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ORIGINAL ARTICLE

A phase II trial of ixabepilone in Asian patients with advanced gastric cancer previously treated with fluoropyrimidine-based chemotherapy

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Abstract
Purpose The highest rates of gastric cancer occur in Eastern Asia. Fluoropyrimidine-based therapy is used initially in unresectable and metastatic disease, but no single standard of care exists following disease progression. Ixabepilone, an epothilone B analog, is a non-taxane microtubule-stabilizing agent with clinical activity across multiple tumor types approved by the United States Food and Drug Administration for treatment of metastatic breast cancer.
Methods Asian patients with unresectable or metastatic gastric adenocarcinoma who had failed fluoropyrimidine-based chemotherapy received ixabepilone 40 mg/m^2 by 3-h intravenous infusion every 3 weeks. The primary endpoint was objective response rate (ORR).
Results Fifty-two patients were treated (65.4 % men; median age: 56.5 years). The ORR was 15.4 % (95 % confidence interval [CI] 6.9–28.1); 8 patients achieved partial responses for a median duration of 3.1 months (95 % CI 2.6–4.1 months) and 26 patients (50.0 %) had stable disease. Median progression-free survival was 2.8 months (95 % CI 2.1–3.5 months). The most common grade 3 non-hematological toxicities were fatigue (9.6 %), decreased appetite (7.7 %), sensory neuropathy (5.8 %),

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and diarrhea (5.8 %). Grade 3/4 neutropenia occurred in 46.2 % of patients.

Conclusions Ixabepilone is active in Asian patients with advanced gastric cancer and shows a toxicity profile similar to those previously reported in other tumor types.

Keywords Gastric cancer · Second-line therapy · Asian patients · Ixabepilone

Introduction

Gastric cancer was newly diagnosed in an estimated 989,600 people and caused an estimated 738,000 deaths worldwide in 2008 [1]; it was the third leading cause of cancer deaths in men and fifth leading cause in women. The highest rates of gastric cancer occur in Eastern Asia, where the age-standardized incidence is 42.4 per 100,000 among men and 18.3 per 100,000 among women [1]. Surgery with curative intent is the mainstay of treatment in localized disease, with perioperative chemotherapy or adjuvant chemoradiation or chemotherapy for patients with stage II or III disease depending on national standards [2–4]. However, more than two-thirds of patients have unresectable disease at the time of diagnosis and 60 % of resectable cases eventually relapse [5, 6]. Non-curative gastrectomy may be used in palliation, but it is associated with high rates of procedure-related morbidity and mortality as well as poor 1-year survival [7].

In the metastatic disease setting, combination chemotherapy with regimens containing a fluoropyrimidine and a platinum agent is widely used initially, with a third cytotoxic agent often included for medically fit patients [2, 3]. Nevertheless, even with the most active regimens, progression-free survival (PFS) remains in the range of 5–7 months and median survival is only 9–11 months [8–11]. In Japan, cisplatin plus the oral fluoropyrimidine S-1 has emerged as a preferred first-line regimen producing median survival of 13 months [12]. Following progression, 20–40 % of patients in Western countries subsequently receive second-line chemotherapy [13], but the number is higher (60–70 %) in Asian countries, particularly Japan and Korea. There is no established second-line regimen; options include paclitaxel, docetaxel, or irinotecan given alone or in doublet regimens, which produced median survival of 4–8 months in prospective clinical trials [14–18]. These survival data underscore the need for more effective therapy in metastatic gastric cancer.

Ixabepilone is the first member of the epothilone class of microtubule-stabilizing drugs to be approved for use in cancer therapy, specifically monotherapy or in combination with capecitabine for treatment of recurrent breast cancer [19, 20]. Ixabepilone is structurally distinct from the taxanes because it binds to a different site on β-tubulin and has reduced susceptibility to common mechanisms that confer resistance to taxanes and other anti-cancer drugs [21, 22]. Phase II clinical studies have demonstrated that ixabepilone has activity against a wide range of tumor types besides breast cancer, including hormone-refractory prostate cancer [23, 24], pancreatic cancer [25], non-small cell lung cancer [26], endometrial carcinoma [27], ovarian cancer [28], and renal cell carcinoma [29].

Ixabepilone administered every 3 weeks produced an objective response rate (ORR) of 5 or 9 % in Western patients with metastatic gastric cancer previously treated with a fluoropyrimidine and/or a platinum [30] or a taxane [31], respectively. Despite this modest activity in Western patients, further evaluation of ixabepilone in Asian patients with gastric cancer is warranted based on growing evidence highlighting epidemiological and genetic differences between Asian and Western populations [32]; gene expression profiling revealed differential expression of multiple genes in Eastern versus Western gastric tumor libraries [33]. Moreover, several retrospective analyses have shown that Asian patients are more likely to be diagnosed with localized tumors and have tumors located in the gastric antrum, whereas Western patients are more likely to have distant metastases and a prognostically less favorable tumor location in the cardia [34–36]. In these retrospective cohorts, median survival was longer in Asian patients than in Western patients, likely reflecting the differences in disease characteristics at presentation.

The present phase II study was designed to evaluate the efficacy and safety of single-agent ixabepilone in Asian patients with advanced gastric adenocarcinomas in which prior fluoropyrimidine-based therapy had failed. The primary objective was to determine the ORR; secondary objectives were to assess time to response, duration of response, disease control rate (DCR), PFS, and safety and tolerability.

Methods

Patients

Men and women of Asian ethnicity aged $\geq$18 years with histologically confirmed unresectable or metastatic gastric adenocarcinoma originating in the stomach or gastroesophageal junction were eligible if a fluoropyrimidine-based chemotherapy regimen had failed in an adjuvant, locally advanced, or metastatic setting. Failure of fluoropyrimidine-based chemotherapy was defined by disease progression while receiving such therapy or by disease recurrence within 12 months of the last dose. Eligibility also required measurable disease by response evaluation criteria in solid tumors (RECIST) guidelines (version 1.1)

[37], Eastern Cooperative Oncology Group performance status 0–1, adequate hematologic, hepatic, and renal function, and life expectancy >12 weeks. Women of childbearing potential required a negative pregnancy test within 72 h before starting ixabepilone and agreed to use an adequate method of contraception to avoid pregnancy for up to 4 weeks after the last dose. All patients provided written informed consent before participating in this study.

Patients were excluded if they had known central nervous system metastasis or neurological signs and symptoms suggestive of such metastasis, prior taxane or ixabepilone therapy, peripheral neuropathy (≥grade 2), or any significant medical illness precluding systemic anticancer therapy. Patients who had received >1 prior chemotherapy regimen for metastatic disease or >2 prior chemotherapy regimens overall were ineligible. Concurrent anti-cancer treatment including investigational agents was not permitted during this study. Strong CYP3A4 inhibitors (e.g., ketoconazole) were discontinued within 1 week prior to starting study treatment.

Study design

This phase II, single-arm, open-label study was conducted at 9 sites in Asia including 2 sites in Japan, 3 sites in Korea, 2 sites in Taiwan, and 1 site each in Hong Kong and Singapore from November of 2009 to June of 2011. The study was run in accordance with ethical principles originating in the 1964 Declaration of Helsinki and in compliance with Good Clinical Practice and national regulatory guidelines. The study protocol and informed consent form were approved by the Institutional Review Board or Independent Ethics Committee at each study site before patient enrollment.

Ixabepilone was administered at a dose of 40 mg/m^2 as a 3-h infusion every 21 days. Premedication with H_1 and H_2 antagonists was given to prevent hypersensitivity reactions. Patients who experienced a hypersensitivity reaction were required to receive additional premedication with intravenous corticosteroids before subsequent ixabepilone doses.

Subsequent cycles of ixabepilone were administered after all treatment-related toxicities had resolved to baseline or grade 1 (or ≤grade 2 for alopecia and fatigue), absolute neutrophil counts were ≥1,500 cells/μL, and platelet counts were ≥100,000 cells/μL. Patients who did not meet these criteria were re-evaluated weekly; those who failed to recover within 3 weeks of a scheduled re-treatment were discontinued from protocol treatment. The duration of treatment was based on a tumor assessment done every other cycle starting from the first dose of the study treatment. Patients achieving a complete response (CR) were treated for a maximum of 4 cycles after documentation of CR or up to a maximum of 8 cycles, whichever came first. Patients with stable disease (SD) or a partial response (PR) were treated until disease progression, unacceptable toxicity, or a maximum of 8 cycles.

Patients experiencing certain toxicities had the dose of ixabepilone reduced in subsequent cycles to 32 mg/m^2, and if toxicity recurred, to 25 mg/m^2. Toxicities mandating dose reduction were grade 4 neutropenia lasting ≥7 days, febrile neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, grade 2 neuropathy lasting ≥7 days, or grade 3 neuropathy lasting <7 days. The reduced dose was then administered in all subsequent cycles. Ixabepilone was discontinued for toxicity requiring more than 2 dose reductions or in the event of grade 3 neuropathy lasting ≥7 days, disabling neuropathy, or any grade 4 nonhematologic toxicity. Palliative and supportive care for disease-related symptoms was allowed during the study.

Assessments

Clinical and radiological evaluation (abdominal and chest computed tomography) of treatment response was conducted every other cycle until disease progression was documented. Treatment response was evaluated according to modified RECIST guidelines (version 1.1) [37]. Patients with CRs or PRs were to have repeat tumor assessments within 4–6 weeks to confirm the response. The ORR was the proportion of patients who achieved either a CR or PR; the DCR was the proportion of patients whose best response was CR, PR, or SD. The time to response was defined as the time interval from the first dose of ixabepilone until measurement criteria for PR or CR were first met, whereas the duration of response was defined as the time interval from when measurement criteria for PR or CR were first met until documented progressive disease or death. PFS was defined as the time interval from the first day of treatment until documented progressive disease or death.

A focused physical examination, including neuropathy assessment, was performed within 2 weeks before the first dose of ixabepilone and then prior to each subsequent dose. Serum chemistry and hematology were measured at the same time, whereas blood counts and differentials were ordered weekly during the first 3 cycles and then as clinically indicated to monitor recovery from hematological toxicity. Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

Statistics

This study used Simon's 2-stage optimal design to determine whether ixabepilone produces an ORR of clinical interest (>8 %); an ORR ≤8 % was not of clinical interest and an ORR ≥20 % was of strong clinical interest. The first stage required 25 response-evaluable patients. Study termination

Table 1 Patient characteristics

Characteristic	$N = 52$
Age, years	
Median (range)	56.5 (29.0–77.0)
≥65 years, *n* (%)	12 (23.1)
Gender, *n* (%)	
Male	34 (65.4)
Female	18 (34.6)
Ethnicity, *n* (%)	
Chinese	23 (44.2)
Japanese	15 (28.9)
Korean	13 (25.0)
Asian other	1 (1.9)
ECOG performance status, *n* (%)	
0	20 (38.5)
1	32 (61.5)
Number of disease sites, *n* (%)	
1	11 (21.2)
2	13 (25.0)
≥3	28 (53.8)
Disease sites, *n* (%)	
Lymph node	37 (71.2)
Gastric	29 (55.8)
Peritoneum (including ascites)	23 (44.2)
Liver	19 (36.5)
Lung	8 (15.4)
Other	30 (57.7)

ECOG Eastern Cooperative Oncology Group

was planned if ≤2 of the 25 patients responded to treatment; otherwise, an additional 27 response-evaluable patients would be treated. The study required at least 8 responders among the 52 evaluable patients at the end of the second stage to reject the null hypothesis of ORR ≤8 %. The test had 80 % power to reject the null hypothesis at a significance level of 5 % if the true ORR is 20 %.

The ORR and DCR were calculated for all treated patients. For each, a 2-sided 95 % exact confidence interval (CI) was computed using the Clopper–Pearson method. Duration of response and PFS were analyzed by Kaplan–Meier methodology, with computation of median values and their 2-sided 95 % CIs. All other parameters, including time to response, demographic and baseline characteristics, and safety variables, were analyzed with descriptive statistics.

Results

Patient disposition and characteristics

Fifty-eight patients were screened, 6 (10.3 %) were not treated because of screening failure, and the remaining 52 patients (89.7 %) were enrolled and received ixabepilone. Of those treated, 4 patients (7.7 %) completed ixabepilone therapy according to the study protocol, 38 patients (73.1 %) discontinued because of disease progression, 5 patients (9.6 %) withdrew consent or requested study drug discontinuation, 4 patients (7.7 %) discontinued because of adverse events, and 1 patient (1.9 %) died.

The median age of the study cohort was 56.5 years (range: 29.0–77.0 years); most were men (65.4 %) and all were of Asian ethnicity (Table 1). The majority of patients had 3 or more disease sites (53.8 %), most frequently in the lymph nodes (71.2 %), stomach (55.8 %), and liver (36.5 %).

Table 2 Best overall response

Parameter	$N = 52$
Best response, *n* (%)	
CR	0 (0)
PR	8 (15.4)
SD	26 (50.0)
Progressive disease	15 (28.8)
Unable to determine	3 (5.8)
ORR (95 % CI)	15.4 (6.9–28.1)
DCR (95 % CI)	65.4 (50.9–78.0)

Exposure

Ixabepilone was administered for a median of 3.5 courses (range: 1–10). Of the 45 patients who received at least 2 courses, 18 (40 %) required at least 1 dose reduction of ixabepilone. The reasons for the first dose reduction included hematologic toxicity in 6 patients (13.3 %), neuropathy in 4 patients (8.9 %), and other non-hematologic toxicity in 8 patients (17.8 %).

Efficacy

The ORR with ixabepilone therapy was 15.4 % (95 % CI 6.9–28.1); all objective responses were PR (Table 2). Twenty-six additional patients (50.0 %) had SD and, therefore, the DCR was 65.4 % (95 % CI 50.9–78.0). For patients achieving PR, the median time to response was 8.9 weeks (range: 5.1–12.1 weeks) and the median duration of response was 3.1 months (95 % CI 2.6–4.1 months). Median PFS was 2.8 months (95 % CI 2.1–3.5 months) (Fig. 1).

Safety

The adverse events reported were consistent with the known safety profile of ixabepilone. Fifty patients (96.2 %) had at least 1 adverse event, most commonly alopecia,

decreased appetite, neutropenia, peripheral sensory neuropathy, and fatigue (Table 3). Most non-hematologic toxicity was grade 1 or 2; the most common grade 3 events were fatigue (9.6 %), decreased appetite (7.7 %), peripheral sensory neuropathy (5.8 %), and diarrhea (5.8 %). Overall, peripheral neuropathies were reported by 33 patients (63.5 %), with the most common forms being peripheral sensory neuropathy (48.1 %) and hypoesthesia (11.5 %). Peripheral motor neuropathy occurred in 1 patient (1.9 %; grade 2). In terms of hematological toxicity, grade 3/4 neutropenia and leukopenia occurred in 24 (46.2 %) and 11 (21.1 %) patients, respectively, with febrile neutropenia in 4 patients (7.7 %). Grade 3 anemia and thrombocytopenia occurred in 3 (5.8 %) and 2 (3.8 %) patients, respectively.

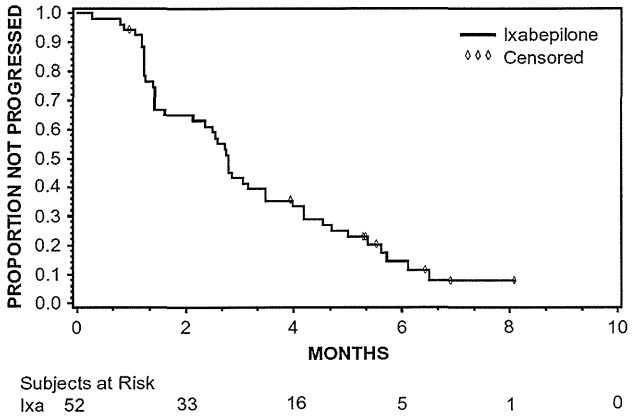

Fig. 1 Kaplan–Meier plot of progression-free survival

Four patients (7.7 %) discontinued treatment because of drug-related adverse events, including 3 patients with peripheral neuropathy and 1 patient with febrile neutropenia. There was 1 death because of drug-related toxicity: a 69-year-old male patient died of pneumonia and neutropenic sepsis during course 6 of ixabepilone therapy. The patient started course 6 with a reduced dose of 32 mg/m^2 because the investigator had considered the patient too weak to continue at the initial dose. The death occurred 18 days after the last treatment. Three other patients died within 30 days of their last dose of ixabepilone, all of which were assessed by the investigator as due to disease progression.

Discussion

The results of this phase II study demonstrate that ixabepilone has activity of clinical interest when administered

Table 3 Treatment-related adverse events (AEs) reported at an incidence ≥10 %

AE	Grade 1	Grade 2	Grade 3	Grade 4	Total
Any AE	7 (13.5)	11 (21.2)	12 (23.1)	19 (36.5)	50 (96.2)[a]
Hematologic AEs					
Neutropenia	0 (0)	2 (3.8)	8 (15.4)	16 (30.8)	26 (50.0)
Leukopenia	0 (0)	1 (1.9)	9 (17.3)	2 (3.8)	12 (23.1)
Non-hematologic AEs					
Alopecia	26 (50.0)	9 (17.3)	0 (0)	0 (0)	35 (67.3)
Decreased appetite	14 (26.9)	11 (21.2)	4 (7.7)	0 (0)	29 (55.8)
Peripheral sensory neuropathy	12 (23.1)	10 (19.2)	3 (5.8)	0 (0)	25 (48.1)
Fatigue	5 (9.6)	12 (23.1)	5 (9.6)	0 (0)	22 (42.3)
Rash	11 (21.2)	5 (9.6)	1 (1.9)	0 (0)	17 (32.7)
Diarrhea	10 (19.2)	1 (1.9)	3 (5.8)	0 (0)	14 (26.9)
Constipation	9 (17.3)	4 (7.7)	0 (0)	0 (0)	13 (25.0)
Nausea	8 (15.4)	4 (7.7)	1 (1.9)	0 (0)	13 (25.0)
Myalgia	9 (17.3)	2 (3.8)	1 (1.9)	0 (0)	12 (23.1)
Arthralgia	7 (13.5)	4 (7.7)	0 (0)	0 (0)	11 (21.2)
Weight decreased	2 (3.8)	9 (17.3)	0 (0)	0 (0)	11 (21.2)
Pruritus	6 (11.5)	3 (5.8)	0 (0)	0 (0)	9 (17.3)
Pyrexia	8 (15.4)	0 (0)	0 (0)	0 (0)	8 (15.4)
Vomiting	5 (9.6)	3 (5.8)	0 (0)	0 (0)	8 (15.4)
Stomatitis	2 (3.8)	3 (5.8)	2 (3.8)	0 (0)	7 (13.5)
Asthenia	1 (1.9)	5 (9.6)	0 (0)	0 (0)	6 (11.5)
Dysgeusia	5 (9.6)	1 (1.9)	0 (0)	0 (0)	6 (11.5)
Hypoesthesia	2 (3.8)	3 (5.8)	1 (1.9)	0 (0)	6 (11.5)
Nail disorder	5 (9.6)	0 (0)	1 (1.9)	0 (0)	6 (11.5)

[a] Includes 1 patient with grade 5 pneumonia and neutropenic sepsis

at a dose of 40 mg/m^2 every 21 days to Asian patients with unresectable or metastatic gastric cancer who had progressed on or within 12 months after receiving fluoropyrimidine-based therapy. In this population, ixabepilone produced an ORR of 15.4 % and DCR of 65.4 %. This is in contrast to the lower ORRs of 5 % and 9 % reported for 50 mg/m^2 ixabepilone administered every 21 days in Western patients with metastatic gastric cancer previously treated with a fluoropyrimidine and/or a platinum [30] or a taxane [31], respectively.

The activity of ixabepilone appears consistent with contemporary studies of taxanes in second-line treatment of Asian patients with advanced gastric cancer. Docetaxel produced ORRs of 14–16 % in phase II trials conducted in Korea [15, 38]. In the largest of these studies, docetaxel was administered to 154 patients who had failed fluoropyrimidine and platinum therapy, of whom 86 were evaluable for response; the ORR and DCR were 14 and 43 %, respectively, and median time to progression was 2.6 months [38]. Rates up to 24 % were reported for docetaxel in Japanese patients with recurrent or metastatic gastric cancer, but these studies were conducted more than a decade ago and, consequently, patients may not have received optimal initial chemotherapy [39, 40]. In a recent Japanese study, biweekly paclitaxel after failure of fluoropyrimidine-based therapy produced an ORR of 17.5 % and DCR of 70.0 % with a median PFS of 3.6 months [16]. Besides taxanes, other cytotoxic agents including irinotecan have shown similar activity in advanced gastric cancer [41], whereas various targeted agents have shown modest single-agent activity in this setting [42].

Although multiple drugs have been evaluated as second-line therapy in phase II trials and retrospective cohorts, there have been no randomized head-to-head trials designed to establish a standard treatment in this setting [43]. Comparisons of second-line therapy across clinical studies are problematic for multiple reasons, including the nature of previous chemotherapy and responses to first-line chemotherapy [13]. This is particularly important in advanced gastric cancer since response duration to first-line chemotherapy is prognostic for the benefit of second-line chemotherapy [44, 45]. With targeted agents being increasingly tested in conjunction with first-line chemotherapy, it will be important to evaluate how they impact the activity of subsequent second-line treatment and, conversely, how second-line therapy affects outcomes measured with first-line regimens [43].

Current treatment options in second-line advanced gastric cancer provide only small overall survival (OS) benefit over best supportive care (BSC). A recent randomized phase III trial of 193 Asian patients assessed the efficacy and safety of BSC combined with either docetaxel (60 mg/m^2 every 3 weeks) or irinotecan (150 mg/m^2 every 2 weeks) compared with BSC alone as a second-line therapy in advanced gastric cancer [17]. The OS of patients randomized to BSC plus docetaxel or irinotecan ($n = 128$) versus BSC alone ($n = 65$) was 5.1 and 3.8 months, respectively; the difference was statistically significant (hazard ratio, 0.63; 95 % CI 0.47–0.86; $P = 0.004$) and was maintained in most of the prospectively defined subgroups including age, gender, performance status, number of prior treatments, number of metastatic sites, hemoglobin levels, and response to prior chemotherapy. Docetaxel or irinotecan improves OS when added to BSC in second-line advanced gastric cancer, but the OS improvement of 1.3 months over BSC only underscores the current unmet medical need for more efficient treatments in this patient population. Another recent phase III trial comparing single-agent irinotecan versus BSC in Germany was closed prematurely after accrual of only 40 patients [18]. Irinotecan produced no objective responses and SD in 53 %, but showed a statistically significant improvement in median OS (4.0 vs 2.4 months; $P = 0.012$).

In Asian gastric cancer patients, ixabepilone showed a safety profile similar to that previously reported in other tumor types. Grade 3/4 toxicity consisted mostly of neutropenia, whereas the most clinically relevant treatment-related non-hematological adverse events were decreased appetite (anorexia), peripheral sensory neuropathy, and fatigue, mostly grade 1 or 2 in severity. In an earlier study conducted in Western patients with gastric cancer, nausea, fatigue, sensory neuropathy, vomiting, and anorexia were commonly seen with ixabepilone given every 3 weeks at a higher dosage (50 mg/m^2) than the one used in this study; frequencies of each of these events except for fatigue reduced when a lower ixabepilone dose was administered over a 5-day period every 3 weeks [31]. At the dose used in this study (40 mg/m^2 every 3 weeks, the approved regimen in breast cancer), the incidence of peripheral sensory neuropathy and fatigue was consistent with rates seen in clinical trials of other tumor types and in other studies of recurrent disease, including breast cancer [19, 20] and endometrial carcinoma [27]. Gastrointestinal adverse events were also common across tumor types, although the nature of these events (e.g., anorexia, nausea) varied in incidence. In general, the safety profile of ixabepilone is better in earlier lines of therapy as demonstrated in the TITAN study of patients with metastatic breast cancer treated in a first-line setting [46].

In summary, ixabepilone showed clinical activity with an ORR of 15.4 % in Asian patients with unresectable or metastatic gastric cancer in whom fluoropyrimidine-based chemotherapy had failed. Ixabepilone therapy was tolerable for most patients and its safety profile was similar to that previously reported in other tumor types.

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ORIGINAL ARTICLE

Fluoropyrimidine plus cisplatin for patients with advanced or recurrent gastric cancer with peritoneal metastasis

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Abstract
Background There are few data on the efficacy of combination chemotherapy with a fluoropyrimidine plus cisplatin for patients with advanced or recurrent gastric cancer (AGC) complicated by peritoneal metastasis, especially massive ascites.
Methods We retrospectively evaluated the efficacy and safety of a fluoropyrimidine (S-1 or capecitabine) plus cisplatin as first-line chemotherapy in 120 patients with AGC and peritoneal metastasis.
Results Ascites was detected in 50 patients, with 11 patients having massive ascites. Median progression-free survival (PFS) and overall survival (OS) of all patients was 6.1 and 15.9 months, respectively. The PFS and OS were shorter in patients with massive ascites ($n = 11$; 3.7 and 9.5 months) compared with patients with small or moderate ascites ($n = 39$; 5.8 and 13.5 months) or patients without ascites ($n = 70$; 6.9 and 18.1 months). The objective response in terms of ascites was similar whether ascites was massive (4 of 11 patients; 36.4%) or small or moderate (16 of 39 patients; 41%). The frequencies of grade 3 or higher toxicity or treatment discontinuation due to toxicity are relatively similar across ascites groups.
Conclusions Fluoropyrimidine plus cisplatin appears to be tolerated in selected patients with peritoneal metastasis.

Keywords Chemotherapy · Cisplatin · Fluoropyrimidine · Gastric cancer · Peritoneal metastasis

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of all malignancies) and the second leading cause of cancer death (737,419 deaths, 9.7% of all cancer deaths) [1]. The prognosis for patients with advanced or recurrent gastric cancer (AGC) remains poor; chemotherapy confers only a minimal survival advantage, with a median overall survival (OS) of approximately 1 year. In a pivotal phase III trial (SPIRITS trial) in Japan that compared S-1 alone with S-1 plus cisplatin (combination = SP), patients treated with SP showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer OS (13 vs. 11 months) than patients receiving S-1 alone [2]. Therefore, SP is now considered to be one of the standard regimens for AGC in Japan. Capecitabine, another oral fluoropyrimidine, when combined with cisplatin (combination = XP), is also reported to have an effectiveness that is statistically indistinguishable from that of 5-fluorouracil (5-FU) plus cisplatin (ML17032 trial [3]), which was used as a reference regimen in recent global studies, including those in Japan [4, 5]. Thus, the most commonly used treatments for AGC are combination

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chemotherapy regimens consisting of a fluoropyrimidine (5-FU or an oral fluoropyrimidine) plus a platinum agent, although docetaxel or anthracyclines are sometimes combined in Western countries [6, 7].

Peritoneal metastasis, a common type of metastasis in AGC, causes several complications such as ascites, bowel obstruction, and hydronephrosis—all leading to a deterioration of the patient's general condition. Several reports have suggested that the presence of peritoneal metastasis or ascites is associated with poor survival in patients with AGC [8–11]. To improve the prognosis for patients with AGC and peritoneal metastasis, several clinical trials have been conducted [12–18]. However, there are few data on the efficacy of a fluoropyrimidine plus cisplatin for peritoneal metastasis as the current standard treatment for patients with AGC. Moreover, since patients with massive ascites have usually been excluded in previous pivotal randomized studies, the efficacy and feasibility in this patient population is also unclear. Therefore, we retrospectively evaluated the efficacy and safety of a fluoropyrimidine plus cisplatin regimen in patients with AGC and peritoneal metastasis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy and safety of first-line chemotherapy with a fluoropyrimidine plus cisplatin (SP and XP) in patients with AGC from January 2005 to March 2011. Since capecitabine was not available in Japan until February 2011, most patients had been treated by SP, although we included patients who had been treated with XP in the context of two global studies [3, 4]. Patients who had received XP plus experimental agents (i.e., trastuzumab or bevacizumab) were excluded from our analysis.

Eligibility criteria were as follows: (1) presence of histologically proven, inoperable AGC; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) sufficient oral intake to take oral agents; (4) adequate bone marrow, hepatic, and renal function; (5) diagnosis of peritoneal metastasis, which could be confirmed either by macroscopic evaluation (upon laparotomy or laparoscopy) with cytology or by imaging data [computed tomography (CT) scan or barium enema] with relevant signs such as ascites, hydronephrosis, and intestinal stenosis; (6) no previous chemotherapy other than adjuvant chemotherapy, which was required to have been finished more than 6 months before enrollment. Written informed consent for chemotherapy was obtained from each patient prior to treatment initiation.

Treatment plan

Patients were treated with either: (1) a standard regimen of SP [S-1 (80 mg/m^2) for 21 consecutive days followed by a 14-day rest; cisplatin (60 mg/m^2) intravenous infusion on day 8] with repetition of the 35-day cycle [2]; or (2) XP [capecitabine (1,000 mg/m^2) for 14 days followed by a 7-day rest; cisplatin (80 mg/m^2) intravenous infusion on day 1] with repetition of the 21-day cycle [4, 5]. Intravenous hydration (1,500 mL) was performed on the day of cisplatin administration and on the next 2 days. Dose modification and scheduling of the two regimens were performed as reported in the literature [2, 4, 5]. Patients could continue with the fluoropyrimidine alone if they experienced severe toxicity with cisplatin. Treatment was discontinued if the tumor progressed, severe toxicity occurred, or at the patient's request.

Evaluation of treatment and statistical analysis

In patients with measurable lesions, the tumor response was assessed objectively according to the guidelines of the Response Evaluation Criteria In Solid Tumors (RECIST, ver. 1.0), and the best overall response was recorded as the antitumor effect for that patient. The objective response rate in these patients was presented as the percentage of patients with a complete response (CR) or partial response (PR). According to the Japanese Classification of Gastric Carcinoma [19], the amount of ascites was assessed by a radiologist using CT. Response rate for ascites represented the percentage of patients with complete disappearance (CR) or a dramatic decrease in ascites (PR). Time to treatment failure (TTF) was measured from the date of initiation of chemotherapy to the date of the last administration of fluoropyrimidine or cisplatin. The PFS was measured from the date of chemotherapy to the date of progressive disease or death from any cause. The OS was estimated from the date of initiation of chemotherapy to the date of death or last follow-up visit. Median PFS and median OS were estimated by the Kaplan–Meier method. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Our primary interest was in comparing the clinical outcomes among patient groups that had different amounts of ascites. The amount of ascites was defined as follows: small (limited to pelvic cavity or around liver); moderate (not small or massive); or massive (continuous ascites from surface of liver to pelvic cavity). This definition of massive ascites was the same as that used in the JCOG 0106 study [13]. The volume of ascites was also estimated by the five-point method, as previously reported [16, 20]. We divided patients into the following three groups: (1) patients

without ascites; (2) patients with small or moderate ascites; and (3) patients with massive ascites.

P values for testing differences in baseline characteristics and response rates of each ascites group were calculated for homogeneity using chi-square tests and for trends using Fisher's exact test. The PFS and OS were compared among the ascites groups by the log-rank test; the hazard ratio (HR) was calculated by the Cox proportional hazards model, and presented as HRs and 95% confidence intervals (95% CIs). Statistical analyses were performed using STATA software (version 10; StataCorp LP, College Station, TX, USA). All tests were two sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 275 patients with AGC had received first-line chemotherapy with a fluoropyrimidine plus cisplatin regimen from January 2005 to March 2011. Of these patients, 120 patients met the inclusion criteria and were analyzed in this study. Patient characteristics are shown in Table 1. Most patients had PS 0 or 1; only 2 patients had PS 2. Peritoneal metastasis was diagnosed by laparotomy or laparoscopy in 45 patients. The other 75 patients were diagnosed by imaging data including CT scan or barium enema. Ascites was detected in 50 patients (42%) by CT scan: 27 patients (23%) had small ascites; 12 patients (10%) had moderate ascites; and 11 patients (9%) had massive ascites. Of the patients with massive ascites, 5 patients underwent paracentesis prior to chemotherapy. The estimated volume of ascites according to this classification was as follows: median of 190 mL in small ascites (range, <100–640 mL); median of 990 mL in moderate ascites (range, 600–1,600 mL); and median of 3,240 mL in massive ascites (range, 1,920–7,200 mL). The proportion of patients with lymph node metastasis or with two or more metastatic organs was higher in the patient group with small or moderate ascites than in the other two groups (Table 1, $P = 0.01$). Human epidermal growth factor receptor 2 (HER2) status was evaluated in 39 patients (22%); four of these patients (10%) were positive, which was defined as immunohistochemistry (IHC) 3+ or IHC 2+ plus amplification by fluorescence in situ hybridization (FISH). Of the 120 patients evaluated, 107 patients (89%) had been treated with SP and 13 patients (11%) with XP.

Treatment results and efficacy

The median TTF among all patients was 5.8 months, and cisplatin was administered a median of four times (range 0–13 times) during the median follow-up period of 34.9 months (Table 2). Three patients (2 patients without ascites and 1 patient with small ascites) started SP, but did not receive cisplatin on day 8 because of toxicity. After the initial dose, the dose of fluoropyrimidines was reduced in 23 patients (19%) and the dose of cisplatin was reduced in 33 patients (28%). One-hundred thirteen patients discontinued S-1 or capecitabine treatment for the following reasons: disease progression ($n = 97$; 81%), toxicity ($n = 6$; 5%), and other ($n = 10$; 8%).

The median numbers of times that cisplatin was administered within the ascites groups were as follows: 4 times in patients without ascites; 3 times in patients with small to moderate ascites; and 2 times in patients with massive ascites. The frequency of discontinuation due to toxicities and dose reduction was not higher in patients with massive ascites than in the other two groups (Table 2).

Of the 55 patients with measurable lesions, 23 patients achieved a CR ($n = 1$) or a PR ($n = 22$) for an overall response rate of 42.0% (95% CI, 28.7–55.9%; Table 3). Of the patients with ascites ($n = 50$), disappearance of ascites was observed in 8 patients (16%), and a decrease of ascites was observed in 12 patients (24%), for an overall response rate in terms of ascites of 40% (95% CI, 26.4–54.8%; Table 3). Response rates in terms of measurable lesions or ascites were relatively similar among the ascites groups (Table 3).

One hundred seven patients had already experienced disease progression at the time of analysis, with a median PFS of 6.1 months (95% CI, 5.3–7.3 months) (Fig. 1). Eighty-four patients (70%) were dead, with a median OS of 15.9 months (95% CI, 12.8–18.4 months) (Fig. 1). Median PFS was shorter in patients with massive ascites (3.7 months; 95% CI, 0.7–6.0 months) than in patients with small or moderate ascites (5.8 months; 95% CI, 4.0–8.8 months; HR 0.45; 95% CI, 0.22–0.93; $P = 0.03$) or patients without ascites (6.9 months; 95% CI, 5.5–9.0 months; HR 0.43; 95% CI, 0.22–0.85; $P = 0.02$) (Fig. 2). Median OS was also shorter in patients with massive ascites (9.5 months; 95% CI, 0.5–not reached) than in patients with small or moderate ascites (13.5 months; 95% CI, 9.4–17.0 months; HR 0.49; 95% CI; 0.21–1.15; $P = 0.1$) or patients without ascites (18.1 months; 95% CI, 14.5–20.0 months; HR 0.31; 95% CI, 0.13–0.71; $P = 0.006$) (Fig. 3).

Ninety-three patients (78%) received second-line chemotherapy, most commonly ($n = 69$) with taxanes (paclitaxel or docetaxel). The proportion of patients having second-line chemotherapy was relatively similar among the ascites groups: 53 patients without ascites (75.7%), 31 patients with small to moderate ascites (79.5%), and 9 patients with massive ascites (81.9%).

Table 1 Patient characteristics

Characteristics	All patients (n = 120%)	Patients without ascites (n = 70%)	Patients with small to moderate ascites (n = 39%)	Patients with massive ascites (n = 11%)
Age				
Median (range)	61 (27–79)	61 (34–79)	61 (27–74)	59 (28–66)
Gender				
Male	62 (52)	39 (56)	19 (49)	4 (36)
Female	58 (48)	31 (44)	20 (51)	7 (64)
ECOG PS				
0	26 (22)	20 (29)	6 (15)	2 (18)
1	92 (77)	50 (71)	31 (79)	9 (82)
2	2 (2)	0	2 (5)	0
Histological type				
Diffuse	96 (80)	61 (87)	28 (72)	7 (64)
Intestinal	24 (20)	9 (13)	11 (28)	4 (36)
Disease status				
Advanced	102 (85)	58 (83)	34 (87)	10 (91)
Recurrent	18 (15)	12 (17)	5 (13)	1 (9)
Previous gastrectomy				
No	86 (72)	45 (64)	31 (79)	10 (91)
Yes	34 (28)	25 (36)	8 (21)	1 (9)
Prior adjuvant chemotherapy				
No	110 (92)	62 (89)	37 (95)	11 (100)
Yes	10 (8)	8 (11)	2 (5)	0
Site of metastasis				
Lymph node	48 (40)	22 (31)	23 (59)	3 (27)
Liver	11 (9)	4 (6)	6 (15)	1 (9)
Ovary	11 (9)	4 (6)	5 (13)	2 (18)
Number of metastatic organs				
1	56 (47)	41 (59)	10 (26)	5 (45)
2 or more	64 (53)	29 (41)	29 (74)	6 (55)

PS performance status, *ECOG* Eastern Cooperative Oncology Group

Toxicity

Toxicity is shown in Table 4. The frequencies of any grade 3–4 hematological toxicity were 27% (19 of 70 patients) in patients without ascites, 41% (16 of 39 patients) in patients with small to moderate ascites, and 27% (3 of 11 patients) in patients with massive ascites; the frequency in patients with massive ascites was not significantly higher. The frequencies of any grade 3–4 nonhematological toxicity also did not differ significantly among patients without ascites (34%; n = 24), patients with small or moderate ascites (26%; n = 10), or patients with massive ascites (45%; n = 5). The frequency of grade 3 or higher anorexia tended to be higher in patients with massive ascites (36%; n = 4) than in patients without ascites (19%; n = 13) or patients with small or moderate ascites (15%; n = 6). No patients experienced grade 3 or higher renal toxicity.

Discussion

We retrospectively evaluated the efficacy and safety of a fluoropyrimidine plus cisplatin regimen for patients with AGC and peritoneal metastasis. Median PFS and OS were similar to that of the SPIRITS trial, in which about 30% of patients had peritoneal metastasis (34% in SP group, 24% in S-1 group) [2]. The frequencies of common toxicities in our analysis were also compatible with that in the SPIRITS trial; therefore, a fluoropyrimidine (S-1 or capecitabine) plus cisplatin regimen is considered to be effective and feasible for treatment of patients with peritoneal metastasis.

In our analysis, PFS and OS were worse in patients with massive ascites than in patients without ascites or patients with small or moderate ascites. Although the incidence of anorexia was higher in patients with massive ascites, the frequencies of discontinuation or dose reduction due to

Table 2 Treatment results

Variables	All patients (n = 120%)	Patients without ascites (n = 70%)	Patients with small or moderate ascites (n = 39%)	Patients with massive ascites (n = 11%)
Median TTF				
Median (months, range)	5.8 (0.3–33.8)	6.5 (0.3–33.8)	5.7 (0.3–28.4)	3.4 (0.4–10.6)
Cisplatin administration				
Median number of times	4 (0–13)	4 (0–13)	3 (0–12)	2 (1–6)
Dose reduction in fluoropyrimidine				
Yes	23 (19)	13 (19)	10 (26)	0 (0)
Dose reduction in cisplatin				
Yes	33 (28)	23 (33)	10 (26)	0 (0)
Cause of discontinuation of cisplatin				
Progressive disease	52 (43)	27 (39)	17 (44)	8 (73)
Toxicities	34 (28)	22 (31)	9 (23)	3 (27)
Other	31 (26)	18 (26)	13 (33)	0 (0)
Ongoing	3 (3)	3 (4)	0	0
Cause of S-1 or capecitabine discontinuation				
Progressive disease	97 (81)	52 (74)	35 (90)	10 (91)
Toxicities	6 (5)	4 (6)	2 (5)	0 (0)
Other	10 (8)	9 (13)	1 (3)	0
Ongoing	7 (6)	5 (4)	1 (3)	1 (9)

TTF time to treatment failure

Table 3 Objective response rates in measurable lesions and ascites

Groups	*N*	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)	*P* value[a]
All patient with target lesions	55	1	22	23	5	4	42.0	28.7–55.9	0.87
No ascites	25	1	10	10	0	4	44.0	24.4–65.1	
Small to moderate ascites	26	0	10	12	4	0	38.5	20.2–59.4	
Massive ascites	4	0	2	1	1	0	50.0	6.8–93.2	
All patient with ascites	50	8	12	17	10	3	40.0	26.4–54.8	0.78
Small to moderate ascites	39	8	8	14	6	3	41.0	25.6–57.9	
Massive ascites	11	0	4	3	4	0	36.4	10.9–69.2	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

[a] Comparison of ORR between 3 groups

toxicity were not higher. Therefore, this treatment may be feasible even for patients with massive ascites if they have good performance status, sufficient oral intake, and adequate organ function. However, median treatment duration and PFS are quite short in patients with massive ascites compared with other patients; therefore, more effective treatments may be necessary to improve the poor prognosis.

To date, several clinical trials have been conducted or are ongoing in patients with peritoneal metastasis. The JCOG 9603 trial showed the efficacy of 5-FU plus methotrexate in patients with AGC with ascites: a response rate in terms of ascites of 35.1% was noted [12]. The JCOG 0106 study was conducted to compare infused 5-FU versus 5-FU plus methotrexate in patients with AGC and peritoneal metastasis, but it did not show a superiority of 5-FU plus methotrexate [13]. Although the JCOG 0106 trial did not include patients with massive ascites and did not evaluate response in terms of ascites, improvement of oral intake was reported in 48% of patients who were unable to eat at the study outset [13]; this finding suggests substantial efficacy of the 5-FU-based therapy in patients with AGC and peritoneal metastasis.

In the SPIRITS trial, combination treatment with cisplatin (SP) showed favorable results compared with S-1 alone in the subset of patients with peritoneal metastasis [2]. Although patients with massive ascites were excluded and detailed information about ascites is not available in

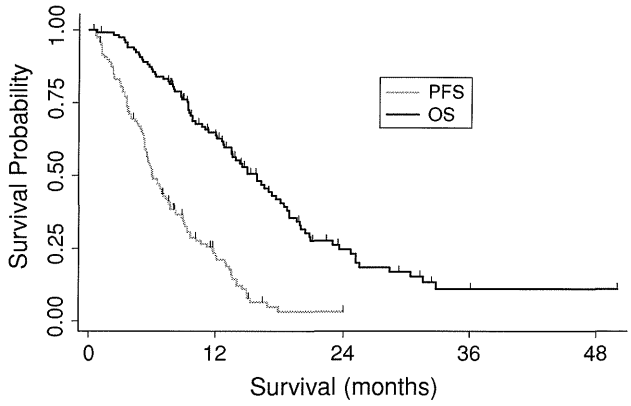

Fig. 1 Progression-free survival and overall survival. Median PFS was 6.1 months (95% CI, 5.3–7.3 months), and median OS was 15.9 months (95% CI, 12.8–18.4 months)

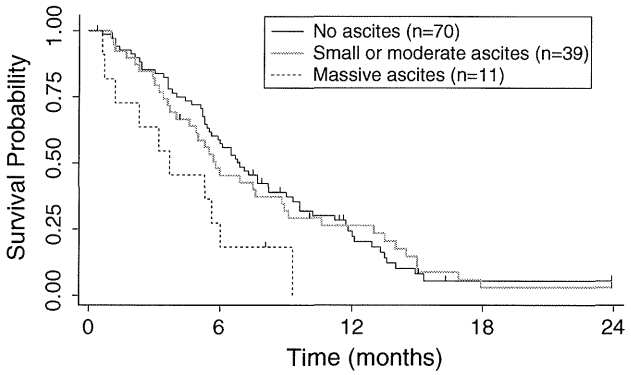

Fig. 2 Progression-free survival by ascites group. Median PFS was shorter in patients with massive ascites (3.7 months; 95% CI, 0.7–6.0 months) than in patients with small or moderate ascites (5.8 months; 95% CI, 4.0–8.8 months; HR 0.45; 95% CI, 0.22–0.93; $P = 0.03$) or patients without ascites (6.9 months; 95% CI, 5.5–9.0 months; HR 0.43; 95% CI, 0.22–0.85; $P = 0.02$)

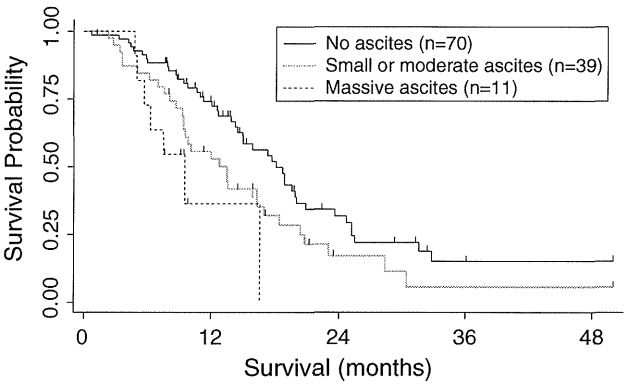

Fig. 3 Overall survival according to ascites group. Median OS was shorter in patients with massive ascites (9.5 months; 95% CI, 0.5–not reached) than in patients with small or moderate ascites (13.5 months; 95% CI, 9.4–17.0 months; HR 0.49; 95% CI, 0.21–1.15; $P = 0.1$) or patients without ascites (18.1 months; 95% CI, 14.5–20.0 months; HR 0.31; 95% CI, 0.13–0.71; $P = 0.006$)

the SPIRITS trial, this result suggests that cisplatin is also an important agent for patients with peritoneal metastasis. Oxaliplatin, another platinum agent, showed noninferior efficacy with significantly less renal toxicity [7] and gastrointestinal toxicity [21] in comparison with cisplatin. A 5-FU and oxaliplatin regimen was also evaluated in patients with AGC and ascites, with a response rate in terms of ascites of 33% with low toxicities [14].

Another effective drug type for patients with peritoneal metastasis is a taxane agent (paclitaxel or docetaxel). The JCOG 0407 trial is a randomized phase II study that compared second-line chemotherapy of weekly paclitaxel with 5-FU-based chemotherapy for patients with AGC and peritoneal metastasis [15]. The efficacy of paclitaxel was suggested by a longer PFS in the paclitaxel arm [15]. A phase II study of weekly paclitaxel for patients with malignant ascites, which included mostly patients with massive ascites (median 2,796 mL), showed a decrease in ascites and improvement of performance status in 39.1% of patients [16]. Combination treatment with 5-FU and paclitaxel also showed a high response rate (44%) in patients with massive ascites [17]. These results suggest the apparent efficacy of paclitaxel in patients with AGC and ascites. In our study, second-line chemotherapy, mainly with taxanes, was used in most patients, including those with massive ascites—possibly contributing to the relatively long survival after first-line chemotherapy. Additionally, a recent phase II study that evaluated S-1 combined with intravenous and intraperitoneal chemotherapy with paclitaxel included 40 patients with peritoneal metastasis in whom overall survival was as impressively long as 22.5 months [18]. Also, in the 30 patients with ascites in that study, the response in terms of ascites was reported to be as high as 60% [18]. These results compare favorably with those from our analysis. The efficacy of intraperitoneal administration of paclitaxel was suggested in a randomized study of patients with ovarian cancer and peritoneal metastasis [22]. Therefore, this treatment may be promising in AGC, especially for patients with peritoneal metastasis. Currently, a randomized study comparing S-1 plus intraperitoneal and intravenous paclitaxel versus S-1 plus cisplatin is ongoing.

It is important to note the limitations of the present study. First, it was a retrospective analysis in a single institution with patients that had sufficient oral intake and adequate organ function. None of the patients had symptoms or complications such as decreased oral intake or renal dysfunction due to hydronephrosis; the treatment regimen used in our study may not be feasible for such patients. Specifically, patients with peritoneal metastasis frequently have an inability to eat [23], making it impossible to use oral agents in such patients, and patients with renal dysfunction should not be given cisplatin. Therefore,

Table 4 Toxicities

	All (n = 120%)		Patients without ascites (n = 70%)		Patients with small or moderate ascites (n = 39%)		Patients with massive ascites (n = 11%)		P value[a]
	All (%)	G3–4 (%)	All (%)	G3–4 (%)	All (%)	G3–4 (%)	All (%)	G3–4 (%)	
Hematological toxicity									
Any	75 (62)	38 (32)	40 (57)	19 (27)	27 (69)	16 (41)	8 (73)	3 (27)	0.31
Leukopenia	58 (48)	15 (12)	29 (41)	9 (13)	22 (56)	5 (13)	7 (64)	1 (9)	0.94
Neutropenia	60 (50)	28 (23)	31 (44)	16 (23)	22 (56)	10 (26)	7 (64)	2 (18)	0.89
Anemia	51 (42)	12 (10)	27 (39)	6 (9)	19 (49)	5 (13)	5 (46)	1 (9)	0.77
Thrombocytopenia	25 (21)	4 (3)	14 (20)	3 (4)	9 (23)	1 (3)	2 (18)	0	0.72
Nonhematological toxicity									
Any	96 (80)	39 (33)	59 (84)	24 (34)	29 (74)	10 (26)	8 (73)	5 (45)	0.45
Nausea	73 (61)	17 (14)	44 (63)	12 (17)	22 (56)	5 (13)	7 (64)	2 (18)	0.71
Vomiting	30 (25)	4 (3)	18 (26)	3 (4)	7 (18)	0 (0)	5 (45)	1 (9)	0.26
Anorexia	80 (67)	23 (19)	45 (64)	13 (19)	28 (72)	6 (15)	7 (64)	4 (36)	0.29
Fatigue	55 (46)	8 (7)	32 (46)	6 (9)	19 (49)	2 (5)	4 (36)	1 (9)	0.51
Diarrhea	25 (20)	5 (4)	18 (26)	4 (6)	5 (13)	1 (3)	2 (18)	0	0.56
Increased creatinine	17 (14)	0	13 (19)	0	4 (10)	0	1 (9)	0	0.43[b]
Stomatitis	17 (14)	2 (2)	11 (16)	2 (3)	4 (10)	0	2 (18)	0	0.48
Rash	4 (3)	0	3 (4)	0	1 (3)	0	0	0	0.78[b]
Hand–foot syndrome	9 (8)	0	5 (7)	0	4 (10)	0	0	0	0.69[b]
Febrile neutropenia	2 (2)	2 (2)	0	2 (3)	0	0	0	0	0.48

[a] Comparison in grade 3 or more

[b] Comparison in all grades

in these types of patients, other treatments such as intravenous 5-FU or combination therapy with taxanes may be the preferred choice. Second, we included both SP and XP in this study, although most patients were treated with SP. Direct comparison of S-1 and capecitabine as well as indirect comparisons of several randomized studies using SP and XP suggest that these two treatments have similar efficacies [2, 3, 24]. Additionally, our retrospective analysis comparing these two treatment regimens showed that they have similar efficacies and safeties [25]. S-1 was suggested to be more efficacious than 5-FU in patients with diffuse-type AGC [26] or AGC associated with high dihydropyrimidine dehydrogenase (DPD), with diffuse-type tumors being more commonly associated with high DPD than intestinal-type tumors are [27]. Since diffuse-type cases are commonly associated with peritoneal metastasis, S-1 may be preferable for the treatment of AGC in this setting. In contrast, several small analyses have suggested that capecitabine is effective at treating high-thymidine phosphorylase (TP) gastric cancer [28, 29]; for such tumors, 5-FU and S-1 are reported to be relatively ineffective compared with their efficacy towards low-TP gastric cancer [30, 31]. The exact impact of using biomarkers or histology to select among 5-FU, S-1, and capecitabine should be evaluated in ongoing randomized studies.

In conclusion, although our findings are limited by the retrospective study design and small number of patients, a regimen consisting of a fluoropyrimidine plus cisplatin appears to be tolerated in selected patients with peritoneal metastasis.

Acknowledgments The manuscript has not been published nor submitted for publication elsewhere, except as a brief abstract in the proceedings of a scientific meeting or symposium (two topics were presented at the 49th Annual Meeting of Japanese Society of Clinical Oncology, October 27–29, 2011).

Conflict of interest None.

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ORIGINAL ARTICLE

A retrospective comparison of S-1 plus cisplatin and capecitabine plus cisplatin for patients with advanced or recurrent gastric cancer

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Abstract
Background Based on the results of the SPIRITS trial, combination chemotherapy of S-1 plus cisplatin (SP) is now considered the standard treatment for patients with advanced gastric cancer (AGC) in Japan. On the other hand, several non-Japanese studies have shown the efficacy of capecitabine plus cisplatin (XP), which has been used as the reference arm in recent global studies of AGC.
Methods We retrospectively compared the efficacy and safety of SP and XP in first-line treatment for patients with AGC.
Results From August 2006 to November 2008, 26 AGC patients received XP in the context of 2 global trials (AVAGAST and ToGA), and 50 patients received SP during the same period. The objective response rate was 43.2 % in the SP group and 50 % in the XP group, with no significant difference ($p = 0.62$). There were also no significant differences in progression-free survival (median 5.8 vs. 5.2 months; $p = 0.91$) and overall survival (median 13.8 vs. 13.5 months; $p = 0.97$) between the SP and XP groups. The frequencies of hematological toxicities of grade 3 or more and non-hematological toxicities were not significantly different between the 2 groups. Although grade 1 or 2 hand–foot syndrome was more common in the XP group, no patients experienced grade 3 or more.
Conclusions Although the retrospective nature of this study and the small number of patients is a major limitation, SP and XP were associated with similar efficacy and safety in patients with AGC.

Keywords Capecitabine · Chemotherapy · Cisplatin · Gastric cancer · S-1

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Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8 % of the total) and the second most prevalent cause of cancer death (737,419 deaths, 9.7 % of the total) [1]. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor; chemotherapy confers only a minimal survival advantage, with a median overall survival (OS) of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine (5-fluorouracil [5-FU] or oral fluoropyrimidine) plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the JCOG 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 was not inferior to 5-FU [9]. In a phase III trial (SPIRITS trial) that compared S-1 alone to S-1 plus cisplatin (SP), SP showed a significantly higher response rate (54 vs. 31 %, $p = 0.002$),

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longer progression-free survival (PFS; 6.0 vs. 4.0 months; hazard ration [HR] = 0.57, 95 % confidence interval [CI] 0.44–0.73), and longer OS (13 vs. 11 months; HR = 0.77, 95 % CI 0.61–0.98) [4]. Therefore, SP is now considered to be one of the standard first-line regimens for AGC in Japan.

Capecitabine is an oral fluoropyrimidine, which is metabolized primarily in the liver and converted in tumor tissues to 5-FU by the enzyme thymidine phosphorylase, which is present in higher concentrations in tumor cells than in normal cells. Kang et al. [5] evaluated capecitabine plus cisplatin (XP) versus 5-FU plus cisplatin. The median PFS showed significant non-inferiority (5.6 vs. 5.0 months; HR = 0.81, 95 % CI 0.63–1.04) [5]. In the REAL-2 study, statistical non-inferiority for OS was achieved for comparisons of capecitabine versus 5-FU (10.9 vs. 9.6 months; HR = 0.86, 95 % CI 0.80–0.99) and oxaliplatin versus cisplatin (10.4 vs. 10.0 months; HR = 0.92, 95 % CI 0.8–1.1) [3]. Additionally, meta-analysis of these 2 trials showed that OS was superior in the patients treated with capecitabine combinations than in the patients treated with 5-FU combinations (HR = 0.87; 95 % CI 0.77–0.98, $p = 0.02$) [10]. On the basis of these results, XP is now considered one of the standard treatments of AGC [11], and recently 2 global studies of molecular targeting agents each adopted XP as the reference arm [12, 13]. However, to date, data are scarce with respect to XP treatment in Japanese patients. In addition, indirect comparison of different clinical trials is difficult due to the possible heterogeneity of the clinical trials and the different time periods. Therefore, we retrospectively compared the efficacy and safety of SP and XP in patients with AGC who were treated during the same period in our institution, adjusting for the patients' characteristics as far as possible.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy and safety of first-line chemotherapy with SP or XP in patients with AGC. Since capecitabine was not available in Japan until February 2011, we evaluated patients who had been treated with XP in our institution from August 2006 to November 2008 in the context of 2 global studies [12, 13]. Patients who had received XP plus experimental agents (i.e. trastuzumab or bevacizumab) were excluded from our analysis. Eligibility for enrollment in the 2 studies has been described previously [12, 13]. In brief, patients meeting the following criteria were eligible: (1) presence of histologically proven, inoperable gastric cancer; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function; (4) measurable or evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.0); (5) no previous chemotherapy other than adjuvant chemotherapy that finished more than 6 months before enrollment; (6) human epidermal growth factor receptor 2 (HER2)-positive, defined as immunohistochemical staining of 3+ (IHC 3+) or IHC 2+ plus positive gene amplification according to fluorescence in-situ hybridization (FISH) (only in the ToGA study).

To compare the clinical outcomes of SP and XP, patients who had been treated with a standard regimen of SP during same period were evaluated in this analysis. To be included in this analysis, patients had to have fulfilled the above criteria (1)–(5) regardless of HER2 status. Patients could be included if they had started chemotherapy with S-1 in another hospital less than 1 month earlier without disease progression. In addition patients could have a history of malignancies which were curatively treated within 5 years. Written informed consent for chemotherapy was obtained from each patient prior to treatment initiation.

Treatment plan

Patients in the SP group had been treated with a standard regimen of S-1 plus cisplatin (repeated 35-day cycles of S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest and cisplatin 60 mg/m^2 intravenous infusion on day 8) [4]. In the XP group, chemotherapy was given every 21 days [12, 13]; capecitabine 1000 mg/m^2 was given orally twice a day for 14 days followed by a 7-day rest; cisplatin 80 mg/m^2 on day 1 was given by intravenous infusion. Chemotherapy dose adjustments were allowed. Treatment was discontinued if the tumor progressed, if severe toxicity occurred, or at the patient's request.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.0, and the best overall response was recorded as the antitumor effect for that patient. The objective response rate represented the percentage of patients with a complete response (CR) or partial response (PR) among patients with measurable lesions. PFS was measured from the date of initiation of chemotherapy to the date of disease progression or death from any cause. Time to treatment failure (TTF) was measured from the date of initiation of chemotherapy to the date of last administration. OS was estimated from the date of initiation of chemotherapy to the date of death or last follow-up visit. Median PFS and median OS were estimated by the Kaplan–Meier method. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

p values for testing differences in baseline characteristics and response rates of both groups were calculated with chi-squared tests for homogeneity or for trend, or with Fisher's exact test. To decrease selection bias as much as possible, survival differences between the 2 patient groups were evaluated not only by univariate analyses but also by multivariate analyses using the Cox proportional hazards model, and presented as hazard ratios (HR) and 95 % confidence intervals (95 % CI). Other variables considered in the multivariate analyses were ECOG PS (0 vs. ≥1), gender, histological type (diffuse vs. intestinal), age (<65 vs. ≥65 years), previous gastrectomy (no vs. yes), disease status (advanced vs. recurrent), prior adjuvant chemotherapy (no vs. yes), presence of liver metastasis (no vs. yes), presence of peritoneal metastasis (no vs. yes), number of metastatic sites (1 vs. ≥2), and HER2 status (positive vs. negative vs. unknown). In this analysis, HER2-positive was defined as IHC 3+ or IHC 2+ plus amplification by FISH, since these criteria were considered indications for the use of trastuzumab by a subset analysis of the ToGA trial [11, 12].

Statistical analyses were performed using STATA software (version 10; StataCorp LP, College Station, TX, USA). All tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

In the time-period of the study, SP- or XP-based therapy was administered in 115 patients. Among them, 51 patients who were included in the ToGA or AVAGAST studies received XP-based therapy. Twenty-five patients with XP plus experimental agents (trastuzumab or bevacizumab) were excluded, and another 26 patients were included in this analysis as the XP group. In contrast, 64 patients received SP-based therapy, and 50 patients were included in this analysis as the SP group after excluding 14 patients for the following reasons: S1 ± cisplatin ± sunitinib (clinical trial) in 5 patients, started SP therapy in another hospital in 4 patients, insufficient organ function in 3 patients; poor performance status in 2 patients. Patient characteristics for both groups are shown in Table 1. No patient had ECOG PS 2. No significant difference was observed between the 2 groups other than HER2 status. HER2 was evaluated in 14 of 50 patients in the SP group, with 2 positive patients (14 %). In contrast, HER2 was evaluated in 20 of 26 patients in the XP group, with 4 positive patients (20 %). Six patients included in the ToGA study were regarded as HER2-negative in this analysis, with IHC staining of 0 or 1. Thirty-seven patients in the SP group (74 %) and 20 patients (77 %) in the XP group had measurable lesions.

Table 1 Patient characteristics

Characteristic	All (n = 76, %)	SP (n = 50, %)	XP (n = 26, %)	p value
Age (years)				
Median (range)	62 (36–79)	61 (36–75)	65 (40–79)	0.36
Gender				
Male	59 (78)	37 (74)	22 (85)	0.29
Female	17 (22)	13 (26)	4 (15)	
ECOG PS				
0	35 (46)	21 (42)	14 (54)	0.33
1	41 (54)	29 (58)	12 (46)	
Histological type				
Diffuse	50 (66)	35 (70)	15 (58)	0.28
Intestinal	26 (34)	15 (30)	11 (42)	
Disease status				
Advanced	59 (78)	40 (80)	19 (73)	0.49
Recurrent	17 (22)	10 (20)	7 (27)	
Previous gastrectomy				
No	48 (63)	31 (62)	17 (65)	0.77
Yes	28 (37)	19 (38)	9 (35)	
Prior adjuvant chemotherapy				
No	69 (91)	45 (90)	24 (92)	0.74
Yes	7 (9)	5 (10)	2 (8)	
Site of metastasis				
Lymph node	49 (64)	30 (60)	19 (73)	0.26
Peritoneum	41 (54)	29 (58)	12 (46)	0.33
Liver	24 (32)	14 (28)	10 (38)	0.35
Lung	6 (8)	4 (8)	2 (8)	0.96
Number of metastatic sites				
1	36 (47)	25 (50)	11 (42)	0.52
≥2	40 (53)	25 (50)	15 (58)	
HER2				
Positive	6 (8)	2 (4)	4 (15)	<0.01
Negative	28 (37)	12 (24)	16 (62)	
Unknown	42 (55)	36 (72)	6 (23)	

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *SP* S-1 plus cisplatin, *XP* capecitabine plus cisplatin, *HER2* human epidermal growth factor receptor 2

Among the patients in the SP group, reasons for non-inclusion in the ToGA or AVAGAST studies were as follows: 13 patients refused, 12 patients were HER2-negative (for ToGA trial), 6 patients had a history of S-1 treatment (<1 month previously) in another hospital, and 5 patients had a history of other cancers. Reasons were not defined for the other 14 patients.

Treatment results and efficacy

The median number of treatment cycles for SP and XP was 4 and 6, respectively. The median TTF was 5.0 months

Table 2 Objective response rate in each treatment regimen

Regimen	*n*	CR	PR	SD	PD	NE	ORR (%)	95 % CI (%)
SP	37	1	15	11	9	1	43.2	27.1–60.5
XP	20	2	8	5	4	1	50.0	27.2–72.8

SP S-1 plus cisplatin, *XP* capecitabine plus cisplatin, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

(95 % CI 3.2–6.9 months) in the SP group and 5.1 months (95 % CI 2.9–5.9 months) in the XP group, with a median duration of follow-up of 32 months in both groups. In the SP group, after the initial dose, the dose of S-1 was reduced in 15 patients (30 %) and the dose of cisplatin was reduced in 15 patients (30 %). In the XP group, the dose of capecitabine was reduced in 11 patients (42 %) and the dose of cisplatin was reduced in 13 patients (50 %). Dose reduction in both groups was mainly due to hematological toxicity. Four patients had their dose of capecitabine decreased due to hand–foot syndrome. The proportion of patients receiving any dose reduction was higher in the XP group ($p = 0.03$). The relative dose intensity of cisplatin in the SP group (0.93) was higher than that in the XP group (0.81). Patients discontinued SP because of disease progression ($n = 42$; 84 %), toxicity ($n = 4$; 8 %), and other reasons ($n = 4$; 8 %); patients discontinued XP because of disease progression ($n = 22$; 85 %), toxicity ($n = 1$; 4 %), and other reasons ($n = 3$; 12 %).

Among the 37 patients with measurable lesions in the SP group, 16 achieved either a CR ($n = 1$) or a PR ($n = 15$), for an objective response rate of 43.2 % (95 % CI 27.1–60.5 %; Table 2). Among the 20 patients with measurable lesions in the XP group, 10 achieved either a CR ($n = 2$) or a PR ($n = 8$), for an objective response rate of 50.0 % (95 % CI 27.2–72.8 %; Table 2) with no statistical difference between the 2 groups ($p = 0.62$).

All patients but 1 experienced disease progression at the time of analysis. The median PFS was 5.8 months (95 % CI 4.0–7.1 months) in the SP group and 5.2 months (95 % CI 3.0–8.0 months) in the XP group (Fig. 1), with no statistical significant difference according to univariate analysis (HR 0.97; 95 % CI 0.60–1.58, $p = 0.91$) or multivariate analysis (HR 0.94; 95 % CI 0.50–1.77, $p = 0.85$). Forty patients (80 %) in the SP group and 21 patients (81 %) in the XP group died; the median OS of patients was 13.8 months (95 % CI 10.3–18.7 months) in the SP group and 13.5 months (95 % CI 10.1–18.5 months) in the XP group (Fig. 2). No statistical difference was observed between OS in the SP group and that in the XP group according to univariate analysis (HR 0.99; 95 % CI 0.58–1.68, $p = 0.97$) or multivariate analysis (HR 1.07; 95 % CI 0.54–2.11, $p = 0.84$). Also, subset analysis

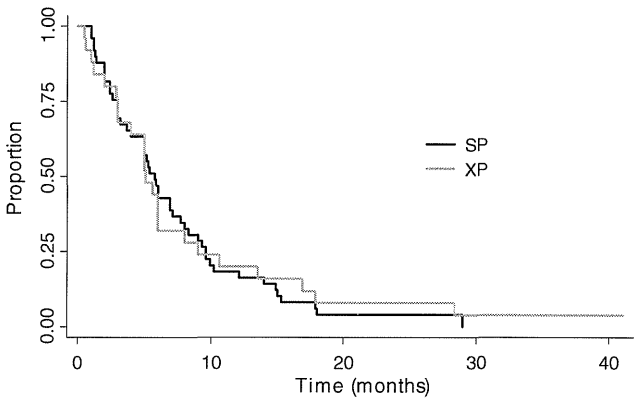

Fig. 1 Progression-free survival under SP and XP treatment regimens. The median PFS was 5.8 months (95 % CI 4.0–7.1 months) in the SP group and 5.2 months (95 % CI 3.0–8.0 months) in the XP group, with no statistical significant difference according to univariate analysis (HR 0.97; 95 % CI 0.60–1.58, $p = 0.91$) or multivariate analysis (HR 0.94; 95 % CI 0.50–1.77, $p = 0.85$). *SP* S-1 plus cisplatin, *XP* capecitabine plus cisplatin

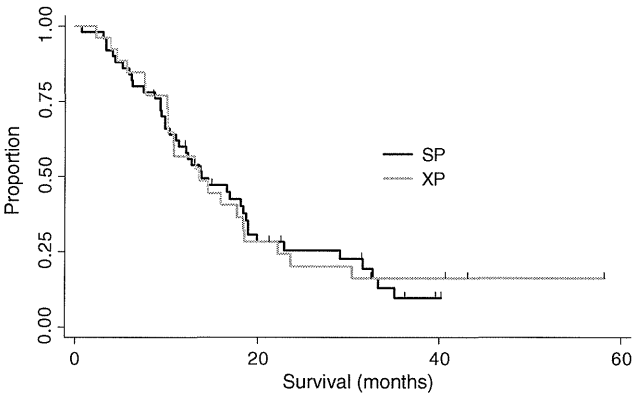

Fig. 2 Overall survival under SP and XP treatment regimens. The median OS of patients in the SP and XP groups was 13.8 months (95 % CI 10.3–18.7 months) and 13.5 months (95 % CI 10.1–18.5 months), respectively, with no statistical difference according to univariate analysis (HR 0.99; 95 % CI 0.58–1.68, $p = 0.97$) or multivariate analysis (HR 1.07; 95 % CI 0.54–2.11, $p = 0.84$). *SP* S-1 plus cisplatin, *XP* capecitabine plus cisplatin

suggested no apparent interaction between the effect of each treatment and patient characteristics (Fig. 3).

Forty-one patients (82 %) in the SP group and 21 patients (81 %) in the XP group received second-line