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Phase II study of S-1, an oral fluoropyrimidine, in patients with advanced or recurrent cervical cancer

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Background: S-1 is an oral fluoropyrimidine. This phase II study was designed to evaluate the efficacy and safety of S-1 in patients with advanced or recurrent uterine cervical cancer.

Patients and methods: S-1 35 mg/m^2 was given twice daily for 28 days repeated every 6 weeks. Eligible patients were women aged 20–74 years, who had Eastern Cooperative Oncology Group performance status of zero or one, who had stage IVB or recurrent uterine cervical cancer, and who had received no more than one platinum-containing chemotherapy regimen for stage IVB or recurrent disease. The primary end point was overall response rate (ORR) determined by RECIST.

Results: A total of 37 patients were enrolled in the trial and 36 were eligible. The median number of cycles administered was 4. The confirmed ORR was 30.6% (95% confidence interval 15.5% to 45.6%). The response rate for patients who had received platinum-based treatment including chemoradiotherapy was 31.8% (7 of 22). After a median follow-up duration of 25 months, the median time to progression and the median survival time were 5.2 and 15.4 months, respectively. The most frequent grade 3 or 4 adverse events were anemia (16%), anorexia (16%), and diarrhea (22%).

Conclusions: This phase II study of S-1 in cervical cancer suggests a promising response rate and a contribution toward prolonging survival, with modest toxic effects. Phase III studies of S-1 in patients with advanced or recurrent cervical cancer are thus warranted.

Key words: cervical cancer, chemotherapy, phase II trial, relapse, S-1

introduction

Cancer of the uterine cervix is the main cause of death from gynecologic malignancy in emerging countries. In the developed world as well, a third of women with cervical cancer die of uncontrolled disease. Although a number of chemotherapeutic agents have been investigated in patients with advanced or recurrent cervical cancer, the prognosis of those patients remains poor. Identification of new agents with activity in cervical cancer is needed.

S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is an oral fluoropyrimidine consisting of tegafur [a prodrug that is metabolized to 5-fluorouracil (5-FU) in blood, largely by the cytochrome P450 system in the liver], gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1 : 0.4 : 1 [1]. S-1 is known to be active against gastric, head and neck, colorectal, lung, breast, pancreatic, and biliary tract cancers [2–9]. This phase II study was designed to evaluate the efficacy and safety of S-1 in patients with uterine cervical cancer and is the first exploration of S-1 for the treatment of any gynecologic cancer. S-1 has also shown activity for cervical cancer in preclinical study (data are available only in investigator's brochure); phase II study of S-1 in patients with cervical cancer has been launched to evaluate the usefulness of S-1 in those patients.

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patients and methods

eligibility criteria

Eligible patients were aged between 20 and 74 years, had Eastern Cooperative Oncology Group performance status of zero or one, and had histological documented primary stage IVB or recurrent cervical carcinoma.

All patients had measurable disease according to the RECIST [10]. Measurable lesions defined unit dimensionally were ≥20 mm using conventional imaging or ≥10 mm with spiral computed topographic scan. Patients had not received more than one prior chemotherapy regimen since diagnosis of metastatic or recurrent disease. Patients who were administered in conjunction with radiation were not counted under prior chemotherapy. Four weeks from prior chemotherapy or radiotherapy were required before study entry. Adequate organ function was required for study entry: neutrophil count ≥2000/μl; platelet count ≥100 000/μl; hemoglobin ≥8.0 g/dl; serum bilirubin level ≤1.5 times upper limit of the institutional normal (ULN); asparate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤2.5 times ULN; and serum creatinine level ≤ ULN. Only patients who could swallow tablets were eligible. Patients with any of the following conditions were excluded from the study: active infection, severe heart disease, interstitial pneumonitis, history of hypersensitivity, malignant or benign effusions requiring drainage, active brain metastasis, or active concomitant malignancy. Patients receiving drugs with potential interactions with S-1 (flucytosine, warfarin, and phenytoin) were excluded. All patients gave informed consent before entering this study, which was approved by the institutional review boards at all participating institutions.

treatment schedule

Patients received two oral doses of S-1 35 mg/m^2 daily for 4 weeks of a 6-week cycle. As S-1 is provided in 20 or 25 mg tablets, the actual dosage of S-1 was decided according to the patient's body surface area as follows: patients with a body surface area of less than 1.25 m^2 received 40 mg; those with a body surface area of 1.25–1.5 m^2 received 50 mg; and those with a body surface area of more than 1.5 m^2 received 60 mg. The schedule was repeated until the occurrence of disease progression, unacceptable toxic effects, or patient's refusal. If a grade 3 or higher hematological toxicity or a grade 2 or higher nonhematological toxicity was observed, the dose was reduced from 60 to 50 mg, 50 to 40 mg, or temporary interruption of S-1 administration was recommended. Patients whose toxic effects necessitated a rest period of >4 weeks were withdrawn from treatment. When initial dose was 40, 50, or 60 mg, dose escalation could be allowed to 50, 60, and 75 mg for subsequent cycles, unless adverse events were observed.

response and toxicity evaluation

The tumor response was assessed according to the guidelines of RECIST. Target lesions included all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total. Target lesions were included the lesions with previously irradiated area. Complete response (CR) was defined as the complete disappearance of all target and nontarget lesions, with no development of new disease. Partial response (PR) was defined as a reduction by ≥30% in the sum of the longest diameter of target lesions. CRs or PRs were confirmed by repeat assessments carried out no <4 weeks after the criteria for response were first met. Progressive disease (PD) was defined as an increase ≥20% in the sum of the longest diameter of all target lesions or the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Stable disease (SD) was defined as neither sufficient lesion shrinkage to qualify for PR nor sufficient increase to qualify for PD. Best response was defined as the most CR achieved by a patient (thus, each patient had a single best response: CR, PR, SD, or PD), and the date of best response was the date it was first detected. Radiological studies were repeated every two cycles. If a patient was documented as having a CR or a PR, the response was confirmed at least 4 weeks after the first evidence of response. An independent response review committee (IRRC) evaluated all tumor responses after the investigators had completed their judgment.

Toxic effects were evaluated with respect to incidence and severity using Common Terminology Criteria of Adverse Events (version 3.0) (www.cancer.gov/).

statistical consideration

The primary end point of this study was to assess the overall response rate determined by the IRRC. The secondary end points were to assess duration of response, time to response, time to progression (TTP), overall survival, and adverse events. Assuming a response rate of 20%, the study was designed with 80% power such that the lower limit of the 95% confidence interval (CI) for the estimate of the response rate was >0.05. A sample size of 32 assessable patients was required. The Kaplan–Meier method was used to determine the TTP and median survival time (MST) in the assessable population. TTP was defined as the time from the first medication to the date of a PD event or death (due to cervical cancer or study drugs).

results

patient population

A total of 37 patients were entered into the study from July 2005 to September 2007 and 36 patients were eligible and assessable. One patient had a lack of absolute neutrophil count for eligibility criteria. All 37 patients were evaluated for safety. Patient characteristics are listed in Table 1. More than half of the patients had distant diseases. Seventeen patients (8 for neoadjuvant chemotherapy, 3 for metastatic disease, and 6 for both) received prior chemotherapy (not including chemoradiotherapy): 14 received platinum-containing regimen and 3 received oral 5-FU derivative drug alone. Thirteen

Table 1. Patient characteristics

Characteristic	No. of patients
No. of patients entered	37
No. of patients eligible	36
Age (years)	
Median	57
Range	33–72
Performance status	
0	26
1	10
Histology	
Squamous cell carcinoma	29
Adenocarcinoma	2
Adenosquamous	4
Small cell carcinoma	1
Site of disease	
Pelvic	23
Distant	26
Both	13
Prior therapy	
Prior radiotherapy	22
Prior chemotherapy[a]	17
Prior chemoradiotherapy	13
Prior platinum therapy	22

[a]Not included chemoradiotherapy.

patients (36%) received chemoradiotherapy. Prior platinum therapy including chemotherapy or chemoradiotherapy was administered for 22 patients.

A total of 167 treatment cycles (median 4, range 1–19) were administered. Nineteen patients (53%) were subjected to dose reduction owing to adverse events. The median relative dose intensity was 0.83 (range 0.45–1.04).

antitumor activity

Table 2 describes the response assessment. The objective response rate assessed by IRRC was 30.6% (95% CI 15.5% to 45.6%). The median duration of response was 134 days (range 73–553 days). The investigators identified one CR and nine PRs. One clinical responded patient who had CR was downgraded to PR, two clinical responded patients who had PR were downgraded to SD and PD, respectively, and three patients who had SD were upgraded to PR by the judgment of IRRC. Therefore, a total of 11 patients were judged PR. Responses according to prior therapy are listed in Table 2. Patients who received chemotherapy alone had a response of 17.6%, patients who received chemoradiotherapy 53.8%, and patients who received platinum-containing chemotherapy or chemoradiotherapy 31.8%. Eighteen patients had target lesions with previously irradiated area and five (27.8%) of them were responded.

After a median follow-up duration of 25 months, the median TTP was 5.2 months (95% CI 4.5–6.6 months; Figure 1) and the MST was 15.4 months (95% CI 11.5–17.8 months; Figure 2). One-year survival was 58.3%.

safety

All 37 patients were assessed for safety. Four patients were discontinued due to toxic effects. Adverse events are listed in Table 3. Grade 3 or 4 hematologic toxic effects were anemia (16%), neutropenia (8%), and thrombocytopenia (5%). Among grade 3 or 4 nonhematologic toxic effects, the most frequent were anorexia (16%) and diarrhea (22%). All other grade 3 or 4 toxic effects were recorded in <10% of patients.

discussion

The prognosis of patients with advanced or recurrent cervical cancer remains poor and there is an urgent need for novel therapeutic agents. This current study was designed to determine the efficacy and tolerability of an oral agent of S-1 for advanced or recurrent cervical cancer and demonstrated a higher response rate of 30.6% with modest toxic effects: grade 3 or 4 anemia (16%), anorexia (16%), and diarrhea (22%).

The most extensively studied agent in the treatment of advanced cervical cancer is cisplatin, which has been used as a single agent, in combination chemotherapy, or with radiotherapy. The eligibility criteria of our study included

Table 2. Responses to S-1 according to the patient characteristics

	n	CR	PR	SD	PD	Response rate (95% CI)
Overall	36	0	11	18	7	30.6 (15.5–45.6)
Prior therapy						
Chemotherapy	17	0	3	9	5	17.6 (0–35.8)
Chemoradiotherapy	13	0	7	5	1	53.8 (26.7–80.9)
Platinum therapy	22	0	7	10	5	31.8 (12.4–51.3)
No platinum therapy	14	0	4	8	7	28.6 (14.9–52.2)

CR, complete response; PR, partial response; SD, stable disease; PD, Progressive disease; CI, confidential interval.

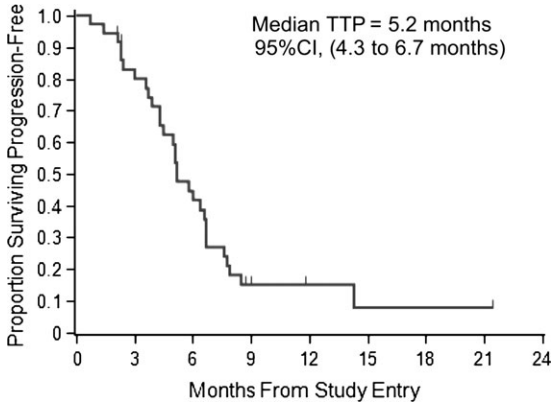

Figure 1. Kaplan–Meier plot for time to progression (TTP; $n = 36$). CI, confidence interval.

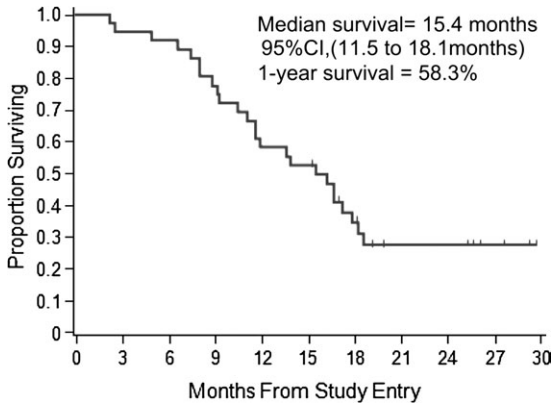

Figure 2. Kaplan–Meier plot for overall survival ($n = 36$). CI, confidence interval.

Table 3. Adverse events ($n = 37$)

Toxicity	Grade				
	1	2	3	4	Grade 3–4(%)
Anemia	6	11	5	1	16
Leukopenia	5	13	2	0	5
Neutropenia	6	9	3	0	8
Thrombocytopenia	6	1	1	1	5
Stomatitis	18	2	0	0	0
Anorexia	14	7	6	0	16
Nausea	21	4	1	0	3
Vomiting	12	2	1	0	3
Diarrhea	13	10	8	0	22
Hyperpigmentation	31	1	0	0	0
Skin rash	7	4	1	0	3
Fatigue	12	11	2	0	5

patients with prior chemotherapy or chemoradiotherapy. Twenty-two of the 36 patients (61%) had previously received platinum therapy including chemoradiotherapy. There may be drug resistance to cisplatin in such patients; however, objective responses were seen in patients who had received prior platinum therapy. Therefore, it is suggested that S-1 is a noncross resistant drug for cisplatin.

Several non-platinum agents, such as paclitaxel [11–13], topotecan [14, 15], irinotecan [16, 17], vinorelbine [18–20], capecitabine [21, 22], and ifosphamide [23–25] were found to have moderate activity in patients with metastatic cervical cancer. However, none of the previously reported phase II studies of non-platinum single-agent chemotherapy for patients with advanced cervical cancer have reported >30% response rate, except paclitaxel and ifosphamide [26]. Paclitaxel is an active agent for cervical cancer and has been evaluated in randomized trial. GOG 0204 compared doublets of paclitaxel, vinorelbine, and gemcitabine plus cisplatin with the combination of topotecan plus cisplatin, and there was a trend favoring treatment with cisplatin/paclitaxel for response rate, progression-free survival (PFS), overall survival, and quality of life [27]. Ifosphamide in combination with cisplatin was tested in randomized trial comparing cisplatin alone and showed a better response rate and PFS but not overall survival and including severe toxic effects. Although our study examined a small number of patients and the CI was wide, notable objective responses were achieved in this single-agent chemotherapy.

Combinations of 5-FU and cisplatin yield synergistic in preclinical studies [28, 29]. A combination therapy of S-1 and cisplatin has been studied in other malignancies, including gastric cancer, lung cancer, and head and neck cancer [30–32]. Phase III trial comparing S-1 in combination with cisplatin versus S-1 alone in advanced gastric cancer demonstrated a significant benefit for combined S-1 plus cisplatin in response rate, PFS, and overall survival [33]. Based on the promising activity of S-1 in the present phase II study, and the experience with S-1 plus cisplatin in other malignancies, we have started phase III trial of S-1 plus cisplatin compared with single-agent cisplatin for metastatic cervical cancer in an Asian trial, including Japan, Korea, and Taiwan.

In conclusion, S-1 is active in patients with metastatic cervical cancer and well tolerated. S-1 plus cisplatin has now entered a prospective randomized phase III trial.

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disclosure

Dr Kamiura has reported honoraria for Taiho Pharmaceutical. Dr Ochiai has reported consultant or advisory role for Taiho Pharmaceutical, and honoraria for Taiho Pharmaceutical, Bristol Myers Squibb, and Sanofi Aventis; he has received research support from Taiho Pharmaceutical, and Bristol Myers Squibb. The other authors have not reported any conflicts of interest.

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