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ORIGINAL ARTICLE

A late phase II study of S-1 for metastatic pancreatic cancer

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Abstract This study evaluated the antitumor effect and safety of S-1, an oral fluoropyrimidine derivative, in patients with metastatic pancreatic cancer. Chemo-naive patients with pancreatic adenocarcinoma, and measurable metastatic lesions were enrolled. S-1 was administered orally twice daily after meals at a dose of 80, 100, or 120 mg/day for body surface areas (BSAs) of less than 1.25 m^2, between 1.25 m^2 and less than 1.5, or 1.5 m^2 or greater, respectively, for 28 consecutive days, followed by a 14-day rest. Fifteen (37.5%) of 40 patients responded to treatment, including 1 complete response and 14 partial responses. The median time to progression and the overall survival time were 3.7 months (95% confidence interval, 2.2–5.6 months) and 9.2 months (95% confidence interval, 7.5–10.8 months), respectively. The major adverse events were anorexia, fatigue, hemoglobin reduction, nausea and pigmentation change, although most were tolerable and reversible. Although disseminated intravascular coagulation occurred in two patients, the condition resolved with anticoagulant therapy. S-1 is an effective and well-tolerated drug. The effectiveness of this drug should be confirmed in a phase III study.

Keywords Pancreatic cancer · Phase II study · Chemotherapy · S-1

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Introduction

Pancreatic cancer is a major leading cause of cancer-related mortality worldwide: it ranks as the fifth leading cause of death in Japan, with an annual incidence of approximately 20,000 cases and a similar mortality rate [1]. Of all the treatments available for pancreatic cancer, only resection offers a chance for a cure. However, owing to the high frequency of local extension and/or metastatic disease at the time of diagnosis, only a small minority of patients are candidates for curative resection. Moreover, surgery alone is limited, with an unsatisfactory prognosis and a high incidence of postoperative recurrence. To improve the survival of patients with pancreatic cancer, effective non-surgical treatments are urgently needed.

A randomized controlled study demonstrated that treatment with gemcitabine exhibited a better clinical benefit response (CBR) (23.8 vs. 4.8%) and median survival period (5.65 vs. 4.41 months) than bolus 5-fluorouracil (5-FU) [2].

However, chemotherapy for pancreatic cancer must be substantially improved because gemcitabine monotherapy offers only a limited survival benefit. Gemcitabine administration via a fixed-dose-rate infusion [3] and gemcitabine-based combined regimens have been investigated, but a meaningful impact on survival, compared with that of gemcitabine monotherapy, was not obtained. Randomized phase III studies of gemcitabine plus erlotinib [4] and gemcitabine plus capecitabine [5] have demonstrated significant survival benefits, but a worldwide consensus regarding these results has not been established.

S-1 is an oral anticancer drug consisting of tegafur (FT), a prodrug of 5-FU, and two biochemical modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) [6]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and allows efficacious concentrations of 5-FU to be maintained in the plasma and tumor tissues. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract and reduces the gastrointestinal toxicity of 5-FU. S-1 has been clinically shown to have a potent antitumor activity against various solid tumors [7–15].

S-1 was also effective against human pancreatic cancer xenografts implanted into nude rats [16]. Furthermore, an early phase II study of S-1 showed promising results, with a 21% response rate and a manageable toxicity profile in 19 patients with metastatic pancreatic cancer [17]. Therefore, we conducted a multi-institutional late phase II study of S-1 to confirm these previous results.

Patients and methods

Patients

Patients with inoperable pancreatic cancer or who were unable to receive radiotherapy were considered for enrollment. The eligibility criteria were as follows: capable of oral intake, histologically or cytologically confirmed pancreatic adenocarcinoma, between 20 and 74 years old, no history of prior treatment other than pancreatic resection, measurable metastatic lesions, a Karnofsky performance status (KPS) of 80–100%, an adequate hematological profile (hemoglobin $\geq$10.0 g/dl; leukocyte count, 4,000–12,000/mm^3; neutrophil count $\geq$2,000/mm^3; platelet count $\geq$100,000/mm^3), adequate hepatic function (total bilirubin level $\leq$3 times the upper limit of normal, transaminases levels $\leq$ 2.5 times the upper limit of normal), adequate renal function (normal serum creatinine level), and a life expectancy $\geq$2 months. The exclusion criteria were as follows: participation in another clinical study; treatment with phenytoin, potassium warfarin or flucytosine; active infection; serious complications; clinically significant ascites or pleural effusion; brain metastasis; abnormal bowel movements, like watery diarrhea or chronic constipation; active secondary malignancies; pregnancy or lactation; and men who were trying to father a child. The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice and was approved by the institutional review boards at each hospital. Written informed consent was obtained from all patients before their participation.

Treatment plan

S-1 (Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily, after breakfast and dinner, for 28 consecutive days followed by a 14-day rest one course. The three initial doses were determined according to the body surface area (BSA) as follows: BSA $<$1.25 m^2, 40 mg/dose; 1.25 m^2 $\leq$ BSA $<$ 1.5 m^2, 50 mg/dose; 1.5 m^2 $\leq$ BSA, 60 mg/dose. Treatment cycles were repeated until the appearance of disease progression, unacceptable toxicities, or the patient's refusal to continue treatment. If a grade 3 or higher hematological toxicity or a grade 2 or higher non-hematological toxicity was observed, dose reduction by 10 mg/dose (minimum, 40 mg/dose) or temporary interruption of S-1 administration was recommended. To enhance treatment efficacy, the rest period was shortened to 7 days or the dose was escalated one step during the next course (maximum, 75 mg/dose), unless adverse events were observed. If a rest period of more than 28 days was required, the study treatment was stopped. Prophylactic granulocyte colony-stimulating factor was not used.

Response and safety

Patients who received at least one dose of S-1 were evaluated for response and toxicity. Tumor response was assessed using computed tomography or magnetic resonance imaging after each course according to the Japan Society for Cancer Therapy (JSCT) Criteria [18], which are similar to the World Health Organization Criteria. Primary pancreatic lesions were considered assessable, but not measurable. The response was secondarily assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels were quantified in each course.

The CBR was evaluated using the KPS and pain score, as described below [2]. The KPS was recorded weekly by the attending physician. Pain was evaluated by measuring the change from the baseline pain intensity and the daily dose of morphine or morphine-equivalent (doses of analgesic agents were converted to morphine-equivalent doses,

i.e., 5.0 mg fentanyl patch = 60 mg morphine). The pain intensity was graded from 0 (no pain) to 100 (worst pain) using a visual analog scale and was recorded on a pain assessment card everyday. Patients who fulfilled at least one of the following criteria were defined as eligible for the CBR analysis: (1) baseline pain intensity ≥20, or (2) baseline morphine consumption ≥10 mg/day. Moreover, all the patients underwent a 'pain stabilization period' for 2 days to ensure that the baseline values were stable before treatment: when the variation in the morphine consumption between 2 days was within 5 mg and the variation of the pain intensity was within 10, the patient was considered eligible for inclusion in the CBR analysis. Any adverse events were evaluated for grading, duration and S-1 causality according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Physical findings were assessed weekly, blood biochemistry and urinalysis were assessed biweekly, and vital signs were assessed as necessary. An independent review committee confirmed the responses and the adverse events.

Statistics

The primary measure of efficacy was the overall response rate, as defined by the tumor measurement. Other measures included the response duration, median survival time (MST) and time to progression (TTP), according to the JSCT Criteria. Response duration was calculated from the first documentation of a response until progressive disease (PD). The MST and median TTP were estimated using the Kaplan–Meier method [20]. The threshold rate was defined as 5%, and the expected rate was set at 20% because the response rate in the previous study had been 21.1% [17]. If the response rate to S-1 was 20%, a sample size of 40 patients would ensure a power of at least 80% at a one-sided significance level of 2.5% to reject the null hypothesis that the response rate was ≤5%. If the lower limit of the 95% confidence interval (95% CI) of the response rate exceeded the 5% threshold, a response rate of 6 out of 40 patients would be required.

Results

Patient characteristics

Between January 2003 and April 2004, 41 patients from 7 institutions were enrolled in the present study. S-1 was not administered in 1 patient because of rapid disease progression: thus, toxicity and response were evaluated in 40 patients. The patient characteristics are listed in Table 1. Most patients had a good Karnofsky performance status of 90–100%. Among the five patients who had undergone resections, three patients received pancreaticoduodenectomies and two patients received distal pancreatectomies. The major sites of metastases were the liver and distal lymph nodes. Ten of the 40 patients fulfilled the eligibility criteria for the CBR evaluation.

Treatment

A total of 144 courses were administered to 40 patients, with a median of 3.0 courses per patient (range 1–16 courses). The S-1 dose was reduced in eight patients for the following reasons: grade 3 hepatotoxicity (one patient); grade 3 gastrointestinal toxicity, including anorexia, nausea and vomiting (one patient each); grade 2 gastrointestinal toxicity (1 patient); grade 2 abdominal pain (one patient); grade 1 pancytopenia (one patient); and a body weight loss of less than 5% (one patient: the body weight of the patient was originally close to the boundary between the 50 and 60 mg dose categories). The dose was increased in eight patients because no adverse events that might have posed an impediment to dose escalation were observed; thereafter, three of the eight patients required a dose reduction to their original dose. Thirty-five (90%) of the 39 patients who completed this study were subsequently treated with gemcitabine, although the treatment periods and responses were not monitored.

Responses and survival

The responses of the 40 patients are shown in Table 2. The overall response rate, as evaluated using the JSCT criteria, was 37.5% (95% CI 22.7–54.2%), including 1 complete response (CR) and 14 partial responses (PRs). The response in the patient who showed a CR according to the JSCT criteria was judged as a PR according to the RECIST criteria because the serum CEA level did not decrease to normal. The serum CA 19-9 level decreased by more than half in 15 (48%) of the 31 patients who had pretreatment levels over 100 U/ml, and the serum CEA level decreased by more than half in 4 (29%) of the 14 patients who had pretreatment levels over 15 U/ml. The median duration of response was 6.9 months (range 4.0–18.6 months). The median TTP, MST, and 1-year survival rate were 3.7 months (95% CI 2.2–5.6 months), 9.2 months (95% CI 7.5–10.8 months), and 32.5% (13/40), respectively (Fig. 1). S-1 treatment was ongoing in 1 of the 40 patients who showed no evidence of disease progression at the time of analysis (617 days).

Clinical benefits

The CBR scores of four (40%) of the ten evaluated patients improved after S-1 therapy. The pain intensity of all four patients decreased, although their daily analgesic consump-

Table 1 Patient characteristics

Characteristics	Median (Range)	No. of patients	(%)
No. of patients enrolled		41	
Assessable for response and toxicity		40	
Sex			
Male		21	52.5
Female		19	47.5
Age, years	59.5 (41–74)		
Karnofsky performance status, %			
100		18	45.0
90		21	52.5
80		1	2.5
First dose, mg			
40		3	7.5
50		18	45.0
60		19	47.5
Pancreatectomy			
(+)		5	12.5
(−)		35	87.5
Metastatic sites			
Liver		36	90.0
Distant lymph nodes		10	25.0
Lung		4	10.0
Peritoneum		1	2.5
CA 19-9, U/ml	1,020 (1.0–250,000)		
No. of cases with more than 100 U/ml		31	77.5
CEA, U/ml	6.95 (1.0–498)		
No. of cases with more than 15 U/ml		14	35.0

tion and KPS scores did not change. In the remaining six patients, the CBR remained unchanged in one patient and increased in five patients. The responses according to the JSCT criteria of the four patients with improved CBR scores were two PR and two no change (NC).

Safety

Treatment-related adverse events are listed in Table 3. The major adverse events were anorexia, fatigue, hemoglobin reduction, nausea, and pigmentation change; however, most

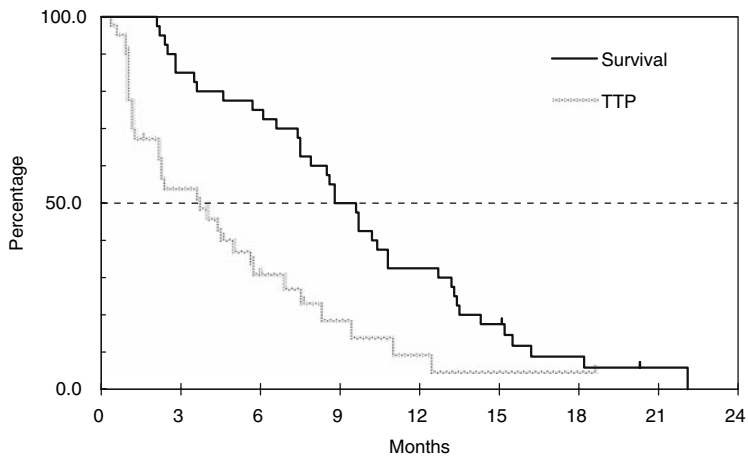

Fig. 1 Kaplan–Meier curves for overall survival (*solid line*) and time to progression (*dotted line*)

Table 2 Tumor response ($n = 40$)

Tumor response	JSCT (%)	RECIST (%)
Complete response	1 (2.5)	0 (0.0)
Partial response	14 (35.0)	15 (37.5)
No change/stable disease	11 (27.5)	11 (27.5)
Progressive disease	13 (32.5)	13 (32.5)
Not evaluable[a]	1 (2.5)	1 (2.5)
Overall response	15 (37.5)	15 (37.5)

[a] Radiographic assessment was not determined

Table 3 Treatment-related adverse events ($n = 40$): worst grade reported during the treatment period

Toxicity	Grade				Grades 1–4	Grades 3–4
	1	2	3	4	(%)	(%)
Hematological						
Leukopenia	10	7	0	0	42.5	0
Neutropenia	4	4	5	0	32.5	12.5
Hemoglobin reduction	8	13	1	1	57.5	5.0
Thrombocytopenia	13	1	1	0	37.5	2.5
Non-Hematological						
Anorexia	10	10	4	1	62.5	12.5
Nausea	11	6	3	0	50.0	7.5
Vomiting	8	6	2	0	40.0	5.0
Diarrhea	12	4	3	0	47.5	7.5
Fatigue	16	9	0	0	62.5	0
Stomatitis	9	1	0	0	25.0	0
Skin rash	6	4	0	0	25.0	0
Pigmentation change	20	0	0	0	50.0	0
DIC[a]	0	0	2	0	5.0	5.0
Colitis	0	0	1	0	2.5	2.5
Hypotension	0	0	1	0	2.5	2.5
Prothrombin time	0	0	1	0	2.5	2.5
T-bilirubin elevation	5	8	2	1	40.0	7.5
AST elevation	3	4	1	0	20.0	2.5
ALT elevation	5	4	1	0	25.0	2.5
γ-GTP elevation	0	0	1	0	2.5	2.5
Albumin reduction	5	3	0	0	20.0	0
T-protein reduction	6	2	0	0	20.0	0
Weight loss	6	1	0	0	17.5	0
LDH elevation	4	1	0	0	12.5	0

Events with a frequency of more than 10.0% or high-grade events (grades 3, 4) are listed

[a] Disseminated intravascular coagulation

of these events were tolerable and reversible. Treatment was discontinued in six patients because of treatment-related adverse events: grade 4 elevation in total bilirubin, grade 4 anorexia, grade 3 disseminated intravascular coagulation (DIC), and grade 3 colitis during the first course, grade 4 anemia (hemoglobin reduction) during the third course, and grade 2 nausea during the fourth course. Most of the events resolved with the cessation of S-1 administration, although an elevated total bilirubin level persisted in 1 patient until his death 41 days after the discontinuation of S-1 and anorexia persisted in 1 patient until the initiation of radiotherapy as a second-line treatment 13 days after the discontinuation of S-1.

Although DIC also occurred in one patient during the first course, it resolved soon after the start of anticoagulant therapy; nonetheless, the S-1 therapy had to be discontinued because of disease progression after the patient recovered from the DIC. Febrile neutropenia or treatment-related deaths did not occur. Ileus, which occurred in three patients during the early phase II study, did not occur in this study. Most of the patients were treated as outpatients.

Discussion

A variety of chemotherapy regimens for the treatment of advanced pancreatic cancer have been evaluated since the introduction of gemcitabine, which aroused renewed interest in clinical research. However, little evidence of significant activity against this disease has been demonstrated, and few agents have reproducibly provided high response rates or a meaningful impact on patient survival or quality of life.

In phase II and III studies for advanced pancreatic cancer, gemcitabine monotherapy produced response rates ranging from 4 to 17% and an MST ranging from 5.4 to 7.3 months [21, 22]. In phase II trials of oral fluoropyrimidines, UFT yielded no objective response (0/21), with an MST of 4.2 months [23], and capecitabine yielded a response rate of 9.5% (4/42), with an MST of 182 days (6.0 months) [24]. For gemcitabine combined therapy, response rates of up to 29% were reported in phase III studies, with MST values ranging from 3.74 to 9.0 months [21, 22].

An early phase II study of S-1 produced a response rate of 21% and an MST of 5.6 months [17]. The present phase II study concluded that S-1 was a promising agent for advanced pancreatic cancer, with a response rate of 37.5%, an MST of 9.2 months, and an acceptable toxicity profile. The efficacy of S-1 in the present study was more favorable than that in the previous study. The reasons for this discrepancy could not be definitively identified because of the small numbers of patients involved, although differences in the patients' backgrounds probably affected the results. A logistic regression analysis suggested that a larger proportion of female patients, fewer measurable lesions, and a lower morphine consumption, compared with the early phase II study, might have contributed to the superior response rate in the present study, although the differences were not statistically significant (data not shown). Moreover,

the larger proportion of patients receiving second-line chemotherapy may have contributed to the longer MST in the present study: the proportion of patients receiving second-line chemotherapy was 26% (5/19, 3 patients receiving 5-FU plus cisplatin, 2 patients receiving gemcitabine) in the previous study and 90% (35/39, 35 patients receiving gemcitabine) in the present study. Gemcitabine was approved for the treatment of pancreatic cancer in Japan in April 2001, after enrollment in the previous study had been completed. Although some divergences in the response rates and survival periods were noted, the results of both studies seemed to favor S-1 over other agents for the treatment of advanced pancreatic cancer.

The toxicity profiles in the previous and present studies on S-1 were similar. However, gastrointestinal toxicities like anorexia and vomiting tended to occur more frequently in the studies for pancreatic cancer than in those for other cancers. We speculated that the higher frequency of toxicity may be related to the clinical features of pancreatic cancer itself, since gastrointestinal symptoms like anorexia are observed in many patients at the time of the initial diagnosis. No treatment-related deaths were observed, but three patients developed ileus during the previous phase II study and two patients developed DIC during the present study. DIC was a noteworthy complication, although this complication can occur even in patients with pancreatic cancer who are receiving only supportive care without chemotherapy. Although the cause of the DIC could not be determined, the possibility that it was caused by the S-1 treatment cannot be excluded. Periodic monitoring of the patients' physical conditions and laboratory parameters is recommended for the early diagnosis of serious complications in patients treated outside of clinical trials, even though most patients were treated as outpatients without any serious complaints.

S-1, an oral anticancer agent, may offer clinical advantages while maintaining quality of life [25]. Since a promising anticancer effect and a relatively long MST were observed in this study, S-1 may be a potentially useful alternative to gemcitabine as a first-line drug for the treatment of advanced pancreatic cancer. Furthermore, S-1 may be useful when administered in combination with gemcitabine, since its toxicity is generally mild and its toxicological profile is distinct from that of gemcitabine. We previously conducted a phase I study to determine the recommended dose of S-1 and gemcitabine in a combination regimen for the treatment of advanced pancreatic cancer [26]. Currently, we are conducting a multi-institutional phase II study. Nakamura et al. [27] reported a 48% (16/33) response rate and an MST of 12.5 months for metastatic pancreatic cancer in a single-institute phase II study of S-1 and gemcitabine. Randomized trials are essential for determining whether chemotherapy with S-1 is equivalent or superior in efficacy to gemcitabine as an initial treatment for advanced pancreatic cancer.

In conclusion, S-1 administered as a single agent showed a promising anticancer effect with acceptable toxicity in patients with metastatic pancreatic cancer. A randomized phase III trial to evaluate the effectiveness of S-1 for advanced pancreatic cancer is warranted.

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References

1. Lowenfels AB, Maisonneuve P (2004) Epidemiology and prevention of pancreatic cancer. Jpn J Clin Oncol 34:238–244
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
3. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R et al (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
4. Moore MJ (2005) Brief communication: a new combination in the treatment of advanced pancreatic cancer. Semin Oncol 32(6 Suppl 8):S5–S6
5. Cunningham D, Chau I, Stocken D, Davies C, Dunn J, Valle J et al (2005) Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl 3:12
6. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K et al (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–557
7. Shirao K, Ohtsu A, Takada H, Mitachi Y, Hirakawa K, Horikoshi N et al (2004) Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. Cancer 100:2355–2361
8. Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K et al (2000) Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. Br J Cancer 83:141–145
9. Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S et al (2001) Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 85:939–943
10. Furuse K, Kawahara M, Hasegawa K, Kudoh S, Takada M, Sugiura T et al (2001) Early phase II study of S-1, a new oral fluoropyrimidine, for advanced non-small-cell lung cancer. Int J Clin Oncol 6:236–241
11. Koizumi W, Kurihara M, Nakano S, Hasegawa K (2000) Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. Oncology 58:191–197

12. Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y et al (1999) An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. Oncology 57:202–210
13. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T (1998) Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 34:1715–1720
14. Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B (2001) Late phase II study of S-1 in patients with advanced head and neck cancer. Gan To Kagaku Ryoho 28:1381–1390
15. Saeki T, Takashima S, Sano M, Horikoshi N, Miura S, Shimizu S et al (2004) A phase II study of S-1 in patients with metastatic breast cancer–a Japanese trial by the S-1 Cooperative Study Group, Breast Cancer Working Group. Breast Cancer 11:194–202
16. Fukushima M, Satake H, Uchida J, Shimamoto Y, Kato T, Takechi T et al (1998) Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluorouracil on human tumor xenografts. Int J Oncol 13:693–698
17. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C (2005) An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology 68:171–178
18. Japan Society for Cancer Therapy (1993) Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. J Jpn Soc Cancer Ther 28:101–130
19. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
20. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
21. Kindler HL (2005) Front-line therapy of advanced pancreatic cancer. Semin Oncol 32(6 Suppl 9):S33–S36
22. Hochster HS, Haller DG, de Gramont A, Berlin JD, Philip PA, Moore MJ et al (2006) Consensus report of the International Society of Gastrointestinal Oncology on therapeutic progress in advanced pancreatic cancer. Cancer 107:676–685
23. Ueno H, Okada S, Okusaka T, Ikeda M, Kuriyama H (2002) Phase II study of uracil-tegafur in patients with metastatic pancreatic cancer. Oncology 62:223–227
24. Cartwright TH, Cohn A, Varkey JA, Chen YM, Szatrowski TP, Cox JV et al (2002) Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 20:160–164
25. O'Neill VJ, Twelves CJ (2002) Oral cancer treatment: developments in chemotherapy and beyond. Br J Cancer 87:933–937
26. Ueno H, Okusaka T, Ikeda M, Ishiguro Y, Morizane C, Matsubara J et al (2005) A phase I study of combination chemotherapy with gemcitabine and oral S-1 for advanced pancreatic cancer. Oncology 69:421–427
27. Nakamura K, Yamaguchi T, Ishihara T, Sudo K, Kato H, Saisho H (2006) Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 94:1575–1579