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ORIGINAL ARTICLE

An early phase II trial of S-1 in Japanese patients with cytokine-refractory metastatic renal cell carcinoma

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Abstract
Purpose S-1, an oral anticancer agent, contains tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo) at a molar ratio of FT:CDHP:Oxo = 1:0.4:1. The aim of this trial was to investigate the efficacy and safety of S-1 in Japanese patients with cytokine-refractory metastatic renal cell carcinoma (RCC).
Methods We conducted a non-randomized, open-label trial in Japanese patients with metastatic RCC who had received nephrectomy and had failed cytokine-based immunotherapy. The primary endpoint was response rate. S-1 40–60 mg based on the body surface area was administered twice daily (80–120 mg/day) for 4 consecutive weeks, followed by a 2-week rest period; cycles were repeated every 6 weeks. Patients continued treatment until disease progression, unacceptable toxicity, or withdrawal of consent.
Results A total of 20 eligible patients were enrolled. Among these, 3 patients had partial response, yielding objective response rate of 15%; 13 patients had no change; 4 patients had progressive disease. The median time-to-progression and median overall survival were 12.0 and 25.7 months, respectively. The initial adverse event was generally mild to moderate in severity. The most common grade 3/4 drug-related hematological and non-hematological adverse events were neutropenia (20.0%) and anorexia (20.0%), respectively.
Conclusions S-1 is active and well tolerated for the treatment of cytokine-refractory metastatic RCC.

Keywords S-1 · Phase II Trial · Cytokine-refractory · Chemotherapy · Renal cell carcinoma

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Introduction

Renal cell carcinoma (RCC) is the most common cancer of the kidney causing an estimated 3,500 annual deaths in Japan. Immunotherapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2) has been the mainstay for the treatment of advanced, metastatic RCC for more than 15 years in Japan. However, response rates with these cytokines are generally low (10–20%), and 5-year survival rates of patients with metastatic RCC treated with these immunotherapies remain less than 20% [1]. Thus, development of alternative treatment is essential.

Recently, the usefulness of several new agents that target the activity of angiogenic growth factors have been demonstrated, and the therapeutic approach to metastatic RCC has changed dramatically. In a phase III randomized controlled

trial, sorafenib and sunitinib demonstrated a better response, progression-free survival (PFS), and overall survival (OS), when compared with placebo [2, 3] and IFN-α [4, 5], respectively. For further improvement of prognosis, however, development of agents with different mechanisms of action such as chemotherapeutic agents is still required. *The targeting agents for RCC came out in Japan after this trial was performed.*

S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) is a novel orally administered drug that is a combination of tegafur (FT) as a prodrug of 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo) in a 1:0.4:1 M concentration ratio [6]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and acts to maintain efficacious concentrations of 5-FU in both plasma and tumor tissues [7]. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, reducing the serious gastrointestinal toxicity associated with 5-FU [8]. Promising anticancer effects of S-1 have been demonstrated in clinical trials for a variety of solid tumors [9–15]. The major drug-related adverse events recognized in such trials were myelosuppression and gastrointestinal toxicities, though most of them were tolerable and reversible. According to these findings, the commercial availability of S-1 for treatment of patients with gastric cancer, colorectal cancer, non-small cell lung cancer, breast cancer, head and neck cancer, pancreatic cancer, and biliary tract cancer has been approved in Japan. However, no previous reports have described the efficacy and safety of S-1 for the treatment of metastatic RCC. Consequently, the present early phase II trial was conducted to evaluate the efficacy and safety of S-1 in Japanese patients with cytokine-refractory metastatic RCC.

Patients and methods

Patients

Patients were required to meet the following eligibility criteria: orally able to ingest drugs, histologically or cytologically confirmed metastatic RCC, had received nephrectomy and failed at least one cytokine-based immunotherapy, at least one bidimensionally measurable lesion, no prior chemotherapy, no radiotherapy for measurable lesion, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1 (2 was allowed in cases of bone metastasis), age 20–79, expected survival 3 months or more, adequate organ function, defined as a hemoglobin level $\geq$10.0 g/dl, a white blood cell count of 4,000–12,000/mm^3 or neutrophil count $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, total bilirubin level $\leq$1.5 mg/dl, an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level $\leq$ 2.5 times the upper normal limits, an alkaline phosphatase (ALP) level $\leq$ 2 times the upper normal limit, serum creatinine level $\leq$ 1.3 mg/dl, and written informed consent from the patients. The exclusion criteria included a history of drug hypersensitivity, severe complications, such as infection, heart disease, brain metastasis, concomitant malignancy, serum calcium $\geq$ 11.5 mg/dl, marked pleural effusion or ascites, watery diarrhea, concomitant peptic ulcer, clinical symptoms of a cardiac disorder, treatment with phenytoin potassium warfarin or flucytosine, pregnancy or lactation, and men who were trying to father a child.

Trial design

This was a non-randomized, open-label, phase II trial in Japanese patients with metastatic RCC who had received nephrectomy and failed at least one cytokine-based immunotherapy. The primary endpoint was to determine the response rate (RR), i.e., the proportion of patients with complete response (CR) plus partial response (PR), confirmed according to the Japan Society for Cancer Therapy (JSCT) criteria [16], which are based on World Health Organization criteria. Secondary endpoints were time-to-progression (TTP), overall response duration, OS, and RR according to the Response Evaluation Criteria in Solid Tumors (RECIST) [17]. We evaluated response according to the JSCT criteria as primary because JSCT criteria were used widely in Japan when we had planned this trial. Lesions identified and measured at baseline were evaluated using the same technique, preferably by the same attending physician. S-1 was administered orally at a dose of 40–60 mg twice daily (80–120 mg/day) based on the body surface area (BSA): BSA $<$ 1.25 m^2, 40 mg; 1.25 m^2 $\leq$ BSA $<$ 1.50 m^2, 50 mg; and 1.50 m^2 $\leq$ BSA, 60 mg. S-1 was administered for 4 consecutive weeks, followed by a 2-week rest; cycles were repeated every 6 weeks. Patients continued treatment until disease progression, unacceptable toxicity according to the clinical judgment of the investigator, or withdrawal of consent. If the daily dose of S-1 was considered to be intolerable, the dose was reduced by 20 mg/day (minimum dose, 80 mg/day). If toxicity required a rest period of more than 28 days, the patient was withdrawn from the trial. During the trial, patients were not allowed to receive concomitant radiation therapy, chemotherapy, immunotherapy, or molecular-targeted therapy. Patients were monitored for adverse events at every visit.

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki [18] and Japanese Good Clinical Practice guidelines. The protocol was approved by the institutional review board of all participating institutions.

Evaluation of efficacy and safety

The response was assessed using computed tomography scan or magnetic resonance imaging at baseline and immediately after each course according to the JSCT criteria. Briefly, CR was defined as the disappearance of all clinical evidence of the tumor for at least 4 weeks. PR was defined as a 50% or more reduction in the sum of the products of the greatest perpendicular dimensions of all measurable lesions for at least 4 weeks. No change (NC) was defined as a reduction in less than 50% or a less than 25% increase in the sum of the products of the greatest perpendicular dimensions of all lesions for at least 4 weeks. Progressive disease (PD) was defined as an increase of 25% or more in the sum of the products of the greatest perpendicular dimensions of all lesions, the appearance of any new lesion, or a deterioration in clinical status consistent with disease progression. The response duration was calculated from the date of the first documentation of a response to the date of disease progression; the TTP was calculated from the date of registration to the date of documented disease progression or death from any cause, whichever *occurred* first. OS was calculated from the date of registration to death from any cause. The median OS and TTP were estimated using the Kaplan–Meier method [19]. The threshold of the RR was defined as 5%, and the expected rate was set at 15% because the RR of IFN-α was estimated at 15%. The maximum number of patients to be enrolled in this trial in the limited study period was decided to be patients from the viewpoint of feasibility of patient recruitment. *So the denominator was planned 20 patients.* If more than 4 patients showed tumor response, we can reject the null hypothesis that RR of S-1 is lower than 5% under condition of two-sided α-error of 10%. Furthermore, response was secondarily assessed according to the RECIST for comparison with other trials. Assessments of the physical findings, blood biochemistry, and urinalysis tests were conducted at baseline and every 2 weeks in the treatment period. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The causal relationship of adverse events to S-1 was first judged by the attending physicians. Subsequently, an external committee consisting of urologists, radiologists, and medical oncologists confirmed objective responses and drug-related adverse events.

Results

Patients characteristics

Twenty patients from 13 institutions were enrolled between June 2003 and December 2004, and the last patient data input was December 2006. All patients were eligible for (full analysis set: 20) and assessable for responses and drug-related adverse events. Patient characteristics are shown in Table 1. Histological tumor subtypes were clear cell carcinoma (90.0%), papillary RCC (5.0%), and unknown (5.0%). The major sites of metastases were the lung, lymph nodes, and liver. The initial dose of S-1 was 100 mg/day in 5 (25.0%), and 120 mg/day in 15 (75.0%), with a median of 3.5 cycles per patient (range, 1–22 cycles).

Efficacy

Confirmed PRs were based on evaluation by an external committee according to the JSCT criteria and RECIST. According to the JSCT criteria, out of the total 20 evaluable patients, 3 patients had PR, for a RR of 15% (90% CI, 4.2–34.4%); 13 patients had NC; 4 patients had PD (Table 2). Response was 21% (3/14) in lung metastases, but no response was seen in lymph node and liver metastases. The median duration of response was 16.2 months (range 2.3–21.2 months), and the median time to response was 2.3 months (range 1.0–4.6 months) in the 3 patients with a best response of PR. According to the RECIST, 2 patients had PR, with an RR of 10% (90% CI, 1.8–28.3%); 17 patients had stable disease (SD); 1 patient had PD. The overall disease control rate (i.e., CR + PR or SD maintained

Table 1 Baseline demographic and clinical characteristics

	No. of pts (n = 20)	%
Gender		
Male	13	65.0
Female	7	35.0
Age, years		
<65 years	11	55.0
≥65 years	9	45.0
ECOG PS		
0	17	85.0
1	3	15.0
Histology		
Clear cell	18	90.0
Papillary renal cell	1	5.0
Unknown	1	5.0
Sites of disease		
Lung	15	75.0
Lymph node	8	40.0
liver	3	15.0
Prior cytokine-based immunotherapy		
IFN-α	13	65.0
IFN-α + IL-2	5	25.0
IFN-α + IFN-γ	2	10.0

Table 2 Best overall response based on an external committee

	No. of pts. (%)	
	JSCT criteria	RECIST
Complete response	0 (0%)	0 (0%)
Partial response	3 (15%)	2 (10%)
No change	13 (65%)	–
Stable disease	–	17 (85%)
Progressive disease	4 (20%)	1 (5%)
Response rate (90% CI)	15% (4.2–34.4%)	10% (1.8–28.3%)

CI confidence interval

for 28 days or more) was 95%. During the trial, a total of 15 patients had some degree of tumor shrinkage from baseline values according to the evaluation by RECIST (Fig. 1). The median TTP was 12.0 months (90% CI, 4.6–18.5 months), and the median OS was 25.7 months (90% CI, 20.4–50.5 months) with a 1-year survival rate of 85.0% (Fig. 2).

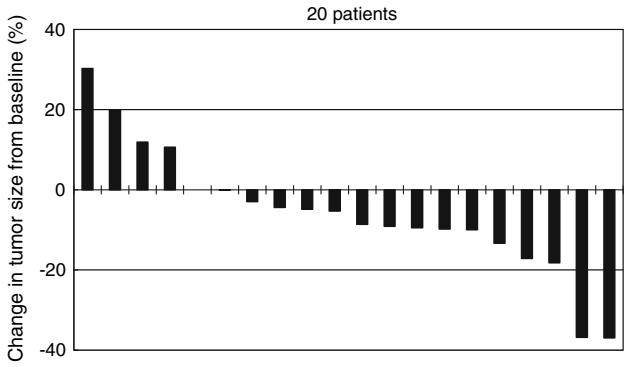

Fig. 1 Maximum percentage of tumor decrease for target lesions by RECIST, assessed by an external committee

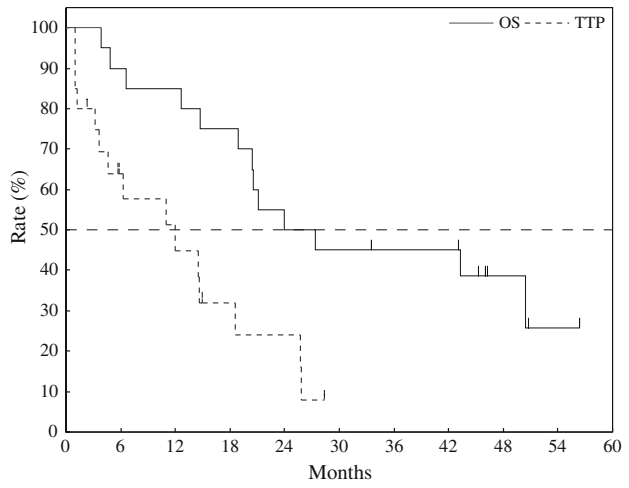

Fig. 2 Kaplan–Meier estimate of TTP (external committee assessment) and OS. The median TTP was 12.0 months (90% CI, 4.6–18.5 months), and the median OS was 25.7 months (90% CI, 20.4–50.5 months) with a 1-year survival rate of 85.0%

Adverse events

S-1 was well tolerated and most patients were treated as outpatients in this trial. Safety analysis was performed in all 20 patients, who had received at least one dose of S-1. All patients experienced at least one drug-related adverse event, but the majority of adverse events were mild to moderate in severity (Table 3). Grade 4 drug-related adverse events were observed in only 1 patient: anorexia (5.0%). The most common grade 3 drug-related hematological and non-hematological adverse event was neutropenia (20.0%) and anorexia (15.0%), respectively. Treatment-related deaths did not occur within 30 days of the last drug administration.

Discussion

5-FU, first synthesized 40 years ago, is still one of the most widely used agents for treatment of gastrointestinal cancers. An oral fluoropyrimidine derivative, S-1, was developed on the basis of biochemical modulation by CDHP, a dihydropyrimidine dehydrogenase inhibitor, and Oxo, a protector against 5-FU-induced gastrointestinal toxicity. The anticancer effect of S-1 monotherapy has already been demonstrated in a variety of solid tumors: the RR for advanced gastric cancer [9], colorectal cancer [10], non-small cell lung cancer [11], breast cancer [12], head and neck cancer [13], pancreatic cancer [14], and biliary tract cancer [15] in the phase II trials conducted in Japan was 44.2, 39.5, 22.0, 41.7, 28.8, 37.5, and 35.0%, respectively. The most studied group of anticancer drugs in RCC is the fluoropyrimidines, including floxuridine [20, 21], fluorouracil [22–24], and tegafur [25]. Response rates of 4 to 11% were seen when fluoropyrimidines were given as monotherapy [26]. *In addition, frequently studied chemotherapeutic agents in metastatic RCC, gemcitabine yielded 6 and 8.1% RR in 2 phase II trials* [27, 28] *and gemcitabine plus capecitabine produced an 8.4% RR in phase II trial* [29]. This small multicenter phase II trial was conducted to investigate the efficacy and safety of S-1 monotherapy for cytokine-refractory metastatic RCC. The RR of S-1 was 15 and 10% according to the JSCT criteria and RECIST, respectively, with good control of tumor growth: objective responses plus SD; 95%. The histology of tumor in responders was clear cell carcinoma. The expected RR of S-1 according to the JSCT criteria was set at 15%. *Expected* RR was achieved, although, the lower limit of the 90% CI (4.2%) was slightly under the 5% *threshold* RR. *This trial did not have enough statistical power to clear that the threshold was exceeded, although, it was planned as a trial of the scales that could evaluate possibility of the effectiveness for the renal cell carcinoma of S-1.* The median TTP and OS

Table 3 Incidence of drug-related adverse events occurring in ≥20.0% of all patients and grade 3/4 drug-related adverse events occurring in patients who were administered at least one dose of S-1 ($n = 20$)

Event category	No. of pts. (%)		
	Any grade	Grade 3	Grade 4
Hematological			
Hemoglobin reduction	15 (75.0)	1 (5.0)	0
Erythropenia	12 (60.0)	1 (5.0)	0
Hematocrit reduction	10 (50.0)	0	0
Neutropenia	10 (50.0)	4 (20.0)	0
Leukopenia	8 (40.0)	0	0
Thrombocytopenia	7 (35.0)	0	0
Lymphocytopenia	6 (30.0)	1 (5.0)	0
Non-hematological			
Anorexia	15 (75.0)	3 (15.0)	1 (5.0)
Nausea	7 (35.0)	0	0
Vomiting	6 (30.0)	0	0
Stomatitis	7 (35.0)	1 (5.0)	0
Taste alteration	5 (25.0)	0	0
Diarrhea	9 (45.0)	2 (10.0)	0
Fatigue	6 (30.0)	0	0
Malaise	9 (45.0)	2 (10.0)	0
Rash	7 (35.0)	2 (10.0)	0
Hyperpigmentation	16 (80.0)	0	0
Laboratory test abnormalities			
Hypoalbuminemia	4 (20.0)	0	0
AST elevation	5 (25.0)	0	0
ALT elevation	5 (25.0)	0	0
LDH elevation	7 (35.0)	0	0
Hyperbilirubinemia	8 (40.0)	0	0
Serum creatinine elevation	5 (25.0)	0	0
Hyponatremia	5 (25.0)	2 (10.0)	0
Hyperglycemia	2 (10.0)	2 (10.0)	0
Glucosuria	2 (10.0)	2 (10.0)	0

were 12.0 and 25.7 months, respectively, with a 1-year survival rate of 85.0%. *Phase II trials of sunitinib in patients with cytokine-refractory RCC demonstrated high RR (40, 34%), but median TTP and PFS were 8.7 months and 8.3 months, respectively* [30, 31]. Furthermore, a randomized phase III controlled trial demonstrated that treatment with sorafenib exhibited a better RR (10 vs. 2%) and median PFS (5.5 vs. 2.8 months) when compared to placebo in patients with cytokine-refractory metastatic RCC [2]. The survival benefit of sorafenib compared with placebo (17.8 vs. 15.2 months) was also reported by Escudier et al. [3]. Although it may be difficult to make a simple comparison between these data and ours, our results suggest that S-1 has a promising anticancer effect on cytokine-refractory metastatic RCC.

The toxicity of S-1 was acceptably mild compared with molecular targeting agents such as sorafenib [2, 3] or sunitinib [4, 5]. Only 1 patient (5%) experienced grade 4 toxicity (anorexia). In S-1 treated patients, there was neither hand-foot skin reaction nor hypertension, which are both characteristic of sorafenib or sunitinib and sometime lead to dose reduction of the agents or interruption of therapy [2–5]. S-1 was easily administered, and most patients could be treated as outpatients, resulting in good compliance. Molecular targeting agents such as sorafenib rarely show myelosuppression, so S-1 may be a good candidate for combination therapy with molecular targeting agents such as sorafenib.

This trial has limitation. Number of subject is small, so we should conduct a large trial. *We are now conducting a late phase II trial. Furthermore, we are planning to conduct the combination trials with targeting agents and S-1 with different mechanisms of action.*

In conclusion, although this trial had a small patient population, S-1 monotherapy was generally well tolerated and was *possibly* effective against cytokine-refractory metastatic RCC.

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Conflict of interest statement None.

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