4 adverse events in patients assigned S-1 were similar to those seen with continuous infusion of fluorouracil, except for a higher rate of diarrhoea. Three treatment-related deaths were reported in the group assigned irinotecan plus cisplatin and one in the S-1 group.

	Fluorouracil (n=232)*	Irinotecan plus cisplatin (n=234)*	S-1 (n=234)
Leucocytes (<2·0×10⁹/L)	0	97 (41)	2 (1)
Neutrophils (<1·0×10⁹/L)	3 (1)†	152 (65)	13 (6)
Haemoglobin (<80 g/L)	36 (16)	92 (39)	30 (13)
Febrile neutropenia	0	22 (9)	0
Infection with neutropenia	0	18 (8)	1 (<1)
Infection without neutropenia	9 (4)	9 (4)	13 (6)
Aspartate aminotransferase (≤99 U/L)	11 (5)	6 (3)	11 (5)
Alanine aminotransferase (≤99 U/L)	8 (3)	6 (3)	8 (3)
Bilirubin (≤25·65 μmol/L)	7 (3)	3 (1)	10 (4)
Creatinine (≤132·6 μmol/L)	0	5 (2)	2 (1)
Hyponatraemia	15 (6)‡	53 (23)	12 (5)‡
Fatigue	4 (2)	24 (10)	12 (5)
Anorexia	29 (13)	77 (33)	29 (12)
Diarrhoea	1 (<1)	21 (9)	18 (8)
Nausea	16 (7)	48 (21)	13 (6)
Stomatitis	7 (3)	0	4 (2)
Hand-foot syndrome	0	0	3 (1)
Neuropathy—motor	0	1 (<1)	2 (1)
Neuropathy—sensory	0	1 (<1)	0
Treatment-related death§	0	3 (1)	1 (<1)

Data are number of patients (%). *Two patients were not treated in each group. †Data for one patient not available. ‡Data for two patients not available. §Judged by data and safety monitoring committee.

Table 2: Adverse events (grade 3 or higher) recorded within 6 months

At the time of the primary analysis (March, 2007), 601 (85%) events had been recorded (figure 1). Median overall survival in patients assigned continuous infusion of fluorouracil was 10·8 (IQR 5·7–17·8) months, in individuals allocated irinotecan plus cisplatin it was 12·3 (8·1–19·5) months, and in those assigned S-1 it was 11·4 (6·4–21·3) months. Irinotecan plus cisplatin was not superior to continuous infusion of fluorouracil (HR 0·85 [95% CI 0·70–1·04]; p=0·0552). Non-inferiority of S-1 to a continuous infusion of fluorouracil was confirmed (0·83 [0·68–1·01]; p=0·0005), but S-1 was not superior to fluorouracil (p=0·0336; one-sided α=0·025).

At the time of the additional analysis (November, 2008), the number of events had risen to 660 (94%; figure 1). Actual 2-year overall survival was 14% in patients assigned continuous infusion of fluorouracil, 18% in individuals allocated irinotecan plus cisplatin, and 21% in those assigned S-1 (figure 2). Irinotecan plus cisplatin was not superior to continuous infusion of fluorouracil (HR 0·82 [95% CI 0·68–0·99]; p=0·0194), whereas S-1 was non-inferior to fluorouracil (0·83 [0·68–1·00]; p=0·0002 for non-inferiority, p=0·0233 for superiority). All HR calculated by multivariate analyses with baseline factors were essentially the same as those measured by univariate analyses (data not shown).

The median time to treatment failure was 2·3 (IQR 1·4–5·4) months for patients assigned continuous infusion of fluorouracil, 3·7 (1·9–5·6) months for those allocated irinotecan plus cisplatin (HR 0·85 [95% CI 0·71–1·02]; p=0·0430), and 4·0 (2·0–6·3) months for individuals assigned S-1 (0·73 [0·61–0·88]; p=0·0004). More than 85% of patients who were allocated either continuous infusion of fluorouracil or S-1 discontinued treatment because of disease progression; a third of those allocated irinotecan plus cisplatin stopped because of toxic effects (figure 1). Median non-hospitalised survival was 7·2 (IQR 2·7–13·3) months for individuals assigned continuous infusion of fluorouracil, 9·5 (4·9–15·7) months for those allocated irinotecan plus cisplatin (0·81 [0·67–0·97]; p=0·0115), and 9·3 (4·2–18·0) months for those assigned S-1 (0·77 [0·63–0·92]; p=0·0025).

Second-line chemotherapy was given to 194 (83%) patients assigned continuous infusion of fluorouracil, 183 (78%) allocated irinotecan and cisplatin, and 173 (74%) assigned S-1 (data not available for 31 individuals). Of those assigned continuous infusion of fluorouracil, 70 crossed over to irinotecan plus cisplatin and 20 moved to S-1. Of those allocated irinotecan plus cisplatin,

127 moved to S-1 and seven to continuous infusion of fluorouracil. Finally, of those in the S-1 arm, two patients crossed over to continuous infusion of fluorouracil and 68 moved to irinotecan plus cisplatin.

Median progression-free survival was 2·9 (IQR 1·7–5·7) months for patients assigned continuous infusion of fluorouracil, 4·8 (2·3–8·2) months for those allocated irinotecan plus cisplatin (HR 0·69 [95% CI 0·58–0·83]; p<0·0001), and 4·2 (2·2–7·1) months for individuals assigned S-1 (0·77 [0·64–0·93]; p=0·0027; figure 2). In patients with a target lesion or lesions, response rates were 9% (15/175) for those assigned continuous infusion of fluorouracil, 38% (68/181) for those allocated irinotecan plus cisplatin, and 28% (49/174, data not available for one patient) for individuals assigned S-1. In this subgroup, median progression-free survival was 2·2 (1·4–5·3) months for patients assigned continuous infusion of fluorouracil, 4·8 (2·3–8·1) months for those allocated irinotecan plus cisplatin (0·56 [0·45–0·69]; p<0·0001) and 3·8 (2·0–5·6) months for those assigned S-1 (0·80 [0·65–0·98]; p=0·0174).

Findings of exploratory subgroup analyses of overall survival (figure 3) showed favourable results for S-1 compared with continuous infusion of fluorouracil for all subgroups except recurrent cases. In the subgroup with target lesions, median survival was 9·0 (IQR 5·4–15·2) months for patients assigned continuous infusion of fluorouracil (n=175), 12·1 (8·1–19·0) months for those allocated irinotecan plus cisplatin (n=181; HR 0·73 [0·59–0·91]; p=0·0022), and 10·5 (5·6–19·2) months for those assigned S-1 (n=175; 0·84 [0·68–1·05]; p=0·0590). In the subgroup without target lesions, median survival was 13·5 (7·9–23·4) months for patients assigned continuous infusion of fluorouracil (n=59), 14·4 (9·0–20·7) months for those allocated irinotecan plus cisplatin (n=55; 1·12 [0·76–1·65]; p=0·7219), and 18·1 (10·5–26·6) months for those assigned S-1 (n=59; 0·79 [0·53–1·16]; p=0·1101).

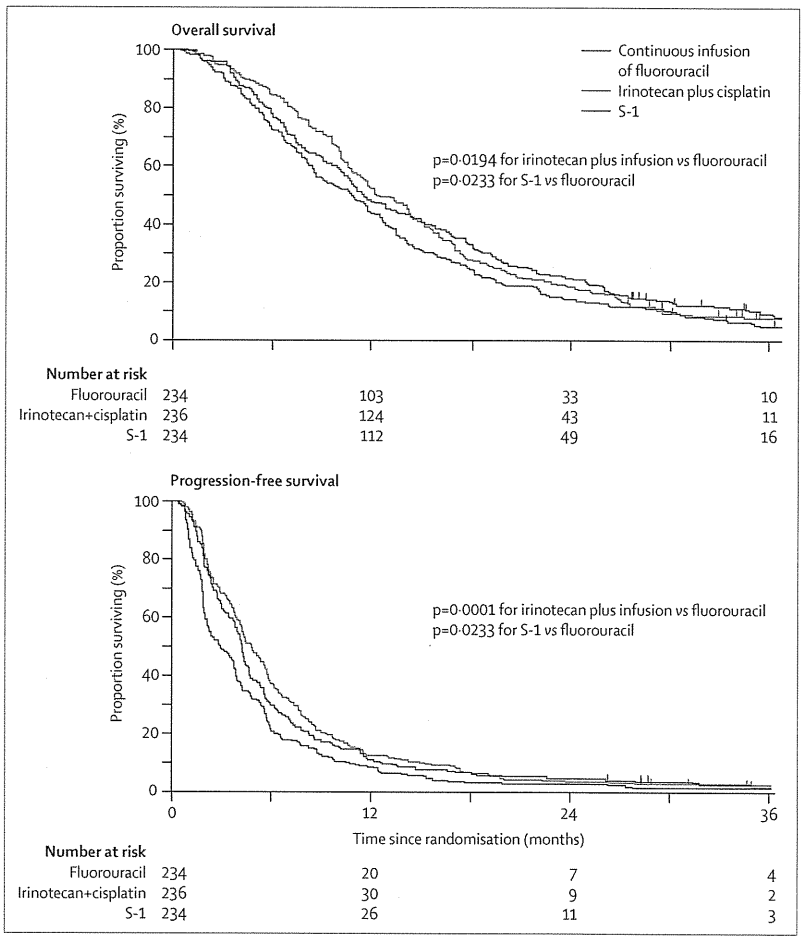

Figure 2: **Survival curves of all randomised patients (November, 2008)**

Discussion

Our findings show that S-1 is non-inferior to continuous infusion of fluorouracil with respect to overall survival. Although S-1 was not superior with respect to overall survival at the primary analysis, patients assigned S-1 had a 7% higher 2-year overall survival rate than those allocated a continuous infusion of fluorouracil. Furthermore, other measures of effectiveness of S-1, such as response rate and progression-free survival, were better than those obtained with continuous infusion of fluorouracil. These findings for S-1 are consistent with those reported in two phase 3 trials containing an S-1 alone arm.[19,20] Drug development for gastric cancer has been focused on replacement of intravenous fluorouracil with oral agents.[21,22] Taken together with our findings, S-1 might have some advantages over continuous infusion of fluorouracil.

Any new treatment, even if non-inferior to standard treatment, should have some benefits, such as for quality of life, cost, or safety. In our study, compared with continuous infusion of fluorouracil, S-1 was associated with almost equivalent safety and longer non-hospitalised survival. Additionally, in Japan, the cost of S-1 (about ¥76 000 per month [about US$834]) is cheaper than that of continuous infusion of fluorouracil (about ¥140 000 per month [US$1537]). In view of the effectiveness, safety, convenience, and cost, continuous infusion of fluorouracil could be replaced by S-1 for first-line chemotherapy of metastatic gastric cancer.

Findings of a meta-analysis of chemotherapy for advanced gastric cancer[23] indicated that survival was slightly better with combination chemotherapy than with a single agent. In the SPIRITS trial,[19] in which S-1 plus cisplatin was compared with S-1 alone for recurrent or unresectable gastric cancer, the combination showed a survival benefit over S-1 alone. In a previous study by us,[13] fluorouracil plus cisplatin could not prolong survival compared with a continuous infusion of fluorouracil, and our findings in this current study suggest that S-1 is non-inferior to continuous infusion of fluorouracil. Therefore, these data support the rationale for S-1 to be a control arm in the SPIRITS trial.[19] Several studies of

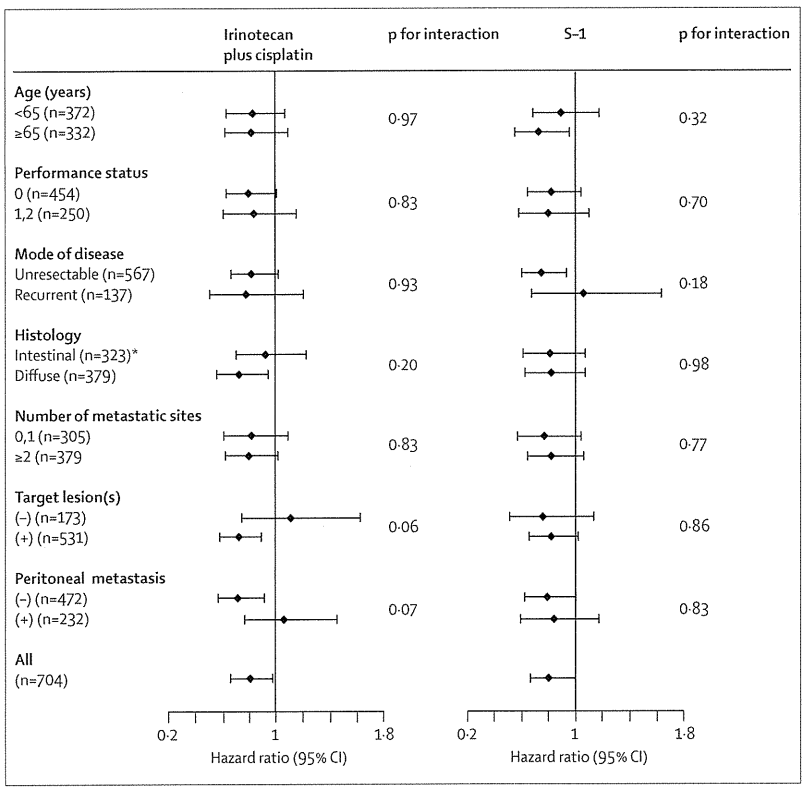

Figure 3: **Forest plot of subgroup analyses**
For every analysis, continuous infusion of fluorouracil is compared with irinotecan plus cisplatin (left) and S-1 (right). *Unknown types were excluded from the analysis.

combination chemotherapy based on S-1 plus cisplatin, including molecular target agents, are ongoing.

Toxic effects of S-1 have been reported to be more severe in individuals from the USA than in Asian patients, resulting in different recommended doses in these populations.[24,25] Since similar discrepancies in toxic effects have been noted with tegafur and uracil,[26] ethnic variations would seem to be a factor with these dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines. In a trial from China,[27] S-1 plus cisplatin was superior to continuous infusion of fluorouracil plus cisplatin. Outside Asia,[28] despite differences in dose and schedule of S-1 from Asian trials, S-1 plus cisplatin was associated with fewer toxic effects, had slightly better survival, and showed non-inferiority compared with fluorouracil plus cisplatin. S-1 plus cisplatin, with an equitoxic dose to fluorouracil plus cisplatin, should be investigated in European and North American populations.

The toxic effects of irinotecan plus cisplatin were the most severe of the three treatment groups in our study, and the rate of treatment failure due to toxic effects was the highest, resulting in a shorter time to treatment failure than that obtained with S-1. In the subgroup with target lesions, of the three treatment groups, irinotecan plus cisplatin showed the best response rate, progression-free survival, survival within 1 year, and overall survival. In North America, divided doses of irinotecan and cisplatin have been investigated,[29] which are associated with a similar response rate to, and fewer toxic effects than, the regimen in our study. Since control of toxic effects of irinotecan plus cisplatin is a big problem, divided doses of irinotecan and cisplatin should be investigated in future phase 3 trials.

Some chemosensitivity-related markers have been suggested to be prognostic factors for irinotecan plus cisplatin treatment.[30] Expression of specific chemosensitivity-related genes is currently being investigated in patients enrolled in our study, and preliminary data suggest that dihydropyrimidine dehydrogenase expression could be a predictive marker for whether irinotecan plus cisplatin or S-1 (plus cisplatin) would be the better treatment in a given patient.[31] We postulate that some populations would benefit from irinotecan plus cisplatin even though chemotherapy regimens containing irinotecan have not shown a survival benefit in phase 3 trials.[20,32] Because clinical behaviour and pathogenesis of gastric cancer are heterogeneous, treatment strategies tailored for optimum chemotherapy according to a patient's clinical and genetic background should be established in the near future, and irinotecan plus cisplatin could then serve as one of the options.

Although median progression-free survival of S-1 and irinotecan plus cisplatin in our study were similar to those reported in other phase 3 trials, median overall survival was somewhat extended.[21,22,32–34] Moreover, median progression-free survival—both in this study and in our previous phase 3 trial[13]—was 2 months for patients who received continuous infusion of fluorouracil. Overall survival of patients with target lesions in this current study was about 2 months longer than that reported by us previously. The proportion of patients who received second-line chemotherapy in our study was more than 70%, which is higher than in our previous study (53%).[13] Since irinotecan and taxanes were approved in the late 1990s in Japan, available active agents for subsequent chemotherapy differed between this current study and our previous study. We postulate that second-line chemotherapy might have contributed to the favourable overall survival in this study, although a survival benefit of second-line chemotherapy has not yet been clarified.

Contributors
NB, HF, and SY wrote the protocol and designed the trial based on discussion with, and agreement from, all authors. All authors (except SY and HF) recruited patients to the study. HF directed the data centre. SY and HF did the statistical analysis. NB wrote the report with revisions from all other authors.

Conflicts of interest
The authors declared no conflicts of interest.

Acknowledgments
We thank A Kimura and N Murata for data management; N Ishizuka, K Yoshimura, and A Kuchiba for statistical analyses; K Nakamura for editorial assistance; and the data and safety monitoring and audit

committees of JCOG. This study was supported mainly by grants-in-aid for cancer research (11S-3, 11S-4, 14S-3, 14S-4, 17S-3, 17S-5) from the Ministry of Health, Labour and Welfare of Japan, and partly by contracts for providing safety data to Taiho Pharmaceutical and Yakult Honsha.

References

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55:** 74–108.

2 Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72:** 37–41.

3 Glimelius B, Hoffman K, Haglund U, Nyrén O, Sjödén PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994; **5:** 189–90.

4 Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus best supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995; **71:** 587–91.

5 Cullinan SA, Moertel CG, Fleming TR, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil versus fluorouracil and doxorubicin versus fluorouracil, doxorubicin, and mitomycin. *JAMA* 1985; **253:** 2061–67.

6 Wils JA, Klein HO, Wagener DJ, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin: a step ahead in the treatment of advanced gastric cancer—a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991; **9:** 827–31.

7 Kelsen D, Atiq OT, Saltz L, et al. FAMTX versus etoposide, doxorubicin and cisplatin: a randomized trial in gastric cancer. *J Clin Oncol* 1992; **10:** 541–48.

8 Cocconi G, Bella M, Zironi S, et al. Fluorouracil, doxorubicin, and mitomycin combination versus PELF chemotherapy in advanced gastric cancer: a prospective randomized trial of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1994; **12:** 2687–93.

9 Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; **15:** 261–67.

10 Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000; **18:** 2648–57.

11 Kim NK, Park YS, Heo DS, et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer* 1993; **71:** 3813–18.

12 Cullinan SA, Moertel CG, Wieand HS, et al. Controlled evaluation of three drug combination regimen versus fluorouracil alone in the therapy of advanced gastric cancer. *J Clin Oncol* 1994; **12:** 412–16.

13 Ohtsu A, Shimada Y, Shirao K, 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:** 54–59.

14 Boku N, Ohtsu A, Shimada Y, et al. A phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. *J Clin Oncol* 1999; **17:** 319–23.

15 Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine aniticancer drug S-1 (1M tegafur-0.4M gimestat-1M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34:** 1715–20.

16 Koizumi W, Kurihara M, Nakano S, Hasegawa K Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. *Oncology* 2000; **58:** 191–97.

17 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.

18 Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979; **6:** 65–70.

19 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:** 215–21.

20 Imamura H, Ilishi H, Tsuburaya A, et al. Randomized phase III study of irinotecan plus S-1 (IRIS) versus S-1 alone as first-line treatment for advanced gastric cancer (GC0301/TOP-002). 2008 Gastrointestinal Cancers Symposium; Orlando, FL, USA; Jan 25–27, 2008. Abstract 5.

21 Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009; **20:** 666–73.

22 Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358:** 36–46.

23 Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24:** 2903–09.

24 Hoff PM, Saad ED, Ajani JA, et al. Phase I study with pharmacokinetics of S-1 on an oral daily schedule for 28 days in patients with solid tumors. *Clin Cancer Res* 2003; **9:** 134–42.

25 Ajani JA, Faust J, Ikeda K, et al. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. *J Clin Oncol* 2005; **23:** 6957–65.

26 Shirao K, Hoff PM, Ohtsu A, et al. Comparison of the efficacy, toxicity, and pharmacokinetics of a uracil/tegafur (UFT) plus oral leucovorin (LV) regimen between Japanese and American patients with advanced colorectal cancer: joint United States and Japan study of UFT/LV. *J Clin Oncol* 2004; **22:** 3466–74.

27 Jin M, Lu H, Li J, et al. Ramdomized 3-armed phase III study of S-1 monotherapy versus S-1/CDDP (SP) versus 5-FU/CDDP (FP) in patients (pts) with advanced gastric cancer (AGC): SC-101 study. 2008 ASCO annual meeting; Chicago, IL, USA; May 30–June 3, 2008. Abstract 4533.

28 Ajani JA, Rodriquez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 (CS) with cisplatin/5-FU (CF) as first-line therapy in patients with advanced gastric cancer (FLAGS): secondary and subset analyses. 2009 ASCO annual meeting; Orlando, FL, USA; May 29–June 2, 2009. Abstract 4511.

29 Ajani JA, Baker J, Pisters PW, 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:** 641–46.

30 Nagashima F, Boku N, Ohtsu A, et al. Biological markers as a predictor for response and prognosis of unresectable gastric cancer patients treated with irinotecan and cisplatin. *Jpn J Clin Oncol* 2005; **35:** 714–19.

31 Yamada Y, Yamamoto S, Ohtsu A, et al. Impact of dihydropyrimidine dehydrogenase status of biopsy specimens on efficacy of irinotecan plus cisplatin, S-1, or 5-FU as first-line treatment of advanced gastric cancer patients in JCOG9912. 2009 ASCO annual meeting; Orlando, FL, USA; May 29–June 2, 2009. Abstract 4535.

32 Dank M, Zaluski J, Barone 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:** 1450–57.

33 Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. 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* 2006; **24:** 4991–97.

34 Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26:** 1435–42.

Gastric Cancer (2009) 12: 206–211
DOI 10.1007/s10120-009-0524-9

Original article

Weekly paclitaxel for heavily treated advanced or recurrent gastric cancer refractory to fluorouracil, irinotecan, and cisplatin

Rai Shimoyama[1,2], Hirofumi Yasui[1], Narikazu Boku[1], Yusuke Onozawa[1], Shuichi Hironaka[1], Akira Fukutomi[1], Kentaro Yamazaki[1], Keisei Taku[1], Takashi Kojima[1], Nozomu Machida[1], Akiko Todaka[1], Hideharu Tomita[1], Takeshi Sakamoto[1], and Takahiro Tsushima[1]

[1] Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Shizuoka 411-8777, Japan
[2] Department of General Surgery, Shonankamakura General Hospital, Kanagawa, Japan

Abstract

Background. **Although triweekly administration of paclitaxel is approved for gastric cancer in Japan, currently, the drug is often delivered with a weekly schedule because of the equivalent efficacy and lesser toxicity of this dosing schedule as compared with the triweekly administration schedule. Weekly administration of paclitaxel as second-line or first-line chemotherapy for gastric cancer has been reported to yield a response rate of about 20%. Because there has been no report of the efficacy of weekly paclitaxel in the third-line setting, this retrospective study investigated the efficacy and toxicities of weekly paclitaxel used in the third-line setting for the treatment of gastric cancer refractory to all three key drugs, fluorouracil, irinotecan, and cisplatin, used in clinical practice.**

Methods. **In 85 patients with advanced or recurrent histologically confirmed gastric adenocarcinoma who had failed to respond to prior chemotherapy regimens containing fluorouracil, irinotecan, and cisplatin, paclitaxel (80 mg/m^2) was administered weekly, three times, for 3 weeks out of 4.**

Results. **The median number of courses was 3 (range, 1–38). The overall response rate was 23.2% (19/82) in the patients with measurable lesions, and ascites disappeared in 15 of 48 patients (31.3%). Progression-free survival was 105 days and the median survival time was 201 days from the initiation of paclitaxel administration. Grade 3 or 4 leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 25 (29%), 25 (29%), 37 (44%), and 3 (4%) patients. Other, nonhematological, toxicities were nausea, vomiting, anorexia, sensory neuropathy, fatigue, and febrile neutropenia.**

Conclusion. **Weekly paclitaxel administration shows activity against advanced gastric cancer also in the third-line setting.**

Key words Metastatic gastric cancer · Weekly paclitaxel · Third-line chemotherapy

Offprint requests to: H. Yasui
Received: July 9, 2009 / Accepted: September 2, 2009

Introduction

Gastric cancer remains the second leading cause of cancer death worldwide, with more than 700000 deaths per year [1]. In Japan, although markedly improved survival has been achieved, its mortality each year remains at approximately 50000, resulting in gastric cancer being the second-leading cause of cancer death in 2007 [2].

For patients with unresectable or recurrent gastric cancer, the main therapeutic option is palliative chemotherapy. Clinical trials of systemic chemotherapy for gastric cancer have shown significantly prolonged survival with the chemotherapy as compared to best supportive care [3–5]. Recently, two phase III studies have been reported from Japan. One was the Japan Clinical Oncology Group (JCOG) 9912 trial, which revealed the noninferiority of S-1 (a combined preparation of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate) alone to 5-fluorouracil (FU) alone and failed to demonstrate the superiority of irinotecan plus cisplatin (CDDP) to 5-FU alone in terms of the overall survival [6]. This trial concluded that 5-FU could be replaced by S-1 in the chemotherapy for advanced gastric cancer. The other study was the S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer (SPIRITS) trial, which showed the superiority of S-1 plus CDDP to S-1 alone in terms of the overall survival [7]. Based on these trials, S-1 plus CDDP has been recognized as the standard first-line therapy for unresectable and recurrent gastric cancer in Japan.

No standard chemotherapy regimen has been established for use after the failure of first-line chemotherapy. For patients with failure in S-1+CDDP therapy, irinotecan and paclitaxel are considered as the key drugs for the subsequent chemotherapy. In clinical practice, two treatment strategies have generally been adopted after the failure of first-line chemotherapy; irinotecan or irinotecan combination chemotherapy as the

second-line treatment followed by paclitaxel or paclitaxel combination chemotherapy as the third-line treatment, or vice versa.

A phase II study of paclitaxel for chemotherapy-naive patients with gastric cancer showed a response rate (RR) of 23% and median survival time (MST) of 340 days, and this result led to the approval of paclitaxel for treating gastric cancer in Japan [8–11]. Paclitaxel may be administered by two methods, in a triweekly schedule and in a weekly schedule (3 weeks on and 1 week off). Studies of paclitaxel for ovarian, breast, and lung cancer treatment showed milder toxicities and equivalent activity of the drug when administered in the weekly schedule as compared with the triweekly schedule [12–16]. In Japan, weekly administration of paclitaxel for gastric cancer after the failure of first-line chemotherapy is very common, and a few trials have reported on the efficacy of weekly paclitaxel in patients with advanced or recurrent gastric cancer, especially in the second-line setting [17–23]. However, no clinical trials have investigated the effect of weekly paclitaxel in the third-line setting.

At our hospital, irinotecan was preferred for the second-line setting (unless the patient had a contraindication for the use of irinotecan (such as intestinal obstruction due to peritoneal dissemination) and subsequently weekly paclitaxel was selected for the third-line setting. In the present retrospective study, we investigated the efficacy and safety of weekly paclitaxel as third-line chemotherapy in patients with gastric cancer who were refractory to all the three key drugs, fluorouracil, CDDP, and irinotecan used in earlier settings.

Patients and methods

Subjects

In total, 119 patients with advanced or recurrent gastric cancer were treated with weekly paclitaxel in the third-line setting between September 2002 and September 2008 at the Shizuoka Cancer Center, Shizuoka, Japan. Among them, the subjects of this retrospective study were 85 patients who were selected according to the following criteria: (1) histologically confirmed adenocarcinoma of the stomach; (2) failure of prior chemotherapy with at least two regimens, including 5-FU or its derivatives (S-1, capecitabine, tegafur/uracil [UFT]), irinotecan, and CDDP; (3) no history of prior chemotherapy with paclitaxel or docetaxel; (4) age 75 years or less; (5) performance status of 2 or less on the Eastern Cooperative Oncology Group scale; (6) adequate bone marrow, hepatic, and renal functions; (7) no synchronous double cancer or other serious disease; and (8) availability of informed consent before the start of treatment. The reasons that the remaining 34 patients were excluded from this study were: age in 3 patients, performance status in 3, double cancer in 3, nonadenocarcinoma in 3, prior history of docetaxel in 2, history of local chemotherapy (CDDP intraperitoneal therapy) in 6, and unknown details in 14.

Treatment

Paclitaxel at 80 mg/m^2 in 250 ml normal saline was administered by intravenous infusion over 1 h, and this was repeated weekly for 3 weeks out of 4, on an outpatient basis as a rule. Short-term premedication was used to prevent paclitaxel-associated hypersensitivity reactions; dexamethasone 8 mg, diphenhydramine 50 mg, ranitidine 50 mg, and granisetron 3 mg were administered 30 min before the infusion of paclitaxel. Treatment was repeated until disease progression, the occurrence of unacceptable toxicities, or the patient's refusal. In the event of serious hematological toxicity, treatment was suspended until recovery.

Although weekly administration of paclitaxel has not been approved in Japan, this schedule is widely used in clinical practice as a community standard. The clinical practice review committee in this hospital reviewed and approved this regimen for gastric cancer, and informed consent to receive this treatment was obtained from each patient.

Response and toxicity evaluation

Response was assessed every 2 months by computed tomography (CT). Objective responses in measurable metastatic lesions were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [25]. Survival time was calculated from the date of initiation of paclitaxel to the date of death or last confirmation of survival. The efficacy for treating ascites was evaluated by the criteria of the *Japanese classification of gastric carcinoma* (13th edition). Symptomatic toxicity and laboratory data were monitored every week at the outpatient clinic. Toxicity was evaluated according to the Common Toxicity Criteria for Adverse Events, version 3.0 (CTCAE 3.0) [25].

Results

Patients' backgrounds

The patients' characteristics are shown in Table 1. Of the 85 patients, 63 (74%) were male. The median age was 61 years (range, 21–75 years). Sixty-nine patients (81%) showed a performance status of 0 or 1. Forty-one patients (48%) had primary lesions, 13 had pleural effu-

Table 1. Patient characteristics ($n = 85$)

	Number	%
Age (years)		
Median (range)	61 (21–75)	
Sex		
Male	63	74
Female	22	26
Performance status (ECOG)		
0	26	31
1	43	51
2	16	18
Histology		
Differentiated	35	41
Undifferentiated	47	55
Unknown	3	4
Primary lesion		
(+)	41	48
(−)	44	52
Metastatic sites		
Lymph node	49	58
Peritoneum	41	48
Liver	34	40
Ovary	12	14
Lung	11	13
Bone	5	6
Number of metastatic sites		
One	35	41
Two	29	34
Three or more	21	25
Pleural effusion	13	15
Ascites	48	56
Prior chemotherapy		
First-line regimen ($n = 85$)		
Oral fluoropyrimidine	57	67
5-FU (i.v.)	14	16
CPT-11	14	16
Second-line regimen ($n = 85$)		
Oral fluoropyrimidine	16	19
5-FU (i.v.)	3	4
CPT-11	66	77
Third-line regimen ($n = 5$)		
CPT-11	4	80
Other	1	20
Number of prior regimens		
One	80	94
Three	5	6
Subsequent chemotherapy after paclitaxel		
None (best supportive care)	38	45
One regimen	36	42
Two regimens	7	8
Three regimens or more	4	5

ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; CPT-11, irinotecan

sion, and 48 had ascites. The number of sites affected by metastasis, including lymph node, peritoneum, liver, ovary, lung and bone, was one in 35 patients, two in 29 patients, and three or more in 21 patients. All patients had received prior chemotherapies with regimens containing fluorouracil or its derivatives, irinotecan, and CDDP.

Table 2. Toxicity ($n = 85$)

	Grade				
	1	2	3	4	3/4 (%)
Hematological					
Leukopenia	21	17	23	2	29
Neutropenia	4	14	19	6	29
Anemia	13	36	23	12	41
Thrombocytopenia	9	6	1	2	4
Nonhematological					
Nausea	10	2	2	0	2
Vomiting	5	7	2	0	2
Diarrhea	12	2	0	0	0
Anorexia	16	11	2	0	2
Mucositis	6	0	0	0	0
Sensory neuropathy	33	9	1	0	1
Motor neuropathy	1	3	2	0	2
Edema	7	0	0	0	0
Allergic reaction	1	0	0	0	0
Fatigue	19	10	2	0	2
Febrile neutropenia	—	—	7	0	8

Dose intensity

The total number of paclitaxel infusions was 870. The median number of courses per patient was 3 (range, 1–38). The dose intensity was calculated as 51.4 mg/m^2 per week, which corresponded to 86% of the planned dose. The dose was reduced in 9 patients; because of myelosuppression in 6, hepatic and renal dysfunction in 1, mucositis in 1, and poor general condition in 1. The treatment was discontinued in all patients: due to disease progression in 79 patients, development of neutropenia in 4, development of neuropathy in 1, and comorbidity (cerebral infarction) in 1 patient.

Toxicity

The hematological and nonhematological toxicities encountered are shown in Table 2. Hematological toxicities were common, and 25 (29%) patients experienced grade 3 or 4 leukopenia and neutropenia. Seven (8%) patients developed febrile neutropenia. Anemia was the most common adverse event, because 82 of the 85 (96%) patients had had anemia before the initiation of paclitaxel, including 18 patients with grade 3 or 4 anemia. Thirty five patients (41%) experienced grade 3 or 4 anemia, with an incidence of grade 3 or 4 thrombocytopenia of only 4%. As nonhematological toxicities, 2 patients (2%) experienced grade 3 nausea/vomiting and anorexia. Grade 3 sensory neuropathy was observed in 1 patient (1%) and motor neuropathy occurred in 2 patients (2%). No severe allergic reactions were reported. One patient (1%) died within 30 days of the last administration of paclitaxel after disease progression was confirmed.

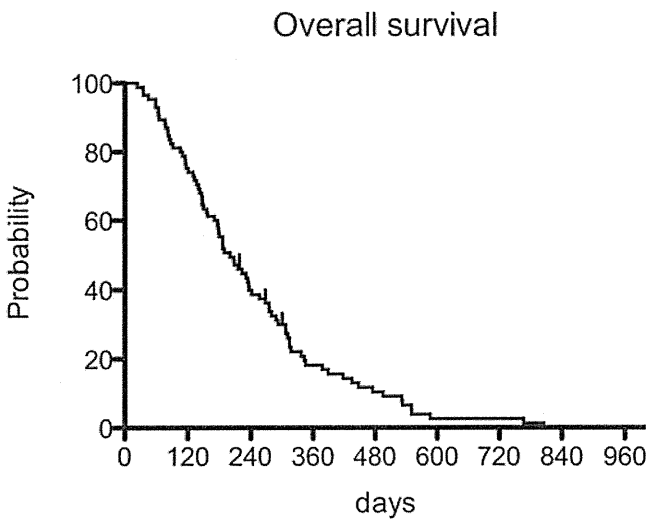

Fig. 1. Overall survival

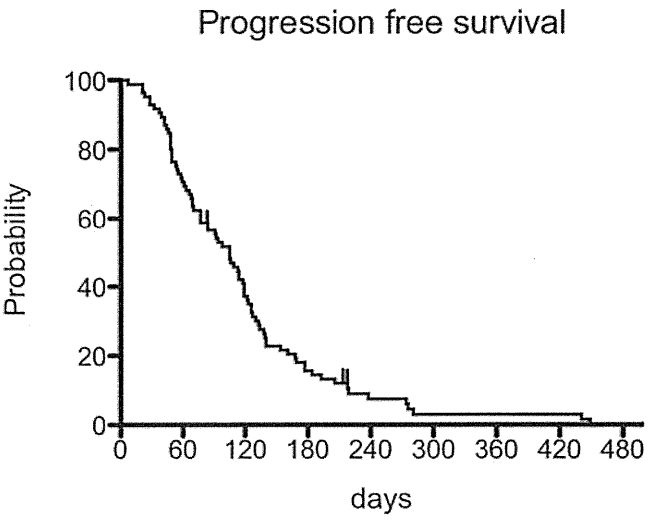

Fig. 2. Progression-free survival

Table 3. Response to weekly paclitaxel (n = 82)

Response	Number of patients	%
CR	0	
PR	19	23.2
SD	35	42.7
PD	27	32.9
NE	1	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

Responses and survival

Eighty-two of the 85 patients were assessable for response, and the remaining 3 patients did not have measurable disease. Nineteen of the 82 patients (23%) showed a partial response, yielding a response rate of 23.2% (Table 3) and a disease control rate (partial response + stable disease) of 65.9%. Ascites disappeared in 7 patients and decreased in size in 8 (31.3%) of the 48 patients who had been noted to have ascites before the start of treatment. The median follow-up period was 561 days when the survival data were updated in March 2009. The median survival time was 201 days after the initiation of paclitaxel administration (Fig. 1). The median progression-free survival (PFS) was 105 days (Fig. 2). After the failure of paclitaxel, 38 patients (45%) received no further chemotherapy or showed disease progression, 36 received one regimen of subsequent chemotherapy, 7 received two regimens, and 4 received three or more regimens.

Discussion

This retrospective study investigated the efficacy and tolerability of weekly paclitaxel in patients with heavily treated advanced gastric cancer. Weekly paclitaxel is one of the most commonly used regimens in the second-line or later setting for gastric cancer in Japan. Five reports of weekly paclitaxel for gastric cancer have revealed similar response rates, of about 15.9%-33.3%, and similar median survival times, of 5.0–7.8 months, despite the differences in the patient background characteristics in each of the studies. The present study, in which all the patients had received two or more treatment regimens containing 5-FU, irinotecan, and cisplatin, showed a response rate of 23% and median survival time of 6.7 months. These results seem to be similar to those of previous studies in the first- or second-line setting. Thus, it is speculated that paclitaxel may show consistent efficacy, irrespective of the previous chemotherapy.

Peritoneal dissemination is a major and serious complication of advanced gastric cancer, often resulting in the development of ascites, intestinal obstruction, and hydronephrosis, especially after failure of chemotherapy. Most patients with peritoneal dissemination or malignant ascites are usually excluded from clinical trials because of the lack of a measureable lesion or their poor general medical condition; hence, the efficacy of chemotherapy for peritoneal dissemination has not yet been confirmed. It has been reported that paclitaxel reaches an effective concentration for the treatment of ascites (8.5 ng/ml) when administered by a weekly schedule [26–29]. In line with several reports of the efficacy of paclitaxel for malignant ascites, showing consistent efficacy [26–28], the present study showed a proportion of patients with decrease or remission of ascites (31.3%) similar to that shown in previous studies [19, 21]. These results may lend support to the notion that paclitaxel still remains effective against malignant ascites in the third-line setting, while irinotecan cannot

be used for patients with severe peritoneal dissemination for fear of severe toxicities.

The greatest concern in third-line chemotherapy for cancer is drug toxicity. The incidences of grade 3 or 4 leukopenia, neutropenia, and anemia in the present study were 29%, 29%, and 44%, with 8% developing febrile neutropenia. These percentages appear to be rather high as compared to those reported previously [19], while the incidence of severe nonhematological toxicities of 2% or less appeared to be consistent with that in previous studies. Especially, anemia was the most frequently encountered severe toxicity in the present study. All of the subjects in this study had been heavily treated before, and chronic anemia due to bleeding from the primary lesion may have occurred in some of the 41 patients (48%) with primary lesions. Indeed, 82 of the 85 (96%) patients were found to have grade 1 or more severe anemia and 18 (22%) had grade 3 or 4 anemia immediately before the start of treatment. Yamada et al. [11] reported an incidence of grade1 or 2 peripheral neuropathy of 73% (44/60) with triweekly paclitaxel therapy. In our present study, the incidence of grade 3 peripheral neuropathy was as low as 4%, and that of grade 1 or 2 was 54%. Short duration of treatment and administration by a weekly schedule may explain the low incidence of neurotoxicity in this study. It is considered that the use of weekly paclitaxel in the third-line setting may be feasible, but it requires careful management of any hematological toxicities.

In conclusion, weekly paclitaxel administration seems to be feasible and show activity for advanced gastric cancer also in the third-line setting. Although careful management of hematological toxicities is required, this therapy can be applied even for patients with severe peritoneal dissemination. Weekly paclitaxel therapy in the third-line setting may be one of the feasible therapeutic strategies for metastatic and recurrent gastric cancer.

References

1. Parki DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
2. Statistics and Information Department, Ministry of Health, Labour and Welfare. Vital statistics in 2007 (in Japanese). http://www.mhlw.go.jp/. Accessed 30 April 2009.
3. Pyrhoenen S, Kuitunen T, Nyandoto P, Kouri M. Randomized 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.
4. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993;72:37–41.
5. Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoeden PO Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 1994;5:189–90.
6. Boku N, Yamamoto S, Shirao K, Doi T, Sawaki A, Koizumi W, et al. Gastrointestinal Oncology Study Group/Japan Clinical Oncology Group. Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG 9912). J Clin Oncol 2007;25(18S):LBA4513.
7. Koizumi W, Narahara H, Hara T, Takagane T, Takagi M, Miyashita K, 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.
8. Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of Taxol in patients with advanced gastric carcinoma. Cancer J Sci Am 1998;4:269–74.
9. Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordano P, Menichetti ET, et al. Phase II study of paclitaxel in pretreated advanced gastric cancer. Anticancer Drugs 1998;9:307–10.
10. Ohtsu A, Boku N Tamura F, Muro K, Shimada Y, Saigenji K, et al. An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. Am J Clin Oncol 1998;21:416–9.
11. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, et al. Phase II trial of paclitaxel by 3-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 2001;12:1133–7.
12. Glantz MJ, Choy H, Akerley W, Kearns CM, Egorin MJ, Rhodes CH, et al. Weekly paclitaxel with and without concurrent radiation therapy: toxicity, pharmacokinetics, and response: Semin Oncol 1996;23(6 Suppl 16):128–35.
13. Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997;15:187–92.
14. Rosenberg P, Anderson H, Boman K, Ridderheim M, Sorbe B, Puistola U, et al: Randomized trial of single agent paclitaxel given weekly versus every 3 weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. Acta Oncol 2002;41:418–24.
15. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B Protocol 9840. J Clin Oncol 2008;26:1642–49.
16. Akerley W, Glantz M, Choy H, Rege V, Sambandam S, Joseph P, et al. Phase I trial of weekly paclitaxel in advanced lung cancer. J Clin Oncol 1998;16:153–8.
17. Cho H, Shotsu A, Konishi K, Kanari M, Tsuburaya A, Kobayasi O, et al. Weekly paclitaxel for the second-line treatment of recurrent and advanced gastric cancer (RAGC). Proc Am Soc Clin Oncol 2002;21 (abstract 2365).
18. Arai T, Hamaguchi T, Shirao K, Yamada Y, Muro K, Matsumura Y, et al. Weekly paclitaxel in patients with heavily treated advanced gastric cancer. Proc Am Soc Clin Oncol 2003;22 (abstract 1291).
19. Arai T, Hamaguchi T, Shirao K, Shimada Y, Yamada Y, Muro K, et al. Weekly paclitaxel (PTX) in patients with heavily treated advanced gastric cancer (AGC). Jpn J Cancer Clin 2003;49: 621–5.
20. Emi Y, Kakeji Y, Baba H, Ishida T, Maehara Y. Weekly paclitaxel therapy as second-line therapy for advanced, recurrent stomach cancer. Jpn J Cancer Clin 2004;50:277–81.
21. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshimo T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9:14–8.
22. 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 (CCOG 0302 study). Anticancer Res 2007;27:2667–72.

23. Emi Y, Yamamoto M, Takahashi I, Orita H, Kakeji Y, Kohnoe S, et al. Phase II study of weekly paclitaxel by 1-hour infusion for advanced gastric cancer. Surg Today 2008;38:1013–20.
24. Japanese translation of common terminology criteria for adverse events (CTCAE), and instructions and guidelines. Int J Clin Oncol 2004;9(Suppl 3):1–82.
25. Gehan EA, Tefft MC. Will there be resistance to the RECIST (response evaluation criteria in solid tumors)? J Natl Cancer Inst 2000;92:179–81.
26. Kobayashi M, Sakamoto J, Namikawa T, Okamoto K, Okabayashi T, Ichikawa K, et al. Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. World J Gastroenterol 2006;12:1412–5
27. Ishida T, Shimokawa H, Kawaguchi K, Nose N, Ikegami T, Itoh H, et al. Effective weekly paclitaxel administration for gastric cancer with malignant ascites: a case report (in Japanese). Jpn J Cancer Chemother (Gan To Kagaku Ryoho) 2002;29:1643–46.
28. Hikino H, Yamada T, Hata T, Nakamura K, Sugimoto S, Kanazawa A, et al. Efficacy of weekly administration of paclitaxel for advanced or recurrent gastric cancer with peritoneal dissemination. Jpn J Cancer Chemother 2004;31:759–61.
29. Kojima T, Matsui T, Uemura T, Fujimitsu Y, Kato J, Kojima H. A case of advanced gastric cancer treated with weekly paclitaxel with measurement of concentrations in blood and ascites. Jpn J Cancer Chemother 2003;30:1529–31.