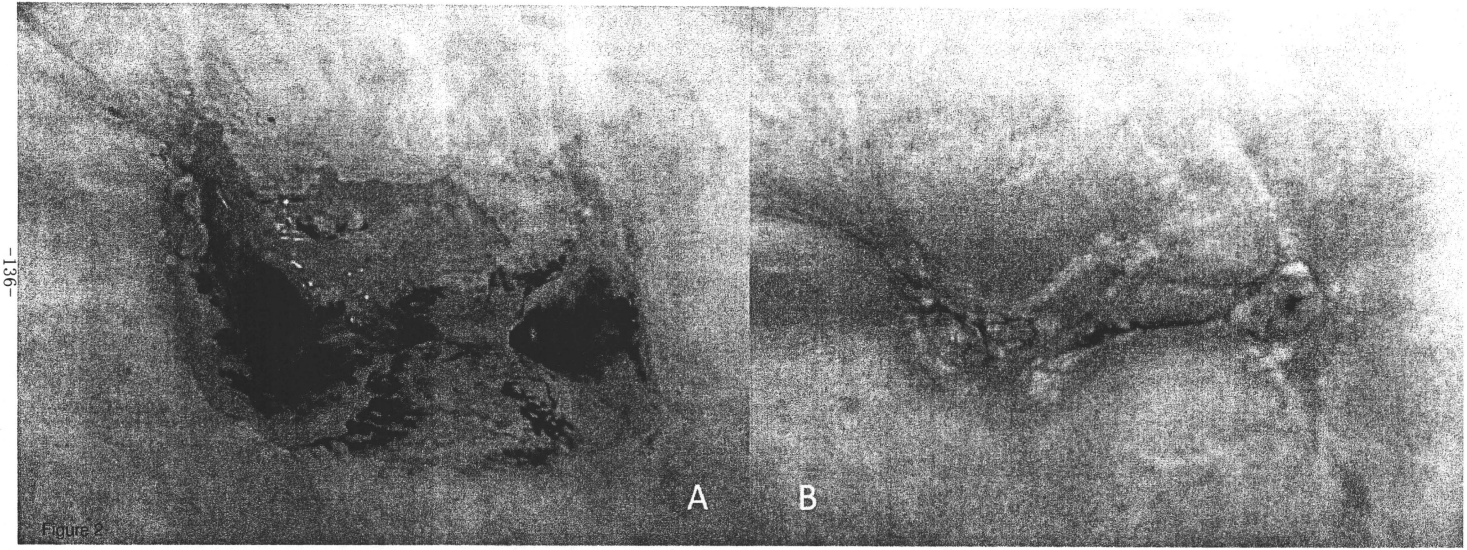

Figure 2

Cancer Chemother Pharmacol
DOI 10.1007/s00280-010-1432-8

ORIGINAL ARTICLE

Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer

D. Takahari · T. Hamaguchi · K. Yoshimura · H. Katai · S. Ito · N. Fuse · T. Kinoshita · H. Yasui · M. Terashima · M. Goto · N. Tanigawa · K. Shirao · T. Sano · M. Sasako

Received: 25 April 2010 / Accepted: 13 August 2010

Abstract
Purpose To evaluate the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III gastric cancer after curative resection.
Methods Japanese patients with stage III gastric cancer who underwent gastrectomy with D2 lymph node resection were enrolled. Treatment consisted of 3 cycles of S-1 (80 mg/m^2/day, b.i.d.) for 21 days followed by a 14-day rest, and cisplatin (60 mg/m^2 iv) on day 8. After that, S-1 monotherapy was given on days 1–28 every 6 weeks until 1-year postsurgery. After protocol amendment, the first chemotherapy cycle consisted of S-1 monotherapy; cisplatin was added to cycles 2, 3, and 4, followed by S-1 monotherapy up to 1-year postsurgery. The primary endpoint was the completion rate of three cycles of S-1 plus cisplatin.

D. Takahari (✉)
Department of Clinical Oncology,
Aichi Cancer Center Hospital, 1-1 Kanokoden,
Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: dtakahari@aichi-cc.jp

T. Hamaguchi
Gastrointestinal Oncology Division,
National Cancer Center Hospital, Tokyo, Japan

K. Yoshimura
Translational Research Center,
Graduate School of Medicine Kyoto University,
Kyoto, Japan

H. Katai
Gastric Surgery Division, National Cancer Center Hospital,
Tokyo, Japan

S. Ito
Department of Gastroenterological Surgery,
Aichi Cancer Center Hospital, Nagoya, Japan

N. Fuse
Division of Gastrointestinal Oncology
and Digestive Endoscopy, National Cancer Center
Hospital East, Kashiwa, Japan

T. Kinoshita
Division of Surgical Oncology,
National Cancer Center Hospital East, Kashiwa, Japan

H. Yasui
Division of Gastrointestinal Oncology,
Shizuoka Cancer Center, Shizuoka, Japan

M. Terashima
Division of Gastric Surgery,
Shizuoka Cancer Center, Shizuoka, Japan

M. Goto
Cancer Chemotherapy Center,
Osaka Medical College, Takatsuki, Japan

N. Tanigawa
Department of General and Gastroenterological Surgery,
Osaka Medical College, Takatsuki, Japan

K. Shirao
Department of Medical Oncology,
Oita University Faculty of Medicine, Yufu, Japan

T. Sano
Department of Surgery, Cancer Institute Hospital,
Japanese Foundation for Cancer Research, Tokyo, Japan

M. Sasako
Department of Surgery, Hyogo College of Medicine,
Nishinomiya, Japan

Published online: 01 September 2010

Results A total of 63 enrolled patients have been evaluated. Grade 3/4 toxicities included neutropenia (40%), anorexia (28%), and febrile neutropenia (4%) before protocol amendment ($n = 25$), and neutropenia (37%), anorexia (8%), and febrile neutropenia (3%) after amendment implementation ($n = 38$). Excluding ineligible cases, treatment completion rates were 57% (12/21) before and 81% (30/37) after the protocol amendment.

Conclusions The amended S-1 plus cisplatin is more feasible than the original protocol because of early dose reduction of S-1 prior to cisplatin addition and greater recovery time from surgery prior to cisplatin. This treatment should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

Gastric cancer (GC) remains a major health problem with approximately 8,03,000 deaths worldwide in 2004, although the mortality rate has steadily decreased in recent years [1]. The primary treatment for GC is surgery, which is almost always curative in early GC (stage I) patients, who have a >90% 5-year survival rate. However, locally advanced (stage II–III) GC often recurs, even after curative resection is performed. Therefore, it is very important to develop adjuvant chemotherapy regimens that can improve survival in GC patients with stage II–III disease after surgical resection.

Until recently, several randomized controlled trials of postoperative adjuvant chemotherapy for GC were conducted [2–12]. Although most of them have failed to show clinical benefit in particular multi-agent anthracycline or cisplatin-based regimens, a recent meta analysis showed that postoperative adjuvant chemotherapy was associated with reduced risk of death compared with surgery alone [13].

S-1 (TS-1, Taiho Pharmaceutical Co.) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the toxic gastrointestinal effects of fluorouracil) [14] approved in Japan, Korea, Singapore, and China for GC. In 2007, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial demonstrated the efficacy of S-1 for stage II–III GC patients who underwent curative resection with D2 lymphadenectomy [15]. S-1 improved the 3-year overall survival (OS) rate from 70.1% for surgery alone to 80.1%, with a low incidence of adverse events and good compliance with treatment for 3 months in 87.4% and for 6 months in 77.9%. However, the 3-year OS rates in stage IIIA and stage IIIB patients receiving S-1 were 77.4 and 63.4%, respectively, which are less satisfactory compared with the rate for stage II (90.7%). Therefore, further investigation into more effective treatments for patients with stage III GC is urgently needed.

Meanwhile, for metastatic or recurrent GC, the phase III trial comparing S-1 alone to S-1 plus cisplatin (S-1 Plus cisplatin vs. S-1 In RCT In the Treatment for Stomach cancer; SPIRITS trial) showed that S-1 plus cisplatin resulted in a significantly higher response rate, longer progression-free survival (PFS), and longer OS [16]. Another phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial) showed that S-1 plus cisplatin was associated with fewer toxic effects and demonstrated noninferiority compared with infusional fluorouracil and cisplatin [17]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent GC, as well as a candidate for an experimental arm in the next adjuvant chemotherapy trial.

Before comparing S-1 monotherapy with S-1 plus cisplatin in a phase III trial, we first evaluated the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III GC after curative resection, to confirm that S-1 plus cisplatin can safely be used.

Patients and methods

Eligibility criteria

The following eligibility criteria were employed: (1) histologically proven adenocarcinoma of the stomach; (2) ≥ D2 lymphadenectomy, with complete resection of the primary tumor (R0 surgery); (3) stage IIIA/IIIB disease (T2, N2; T3, N1–2; or T4, N0–1 [Japanese classification]); (4) ECOG performance status 0–1; (5) age 20–75 years; (6) no prior chemotherapy or radiotherapy; (7) able to be enrolled 4–8 weeks after surgery; (8) sufficient oral food intake; (9) adequate organ function (white blood cells [WBCs] $\geq$3,000/mm^3 and $\leq$1,20,000/mm^3, neutrophils $\geq$1,500/mm^3, hemoglobin $\geq$8.0 g/dl, platelets $\geq$1,00,000/mm^3, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels $\leq$100 IU/l, total serum bilirubin $\leq$2.0 mg/dl, serum creatinine concentration $\leq$1.2 mg/dl, estimated creatinine clearance $\leq$60 ml/min, normal electrocardiogram); and (10) written informed consent obtained from the patient. Disease stage was classified according to Japanese Gastric Cancer Association guidelines [18]. The protocol was approved by the institutional review board at each participating center.

Treatment and toxicity assessment

Treatment according to the original protocol was begun 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin ("S-1+ cisplatin [SP] step") followed by S-1 monotherapy ("S-1 step") up to 1 year after surgery. In the "SP step", each cycle consisted of 40 mg/m^2 of S-1 taken orally twice daily for 21 days plus a 2-hour infusion of 60 mg/m^2 of cisplatin on day 8. Each cycle was administered at 5-week intervals. In the "S-1 step", 40 mg/m^2 of S-1 was taken orally twice daily as monotherapy for 28 days at 6-week intervals. All patients received 5-HT3 antagonists and dexamethasone on administration of cisplatin as antiemetics.

Patients were assessed before registration, on days 1, 8, and 15 during the "SP step", and every 2 weeks during the "S-1 step". The baseline assessment included physical examination and laboratory tests. Patients were monitored for adverse effects throughout the treatment period, in addition to receiving follow-up for treatment-related adverse effects. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

For adverse effects, the subsequent chemotherapy cycle was delayed until patient recovery, which included the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, hemoglobin $\geq$8.0 g/dl, platelets >75,000/mm^3, AST or ALT levels $\leq$100 IU/l, total serum bilirubin level $\leq$2.0 mg/dl, and serum creatinine concentration <1.5 mg/dl. Nonhematological toxicities, excluding stomatitis, alopecia, pigmentation changes, nail changes, and watery eyes, were required to be grade 0/1. Cisplatin administration was delayed and administered within 1 day of recovery of the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, platelets >75,000/mm^3, and serum creatinine <1.5 mg/dl. Both S-1 and cisplatin doses were reduced in the event of grade 4 leukopenia or neutropenia, grade 3/4 thrombocytopenia, serum creatinine $\geq$1.5 mg/dl, or other drug-related nonhematological grade 3/4 toxicities. For level −1 dose reduction, S-1 was reduced from 120 to 100 mg/day, from 100 to 80 mg/day, or from 80 to 50 mg/day, while cisplatin was reduced from 60 to 50 mg/m^2. Dose reduction was permitted twice. When dose-limiting toxicities as described previously occurred again at level −2 (S-1 reduced from 100 to 80 mg/day or from 80 to 50 mg/day [if the −1 level of S-1 was already 50 mg, the patient was withdrawn from the study]; cisplatin administration reduced from 50 to 40 mg/m^2), the patient was withdrawn from the study. A patient was also withdrawn from the study whenever the beginning of the subsequent cycle was delayed by toxicity for more than 3 weeks. When cisplatin administration was delayed beyond day 15, the cisplatin portion of the cycle was skipped.

Protocol amendment

During enrollment, some toxicity was reported during the first cycle of SP, especially neutropenia and anorexia. To minimize patient risk, the Data and Safety Monitoring Committee recommended that patient enrollment be halted and that an interim analysis be conducted using the first 25 registered cases (see "Results"). After the analysis, we decided to amend the protocol.

Treatment according to the amended protocol was begun 4–6 weeks after surgery as in the ACTS-GC trial, and consisted of the following: (1) The first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 monotherapy was administered up to 1 year after surgery; (2) The dose of S-1 in the first SP cycle was reduced in case of severe toxicity during the first cycle of S-1 monotherapy; (3) The criterion for delaying cisplatin administration was changed from a neutrophil count of <1,500/mm^3 to <1,200/mm^3; (4) Dexamethasone was recommended for treatment-induced nausea with 20 mg on day 8 (the day of cisplatin administration) and 16 mg on days 9 and 10.

Statistical analysis

The primary endpoint was the rate of completion of 3 cycles of S-1 plus cisplatin; secondary endpoints were the rate of completion of 2 cycles of S-1 plus cisplatin, the proportion of patients receiving treatment according to protocol, and adverse events. Treatment completion was defined as administration of S-1 for more than 14 days in each cycle plus administration of cisplatin. Completion rate of S-1 plus cisplatin was evaluated in all eligible patients. Toxicity was evaluated among patients who received more than one cycle of S-1 plus cisplatin.

In the present trial, the rate of treatment completion was expected to be lower than compliance in the ACTS-GC trial because of the addition of cisplatin. Moreover, if the rate of treatment completion using 3 cycles of S-1 plus cisplatin were lower than 50%, this regimen would be considered inappropriate for adjuvant therapy and would not be evaluated in a phase III trial. Assuming a null hypothesis of 50% for the rate of completion of 3 cycles and an alternative hypothesis of 70%, and using a 1-sided alpha of 0.1 and a statistical power of 0.1, it is necessary to enroll a minimum of 44 patients. Therefore, the target enrollment was 50 patients, in order to make accommodations for ineligible patients.

After protocol amendment, a minimum of 33 patients is needed for a 1-sided alpha of 0.1 and a statistical power of 0.2. Therefore, 38 more patients were added to allow for ineligible patients. Statistical analysis was performed independently for patients enrolled before and after amendment.

Table 1 Patient characteristics

Characteristic	Original ($n = 25$)	Amended ($n = 38$)
Median age, years (range)	60 (47–72)	62 (40–74)
Gender		
Male	16	25
Female	9	13
PS (ECOG)		
0	17	26
1	8	12
Pathological type		
Intestinal	14	5
Diffuse	11	33
Type of gastrectomy		
Total	8	13
Distal	16	25
Proximal	1	0
T stage		
pT1	2	0
pT2	8	9
pT3	14	28
pT4	1	1
N stage[a]		
pN0	1	0
pN1	10	8
pN2	14	30
Cancer stage[a]		
IB	1[b]	0
II	2[b]	0
IIIA	17	16
IIIB	5	21
IV	0	1[b]

Original before protocol amendment, *Amended* after protocol amendment, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

[a] Japanese classification; [b] excluded after enrollment

Table 2 Toxicities

Toxicities	Original ($n = 25$)				Amended ($n = 38$)			
	All		Grade 3/4		All		Grade 3/4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
(A) Hematological toxicities								
Leucopenia	19	(76)	1	(4)	26	(68)	2	(5)
Neutropenia	20	(80)	10	(40)	30	(79)	14	(37)
Anemia	23	(92)	5	(20)	35	(92)	3	(8)
Thrombocytopenia	10	(40)	1	(4)	17	(45)	1	(3)
Febrile Neutropenia	1	(4)	1	(4)	1	(3)	1	(3)
(B) Nonhematological toxicities								
Anorexia	23	(92)	7	(28)	34	(89)	3	(8)
Nausea	17	(68)	2	(8)	31	(82)	1	(3)
Vomitting	7	(28)	0	(0)	8	(21)	0	(0)
Diarrhea	13	(52)	0	(0)	24	(63)	1	(3)
Fatigue	17	(68)	0	(0)	34	(89)	2	(5)
Stomatitis	2	(8)	0	(0)	8	(21)	0	(0)
AST	5	(20)	0	(0)	10	(40)	0	(0)
ALT	5	(20)	0	(0)	8	(36)	0	(0)
Total bilirubin	6	(30)	0	(0)	22	(22)	0	(0)
Creatinine	5	(20)	0	(0)	11	(10)	0	(0)

Original before protocol amendment, *Amended* after protocol amendment, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Results

Patient characteristics

From August 2007 to July 2009, 63 patients (25 patients in the original protocol/38 patients in the amended protocol) were accrued from 5 Japanese hospitals. To date, all 63 patients have finished the "SP step" and have been evaluated. Clinical characteristics are summarized in Table 1. The median age was 60/62 (original/amended protocol) years (range, 47–72/40–74 years), and the following types of resection were performed: total gastrectomy ($n = 8/13$), distal gastrectomy ($n = 16/25$), and proximal gastrectomy ($n = 1/0$). In the original protocol, 17 patients had stage IIIA disease and 5 had stage IIIB disease; whereas 16 had stage IIIA and 21 had stage IIIB disease in the amended protocol. After enrollment, 4 patients were deemed ineligible during the original protocol because of confirmed stage II disease ($n = 2$), stage IB disease ($n = 1$), and cancer other than GC ($n = 1$), and 1 patient was considered ineligible during the amended protocol because of pathological stage IV ($n = 1$) disease.

Toxicity

A total of 202 cycles from the 63 cases were assessable for toxicity (Table 2). Under the original protocol ($n = 25$), neutropenia was the most common hematological toxicity, with grade 3/4 neutropenia observed in 10 patients (40%). Additional grade 3/4 hematological toxicities included anemia in 5 patients (20%), and leucopenia, thrombocytopenia, and febrile neutropenia in 1 patient (4%) each. Grade 3/4 anorexia was the most frequent nonhematological toxicity ($n = 7$ [28%]), followed by nausea ($n = 2$ [8%]). There was no grade 3/4 creatinine elevation seen.

Under the amended protocol ($n = 38$), the frequency of grade 3/4 neutropenia was similar to the original; it was seen in 14 patients (37%). Grade 3/4 anemia decreased to 3 patients (8%), and the frequencies of grade 3/4 leukopenia ($n = 2$

[5%]), thrombocytopenia ($n = 1$ [3%]), and febrile neutropenia ($n = 1$ [3%]) were also similar to the original. Among nonhematological toxicities, grade 3/4 anorexia was remarkably reduced to 3 patients (8%) and nausea also decreased to 1 patient (3%). The incidences of grade 3/4 fatigue and diarrhea slightly increased to 2 (5%) and 1 (3%) patients, respectively. There was no grade 3/4 creatinine elevation seen. There were no treatment-related deaths occurring within 30 days after completion of "SP step" treatment.

Compliance

As mentioned previously, 4 and 1 patients were determined to be ineligible after enrollment in the original and amended protocols, respectively, and therefore 21 and 37 patients were analyzed for compliance, respectively. Under the original protocol, 57% (12/21; 95% CI 34–78%) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 76% (16/21; 95% CI 53–92%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 57% (12/21; 95% CI 34–78%). Of note, 6/21 (29%) patients did not complete the first cycle of the "SP step". Reasons for not completing the first cycle included neutropenia on the day of cisplatin administration (day 8) in 3 patients, anorexia in 2 patients, and infection in 1. Dose reductions of S-1 and cisplatin were required once in 9 (43%) and 8 (38%) patients, respectively, and twice in 1 (5%) and 1 (5%) patients, respectively. There were 6 patients (29%) withdrawn from treatment as follows: 3 because of toxicity (neutropenia), 2 because of patient refusal of additional treatment because of toxicity, and 1 because of refusal of additional treatment for other reasons.

Under the amended protocol, 81% (30/37; 95% CI 65–92%; $P < 0.001$ under the null hypothesis) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 95% (35/37; 95% CI 82–99%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 78% (29/37; 95% CI 62–90%). The number of patients not completing the first cycle of the "SP step" was remarkably decreased to only 1 (3%) patient. There were 10 (27%) patients requiring S-1 dose reduction after the first chemotherapy cycle of S-1 monotherapy. Dose reductions of S-1 and cisplatin were required once in 12 (32%) and 8 (22%) patients, respectively, and twice in 7 (19%) and 6 (16%) patients, respectively. Withdrawal of treatment occurred in 2 (5%) patients as follows: one because creatinine elevation did not recover and the other because of patient refusal of additional treatment because of toxicity.

The relative dose intensities (RDIs) of S-1 were 0.67 in the original and 0.78 in the amended protocol, and for cisplatin were 0.65 and 0.81, respectively.

Discussion

To the best of our knowledge, this is the first report on a safety analysis of S-1 plus cisplatin treatment for stage III GC patients who have undergone curative resection with D2 lymphadenectomy. The overall frequencies of major toxicities under the original protocol were almost similar to those of the SPIRITS trial [16] (neutropenia 40 vs. 40%; anemia 20 vs. 26%; and anorexia 28 vs. 30% in this study and the SPIRITS trial, respectively). However, the completion rate of 3 cycles of S-1 plus cisplatin as a primary endpoint (57%) and RDI of S-1 or cisplatin were unexpectedly low in this study. Among the 9 patients who could not complete the 3 cycles of S-1 plus cisplatin, 6 patients could not complete treatment even during the first cycle, mainly because of neutropenia on day 8 and anorexia. We found that toxicity of chemotherapy was more likely to occur during the first cycle.

Therefore, to improve the completion rate of the treatment, we decided to amend the protocol by establishing S-1 monotherapy as the first cycle of chemotherapy, followed by 3 cycles of S-1 plus cisplatin. Although it might be possible that efficacy is decreased by changing the first cycle to S-1 monotherapy, we prioritized complying with postoperative adjuvant chemotherapy, which might also be important in improving survival [19, 20].

In our amended protocol, not only was cisplatin administration omitted in the first cycle, but also the dose of S-1 in subsequent combination cycles was reduced if there were severe toxicities during the "first-cycle" administration of S-1 monotherapy. In addition, the neutropenia count for delaying cisplatin administration was also changed, from $<1{,}500/mm^3$ to $<1{,}200/mm^3$. As a result, 81% of patients achieved treatment completion with 3 cycles of S-1 plus cisplatin with improved RDIs of both S-1 (0.78 from 0.65) and cisplatin (0.81 from 0.65). The frequency of grade 3/4 anorexia and nausea also decreased, from 28 to 8% and 8 to 3%, respectively, although we do not use Substance P inhibitor in both protocol because it was not approved in Japan at that time.

The actual cause of the poor compliance during the early post-gastrectomy course in this study was not discovered. There are several reports about the effect of gastrectomy on S-1 pharmacokinetics [21–23], although this issue remains controversial. Kim et al. reported that total gastrectomy significantly increased the maximum concentration and the areas under the curves of plasma fluorouracil and 5-chloro-2,4-dihydroxypyridine (CDHP) after S-1 administration, which may be one explanation for the toxicity seen in this study [23]. Additionally, there may be a hidden cause, such as relatively poor nutritional status due to gastrectomy, although this study included patients with sufficient oral intake and adequate organ function.

Although this was not a randomized study, in comparison with the original protocol, the amended protocol was more feasible, with a higher completion rate and higher RDIs. Relapse-free survival and overall survival were not reached in this study; therefore, it is difficult to speculate that the addition of 3 cycles of cisplatin might improve the prognosis compared with S-1 alone. Now in Japan, another feasibility study of S-1 plus docetaxel as postoperative adjuvant chemotherapy is ongoing [24]. The addition of any other agent to S-1 as an adjuvant chemotherapy needs to be validated in a randomized phase III trial with S-1 as the control arm.

In conclusion, the postoperative adjuvant S-1 plus cisplatin regimen of the amended protocol is more feasible than the original protocol, because of (1) early dose reduction of S-1 prior to cisplatin addition (2) greater recovery time from surgery prior to cisplatin. It should be regarded as a feasible experimental arm for the next adjuvant phase III trial comparing this S-1 plus cisplatin regimen and S-1 alone as adjuvant chemotherapy for stage III GC patients who have undergone curative resection with D2 lymphadenectomy.

Acknowledgments We thank Mr. Yushi Nagai and Ms. Michiyo Tada for help in collecting and organizing the database. We received no financial support.

Conflicts of interest T. Sano has received lecture fees from Taiho Pharmaceutical (Tokyo, Japan). All other authors declared no conflicts of interest.

References

1. http://www.who.int/mediacentre/factsheets/fs297/en/index.html
2. Cirera L, Balil A, Batise-Alentorn E et al (1999) Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. J Clin Oncol 17:3810–3815
3. Nakajima T, Nashimoto A, Kitamura M et al (1999) Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Lancet 354:273–277
4. Neri B, Cini G, Andreoli F et al (2001) Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. Br J Cancer 84:878–880
5. Bajetta E, Buzzoni R, Mariani L et al (2002) Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian trials in medical oncology (ITMO) group. Ann Oncol 13:299–307
6. Nashimoto A, Nakajima T, Furukawa H et al (2003) Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan clinical oncology group 9206-1. J Clin Oncol 21:2282–2287
7. Chipponi J, Huguier M, Pezet D et al (2004) Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. Am J Surg 187:440–445
8. Popiela T, Kulig J, Czupryna A et al (2004) Efficiency of adjuvant immunochemotherapy following curative resection in patients with locally advanced gastric cancer. Gastric Cancer 7:240–245
9. Bouche O, Ychou M, Burtin P et al (2005) Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol 16:1488–1497
10. Nitti D, Wils J, Santos GD et al (2006) Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI group and the ICCG. Ann Oncol 17:262–269
11. De Vita F, Giuliani F, Orditura M et al (2007) Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). Ann Oncol 18:1354–1358
12. Nakajima T, Kinoshita T, Nashimoto A et al (2007) Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg 94:1468–1476
13. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group (2010) Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 303:1729–1737
14. Shirasaka T, Shimamoto Y, Ohshimo H et al (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–557
15. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820
16. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
17. Ajani JA, Rodriguez W, Bodoky G et al (2010) Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 28(9):1547–1553
18. Japanese Gastric Cancer Association (1998) Japanese classification of gastric carcinoma, 2nd english ed. Gastric Cancer 1:10–24
19. Cascinu S, Labianca R, Barone C et al (2007) Adjuvant treatment of high-risk, radically resected gastric cancer patients with 5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. J Natl Cancer Inst 99:601–607
20. Ellenberg SS, Sun W (2007) Adjuvant therapy for gastric cancer: how negative results can help patients. J Natl Cancer Inst 99:580–582
21. Tsuruoka Y, Kamano T, Kitajima M et al (2006) Effect of gastrectomy on the pharmacokinetics of 5-fluorouracil and gimeracil after oral administration of S-1. Anticancer Drugs 17:393–399
22. Kochi M, Fujii M, Kanamori N et al (2007) Effect of gastrectomy on the pharmacokinetics of S-1, an oral fluoropyrimidine, in resectable gastric cancer patients. Cancer Chemother Pharmacol 60:693–701
23. Kim WY, Nakata B, Hirakawa K (2007) Alternative pharmacokinetics of S-1 components, 5-fluorouracil, dihydrofluorouracil and alpha-fluoro-beta-alanine after oral administration of S-1 following total gastrectomy. Cancer Sci 98:1604–1608
24. Kinura Y, Tamura S, Fujitani K et al (2010) Phase II study of adjuvant S-1 plus docetaxel for stage III gastric cancer patients after curative D2 gastrectomy(OGSG0604). In: 2010 Gastrointestinal cancers symposium abstr #100

Int J Clin Oncol (2010) 15:287–293
DOI 10.1007/s10147-010-0054-9

ORIGINAL ARTICLE

Comparison of combination chemotherapy with irinotecan and cisplatin regimen administered every 2 or 4 weeks in pretreated patients with unresectable or recurrent gastric cancer: retrospective analysis

Takeshi Sakamoto · Hirofumi Yasui · Narikazu Boku · Yusuke Onozawa · Shuichi Hironaka · Akira Fukutomi · Kentaro Yamazaki · Keisei Taku · Nozomu Machida · Akiko Todaka · Hideharu Tomita · Takahiro Tsushima · Hiroya Taniguchi · Satoshi Hamauchi

Received: 6 January 2010 / Accepted: 29 January 2010 / Published online: 10 March 2010

Abstract
Background Efficacy and safety of irinotecan and cisplatin administration every 2 weeks (biweekly regimen) or 4 weeks (4-weekly regimen) in patients with pretreated unresectable or recurrent gastric cancer was retrospectively evaluated.
Methods Study patients comprised two cohorts: cohort 1, consisting of 31 patients received chemotherapy on a 4-weekly regimen; and cohort 2, consisting of 32 patients received chemotherapy on a biweekly regimen. In cohort 1, patients received irinotecan (70 mg/m^2) on days 1 and 15 and cisplatin (80 mg/m^2) on day 1 every 4 weeks; in cohort 2, patients received irinotecan (60 mg/m^2) on day 1 and cisplatin (30 mg/m^2) on day 1 every 2 weeks.
Results Response rates were for cohorts 1 and 2 were 26% (7/27) and 28% (7/25) in patients with measurable lesions, median progression-free survivals were 3.5 and 4.3 months, and median survival times after irinotecan and cisplatin initiation were 9.5 and 10.1 months, respectively. The incidence of grades 3 and 4 hematological toxicities in cohorts 1 and 2 were 74% and 44% for leukopenia, 81% and 53% for neutropenia, and 45% and 28% for anemia, respectively. Incidences of grades 3 and 4 nonhematological toxicities were 23% and 12% for nausea, 23% and 9% for vomiting, 19% and 12% for anorexia, and 6% and 6% for febrile neutropenia, respectively.
Conclusion Irinotecan plus cisplatin chemotherapy administered on a biweekly regimen was comparable in efficacy to a 4-weekly regimen and might be more feasible than the 4-weekly regimen.

Keywords Irinotecan · Cisplatin · Pretreated · Gastric cancer

T. Sakamoto (✉) · H. Yasui · N. Boku · Y. Onozawa · S. Hironaka · A. Fukutomi · K. Yamazaki · K. Taku · N. Machida · A. Todaka · H. Tomita · T. Tsushima · H. Taniguchi · S. Hamauchi
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: t.sakamoto@scchr.jp

Introduction

Gastric cancer is a major cause of death from cancer worldwide and remains the second most common cause in Japan of cancer-related death. For patients with unresectable or recurrent gastric cancer, the main therapeutic option is palliative chemotherapy. Chemotherapy treatment with 5-fluorouracil (5-FU) has been shown to have a survival benefit over best supportive care (BSC) [1–3] and is widely used. Recently, two pivotal phase III studies conducted in Japan were reported. The first, the Japan Clinical Oncology Group (JCOG) 9912 trial revealed no inferiority of S-1 alone to 5-FU alone and failed to demonstrate superiority of irinotecan (CPT-11) plus cisplatin (CDDP) to 5-FU alone in terms of overall survival (OS) [4]. The study concluded that S-1 alone could replace continuous 5-FU infusion for treating advanced gastric cancer. The second study was the Randomized phase III study of S-1 alone versus S-1 + cisplatin in the treatment for advanced gastric cancer (SPIRITS) trial, which showed superiority of S-1 plus CDDP to S-1 alone in terms of overall survival [5]. From these results, S-1 plus CDDP has been recognized in Japan as the standard first-line chemotherapy for unresectable and recurrent gastric cancer. In an adjuvant setting, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial reported that adjuvant therapy

with S-1 showed a better survival outcome than surgery alone in patients with stage II or III gastric cancer who had undergone gastrectomy with extended (D2) lymph-node dissection [6]. Based on the results of that study, S-1 alone is recognized in Japan as the standard adjuvant chemotherapy for stage II or III gastric cancer. These studies indicate that S-1 is a key drug for the initial treatment of gastric cancer. However, although a considerable number of patients experience disease progression or recurrence during or after initial therapy, a standard chemotherapy regimen after failure in initial therapy containing S-1 has not yet been established.

CPT-11 is a semisynthetic compound derived from the plant alkaloid camptothecin, which is extracted from *Camptotheca acuminate*. This compound inhibits DNA topoisomerase I [7]. Recently, Thuss-Patience et al. [8] reported a phase III study comparing CPT-11 to BSC as a second-line therapy for advanced gastric cancer. Although the trial was closed prematurely because of poor accrual, this study suggested a survival benefit of second-line chemotherapy by CPT-11 alone [OS 123 vs. 73 days, $p = 0.023$; hazard ratio (HR) 0.48; 95% confidence interval (CI) 0.25–0.92]. Thus, CPT-11 can be considered an option for second-line therapy. In our hospital, CPT-11 is preferred in second-line settings unless the patient has a contraindication for CPT-11 therapy, such as intestinal obstruction due to peritoneal dissemination. In particular, combination chemotherapy with CPT-11 plus CDDP is frequently used after failure of S-1 monotherapy.

Combination chemotherapy with CPT-11 and CDDP administered every 4 weeks (4-weekly regimen) was reported by Boku et al. [9]. CPT-11 (70 mg/m^2) was administered on days 1 and 15 and CDDP (80 mg/m^2) on day 1 by intravenous infusion every 4 weeks. The response rate (RR) when administered as a first-line therapy for advanced gastric cancer was 59%, and the median survival time (MST) was 12.3 months. Additionally, Ueda et al. [10] reported a RR of 28%, a median time to progression of 3.5 months, and a MST of 9.4 months when administered to patients with pretreated gastric cancer. Subsequently, a regimen comprised of CPT-11 (60 mg/m^2) on day 1 and CDDP (30 mg/m^2) on day 1 every 2 weeks (biweekly regimen) was reported by Koizumi et al. [11]. The response for this regimen in second-line therapy for advanced gastric cancer was 20%, and MST was 9.1 months.

As for toxicities, the biweekly regimen seems to be less toxic than the 4-weekly regimen. After Koizumi et al.'s report, biweekly regimen was adopted at our institution in 2007 (with the approval of the clinical practice committee of Shizuoka Cancer Center) for treating patients with pretreated advanced gastric cancer. However, these two regimens, every 2 or 4 weeks, have not been compared. The objective of this retrospective study was to historically compare the efficacy and safety between CPT-11 plus CDDP administered on a biweekly and 4-weekly regimen in patients with pretreated advanced gastric cancer.

Patients and methods

Patients

Sixty-three patients with unresectable or recurrent gastric cancer were treated with CPT-11 plus CDDP administered on either a biweekly or 4-weekly regimen between September 2002 and July 2009. Thirty-one patients were treated on the 4-weekly regimen (cohort 1), which was initiated before May 2007; 32 patients were treated on the biweekly regimen (cohort 2) between February 2007 and July 2009. Selection criteria for this retrospective analysis were: (1) histological diagnosis of adenocarcinoma, (2) history of having undergone one or two prior chemotherapy regimens that did not contain either CPT-11 or CDDP, (3) age $\leq$75 years, (4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\leq$2, (5) preserved organ functions [bone marrow: white blood cell (WBC) count $\geq$3,000/μl and platelet count $\geq$10,000/μl; hepatic function: serum bilirubin level $\leq$1.5 mg/dl, serum transaminase level $\leq$2.5$\times$ the upper limit of the normal range; renal function: serum creatinine level $\leq$1.5 mg/dl, and blood urea nitrogen level $\leq$25 mg/dl), (6) no other serious diseases, (7) no other active malignancy, and (8) provision of written informed consent for treatment.

Treatment methods

In cohort 1, CPT-11 (70 mg/m^2) was administered by intravenous infusion for 90 min on day 1 followed by a 2-h interval and then intravenous infusion of CDDP (80 mg/m^2) for 120 min. The same dose of CPT-11 was administered on day 15. This treatment was repeated every 4 weeks. In cohort 2, CPT-11 (60 mg/m^2) was administered by intravenous infusion for 90 min, followed by CDDP (30 mg/m^2) for 120 min on day 1. This treatment was repeated every 2 weeks. Treatments in both cohorts were continued until disease progression, patient's refusal, or unacceptable toxicity. Treatments were given after confirming a leukocyte count $\geq$3,000/μl, a platelet count $\geq$100,000/μl, grade 0 diarrhea, and absence of infection on day 1. In cohort 1, if the patient had a leukocyte count $<$3,000, a platelet count $<$100,000, diarrhea of grade 1 or higher, or an infection on day 15, then administration of CPT-11 on day 15 was postponed until the patient had recovered from these adverse reactions. If these adverse reactions persisted beyond day 22, then the CPT-11 dosage scheduled on day 15 was skipped. If a hematological

adverse reaction of grade 4 or a nonhematological adverse reaction of grade 3 or higher occurred, then administration of CPT-11 on day 15 was skipped, and the subsequent dose of CPT-11 was reduced to 60 mg/m^2. In cohort 2, if the patient had a leukocyte count <3,000, a platelet count <100,000, diarrhea of grade 1 or higher, or an infection on day 1, administration of CPT-11 and CDDP was postponed until the patient had recovered from these adverse reactions. If these adverse reactions continued beyond day 22 or if a hematological adverse reaction of grade 4 or a nonhematological adverse reaction of grade 3 or higher occurred, then the subsequent dose of CPT-11 was reduced to 50 mg/m^2.

Evaluation

Response was assessed using computed tomography (CT) every 1 or 2 months, and the results were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST v.1.0) [12]. Toxicities were evaluated according to the Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE 3.0). Progression-free survival (PFS) was calculated using the Kaplan–Meier method as the period from the date of treatment initiation (CPT-11 plus CDDP) until the first observation of disease progression or death from any cause. Similarly, overall survival was calculated as the period from the date of treatment initiation until the date of death or the last confirmed date of survival (censored).

Results

Patient characteristics

Thirty-one patients in cohort 1 and 32 patients in cohort 2 received CPT-11 plus CDDP administered on a 4-weekly or biweekly regimen, respectively. Patient characteristics are summarized in Table 1. Whereas most patients had a good PS, the proportion of patients with PS 2 was larger in cohort 2 than in cohort 1. All previous therapies are summarized in Table 2. The proportion of patients receiving CPT-11 plus CDDP as a third-line treatment was larger in cohort 2 than in cohort 1.

Response and survival

Responses are summarized in Table 3. Twenty-seven patients in cohort 1 and 25 in cohort 2 had measurable lesions, respectively. Seven patients (26%) in cohort 1 and 7 (28%) in cohort 2 achieved a partial response (PR). Ten patients (37%) in cohort 1 and 9 (36%) in cohort 2 showed stable disease (SD). Thus, the RR in cohorts 1 and 2 were 26% and 28%, and disease control rates were 63% and 64%, respectively. At the time of analysis, treatment was continued in one patient in cohort 2. The median PFS for cohorts 1 and 2 were 3.5 and 4.3 months, respectively (Figs. 1, 2), and MSTs were 9.5 and 10.1 months, respectively (Figs. 3, 4).

Table 1 Patient characteristics

	Four-weekly regimen cohort 1	Biweekly regimen cohort 2
No. of patients	31	32
Age		
Median (range)	58 (37–75)	66 (40–76)
Sex		
Male/female	25/6	21/11
ECOG performance status		
0/1/2	15/14/2	14/11/7
Macroscopic type		
1,2/3,4/unknown	6/18/7	8/19/5
Histological type		
Intestinal/diffuse/unknown	16/12/3	13/15/4
No. of metastatic sites		
0,1/2/≥3	15/12/4	14/12/6
Metastatic site		
Lymph node	22	17
Peritoneal dissemination	13	16
Liver	8	12
Lung	4	3
Bone	0	2

ECOG Eastern Cooperative Oncology Group

Table 2 Previous chemotherapeutic regimen

	Four-weekly regimen cohort 1 No. of patients	Biweekly regimen cohort 2 No. of patients
No. of prior regimens		
1/2	26/5	18/14
Prior therapy		
Oral fluoropyrimidine	18	27
Paclitaxel	3	10
5-FU bolus (MTX + 5-FU)	5	5
5-FU CIV	10	2
Others	0	2

5-FU 5-fluorouracil, *MTX* methotrexate, *CIV* continuous intravenous infusion

Toxicity

Grade 3 and 4 toxicities observed in each cohort are summarized in Table 4. Incidence in cohorts 1 and 2 were

Table 3 Response rate

	Four-weekly regimen cohort 1		Biweekly regimen cohort 2	
	No. of patients	%	No. of patients	%
Total	27		25	
CR	0	0	0	0
PR	7	26	7	28
SD	10	37	9	36
PD	10	37	9	36
RR		26		28
DCR		63		64

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate, *DCR* disease control rate

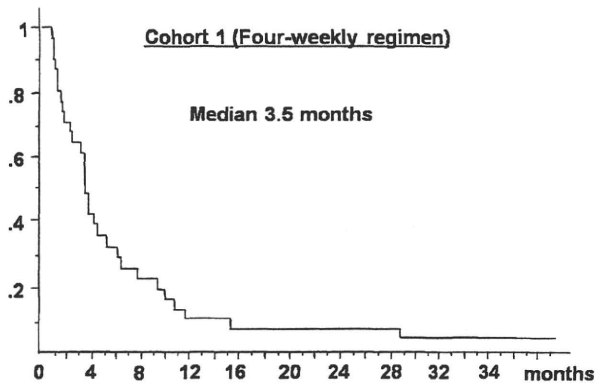

Fig. 1 Kaplan–Meier curve for progression-free survival curve in cohort 1. Median progression-free survival was 3.5 months

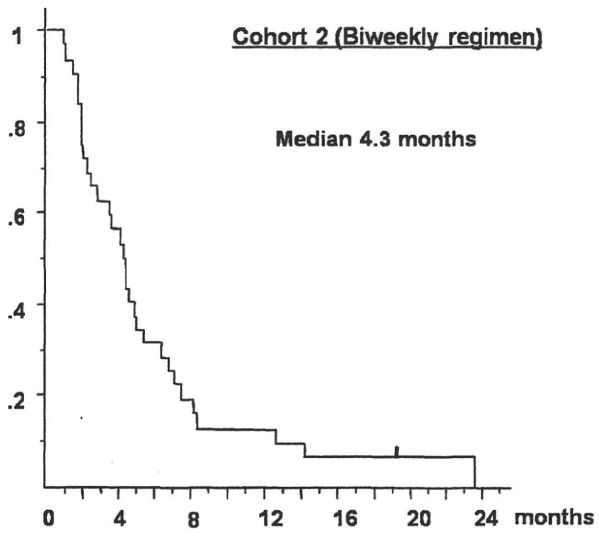

Fig. 2 Kaplan–Meier curve for progression-free survival curve in cohort 2. Median progression-free survival was 4.3 months

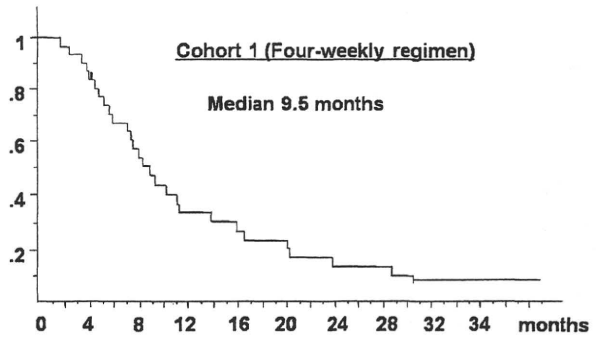

Fig. 3 Kaplan–Meier curve for overall survival curve in cohort 1. Median overall survival was 9.5 months

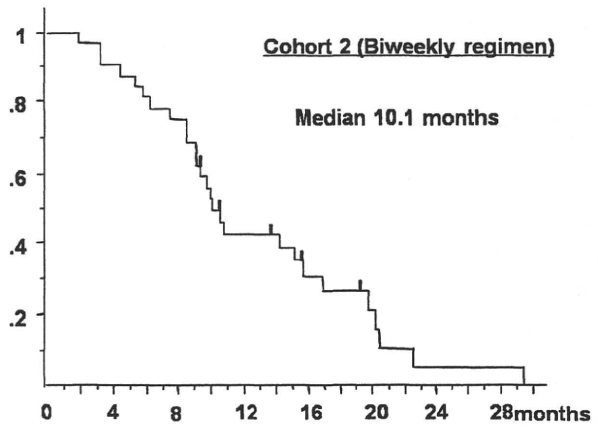

Fig. 4 Kaplan–Meier curve for overall survival curve in cohort 2. Median overall survival was 10.1 months

81% and 53% for neutropenia 45% and 28% for anemia, respectively. Incidences of grade 3 nausea were 23% and 12%, of grade 3 vomiting 23% and 9%, and of grade 3 anorexia 19% and 12%, respectively. No grade 4 nonhematological toxicities or treatment-related deaths occurred in this series.

Dose intensity

In cohort 1, the total number of courses was 67. Dose reduction of CPT-11 was required in 7 (23%) patients. The total number of skipped CPT-11 scheduled on day 15 was 10. Leukopenia was the most frequent reason for skipping the dose and for dose reduction. Thus, the actual dose intensity of CPT-11 was 24.5 mg/m^2 per week, whereas that of CDDP was 15.4 mg/m^2 per week. These values correspond to 70% and 77% of the planned doses, respectively.

In cohort 2, the total number of courses was 283. Dose reduction of CPT-11 was required in 5 (16%) patients. The total number of delays in treatment schedule was 24 (8%). Leukopenia was the most frequent reason both for

Table 4 Adverse events

	Four-weekly regimen (cohort 1)					Biweekly regimen (cohort 2)				
	Grade 3		Grade 4		Grade 3–4	Grade 3		Grade 4		Grade 3–4
	No.	%	No.	%	%	No.	%	No.	%	%
Hematological										
Leukopenia	16	52	7	22	74	12	38	2	6	44
Neutropenia	3	10	22	71	81	13	41	4	12	53
Anemia	9	29	5	16	45	6	19	3	9	28
Thrombocytopenia	2	6	0	0	6	2	6	1	3	9
Nonhematological										
Nausea	7	23	0	0	23	4	12	0	0	12
Vomiting	7	23	0	0	23	3	9	0	0	9
Anorexia	4	13	2	6	19	4	12	0	0	12
Diarrhea	1	3	0	0	3	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	2	6	0	0	0	2	6	0	0	6

Table 5 Subsequent chemotherapy

	Four-weekly regimen (cohort 1) ($n = 31$)		Biweekly regimen (cohort 2) ($n = 32$)	
	No. of patients	%	No. of patients	%
No. of regimens				
0 (BSC)	8	26	7	22
1	8	26	20	63
2	10	32	4	13
3	4	13	1	3
No follow-up	1	3	0	0
Regimen				
Paclitaxel	21	68	18	58
Contained 5-FU bolus	7	23	7	
mFOLFOX6	0	0	2	6
5-FU i.a. (WHF)	0	0	2	6
Oral fluoropyrimidine	0	0	2	6
CDDP i.p.	4	13	0	0
MMC	3	10	0	0
Others	2	6	1	3

i.a. intra-arterial injection, *mFOLFOX6* 5-fluorouracil (5-FU), leucovorin, and oxaliplatin, *WHF* weekly high dose 5-FU, *i.p.* intraperitoneal injection, *MMC* mitomycin C

treatment delay and dose reduction. Thus, the dose intensity of CPT-11 was 27.1 mg/m^2 per week, whereas that of CDDP was 14.1 mg/m^2 per week. These values correspond to 90% and 94% of the planned doses, respectively.

Subsequent chemotherapy

Subsequent chemotherapies administered in each cohort are summarized in Table 5. Twenty-three patients (74%) in cohort 1 and 25 (81%) in cohort 2 received subsequent chemotherapy. Eighteen patients (58%) in cohort 1 and 21 (68%) in cohort 2 received monotherapy with paclitaxel.

Discussion

There are few reports of CPT-11 alone for pretreated patients with advanced gastric cancer. Futatsuki et al. [13]

reported a response rate of 20% as a CPT-11 single agent in pretreated patients. For combination therapy with CPT-11 and CDDP, administration by 4-weekly or biweekly regimen has been widely used after the failure of S-1 or 5-FU monotherapy. Boku et al. [9] reported a response rate of 27% in a prospective study examining administration by 4-weekly regimen, and Ueda et al. [10] recapitulated these results with a response rate of 28% in a retrospective analysis of their clinical practice. On the other hand, response rates of 20–29% have been reported for administration of a biweekly regimen [11, 14, 15]. Although a randomized trial in pretreated patients with advanced gastric cancer has not yet been performed, combination therapy with CPT-11 plus CDDP seems to be more effective than CPT-11 alone, at least with regard to the response rate. CPT-11 plus CDDP seems to be one of the most common chemotherapy regimens after failure in first-line chemotherapy of S-1 or 5-FU alone.

In our clinical practice, in 2007, we replaced the administration of CPT-11 plus CDDP on a 4-weekly regimen with a biweekly regimen. Consequently, the clinical outcomes of the administration of these agents every 4 weeks or every 2 weeks were not simultaneously compared. Because the administration of CPT-11 is contraindicated for patients with complications myelosuppression, infection, diarrhea, ileus, interstitial pneumonia, or obstructive jaundice due to its severe toxicity, we limited the administration of CPT-11 for both second- and third-line chemotherapy to patients with a PS 0–2 and no or only mild peritoneal dissemination in clinical practice. There seemed to be no intended differences in indication between these two cohorts. However, cohort 2 included more patients in a third-line setting and with PS 2 than did cohort 1. Actually, the patient background was rather worse in cohort 2 than in cohort 1.

Despite these background differences, RR, PFS, and OS of cohort 2 were comparable with those of cohort 1. These parameters seem to be consistent with those in previous reports of CPT-11 plus CDDP administered on a biweekly regimen. In this study, the incidence of grade 3 or 4 toxicities was lower in cohort 2 than in cohort 1. In particular, the incidences of grade 4 leukopenia (74% vs. 44% for cohort 1 and 2, respectively), neutropenia (81% vs. 53%), grade 3 nausea (23% vs. 12%), and grade 3 vomiting (23% vs. 9%) were much higher in cohort 1. These toxicities sometimes caused dose reduction and skipped administrations. Dose intensities of CPT-11 and CDDP in cohort 2 were equivalent to those in cohort 1, although the planned doses were higher in cohort 1 than in cohort 2. These results suggest that a biweekly regimen might exert a comparable activity to a 4-weekly regimen, in addition to being more feasible.

For second-line chemotherapy after the failure of fluoropyrimidine-based chemotherapy, taxanes (paclitaxel and docetaxel) are another option. Arai et al. [16] reported that the RR of paclitaxel in heavily treated patients was 23% and the median survival was 6.9 months. These results seem comparable with those for CPT-11-containing chemotherapy as a second-line treatment for advanced gastric cancer. Whereas a randomized phase III trial of CPT-11 versus paclitaxel in a second-line setting after failure of first-line chemotherapy with fluoropyrimidine and platinum is ongoing in Japan [West Japan Oncology Group (WJOG) 4007]. Today in Japan, combination therapy with S-1 and CDDP is recognized as the standard first-line therapy for advanced gastric cancer. In this situation, CPT-11 plus CDDP is not applicable in a second-line setting for many initially unresectable patients. However, for patients who develop recurrence during or immediately after adjuvant therapy with S-1, combination therapy with CPT-11 and CDDP might be a promising regimen. Another phase III trial comparing taxane and CPT-11 plus CDDP is also underway for patients in whom S-1 monotherapy has failed, especially in an adjuvant setting.

In conclusion, this study suggests that administration of CPT-11 plus CDDP on a biweekly regimen might have comparable activity with administration of these agents on a 4-weekly regimen, in addition to being associated with milder toxicities. A biweekly regimen could be considered as the preferred test arm in a comparison with a 4-weekly regimen in future trials.

Conflict of interest statement No author has any conflict of interest.

References

1. Glimelius B, Ekstrom K, Hoffman K et al (1997) Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 8:163–168
2. Pyrhonen S, Kuitunen T, Nyandoto P et al (1995) 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 71:587–591
3. Murad AM, Santiago FF, Petroianu A et al (1993) Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 72:37–41
4. Boku N, Yamamoto S, Fukuda H et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069
5. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
6. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820

7. Hsiang YH, Liu LF, Wall ME et al (1989) DNA topoisomerase I-mediated DNA cleavage and cytotoxicity of camptothecin analogues. Cancer Res 49:4385–4389
8. Thuss-Patience PC, Kretzschmar A, Deist T et al (2009) Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol 27:15(Suppl) abstr 4540
9. Boku N, Ohtsu A, Shimada Y et al (1999) Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol 17:319
10. Ueda S, Hironaka S, Boku N et al (2006) Combination chemotherapy with irinotecan and cisplatin in pretreated patients with unresectable or recurrent gastric cancer. Gastric Cancer 9:203–207
11. Koizumi W, Kurihara M, Satoh A et al (2005) Phase 1/11 study of bi-weekly irinotecan plus cisplatin in the treatment of advanced gastric cancer. Anticancer Res 25:1257–1262
12. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) 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 92:205–216
13. Futatsuki K, Wakui A, Nakao I et al (1994) Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. Gan To Kagaku Ryoho 21:1033–1038
14. Yoshida T, Yoshikawa T, Tsuburaya A et al (2006) Feasibility study of biweekly CPT-11 plus CDDP for S-1- and paclitaxel-refractory, metastatic gastric cancer. Anticancer Res 26:1595–1598
15. Nakae S, Hirao M, Kishimoto T et al (2008) Phase II study of biweekly CPT-11+CDDP for patients with gastric cancer refractory to S-1 (OGSG 0504 study). J Clin Oncol 26:(May 20 Suppl) abstr 4571
16. Arai T, Hamaguchi T, Shirao K et al (2003) Weekly paclitaxel in patients with heavily treated advanced gastric cancer. Proc Am Soc Clin Oncol 22:321

VOLUME 28 · NUMBER 11 · APRIL 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer

Toshihiko Doi, Kei Muro, Narikazu Boku, Yasuhide Yamada, Tomohiro Nishina, Hiroya Takiuchi, Yoshito Komatsu, Yasuo Hamamoto, Nobutsugu Ohno, Yoshie Fujita, Matthew Robson, and Atsushi Ohtsu

From the National Cancer Center Hospital East, Chiba; Aichi Cancer Center, Aichi; Shizuoka Cancer Center, Shizuoka; National Cancer Center Hospital; Novartis K.K., Tokyo; Shikoku Cancer Center, Ehime; Osaka Medical College, Osaka; Hokkaido University Hospital, Hokkaido; Tochigi Cancer Center, Tochigi, Japan; and Novartis Pharmaceutical Corp, East Hanover, NJ.

Submitted October 1, 2009; accepted December 11, 2009; published online ahead of print at www.jco.org on March 15, 2010.

Supported by Novartis.

Presented at the 2009 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, January 15-17, 2009, San Francisco, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Toshihiko Doi, MD, PhD, National Cancer Center Hospital East, 5-1, Kashiwanoha 6-chome, Kashiwa-shi, Chiba 277-8577, Japan; e-mail: tdoi@east.ncc.go.jp.

0732-183X/10/2811-1904/$20.00

DOI: 10.1200/JCO.2009.26.2923

ABSTRACT

Purpose
Everolimus, an oral inhibitor of the mammalian target of rapamycin, has shown antitumor activity in gastric cancer in preclinical and phase I studies. This phase II study evaluated the efficacy and safety of everolimus in pretreated patients with advanced gastric cancer.

Patients and Methods
Patients with advanced gastric cancer who experienced progression despite prior chemotherapy received everolimus 10 mg orally daily until disease progression or study discontinuation. The primary end point was disease control rate (DCR; ie, complete response, partial response, or stable disease). Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

Results
Fifty-three patients were assessable (median age, 63 years; 51% and 49% received one or two prior chemotherapy regimens, respectively). Although no complete or partial response was obtained, a decrease in tumor size from baseline was observed in 45% of patients by central review. The DCR was 56.0% (95% CI, 41.3% to 70.0%); median PFS was 2.7 months (95% CI, 1.6 to 3.0 months). At a median follow-up time of 9.6 months, median OS was 10.1 months (95% CI, 6.5 to 12.1 months). Common grade 3 or 4 adverse events included anemia, hyponatremia, increased γ-glutamyltransferase, and lymphopenia. Grade 1 or 2 pneumonitis was reported in eight patients (15.1%).

Conclusion
Everolimus monotherapy resulted in a promising DCR in patients with previously treated advanced gastric cancer. Adverse events are consistent with the reported safety profile of everolimus. These results warrant further evaluation in patients with advanced gastric cancer.

J Clin Oncol 28:1904-1910. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide, with 603,003 and 330,290 new cases among men and women, respectively, reported annually between 1993 and 2001.[1,2] Globally, it is the second most common cause of cancer death, with an estimated 700,000 deaths annually.[1,2] In Japan, gastric cancer is the second leading cause of cancer death (50,415 deaths in 2006), accounting for 15.3% of all cancer deaths.[3]

Only surgical resection is curative; however, patients with gastric cancer commonly present with unresectable disease.[4] Even after curative surgical resection, 60% of these patients eventually experience relapse.[5] Systemic chemotherapy has been evaluated extensively in patients with unresectable and recurrent gastric cancer.[4,5] At present, although fluoropyrimidine-based therapy is used worldwide, there is no globally accepted standard first-line chemotherapy for advanced gastric cancer. In randomized studies, combination chemotherapy regimens including fluorouracil (FU) or its derivatives, taxanes, irinotecan, and platinum derivatives generally achieved median overall survival (OS) times of less than 1 year in the first-line setting.[6-12] In Japan, S-1 (tegafur + gimeracil + oteracil potassium) is an established first-line agent for advanced gastric cancer. A recent phase III trial demonstrated a median OS time of 13 months with the combination of S-1 plus cisplatin as first-line therapy for patients (n = 148) with advanced gastric cancer.[13]

The poor long-term outcomes associated with chemotherapies to date strongly suggest considerable unmet needs in gastric cancer and a need for new agents, particularly targeted agents that will confer a survival benefit with acceptable tolerability. This is especially true in the second- and third-line

settings, in which to date there are no phase III studies demonstrating survival benefit for chemotherapy compared with best supportive care.

Inhibition of the mammalian target of rapamycin (mTOR) pathway represents a new therapeutic target in the treatment of various human cancers. mTOR, a key protein kinase that regulates cell growth and proliferation, cellular metabolism, and angiogenesis,[14] is mainly activated via the PI3 kinase pathway through Akt/PKB and tuberous sclerosis complex. Mutations in these components or in PTEN, a negative regulator of PI3 kinase, result in inappropriate mTOR activation.[14] The mTOR pathway has been shown to be frequently dysregulated in a variety of human cancers, including gastric cancer.[15] Oncogenic transformation maintained by a dysregulated mTOR pathway may sensitize tumor cells to mTOR inhibitors.[14] Overexpression of the mTOR downstream effectors[14] eIF4E and 4E binding protein 1 (4E-BP1) was shown in GI cancer cells. Everolimus reduced 4E-BP1 phosphorylation and attenuated production of the proangiogenic factors hypoxia-inducible factor 1α and vascular endothelial growth factor in these gastric cancer cell lines.[15]

Everolimus is an orally bioavailable mTOR inhibitor that binds with high affinity to its intracellular receptor FKBP12.[16] Everolimus has demonstrated antitumor activity in gastric cancer in preclinical studies[14,15,17] and a phase I study involving patients with advanced gastric cancer.[18] The current phase II study evaluated the efficacy and safety of everolimus monotherapy in patients with advanced gastric cancer who had experienced treatment failure with one or two prior chemotherapy regimens.

PATIENTS AND METHODS

Patient Eligibility

This open-label, single-arm, multicenter, proof-of-concept, phase II study was conducted in Japan and included patients ≥ 20 years of age with pathologically confirmed advanced gastric adenocarcinoma who had received one or two prior chemotherapy regimens (one regimen was required to contain any of the following: FU or its derivatives, platinum derivatives, taxanes, or irinotecan) and who had ≥ one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients were required to have documented progressive disease (PD) based on imaging during or after last prior treatment. Before study entry, prior therapies had to be completed for ≥ 2 weeks for anticancer agents and for ≥ 4 weeks for surgery or radiotherapy, and patients had to recover from adverse reactions of prior therapy. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate organ function (bone marrow function: neutrophils ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, hemoglobin ≥ 8.5 g/dL; liver function: serum bilirubin ≤ 1.5 mg/dL and ALT and AST ≤ 2.5 × upper limit of normal [ULN] if no evidence of liver metastasis or serum bilirubin ≤ 1.5 mg/dL and ALT and AST ≤ 5.0 × ULN with liver metastases; renal function: serum creatinine ≤ 2 × ULN). Exclusion criteria were CNS metastases already detected, malignant ascites requiring invasive treatment (eg, ascites drainage), or severe or uncontrolled medical conditions (eg, impaired heart and lung function, diabetes, active infections, or liver disease).

This study was conducted according to the ethical principles of the Declaration of Helsinki and approved by the institutional review board of each center. All patients provided written informed consent.

Study Treatment and Assessment

All patients were treated with everolimus 10 mg/d orally in continuous 28-day cycles until tumor progression, unacceptable toxicity, or study discontinuation for any other reason. Two levels of dose reduction were permitted (5 mg/d and then 5 mg every other day) for tolerability. For the baseline tumor assessment, radiographic assessments (computed tomography or magnetic resonance imaging scans of the chest, abdomen, and pelvis) were performed within 2 weeks before the first dose of everolimus. Tumor response was assessed every 4 weeks from cycle 2 to cycle 4 and then every two cycles until determination of disease progression and/or at the end of the study. Disease status was assessed by a local radiologist with the investigator and reviewed by central review of radiology using RECIST criteria.

Safety assessments consisted of continuous monitoring and recording of all adverse events (AEs) and regular monitoring of hematology, serum chemistry, vital signs, weight, ECOG PS, chest computed tomography scans, and physical condition. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Statistical Considerations

The primary efficacy objective was to assess disease control rate (DCR), which was defined as the proportion of patients with complete response, partial response, or stable disease (SD) as the best overall response according to RECIST. DCR was summarized in terms of percentage, with a 95% CI. The DCR was calculated primarily based on the assessment of the central radiologic review. All results were analyzed in the full analysis set (FAS), which included all patients who received at least one dose of everolimus. DCR as primary end point was also analyzed in the per-protocol set (PPS), which consisted of patients from the FAS who completed a minimum exposure requirement (dose-intensity ≥ 0.5) or experienced progression before the minimum exposure requirement without any major protocol deviation and was defined as the primary analysis population. This study adopted a Simon two-stage design for sample size determination,[19] which required disease control in ≥ eight of the first 21 patients enrolled onto the first stage to proceed to the second stage, in which an additional 27 patients were planned to be enrolled. The null hypothesis was a DCR of ≤ 30%. DCRs of 30% (futility rate) and 50% (targeted antitumor activity rate) were used for power setting.[20,21] If ≥ 20 of 48 patients achieved disease control, the null hypothesis would be rejected, and everolimus would be considered to have antitumor activity in this population.

The secondary end points of the study were to assess objective response rate, progression-free survival (PFS), OS, and the safety profile of everolimus. PFS and OS curves were generated using the Kaplan-Meier product-limit method. Median PFS and OS were obtained with a 95% CI. Safety analysis was performed in the safety population, which consisted of all patients who received ≥ one dose of everolimus and had ≥ one postbaseline safety assessment.

As an exploratory end point, the influence of gastrectomy on the pharmacokinetics (PKs) of everolimus was investigated. Blood samples for PK analyses were collected from patients enrolled onto the first stage before dose and at 1, 2, 3, and 4 hours after dose on day 1 of cycles 1 and 2 and from all patients before dose on day 1 of cycles 1, 2, 3, and 4. Everolimus concentrations in whole blood were determined by liquid chromatography–mass spectrometry. The PK population consisted of all patients from the safety population who had PK samples available. Noncompartmental methods with WINNonlin Pro (Version 5.2; Pharsight, St Louis, MO) were used to determine the PK parameters of area under the concentration-time curve from 0 to 4 hours after drug administration [$AUC_{(0\text{-}4)}$], observed predose concentration (C_{min}), maximum blood drug concentration (C_{max}), and time to reach maximum concentration after drug administration (T_{max}).

RESULTS

Patient Disposition

A total of 26 patients were enrolled onto the first stage to ensure 21 patients in the PPS population at week 8. Central radiologic review confirmed that ≥ eight patients achieved disease control, and an additional 28 patients were enrolled onto stage 2 (Fig 1). The FAS population included 53 patients; the remaining patient did not receive study medication because of ineligibility. Three patients were not

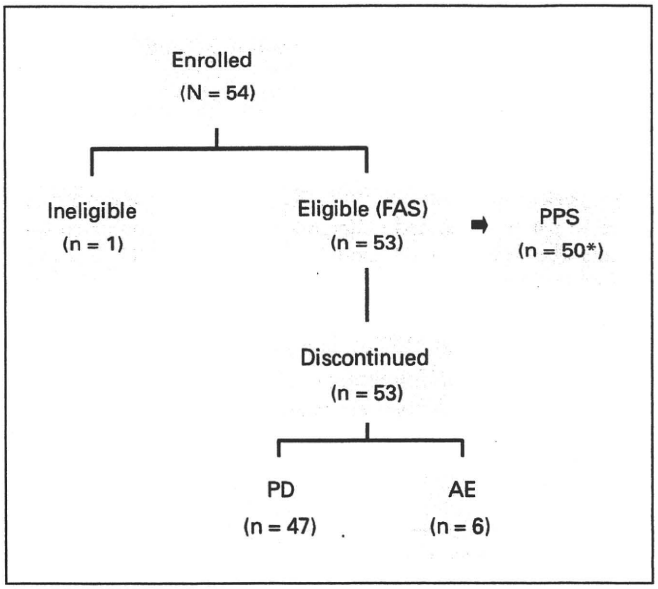

Fig 1. Patient disposition. (*) Three patients were excluded from the per-protocol set (PPS), two with unknown best response and one with dose intensity less than 50% during the first 8 weeks of treatment. FAS, full analysis set; PD, progressive disease; AE, adverse event.

included in the PPS population (n = 50); two patients were not assessable for best overall response, and one patient had a dose-intensity of less than 50% during the first 8 weeks of treatment. At study completion, 47 patients had discontinued treatment as a result of disease progression (Fig 1).

Patient Characteristics

Most patients were men (77%), and the median age was 63 years (Table 1). All treated patients had an ECOG PS of 0 or 1 (PS 0 = 60%; PS 1 = 40%). Most patients had moderately (47%) or poorly (42%) differentiated adenocarcinomas. Most patients had been previously treated; 25 of 53 patients had a gastrectomy, and all patients had received chemotherapy (51% with one prior line; 49% with two prior lines). The most commonly used prior chemotherapy agents in the study population were FU derivatives (S-1) as monotherapy (49%) and in combination with cisplatin (55%), and the most common second-line agents were paclitaxel (17%) or irinotecan (11%) as monotherapy (Table 1).

Efficacy

Best overall responses per central radiology review are listed in Table 2; 28 (56.0%) and 22 patients (44.0%) in the PPS population and 29 (54.7%) and 22 patients (41.5%) in the FAS population had SD and PD, respectively. Disease control was observed in more than 20 patients in the first 48 patients (out of 50 patients) in the PPS population, and the null hypothesis (DCR $\leq$ 30%) was rejected at the one-sided $\alpha = .05$. At the final analysis, disease control was observed in 28 patients (56.0%; 95% CI, 41.3% to 70.0%) in the PPS population. The lower limit 95% CI value (41.3%) exceeded the threshold (30%) for futility. Results in the FAS population (DCR = 54.7%; 95% CI, 40.4% to 68.4%) were consistent with the results observed in the PPS population. Although no complete or partial response was obtained, a decrease in tumor size from baseline was observed in 45% of patients by central review. The maximum best change observed was a 34% decrease in sum of longest diameters when compared with baseline (Fig 2). Subgroup analysis by number of previous chemotherapies indicated that the effect of everolimus was consistent in the second- and third-line PPS populations, with the same proportions of patients with SD (56.0%) and PD (44.0%) observed in each group.

Table 1. Patient Demographic and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 53)	%
Age, years		
Median	63	
Range	30-77	
Asian	53	100
Male	41	77
ECOG performance status (0/1)		
0	32	60
1	21	40
Degree of tumor differentiation		
Well	6	11
Moderate	25	47
Poor	22	42
Gastrectomy	25	47
No. of prior chemotherapy regimens		
1	27	51
2	26	49
Contents of prior chemotherapy regimens		
FU monotherapy*	26	48
FU plus cisplatin	29	55
Paclitaxel monotherapy	9	17
Irinotecan monotherapy	6	11
Other†	9	17
Site of measurable lesion		
Abdominal lymph node	26	49
Liver	25	47
Distant lymph node	11	21
Peritoneum	4	8
Lung	3	6
Ovary	3	6
Other‡	5	9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil.
*Including FU derivatives S-1, capecitabine, and so on.
†Other includes irinotecan plus cisplatin (n = 4), FU plus paclitaxel (n = 3), FU plus irinotecan (n = 1), and FU plus methotrexate (n = 1).
‡Other measurable lesion sites include abdominal mass, adrenals, thyroid gland, pleura, pulmonary lymphangitic spread (n = 1 each).

Table 2. Best Overall Response and DCR per Central Review

Best Overall Response and DCR	PPS (n = 50) No. of Patients	PPS (n = 50) %	FAS (N = 53) No. of Patients	FAS (N = 53) %
Best overall response				
CR	0	0	0	
PR	0	0	0	
SD	28	56.0	29	54.7
PD	22	44.0	22	41.5
Unknown	0	0	2	3.8
DCR (CR + PR + SD)	28	56.0	29	54.7
95% CI, %	41.3 to 70.0		40.4 to 68.4	

Abbreviations: DCR, disease control rate; PPS, per-protocol set; FAS, full analysis set; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

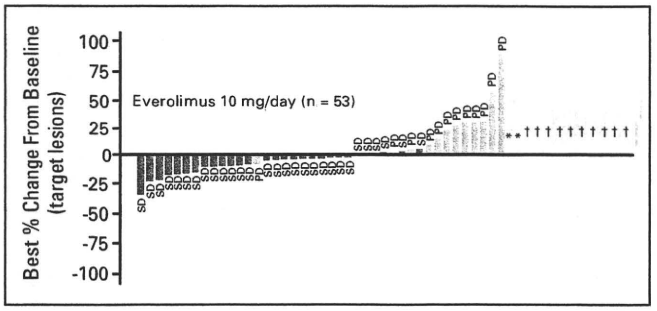

Fig 2. Maximum best change in tumor size from baseline. Decrease in best percent change from baseline = 45.28%; increase in best percent change or no percent change from baseline = 32.08%. (*) Percent change in target lesion was available but contradicted by overall lesion response = unknown 3.77%. (†) Percent change in target lesion was available but contradicted by overall lesion response = progressive disease (PD) 18.87%. SD, stable disease.

Median PFS was 2.7 months (95% CI, 1.6 to 3.0 months; Fig 3A). At 4 months, 28.3% (Kaplan-Meier estimate) of patients were progression free. Subgroup analysis did not reveal a difference in PFS stratified by number of prior chemotherapy regimens; in the second-line setting, median PFS was 2.6 months (95% CI, 1.0 to 3.0 months), and in the third-line setting, median PFS was 2.8 months (95% CI, 1.6 to 4.0 months). At a median follow-up time of 9.6 months, median OS was 10.1 months (95% CI, 6.5 to 12.1 months; Fig 3B); in the second-line setting, median OS was 9.8 months (95% CI, 6.2 to 12.3 months), and in the third-line setting, median OS was 10.7 months (95% CI, 6.3 months to not reached).

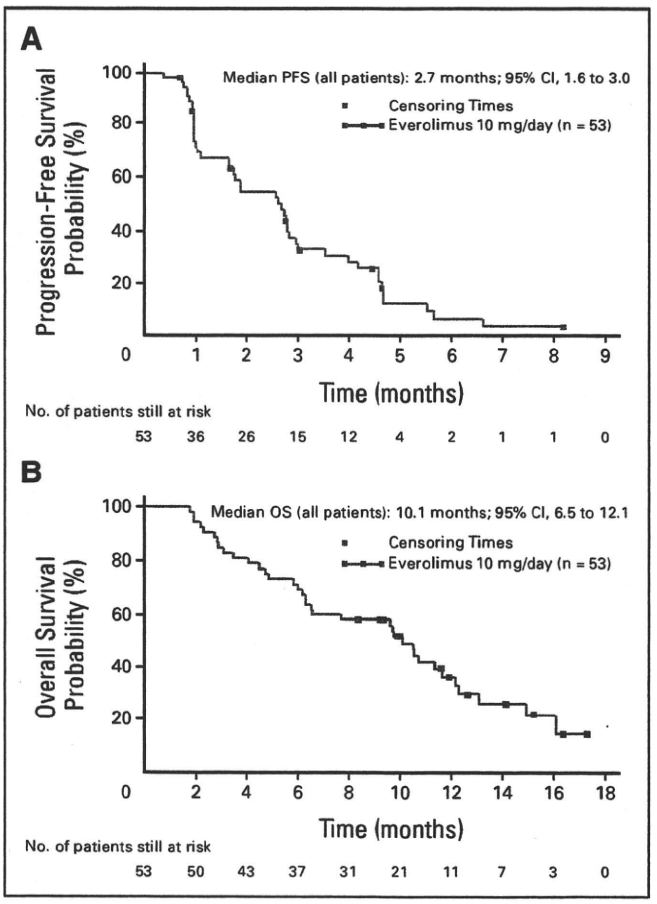

Fig 3. Kaplan-Meier plots of (A) median progression-free survival (PFS) and (B) median overall survival (OS) in all patients.

PK Analysis

On day 1 of cycle 1 and at steady-state (day 1 of cycle 2), slightly higher peak plasma concentrations (C_{max}) of everolimus were observed in patients who had undergone gastrectomy compared with patients who had not. In addition, T_{max}, C_{max}, and $AUC_{(0-4)}$ data on day 1 of cycle 1 and at steady-state also suggest that the rate of absorption of everolimus was faster in patients who had undergone gastrectomy [higher C_{max} and $AUC_{(0-4)}$ and shorter T_{max}] than in patients who had not (Table 3). However, mean C_{min} values on day 1 of cycles 1, 2, 3, and 4 were similar between patients with and without gastrectomy, as were AUC during dosing interval values at steady-state,

Table 3. PK Parameters of Everolimus

PK Parameter	No. of Patients	PK Value Mean	PK Value SD
Day 1 of cycle 1			
C_{max}, ng/mL			
No gastrectomy	14	78.3	39.7
Gastrectomy	12	122	33.2
T_{max}, hours			
No gastrectomy	14	1.5	0.92
Gastrectomy	12	1.1	0.29
$AUC_{(0-4)}$, h · ng/mL			
No gastrectomy	14	172	84
Gastrectomy	12	271	84
Day 29 (day 1 of cycle 2)			
C_{max}, ng/mL			
No gastrectomy	6	98.7	33.4
Gastrectomy	10	134	33.0
T_{max}, hours			
No gastrectomy	6	2.0	1.29
Gastrectomy	10	1.0	0.11
$AUC_{(0-4)}$, h · ng/mL			
No gastrectomy	6	254	101
Gastrectomy	10	324	94
C_{min}, ng/mL			
Day 1 (day 1 cycle 1)			
No gastrectomy	9	11.2	2.43
Gastrectomy	6	15.4	2.96
Day 29 (day 1 cycle 2)			
No gastrectomy	16	27.6	22.3
Gastrectomy	21	25.5	14.4
Day 57 (day 1 cycle 3)			
No gastrectomy	11	25.0	10.2
Gastrectomy	11	17.7	6.87
Day 85 (day 1 cycle 4)			
No gastrectomy	6	23.3	7.48
Gastrectomy	12	18.0	6.31
AUC0-τ on day 29 (day 1 of cycle 2), ng · h/mL			
No gastrectomy	6	1,080	744
Gastrectomy	10	1,100	417

Abbreviations: PK, pharmacokinetic; SD, standard deviation; C_{max}, maximum blood concentration; T_{max}, time to reach maximum plasma concentration; $AUC_{(0-4)}$, area under the concentration time curve during the first 4 hours after drug administration; C_{min}, minimum blood concentration; AUC0-τ, area under the concentration time curve during the dosing interval.

suggesting that the extent of oral absorption was similar between the two groups (Table 3).

Safety

The median duration of everolimus therapy was 57.0 days (range, 11 to 249 days), with a median cumulative dose of 540 mg (range, 110 to 1,960 mg). Although 23 patients (43.4%) had a dose reduction or interruption, the mean relative dose-intensity was 0.9.

The major AEs observed with everolimus were grade 1 or 2 in severity. The most common AEs were stomatitis (73.6%), anorexia (52.8%), fatigue (50.9%), rash (45.3%), nausea (32.1%), peripheral edema (22.6%), diarrhea (20.8%), and pruritus (18.9%). Grade 3 or 4 AEs observed during the study are listed in Table 4. Grade 3 AEs occurred in 20 patients (37.7%), including anemia (11.3%), hyponatremia (9.4%), increased γ-glutamyltransferase (7.5%), lymphopenia (7.5%), fatigue (5.7%), stomatitis (5.7%), anorexia (5.7%), abnormal hepatic function (5.7%), hyperglycemia (3.8%), hypophosphatemia (3.8%), and ileus (3.8%). Grade 4 AEs suspected to be related to treatment were reported in four patients; one patient each had tumor hemorrhage, increased γ-glutamyltransferase, lymphopenia, and cerebral infarction. Six patients discontinued the protocol treatment as a result of AEs; five of these patients had AEs suspected to be related to everolimus (grade 2 pneumonitis, n = 2; grade 3 stomatitis, n = 1; liver dysfunction, n = 1; and tumor hemorrhage, n = 1). Pneumonitis related to everolimus was observed in eight patients (15.1%); the maximum severity was grade 2.

At the time of this analysis, 36 (67.9%) of 53 patients had died; 33 of these patients died of gastric cancer, two patients died of aspiration pneumonia (not suspected to be related to everolimus), and one patient died 313 days after last dose of study drug with the cause of death unknown.

DISCUSSION

Everolimus monotherapy demonstrated a promising DCR of 56% in pretreated patients with advanced gastric cancer. In addition, 45% of patients demonstrated tumor shrinkage from baseline, the median PFS was 2.7 months, and the median OS was 10.1 months. All efficacy data except survival were judged by an independent central radiologic review committee.

The choice of DCR as the primary end point in this study was considered appropriate because it reflects clinical practice where progression usually necessitates a change of treatment; its use is also appropriate in a proof-of-concept study in the second- and third-line settings. Patients in this study were previously treated; nearly half (49%) received everolimus as a third-line therapy. The reasons for the choice of this population were the recent establishment of S-1 plus cisplatin as a standard first-line regimen in Japan and the lack of any evidence, at the time of the study, to support a survival benefit of chemotherapy over best supportive care in the second- or third-line setting in advanced gastric cancer.

The clinical evaluation of everolimus in patients with gastric cancer is supported by research regarding the mTOR pathway in preclinical models[14,15,17,22,23]; blockade of PI3 kinase signaling via mTOR inhibition has shown antitumor activity in experimental models of gastric cancer.[22,23] It is noteworthy that the efficacy results were similar in patients who had received one or two prior chemotherapy regimens. A number of other agents and combinations have been evaluated as second-line therapy in patients with advanced gastric cancer, including docetaxel, paclitaxel, irinotecan/cisplatin, paclitaxel/doxifluridine, paclitaxel/cisplatin, and S-1/mitomycin.[20,24-29] Median OS ranged from 3.5 months[24] to 7.2 months[30] in the single-agent trials and from 6 months[28] to 10.5 months[29] in the combination therapy trials. In this trial, median OS was 10.1 months (9.8 months in the second-line setting and 10.7 months in the third-line setting). These results seem to compare favorably with those observed in the other trials evaluating single-agent and combination therapy in the second-line setting. Although the number of patients in the third-line setting in this study is small, their median OS of more than 10 months is encouraging when compared with other studies in this patient population.

In earlier studies comparing FU monotherapy with FU plus cisplatin, uracil/tegafur plus mitomycin,[31] or irinotecan plus cisplatin,[32] the combinations had no survival advantage over FU monotherapy. One potential explanation for this observation is that therapy with a single agent preserved the patients' PS, allowing them to receive additional lines of chemotherapy. The same effect may have been seen in this study, where the majority of patients (n = 45) received additional chemotherapy after discontinuation of everolimus, again potentially implying that the single-agent therapy with everolimus preserved the patients' PS, making them suitable candidates for further line(s) of therapy. At the time of study discontinuation, 85% of patients (45 of 53 patients) had PS of 0 to 1, and 92% of patients (49 of 53 patients) had PS of 0 to 2.

Everolimus was generally well tolerated, and no new safety concerns were identified in the study. Grade 3 stomatitis was reported in three patients. Other major grade 3 or 4 AEs included anemia (11.3%), hyponatremia (9.4%), increased γ-glutamyltransferase (7.5%), and lymphopenia (7.5%). Pneumonitis related to everolimus was observed in eight patients (15.1%), with no grade 3 or 4 pneumonitis observed. There were no treatment-related deaths and no deaths within 28 days after discontinuation of study drug. The frequency and severity of AEs in this study, including pneumonitis, seem to be consistent with those in a large phase III placebo-controlled trial in patients with advanced renal cell carcinoma.[33] Compared with other

Table 4. Grade 3 or 4 Adverse Events > 3% Regardless of Relationship to Study Drug (N = 53)

Adverse Event	No. of Patients: Grade 3	No. of Patients: Grade 4	Total Grade 3 or 4: No. of Patients	Total Grade 3 or 4: %
Anemia	4	1	5	9.4
Hyponatremia	5	0	5	9.4
Increased GGT	2	2	4	7.5
Lymphopenia	2	2	4	7.5
Fatigue	3	0	3	5.7
Stomatitis	3	0	3	5.7
Anorexia	3	0	3	5.7
Abnormal hepatic function	2	1	3	5.7
Hyperglycemia	2	0	2	3.8
Hypophosphatemia	2	0	2	3.8
Ileus	2	0	2	3.8

Abbreviation: GGT, γ-glutamyltransferase.

second-line advanced gastric carcinoma trials,[20,25,28,30] everolimus monotherapy exhibits less bone marrow suppression in this setting. These results suggest that everolimus monotherapy is suitable for use on an outpatient basis.

PK analyses in this trial suggested that although the rate of oral absorption seems to be faster in patients who had undergone gastrectomy compared with patients who did not [as evidenced by a higher C_{max} and $AUC_{(0-4)}$ and shorter T_{max}], no differences in the extent of oral absorption were observed because the mean C_{min} and steady-state AUC over the dosing interval values were similar between patients with and without gastrectomy. Further investigation is needed because the sample size of this study is limited. In conclusion, everolimus monotherapy showed a promising rate of disease control and was well tolerated in previously treated patients with advanced gastric cancer, warranting further evaluation in a phase III trial of everolimus monotherapy in this population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Nobutsugu Ohno, Novartis (C); Yoshie Fujita, Novartis (C); Matthew Robson, Novartis (C) **Consultant or Advisory Role:** None **Stock Ownership:** Matthew Robson, Novartis Pharma **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Toshihiko Doi, Nobutsugu Ohno, Yoshie Fujita, Matthew Robson, Atsushi Ohtsu

Administrative support: Nobutsugu Ohno, Yoshie Fujita

Provision of study materials or patients: Toshihiko Doi, Kei Muro, Narikazu Boku, Yasuhide Yamada, Tomohiro Nishina, Hiroya Takiuchi, Yoshito Komatsu, Yasuo Hamamoto, Nobutsugu Ohno, Yoshie Fujita, Atsushi Ohtsu

Collection and assembly of data: Toshihiko Doi, Kei Muro, Yasuhide Yamada, Tomohiro Nishina, Hiroya Takiuchi, Yoshito Komatsu, Yasuo Hamamoto, Nobutsugu Ohno, Atsushi Ohtsu

Data analysis and interpretation: Toshihiko Doi, Yasuhide Yamada, Hiroya Takiuchi, Nobutsugu Ohno, Yoshie Fujita, Matthew Robson, Atsushi Ohtsu

Manuscript writing: Toshihiko Doi, Kei Muro, Narikazu Boku, Yasuhide Yamada, Tomohiro Nishina, Hiroya Takiuchi, Yoshito Komatsu, Yasuo Hamamoto, Nobutsugu Ohno, Yoshie Fujita, Matthew Robson, Atsushi Ohtsu

Final approval of manuscript: Toshihiko Doi, Kei Muro, Narikazu Boku, Yasuhide Yamada, Tomohiro Nishina, Hiroya Takiuchi, Yoshito Komatsu, Yasuo Hamamoto, Nobutsugu Ohno, Yoshie Fujita, Matthew Robson, Atsushi Ohtsu

REFERENCES

1. Kamangar F, Dores GM, Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137-2150, 2006
2. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005
3. Editorial Board of Cancer Statistics in Japan: Cancer Statistics in Japan 2008. Tokyo, Japan, Foundation for Promotion Cancer Research, 2008
4. Menges M, Hoehler T: Current strategies in systemic treatment of gastric cancer and cancer of the gastroesophageal junction. J Cancer Res Clin Oncol 135:29-38, 2009
5. Ajani JA: Evolving chemotherapy for advanced gastric cancer. Oncologist 10:49-58, 2005 (suppl 3)
6. 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 15:261-267, 1997
7. Ross P, Nicolson M, Cunningham D, et al: Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5- FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 20: 1996-2004, 2002
8. 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 19:1450-1457, 2008
9. 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 20:666-673, 2009
10. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil and first-line therapy for advanced gastric cancer: A report of the V325 Study Group. J Clin Oncol 24: 4991-4997, 2006
11. Cunningham D, Rao S, Starling N, et al: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36-46, 2008
12. Al-Batran S, Hartmann J, 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 26: 1435-1442, 2008
13. 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 9:215-221, 2008
14. Bjornsti MA, Houghton PJ: The TOR pathway: A target for cancer therapy. Nat Rev Cancer 4:335-348, 2004
15. Martín ME, Pérez MI, Redondo C, et al: 4E binding protein 1 expression is inversely correlated to the progression of gastrointestinal cancers. Int J Biochem Cell Biol 32:633-642, 2000
16. Wan X, Helman LJ: The biology behind mTOR inhibition in sarcoma. Oncologist 12:1007-1018, 2007
17. Cejka D, Preusser M, Woehrer A, et al: Everolimus (RAD001) and anti-angiogenic cyclophosphamide show long-term control of gastric cancer growth in vivo. Cancer Biol Ther 7:1377-1385, 2008
18. Okamoto I, Doi T, Ohtsu A, et al: Phase I clinical and pharmacokinetic study of RAD001 (Everolimus) administered daily to Japanese patients with advanced solid tumors. Jpn J Clin Oncol 40:17-23, 2010
19. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989
20. Hironaka S, Zenda S, Boku N, et al: Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 9:14-18, 2006
21. Yamada Y, Shirao K, Ohtsu A, et al: Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 12:1133-1137, 2001
22. Lang SA, Gaumann A, Koell GE, et al: Mammalian target of rapamycin is activated in human gastric cancer and serves as a target for therapy in an experimental model. Int J Cancer 120:1803-1810, 2007
23. Michl P, Downward J: Mechanisms of disease: PI3K/AKT signaling in gastrointestinal cancers. Z Gastroenterol 43:1133-1139, 2005
24. Graziano F, Catalano V, Baldelli AM, et al: A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. Ann Oncol 11:1263-1266, 2000
25. Lee K-W, Kim JH, Yun T, et al: Phase II study of low-dose paclitaxel and cisplatin as a second-line therapy after 5-fluorouracil/platinum chemotherapy