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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**

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**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

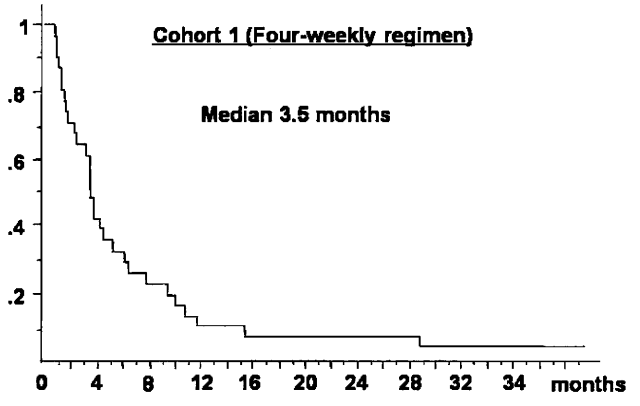


**Fig. 1** Kaplan–Meier curve for progression-free survival curve in cohort 1. Median progression-free survival was 3.5 months

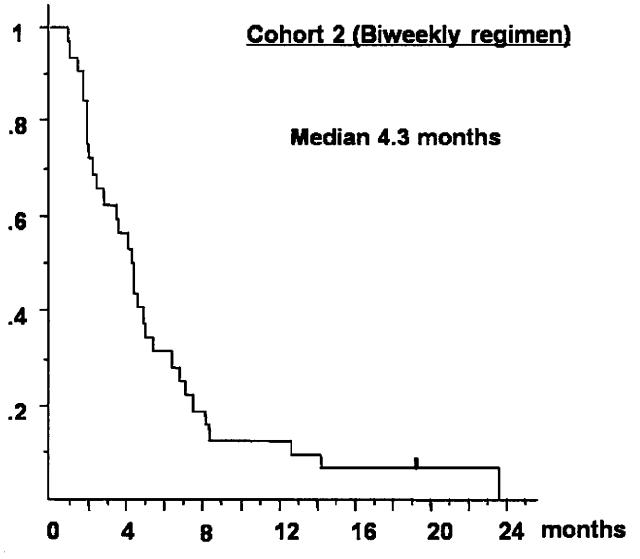


**Fig. 2** Kaplan–Meier curve for progression-free survival curve in cohort 2. Median progression-free survival was 4.3 months

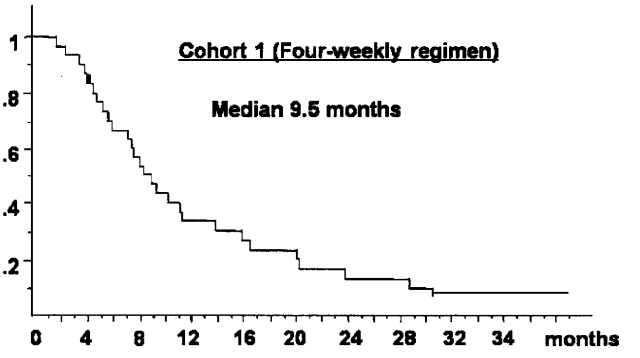


**Fig. 3** Kaplan–Meier curve for overall survival curve in cohort 1. Median overall survival was 9.5 months

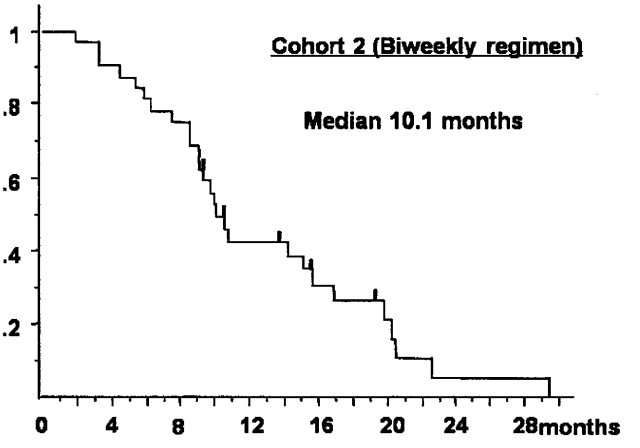


**Fig. 4** Kaplan–Meier curve for overall survival curve in cohort 2. Median overall survival was 10.1 months

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.

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ORIGINAL PAPER

# Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate?

**Hirofumi Asakura · Takayuki Hashimoto · Hideyuki Harada · Masashi Mizumoto · Kazuhisa Furutani · Noriaki Hasuike · Masaki Matsuoka · Hiroyuki Ono · Narikazu Boku · Tetsuo Nishimura**

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**Abstract**
*Purpose* To evaluate the effectiveness of short-course radiotherapy (RT) with 30 Gy in 10 fractions for bleeding from advanced gastric cancer.
*Methods* We reviewed the data for all patients with gastric cancer requiring blood transfusions due to gastric bleeding who were treated with RT at the Shizuoka Cancer Center Hospital between September 2002 and March 2007. Patients with curative-intent chemoradiotherapy or previous irradiation were excluded. RT was planned to deliver a total of 30 Gy at 3 Gy per fraction. We defined RT as effective if the patients did not require blood transfusions for 1 or more months after RT.
*Results* Twenty-two out of 30 patients (73%) responded to RT, and rebleeding occurred in 11 (50%) of 22 patients responding to RT. The median actuarial time to rebleeding was 3.3 months. Twelve patients received concurrent chemoradiotherapy and had a significantly lower rebleeding rate than patients undergoing RT alone ($P = 0.001$). Among patients receiving CRT, 1 with grade 3 nonhematological toxicity and 5 with grade 3–4 hematological toxicity were observed. No Grade 3 or higher adverse events were observed in patients treated with RT alone.
*Conclusions* RT with 30 Gy in 10 fractions is an adequate treatment for bleeding from advanced gastric cancer, especially in patients with poor prognosis.

**Keywords** Gastric cancer · Bleeding · Palliation · Radiotherapy · Chemoradiotherapy

H. Asakura (✉) · T. Hashimoto · H. Harada · M. Mizumoto · K. Furutani · T. Nishimura
Division of Radiation Oncology, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi, Shizuoka 411-8777, Japan
e-mail: h.asakura@scchr.jp

N. Hasuike · H. Ono
Division of Endoscopy, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi, Shizuoka 411-8777, Japan

M. Matsuoka · N. Boku
Division of Gastrointestinal Oncology, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi, Shizuoka 411-8777, Japan

## Introduction

For patients with resectable gastric cancer, the standard treatment with curative intent is radical surgery. Radiotherapy (RT) is mainly used with concurrent chemotherapy as adjuvant therapy in gastric cancer treatment (Xiong et al. 2003; Macdonald et al. 2001; Foukakis et al. 2007). The majority of patients with unresectable gastric cancer are treated with chemotherapy. Many clinical trials have shown the effectiveness of chemotherapy in unresectable gastric cancer (Wöhrer et al. 2004; Wagner et al. 2006; Rivera et al. 2007).

Gastric bleeding from the primary tumor frequently occurs in patients with unresectable gastric cancer. RT has been used to manage hemorrhage from lung cancer, cervical cancer, bladder cancer, and skin cancer (Pereira and Phan 2004). Although RT has also been used for palliation of symptoms including hemorrhaging in patients with unresectable gastric cancer, there have been only a few reports on this topic (Tey et al. 2007; Kim et al. 2008; Hashimoto et al. 2009), and various dose-fractionation regimens were used in these previous studies. Although 30 Gy in 10 fractions is one of the most commonly used dose-fractionation regimens for palliative RT, it has remained unclear whether this regimen is effective in

treating bleeding from advanced gastric cancer. The purpose of this study was therefore to evaluate the effectiveness and safety of short-course RT with 30 Gy in 10 fractions for bleeding from advanced gastric cancer.

## Methods

### Patients

The medical and radiation records of all patients with gastric cancer requiring blood transfusions due to gastric bleeding who were treated with RT at the Shizuoka Cancer Center Hospital between September 2002 and March 2007 were retrospectively reviewed. Patients with curative-intent chemoradiotherapy or previous irradiation were excluded.

### Radiotherapy

RT was planned to deliver a total of 30 Gy at 3 Gy per fraction using a linear accelerator with a 6-, 10-, or 18-MV photon beam. Three-dimensional dose calculations were performed using *Pinnacle3* software (ADAC, Milpitas, CA) with tissue-density inhomogeneity correction. The treatment planning was based on 3.8- to 5-mm-thick CT scans obtained in the treatment position. The clinical target volume (CTV) was based on clinical examinations including CT scan and endoscopy. Regional lymph nodes were not intended to be included in the CTV. The radiation fields were designed to cover the CTV with an adequate margin. The majority of patients were treated with anteroposterior–posteroanterior opposed beams or oblique opposed beams.

### Evaluation

We defined RT as effective if the patients did not require blood transfusions for 1 or more months after the beginning of RT. Treatment toxicities were assessed according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0). Overall survival, rebleeding-free survival, and time to rebleeding were estimated from the beginning of RT using the Kaplan–Meier method, and the differences between groups with or without concurrent chemotherapy were compared using the log-rank test. For the estimation of time to rebleeding, patients without rebleeding were censored at the time of death or last follow-up. Patients who did not achieve a 1-month blood transfusion–free survival time or who underwent other concomitant treatments for hemostasis were considered as failure to achieve bleeding control (i.e. rebleeding) at day 0. Comparisons of the amount of blood transfused and the hemoglobin (Hb) levels before and after treatment were carried out using the Wilcoxon signed rank test. Data were considered statistically significant at $P$ values $<0.05$.

## Results

### Subjects

During the four and a half years of the study, there were 37 patients at Shizuoka Cancer Center Hospital who required blood transfusions due to bleeding from gastric cancer and were treated with RT. In each patient, the diagnosis was confirmed histopathologically. A total of 30 patients were analyzed, and the other 7 patients were excluded from the analysis because of curative-intent chemoradiotherapy ($n = 6$) or previous RT ($n = 1$).

The patient characteristics are shown in Table 1. There were 21 men and 9 women with a median age of 69 years (range, 36–82 years). Twenty-one patients received chemotherapy before RT. The number of chemotherapy regimens carried out before RT was one in 7 patients, two in 9 patients, and three or more in 5 patients. All patients underwent upper gastrointestinal endoscopy prior to radiotherapy, which confirmed the bleeding from the primary tumors. Seven patients had been treated for bleeding by endoscopic interventions within 1 month before starting RT and had not achieved hemostasis. Twenty-six patients had symptoms including melena or hematemesis.

### Treatment

Twelve patients received concurrent chemoradiotherapy (CRT). The concurrent chemotherapy regimens were as follows: S-1/cisplatin in 6 patients, S-1 in 1 patient, methotrexate/5-fluorouracil in 2 patients, 5-fluorouracil in 2 patients, and paclitaxel in 1 patient. Seven of 9 patients without previous chemotherapy received CRT. Nineteen patients received additional chemotherapy after completing RT. Ten of 12 patients with CRT received additional chemotherapy. Only 1 patient never received previous, concurrent, or additional chemotherapy.

Twenty-seven patients received a total of 30 Gy in 10 fractions. One patient was scheduled to receive a total of 27 Gy in 9 fractions due to the machine operating schedule resulting from a long holiday period. Two patients discontinued RT due to a poor general condition at a total dose of 21 Gy and 27 Gy, respectively. The CTV was determined as the whole stomach in 6 of the 30 patients.

### Efficacy

The median follow-up from the beginning of RT for the 30 patients was 3.5 months (range, 0.5–19.6 months).

**Table 1** Patient characteristics ($n = 30$)

| | No. (%) |
|---|---|
| Age (year) | |
| Range | 36–82 |
| Median | 69 |
| Sex | |
| Male | 21 (70) |
| Female | 9 (30) |
| Performance status (ECOG) | |
| 0–1 | 9 (30) |
| 2 | 9 (30) |
| 3 | 11 (37) |
| 4 | 1 (3) |
| Lowest Hb level before RT (g/dl) | |
| Range | 3.8–8.5 |
| Median | 5.1 |
| Distant metastasis | |
| No | 2 (4) |
| Yes | 28 (96) |
| Previous chemotherapy | |
| No | 9 (30) |
| Yes | 21 (70) |
| Radiation dose | |
| 21 Gy/7 fr | 1 (3) |
| 27 Gy/9 fr | 2 (7) |
| 30 Gy/10 fr | 27 (90) |
| Treatment field | |
| Local | 24 (80) |
| Whole stomach | 6 (20) |
| Concurrent chemotherapy | |
| No | 18 (60) |
| Yes | 12 (40) |
| Additional chemotherapy after RT | |
| No | 11 (37) |
| Yes | 19 (63) |

Figure 1 shows the overall survival curve for all 30 patients in the study. Twenty-nine (97%) of 30 patients died, and 1 patient was lost to follow-up. The median survival time from the beginning of RT was 3.6 months. Twenty-two (73%) of 30 patients responded to RT (i.e., patient did not require blood transfusion for 1 or more months). Six patients did not achieve a 1-month blood transfusion–free survival time, including 3 patients who died due to metastatic disease within 1 month of the beginning of RT, and 2 patients underwent other concomitant treatments for hemostasis (one patient was treated with an endoscopic argon plasma coagulator system and the other received arterial embolization). Of the 26 patients with melena or hematemesis, 20 (77%) showed an improvement in their

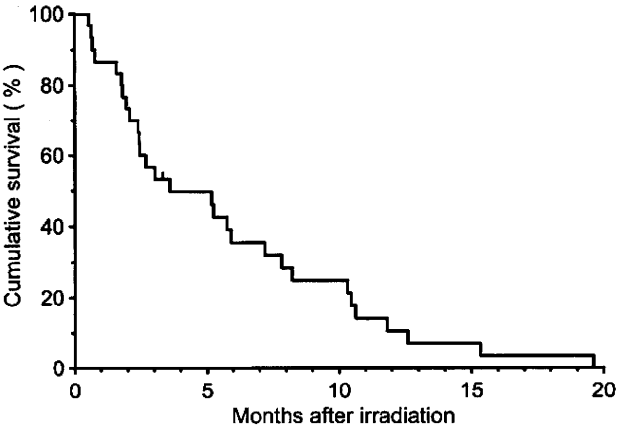


**Fig. 1** Overall survival for the entire patient population

symptoms. Figure 2a shows the amounts of blood transfused for 22 patients responding to RT before and after completion of RT. The mean amount of total blood that corresponds to transfused red blood cells in the 1-month periods before and after completion of RT were 2236 and 273 ml, respectively ($P < 0.0001$). Figure 2b shows the Hb levels of 22 patients responding to RT before and after treatment. The median Hb level 1 month after the last blood transfusion was 8.2 g/dl (range, 6.1–11.4 g/dl), compared to the median value of the lowest Hb level before the last blood transfusion of 4.9 g/dl (range, 3.8–8.5 g/dl) ($P < 0.0001$).

Figure 3a shows the rebleeding-free survival curve. The median rebleeding-free survival time from the beginning of RT was 2.6 months. The rebleeding-free survival curves in those with and without concurrent chemotherapy are shown in Fig. 3b. The median rebleeding-free survival was 1.7 months for RT alone compared with 5.5 months for CRT ($P = 0.002$). The median actuarial time to rebleeding was 3.3 months (Fig. 4a). The cumulative incidence curves for rebleeding in those with and without concurrent chemotherapy are shown in Fig. 4b. The 3-month cumulative incidences of rebleeding were 60% for RT alone compared with 17.5% for CRT ($P = 0.001$).

Of the 22 patients responding to RT, rebleeding occurred in 7 of 11 patients receiving RT-alone and 4 of 11 patients receiving CRT, respectively.

## Toxicities

Most patients experienced only minimal toxicity. A total of four grade 3 and two grade 4 treatment-related adverse events were observed in 4 patients receiving CRT. Of these patients, one experienced grade 3 gastric bleeding as a late toxicity. No grade 3 or higher adverse events were observed in patients treated with RT alone (Table 2).

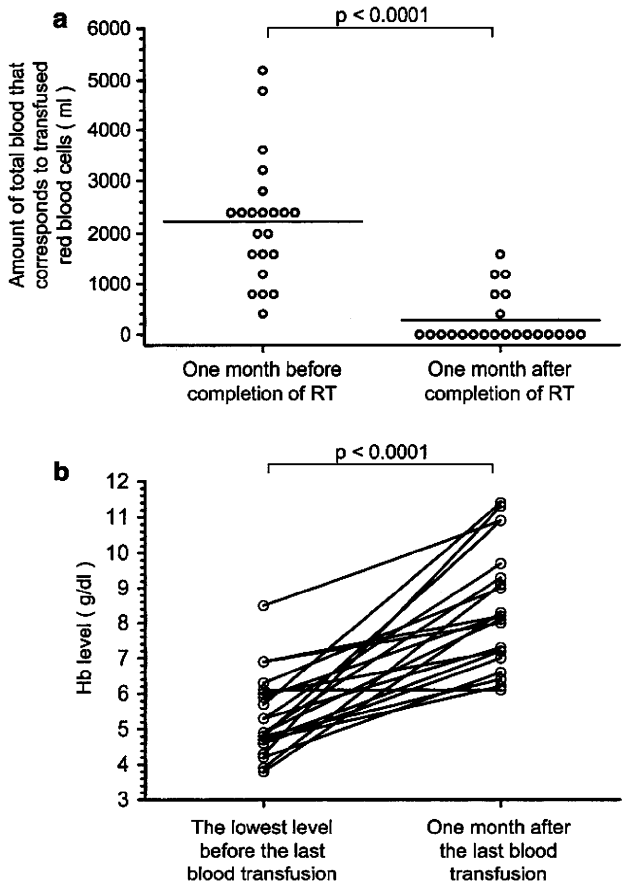


**Fig. 2** **a** Comparison of the amount of blood transfused in the 1 month before and after completion of RT for 22 patients responding to RT. Each *circle* on this plot represents the individual amount of total blood that corresponds to transfused red blood cells. The *black bars* are the mean amounts of total blood that correspond to transfused units across patients. **b** The Hb levels of 22 patients responding to RT before and after treatment. Each *circle* on this plot represents the individual Hb level, and *black lines* connect the Hb levels before and after treatment for each patient

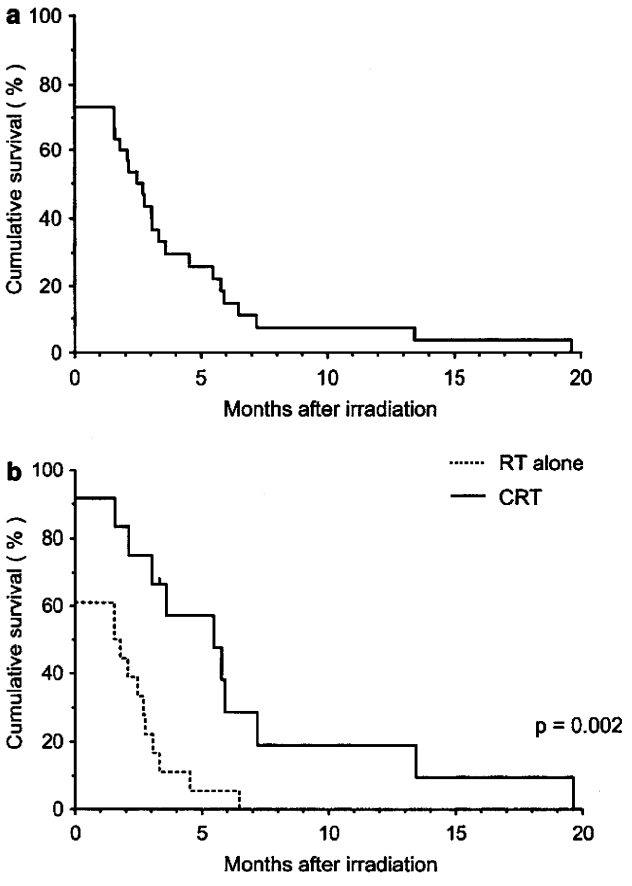


**Fig. 3** **a** Rebleeding-free survival for the entire patient population. **b** Rebleeding-free survival of patients with and without concurrent chemotherapy

## Discussion

Apart from three recent studies (Tey et al. 2007; Kim et al. 2008; Hashimoto et al. 2009) on the topic, there have been few reports regarding palliative RT for gastric cancer. The rates of bleeding control ranged from 57 to 70% in these studies. However, various dose fractionation regimens were used in each study, and there were also differences in the evaluation of treatment efficacy among the studies. These differences should be considered when comparing the bleeding control rates in the present study and other publications. In the present study, all patients received blood transfusions before RT, and the majority of patients received blood transfusions during RT, so RT was assumed to be effective when the patient did not require blood transfusions for 1 month or longer. Hashimoto's study and our study used similar methods for the evaluation of treatment efficacy, and treatment success was observed in 68% (13/19) of patients in their paper. A biologically effective dose (BED), calculated by the linear quadratic formula with an $\alpha/\beta$ ratio of 10 Gy, of 50 $Gy_{10}$ or more was significantly correlated with treatment success compared with a BED of <50 $Gy_{10}$, and so they recommended a dose of 40 Gy in 16 fractions. However, the dose-fractionation regimen of 30 Gy in 10 fractions used in our study corresponds to 39 $Gy_{10}$, and the rate of bleeding control was 73% on an intention-to-treat basis in the present study. As Hashimoto et al. mentioned in their discussion, patients treated with a BED of <50 $Gy_{10}$ included more than a few patients who discontinued RT, and the dose–response relationships in their study might also have been biased.

A dose-fractionation regimen of 30 Gy in 10 fractions is commonly used for palliative radiotherapy such as for brain metastasis and bone metastasis, and also showed a high response rate of 73% for palliating bleeding from advanced gastric cancer in our study. This schedule appears to have the benefit of being able to reduce the treatment period relative to 40 Gy in 16 fractions or 35 Gy in 14 fractions, doses which have been used for a large portion of

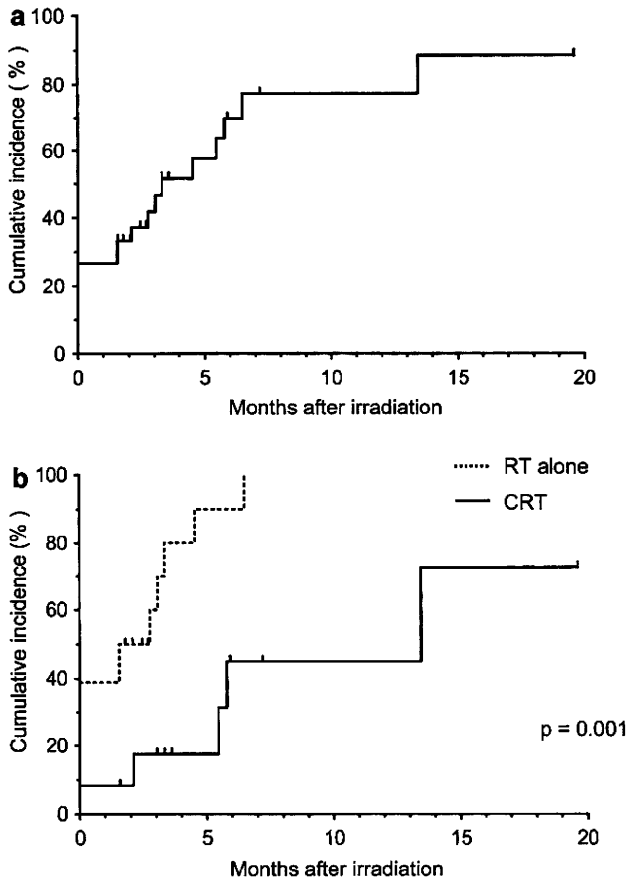


**Fig. 4** **a** Actuarial rebleeding rate for the entire patient population. **b** Actuarial rebleeding rate of patients with and without concurrent chemotherapy

**Table 2** Toxicity (CTCAEv3.0 Grade ≥ 2)

| | | RT alone ($n = 18$) | CRT ($n = 12$) | Total |
|---|---|---|---|---|
| Leukocytes | Grade 2 | 1 | 2 | 3 |
| | Grade 3 | 0 | 3 | 3 |
| | Grade 4 | 0 | 1 | 1 |
| Platelets | Grade 2 | 0 | 0 | 0 |
| | Grade 3 | 0 | 0 | 0 |
| | Grade 4 | 0 | 1 | 1 |
| Nausea/vomiting/anorexia/ heartburn | Grade 2 | 5 | 5 | 10 |
| Hemorrhage, GI-stomach | Grade 3 | 0 | 1 | 1 |

patients in previous studies regarding palliative RT for gastric cancer. In fact, of the patients in this study, 2 received RT on an outpatient basis, and the majority of patients who needed to be hospitalized were discharged from the hospital after achieving hemostasis. Reduction of the treatment period would be beneficial for these patients. Although 73% of patients responded to RT, the median actuarial time to rebleeding was 3.3 months in the current study. Kim et al. (2008) have reported that 6-month local control is better in patients treated with a BED of ≥41 $Gy_{10}$. The longer the patient lives after the end of RT, the greater the risk of rebleeding. Survival time will be influenced by various factors such as the time from the initial treatment, previous chemotherapy, performance status, and the existence of metastasis. Further clinical studies are required to assess the optimal dose-fractionation regimen, especially for patients expected to survive for a relatively long period.

The rate of patients free from rebleeding was better among the CRT group than the RT-alone group. However, there are limitations to this study, in that it was retrospective with a small sample size. Since systemic chemotherapy is the standard treatment for metastatic or unresectable gastric cancer, 70% (21/30) of patients received chemotherapy as the first-line treatment, and gastric bleeding occurred as a result of the disease progression in these patients in the present study. The CRT group tended to include patients without previous chemotherapy (7 of 12 patients) compared to the RT-alone group (2 of 18 patients). Selection biases might be relevant to an evaluation of this study. Considering that short-course RT with concomitant use of chemotherapy was feasible in the present study, indications for CRT should be determined based on whether there are chemotherapeutic regimens effective for the patients, by assessing the treatment history of the patients.

In conclusion, RT with 30 Gy in 10 fractions was found to be an effective and safe treatment option for bleeding from advanced gastric cancer. Seventy-three percent of patients achieved hemostasis in this study. Considering the median actuarial time to rebleeding (3.3 months), this dose-fractionation regimen appears to be adequate, especially for patients with poor prognosis.

**Conflict of interest statement** We declare that we have no conflict of interest.

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*Original article*

# Safety and efficacy of S-1 monotherapy in elderly patients with advanced gastric cancer

Takahiro Tsushima[1], Shuichi Hironaka[1,2], Narikazu Boku[1], Nozomu Machida[1], Kentaro Yamazaki[1], Hirofumi Yasui[1], Keisei Taku[1], Akira Fukutomi[1], and Yusuke Onozawa[1]

[1] Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Shizuoka 411-8777, Japan
[2] Clinical Research Promotion Department, Chiba Cancer Center, Chiba, Japan

**Abstract**

***Background.*** **Although S-1 is effective against advanced gastric cancer (AGC), its efficacy in elderly patients has not yet been investigated sufficiently. We assessed the efficacy and safety of S-1 monotherapy in elderly patients with AGC.**

***Methods.*** **We conducted a retrospective review of the data of 153 patients with unresectable/recurrent gastric adenocarcinoma who received S-1 monotherapy as first-line chemotherapy at our institution. S-1 was administered orally twice daily at the dose of 40 mg/m$^2$, on days 1–28, every 6 weeks. We categorized the patients into three groups, the young (≤65 years old), the middle-aged (66–75 years old), and the elderly (≥76 years old); and the drug toxicity, objective responses, progression-free survivals, and overall survivals were compared among the three groups.**

***Results.*** **The incidence of leukopenia of grade 3 or greater in the three groups was 7%, 5%, and 13%, and that of anemia was 9%, 18%, and 27%, respectively. In regard to nonhematological toxicities, the incidence of nausea of grade 3 or greater was 3%, 5%, and 13%; that of fatigue was 5%, 11%, and 20%; and that of anorexia was 5%, 6%, and 27%, respectively. As for the treatment efficacy, the objective response rates, median progression-free survivals, and overall survivals in the young, middle-aged, and elderly groups were 53%, 46%, and 33%; 7.8, 5.6, and 3.9 months; and 16.9, 17.1; and 7.7 months, respectively.**

***Conclusion.*** **Although S-1 monotherapy showed moderate efficacy in elderly (≥76 years) patients with AGC, patients in this age group showed higher incidences of severe toxicities than the younger patients.**

**Key words** S-1 · Elderly · Gastric Cancer · Safety · Efficacy

## Introduction

Gastric cancer is the second leading cause of death from malignant disease in the world [1, 2]. In Japan, gastric cancer is the most frequently encountered malignancy and the second leading cause of cancer-related death [3]. The prognosis of unresectable or recurrent tumors is very poor: the median survival time is about 4 months with best supportive care [4–6]. Although several randomized trials of treatments for advanced gastric cancer were conducted during the 1990s, with anthracyclines, mitomycin C, 5-fluorouracil (5-FU), methotrexate, and cisplatin [7–15], no standard treatment for advanced gastric cancer was established.

S-1 is an oral fluoropyrimidine, consisting of tegafur (a prodrug of fluorouracil), 5-chloro-2, 4-dihydropyrimidine (CDHP), and potassium oxonate. CDHP is an inhibitor of dihydropyrimidine dehydrogenase (DPD), which is the rate-limiting enzyme for the degradation of fluorouracil [16]. Three randomized controlled trials of S-1 monotherapy have been reported from Japan. One was the Japan Clinical Oncology Group (JCOG) 9912 trial, which showed the noninferiority of S-1 to continuous infusion of 5-FU, adopted as the reference arm for patients with unresectable or recurrent gastric cancer, based on the result of the JCOG9205 trial [15, 17]. The second trial was the S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer (SPIRITS) trial, conducted in 2007, which showed the superiority of S-1 plus cisplatin to S-1 alone in patients with advanced gastric cancer [18]. The third trial was the 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), which did not demonstrate the superiority of S-1 plus irinotecan (CPT-11) to S-1 alone [19]. From the results of these three phase III trials, S-1 plus cisplatin came to be recognized as the standard of care for patients with advanced gastric cancer in Japan, while S-1 monotherapy was a community standard until 2007.

In recent years, the percentage of elderly people in the general population in Japan has increased remarkably, to more than 20%, owing to the prolonged lifespan of the

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Japanese. Considering this social background, chemotherapy for elderly cancer patients is an important issue that must be addressed. However, because gastric cancer patients who were more than 75 years old were not included in the three aforementioned Japanese phase III trials, elderly patients are generally administered monotherapy with S-1, which is not as intensive as S-1 plus cisplatin. However, the efficacy and toxicity of S-1 monotherapy in elderly patients has not yet been clarified.

In this study, we assessed the safety and efficacy of S-1 monotherapy as a function of the age of patients with advanced gastric cancer.

## Subjects, materials, and methods

### *Patients*

The subjects were patients with unresectable or recurrent gastric cancer who received S-1 monotherapy at our hospital. The patient selection criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; histologically proven adenocarcinoma; no previous history of chemotherapy; adequate oral intake; adequate bone marrow, renal, and hepatic functions (defined as an absolute neutrophil count of ≥1500/μl, hemoglobin of ≥8.0 g/dl, serum creatinine of ≤1.5 mg/dl, serum transaminase levels less than threefold the upper limit of normal); and no concomitant malignancy. The presence of measurable lesions was not mandatory.

We categorized the patients into three groups, as follows; the young group (less than 66 years old), the middle-aged group (66 years or older, but not older than 75 years), and the elderly (more than 75 years old).

### *Treatment dose and schedule*

S-1 was administered orally twice daily at the dose of 40 mg/m$^2$ from day 1 to day 28, followed by 14 days' rest, and this regimen was repeated every 42 days until disease progression, the appearance of unacceptable toxicities, or the patient's refusal to continue treatment. The dosage of S-1 was determined according to the body surface area (BSA), as follows: BSA less than 1.25 m$^2$, 40 mg bid; BSA 1.25 to 1.5 m$^2$, 50 mg bid; BSA more than 1.5 m$^2$, 60 mg bid. We suspended treatment during the cycle or delayed the treatment cycle until nonhematological toxicities recovered to grade 1 or lower, the neutrophil count was 1500/μl, and the platelet count was 7.5 × 10$^4$/μl. The dose of S-1 was reduced by 20% (level 1) in the event of any of the following occurrences during the previous cycle: grade 4 decrease in the leukocyte count, hemoglobin, or platelet count; and/or grade 3 or higher nonhematological toxicities. If these toxicities appeared again at the reduced dose, an additional reduction of the dose of S-1 by 20% (level 2) was made. The treatment schedule of 2 weeks' administration every 3 weeks was permitted if severe adverse events were seen after the second week in each course. A dose reduction of S-1 by one level at the initiation of the therapy was also permitted considering the patient's age, PS, and organ functions.

### *Response and toxicity evaluation*

We obtained all the clinical data from the medical records retrospectively. We repeated physical examinations and laboratory tests at least once every 2 weeks. Objective response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0, and toxicity was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

### *Statistical analysis*

Overall survival (OS) was defined as the period from the date of the first administration of S-1 to the date of death from any cause or the last date on which the patient was confirmed to be alive. Progression-free survival (PFS) was defined as the period from the date of the first administration of S-1 to the date of confirmation of tumor progression by imaging, or the date of symptomatic deterioration by clinical judgment, or the last date on which the patient was confirmed to be alive without disease progression. Patients who had only the one noncurative factor of positive peritoneal washing cytology were excluded from the PFS and OS analyses, because it was suggested that these patients would survive longer than patients with other noncurative factors; however these patients' toxicities were assessed. Patients who did not have target lesions were also excluded from the response rate (RR) analysis. The survival curves were calculated by the Kaplan-Meier method, using StatView, version 5.0 (Abacus Concepts, Berkeley, CA, USA). Written informed consent was obtained from each of the patients prior to their starting the chemotherapy.

## Results

### *Patient characteristics*

A total of 165 patients received S-1 monotherapy between September 2002 and October 2007. Of these, 12 patients were excluded, for the following reasons: hepatic function disorder (5 patients), concomitant malignancy (3 patients), severe anemia (2 patients), renal failure (1 patient), and massive pleural effusion and/or ascites (1 patient).

**Table 1.** Patient characteristics at baseline

| | | Young ($n = 76$) | Middle-aged ($n = 62$) | Elderly ($n = 15$) | $P$ value |
|---|---|---|---|---|---|
| Age (years) | Median | 59.5 | 70 | 77 | <0.0001 |
| | (range) | (34–65) | (66–75) | (76–80) | |
| Sex | Male | 52 | 49 | 10 | 0.33 |
| | Female | 24 | 13 | 5 | |
| PS | 0 | 43 | 26 | 4 | 0.02 |
| | 1 | 32 | 35 | 8 | |
| | 2 | 1 | 1 | 3 | |
| Tumor status | Unresectable | 59 | 54 | 14 | 0.18 |
| | Recurrent | 17 | 8 | 1 | |
| CCr (ml/min)[a] | Median | 88.3 | 65.4 | 59.9 | <0.0001 |
| | (range) | (35.5–143.7) | (35.9–104.9) | (41.3–93.9) | |
| Macroscopic type | 1 | 0 | 2 | 2 | 0.16 |
| | 2 | 19 | 16 | 7 | |
| | 3 | 35 | 32 | 2 | |
| | 4 | 20 | 9 | 4 | |
| | Unknown | 2 | 3 | 0 | |
| Histological type | Intestinal | 15 | 26 | 8 | 0.01 |
| | Diffuse | 60 | 32 | 7 | |
| | Unknown | 1 | 4 | 0 | |
| No. of metastatic sites | 1 | 54 | 28 | 5 | 0.003 |
| | 2 | 18 | 31 | 7 | |
| | ≥3 | 4 | 3 | 3 | |
| Target lesions | + | 32 | 35 | 12 | 0.02 |
| | – | 44 | 27 | 3 | |
| Noncurative factors | Only CY1 | 20 | 12 | 1 | 0.21 |
| | Others | 56 | 50 | 14 | |

The $P$ values were determined using the Kruskal-Wallis test
PS, performance status; CCr, creatinine clearance; CY1, positive peritoneal washing cytology
[a] Cockcroft-Gault equation

The baseline characteristics of the patients in the three groups are shown in Table 1. The median age was 59.5 years (range, 34 to 65 years) in the young group, 70 years (range, 66 to 75 years) in the middle-aged group, and 77 years (range, 76 to 80 years) in the elderly group. The percentage of patients with PS 2 was higher (20%) in the elderly group than in the other two groups. The median creatinine clearance (calculated by the Cockcroft-Gault equation) was 88.3 ml/min in the young group, 65.4 ml/min in the middle-aged group, and 59.9 ml/min in the elderly group. There were 32 (42%), 35 (56%), and 12 (80%) patients with target lesions, and 20 (26%), 12 (19%), and 1 (6%) patients with positive peritoneal washing cytology as the only noncurative factor in the young, middle-aged, and elderly groups, respectively.

*Exposure to treatment*

The median number of treatment cycles was 5.5 (range, 1 to 28) in the young group, 5 (range, 1 to 18) in the middle-aged group, and 3 (range, 1 to 13) in the elderly group. Dose reduction of S-1 was required in some patients in all three groups: in 12 patients (16%) in the young group, 14 patients (23%) in the middle-aged group, and 8 patients (53%) in the elderly group. Delay of the subsequent treatment cycle was also necessitated in some patients in all three groups: in 23 patients (30%) in the young group, 26 patients (42%) in the middle-aged group, and 5 patients (33%) in the elderly group.

The median relative dose intensity (RDI) per patient in the elderly group was only 75.8%, whereas the corresponding values in the young and middle-aged groups were 99.5% and 96.3%. In 7 (47%) of the 15 patients in the elderly group, S-1 was administered at a reduced dose from the start, and in 8 patients in the elderly group (53%), the dose of S-1 was reduced due to the appearance of toxicity during the treatment courses, and 3 of these 8 patients needed additional dose reduction because of the development of severe adverse events.

The reasons for treatment discontinuation are shown in Table 2. The most frequent reason in all three groups was disease progression. While two patients in the young group required treatment discontinuation because of the development of adverse events (grade 3 pneumonitis in one, and grade 2 skin rash in the other), none of the patients in the elderly group required treatment

**Table 2.** Reasons for treatment discontinuation

| | Young ($n = 76$) | Middle-aged ($n = 62$) | Elderly ($n = 15$) |
|---|---|---|---|
| S-1 discontinuation | 74 (97%) | 62 (100%) | 15 (100%) |
| Disease progression | 60 | 52 | 13 |
| Adverse events | 2 | 0 | 0 |
| Patient's refusal | 0 | 3 | 0 |
| Lost to follow-up | 1 | 1 | 1 |

**Table 3.** Adverse events

| | Young ($n = 76$) | | | | Middle-aged ($n = 62$) | | | | Elderly ($n = 15$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1/2 | G3 | G4 | ≥G3 (%) | G1/2 | G3 | G4 | ≥G3 (%) | G1/2 | G3 | G4 | ≥G3 (%) | *P* value |
| Hematological | | | | | | | | | | | | | |
| Leukopenia | 41 | 5 | 0 | 7 | 36 | 3 | 0 | 5 | 3 | 2 | 0 | 13 | 0.28 |
| Neutropenia | 26 | 10 | 1 | 14 | 25 | 5 | 0 | 8 | 2 | 2 | 0 | 13 | 0.45 |
| Anemia | 63 | 7 | 0 | 9 | 51 | 10 | 1 | 18 | 9 | 4 | 0 | 27 | 0.08 |
| Thrombocytopenia | 21 | 1 | 0 | 1 | 15 | 1 | 0 | 2 | 6 | 0 | 0 | 0 | 0.59 |
| Nonhematological | | | | | | | | | | | | | |
| Nausea | 28 | 2 | 0 | 3 | 16 | 3 | 0 | 5 | 7 | 2 | 0 | 13 | 0.08 |
| Vomiting | 16 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0.24 |
| Anorexia | 40 | 4 | 0 | 5 | 34 | 4 | 0 | 6 | 8 | 4 | 0 | 27 | 0.07 |
| Diarrhea | 29 | 0 | 0 | 0 | 16 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0.31 |
| Mucositis | 25 | 1 | 0 | 1 | 22 | 4 | 0 | 6 | 6 | 0 | 0 | 0 | 0.53 |
| Fatigue | 19 | 4 | 0 | 5 | 21 | 7 | 0 | 11 | 8 | 3 | 0 | 20 | 0.004 |
| Febrile neutropenia | — | 0 | 0 | 0 | — | 0 | 0 | 0 | — | 0 | 0 | 0 | |
| Death within 30 days | | | | 0 | | | | 0 | | | | 1 | |

The *P* values were determined using the Kruskal-Wallis test

discontinuation because of adverse events or the patient's refusal.

*Adverse events*

Table 3 shows the adverse events until 30 days from the last administration of S-1 or the day of initiation of second-line treatment, whichever was earlier. The incidences of grade 3/4 decreases in the leukocyte count and serum hemoglobin were 7% and 9% in the young group, 5% and 18% in the middle-aged group, and 13% and 27% in the elderly group, respectively. One patient in the middle-aged group showed a grade 4 decrease in serum hemoglobin, and one patient in the young group showed grade 4 neutropenia. In regard to the nonhematological toxicities, the incidences of grade 3/4 nausea, anorexia, and fatigue seemed to be higher in the elderly group than in the other two groups. Thus, it would appear that patients in the elderly group experienced more severe hematological and nonhematological toxicities than those in the young and middle-aged groups, while the incidences of toxicities were similar in the young and middle-aged groups. One patient in the elderly group died within 30 days from the last administration of S-1. He was 80 years old, with PS 2, and the estimated creatinine clearance was 56 ml/min at the baseline. He received S-1 administration at a reduced dose even from the first cycle because of his advanced age and anorexia caused by primary cancer. When he visited our hospital on day 17, he was found to have grade 2 mucositis. On day 23, he was admitted to another hospital because of severe anorexia and fatigue, and received some infusion therapy. However, he died on day 30 after the last administration of S-1. The attending physician judged that the cause of death was disease progression.

*Response and survival*

Among the patients with target lesions, the RR was 53% (17/32) in the young group, 46% (16/35) in the middle-aged group, and 33% (4/12) in the elderly group. Two patients (6%) in the middle-aged group showed a complete response (CR).

The data of 56 patients in the young group, 50 in the middle-aged group, and 14 in the elderly group were analyzed in the calculations of the PFS and OS. The median PFS values in the young group, middle-aged group, and elderly group were 7.8 months, 5.6 months, and 3.9 months (Fig. 1), and the median overall survivals

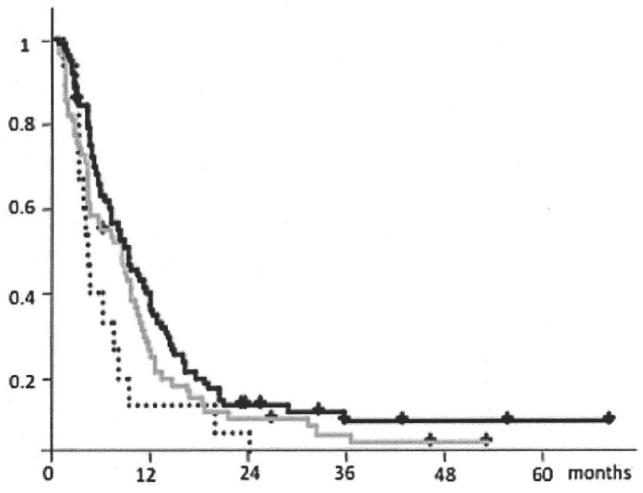


**Fig. 1.** The median progression-free survival (PFS) was 7.8 months in the young group (*solid line*), 5.6 months in the middle-aged group (*faint line*), and 3.9 months in the elderly group (*dotted line*)

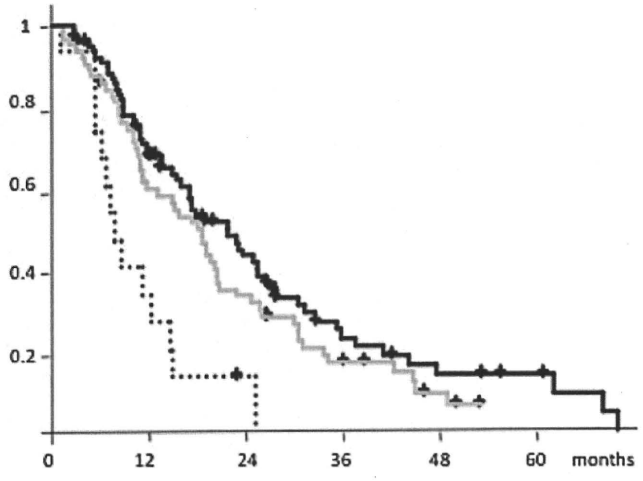


**Fig. 2.** The median OS was 16.9 months in the young group (*solid line*), 17.1 months in the middle-aged group (*faint line*), and 7.7 months in the elderly group (*dotted line*)

in the three groups were 16.9 months, 17.1 months, and 7.7 months, respectively (Fig. 2). It would seem that the treatment efficacy in the elderly group was inferior to that in the other two groups, while the young and middle-aged groups showed similar treatment efficacy.

## Discussion

It still remains under debate whether standard chemotherapies established by pivotal phase III trials might also be applicable to elderly patients with advanced gastric cancer [20–23]. Lee et al. [24] conducted a randomized phase II study comparing capecitabine and S-1 in patients older than 65 years, and showed satisfactory efficacy of S-1 (RR, 29%; median time to progression, 4.2 months; median OS, 8.1 months). In Japan, Koizumi et al. [25] conducted a phase II study of S-1 in patients older than 75 years and demonstrated a RR of 21%, median PFS of 3.9 months, and median OS of 15.7 months. Similar results were obtained in the elderly group in the present study. Because these results are consistent with those of the previous phase III studies in Japan [17–19] (RR of about 30% and PFS of about 4 months), it is considered that S-1 monotherapy may be effective in elderly patients with gastric cancer.

However, elderly cancer patients often have comorbidities and age-related physiological problems, such as organ dysfunction. The kidney is a very common route for the excretion of drugs; however, it is reported that the glomerular filtration rate generally decreases by approximately 0.75 ml/min per year after the age of 40, on average [26]. In several pharmacokinetic studies of chemotherapeutic drugs, such as paclitaxel, vinorelbine, etoposide, cisplatin, and doxorubicin, an age-related decrease in creatinine clearance has been reported [23].

Lee et al. [24] and Koizumi et al. [25] reported the following incidences of grade 3/4 toxicities: decrease in serum hemoglobin, 9%–14.3%; anorexia, 9.5%–12%; and nausea, 4.8%–6%. These data are similar to those in the middle-aged group in the present study (decrease in serum hemoglobin, 18%; anorexia, 6%; nausea, 5%). In the elderly group in the present study, the incidences of severe toxicities (decrease in serum hemoglobin, 27%; anorexia, 27%; nausea, 13%) were higher than those reported from the previous trials, despite about half of our elderly patients having received S-1 at a reduced dose from the first administration. The conditions of patients in daily clinical practice are generally worse than those in patients participating in clinical trials. Actually, in the present study, the median creatinine clearance, estimated by the Cockcroft-Gault equation, was lower in the elderly group (59.9 ml/min) than the values in the middle-aged (65.4 ml/min) and younger (88.3 ml/min) groups. It is known that the clearance of CDHP is reduced by renal dysfunction, resulting in a high blood concentration of 5-FU due to decreased DPD activity [27, 28]. In a post-marketing survey of S-1, it was reported that the incidence of toxicities was greater in patients with renal dysfunction than in those with normal renal function [29]. Thus, it is considered that renal dysfunction is the main reason for the high incidence of severe S-1 toxicities in elderly patients. Therefore, careful evaluation of the renal function prior to the initiation of S-1 monotherapy is strongly recommended.

In conclusion, in the present study, although S-1 monotherapy exhibited moderate efficacy in elderly

patients (≥76 years of age) with advanced gastric cancer, this subject population is at a higher risk of severe toxicities than the other two age groups (66–75 years old and younger) examined in this study. Careful monitoring of renal function and toxicities during treatment is recommended, especially in elderly patients.

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**Original Articles**

# Phase I Study of Docetaxel, Cisplatin and S-1 in Patients with Advanced Gastric Cancer

**Shuichi Hironaka[1,2,*], Kentaro Yamazaki[1], Keisei Taku[1], Tomoya Yokota[3], Kohei Shitara[3], Takashi Kojima[1,4], Shinya Ueda[1,5], Nozomu Machida[1], Kei Muro[3] and Narikazu Boku[1]**

[1]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, [2]Clinical Trial Promotion Department, Chiba Cancer Center, [3]Division of Clinical Oncology, Aichi Cancer Center, [4]Division of Gastrointestinal Oncology, National Cancer Center Hospital East and [5]Department of Medical Oncology, Kinki University School of Medicine, Japan

*For reprints and all correspondence: Shuichi Hironaka, Clinical Trial Promotion Department, Chiba Cancer Center, 666-2 Nitona-cho Chuo-ku Chiba, 260-8717, Japan. E-mail: shironaka@ta2.so-net.ne.jp

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**Objective:** S-1 plus cisplatin is standard treatment for advanced gastric cancer in Japan. Triplet therapy with docetaxel, cisplatin and fluoropyrimidine showed a survival benefit over doublet therapy, but was associated with substantial toxicities. We investigated the maximum tolerated dose of combination chemotherapy with divided-dose docetaxel added to standard-dose S-1 plus cisplatin in advanced gastric cancer patients.

**Methods:** Patients with advanced gastric cancer, naive to chemotherapy or not refractory to fluoropyrimidine, were enrolled. Fixed doses of S-1 (40 mg/m$^2$ twice daily for 3 weeks) and cisplatin (60 mg/m$^2$ on day 1) were administered with increasing docetaxel dose levels of 20 mg/m$^2$ (dose level 1), 25 mg/m$^2$ (dose level 2) and 30 mg/m$^2$ (dose level 3) on days 1, 8 and 15, or 40 mg/m$^2$ (dose level 4) on days 1 and 15 of a 5-week cycle. Treatment cycles were repeated until disease progression, patient's refusal or unacceptable toxicity occurred.

**Results:** Fifteen patients were enrolled. During the first cycle, no dose-limiting toxicity was observed at dose levels 1 and 2. At dose level 3, grade 3 febrile neutropenia was seen in one patient. At dose level 4, grade 3 infection and grade 3 abdominal pain were observed. Thus, dose level 4 was determined to be the maximum tolerated dose. The response rate was 54% (7/13), and median progression-free survival and overall survival were 243 and 383 days, respectively.

**Conclusions:** The recommended dose of docetaxel added to standard-dose S-1 (80 mg/m$^2$ days 1–21) plus cisplatin (60 mg/m$^2$ day 1) was 40 mg/m$^2$ on days 1 and 15 of a 5-week cycle.

*Key words: docetaxel – cisplatin – s-1 – DCS – gastric cancer*



## INTRODUCTION

Gastric cancer is more prevalent in Eastern Asia, Eastern Europe and Central and South America than in other regions. In Japan, gastric cancer is the second most frequent cause of cancer mortality, accounting for 50 597 of the 336 468 cancers occurring in 2007 (1). Because of the vague and non-specific symptoms associated with gastric cancer, the disease is often advanced at the time of diagnosis. Despite the identification and development of several new types of anti-cancer agents, gastric cancer remains an aggressive malignancy with a median survival of 9–13 months in patients with metastatic or recurrent disease (2–5).

There is no global consensus on a standard regimen for gastric cancer; however, a combination of 5-fluorouracil (5-FU) plus cisplatin is the most commonly used treatment worldwide. In Japan, 5-FU alone was used as the control