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Biweekly gemcitabine with S-1 combination chemotherapy in locally advanced or metastatic pancreatic cancer

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Objective: Gemcitabine (GEM)-based combination chemotherapy has been studied to determine whether or not it improves outcomes, but results have generally been disappointing. We retrospectively compared chemotherapy with biweekly GEM plus a novel form of an oral 5-fluorouracil derivative (S-1) (GEM+S-1) with GEM alone in locally advanced or metastatic pancreatic cancer.

Patients and Methods: We studied patients with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer with measurable lesions. Ninety-six patients received GEM+S-1 (GEM 800-1,000 mg/m^2 intravenously on days 1 and 15 plus S-1 40 mg/m^2 twice daily orally on days 1-7 and days 15-21 of a 28-day cycle), and 66 patients received GEM alone (GEM alone, 1,000 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle). Treatment was repeated every 4 weeks.

Results: The overall response rate was 36.5% in the GEM+S-1 group and 7.6% in the GEM-alone group (P = 0.0028). The median survival time was 16.2 months in the GEM+S-1 group and 7.8 months in the GEM-alone group (P = 0.008).

Conclusions: This regimen for GEM+S-1 combination chemotherapy is feasible, well tolerated, and more effective than GEM alone in patients with locally advanced or metastatic pancreatic cancer.

Key words: pancreatic cancer, gemcitabine, oral 5-fluorouracil derivative (S-1)

Introduction

Pancreatic cancer has one of the poorest prognoses among all neoplasms because it is difficult to detect it in an early stage, has a very high rate of postoperative recurrence, and is relatively insensitive to chemotherapy and radiotherapy. Surgery is the only curative treatment for pancreatic cancer, but few tumors are resectable at the time of the diagnosis.

Gemcitabine (GEM) has been the standard chemotherapeutic agent for unresectable pancreatic cancer since the time that Burris et al. reported that GEM is more effective than 5-fluorouracil (5-FU) for alleviating some disease-related symptoms in patients with advanced, symptomatic pancreatic cancer.[1] GEM was also reported to confer a modest survival advantage over 5-FU.[2] However, the benefits were limited, with an objective response rate of less than 15% and a median survival of less than 6 months. GEM-based combined chemotherapy has been studied to improve outcomes,[3-8] but it is insufficient to merely prolong survival as compared with that in patients given GEM monotherapy.

Recently, the National Cancer Institute of Canada Clinical Trials Group reported that erlotinib plus GEM significantly prolonged overall survival as compared with GEM alone in patients with advanced pancreatic cancer (P = 0.038, median 6.24 months vs. 5.91 months).[9] However, the overall survival benefit was only 2 weeks. Phase III randomized studies of GEM alone vs. GEM plus capecitabine have demonstrated a significant survival benefit, but a worldwide consensus has yet to be reached.[10,11]

The oral 5-FU derivative (S-1) is a fluorinated pyrimidine preparation, combining tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate in a 1:0.4:1 molar concentration ratio. Tegafur is a prodrug of 5-FU that is gradually converted to 5-FU but rapidly metabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. CDHP is a competitive inhibitor of 5-FU metabolism that is about 180 times more potent than

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uracil in inhibiting DPD. Inhibition of 5-FU metabolism by CDHP results in prolonged active concentrations of 5-FU in both plasma and tumors. Potassium oxonate, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract and reduces gastrointestinal toxicity associated with 5-FU.[12-15]

Since 2001, we have used the single-agent GEM to treat locally advanced or metastatic pancreatic cancer. After 2003, we started to use GEM biweekly in combination with S-1 (GEM+S-1) for this indication. In the present study, we retrospectively evaluated and compared the safety and effectiveness of GEM+S-1 with those of GEM alone.

Patients and Methods

Patients

The study group was comprised of patients with a histologically or cytologically confirmed diagnosis of inoperable, locally advanced or metastatic pancreatic cancer with measurable lesions. None of the patients had previously received chemotherapy or radiotherapy. All of the patients were 20 to 83 years of age and had a Karnofsky performance status of 70% to 100%, an adequate hematologic profile (white cell count >3,000/mm^3, neutrophil count >2,000/mm^3, hemoglobin concentration >10.0 g/dl, platelet count >100,000/mm^3), adequate liver function (transaminase levels <5 times the upper limit of normal), adequate renal function (normal serum creatinine level), and a life expectancy of more than 2 months. Patients were excluded if they were receiving treatment with phenytoin, warfarin potassium, or flucytosine or had active infections, severe heart disease, mental disorders, or uncontrolled diabetes mellitus.

Treatments

Patients received either GEM+S-1 or GEM alone. In the GEM+S-1 group, GEM 1,000 mg/m^2 (under 75 years old) or 800 mg/m^2 (over 75 years old) was administered as a 30-minute intravenous infusion on days 1 and 15 (biweekly) and S-1 40 mg/m^2 twice daily was administered on days 1 to 7 and days 15 to 21 of a 28-day cycle. In the GEM-alone group, GEM 1,000 mg/m^2 was given on days 1, 8, and 15 of a 28-day cycle. Treatment was repeated every 4 weeks and continued until disease progression, unacceptable adverse events, or withdrawal of informed consent by the patient.

Complete blood cell counts and serum chemical analyses, including serum total bilirubin, transaminases, and alkaline phosphatase, were performed before each dose of GEM. If leukopenia (<2,000/mm^3), neutropenia (<1,000/mm^3), thrombocytopenia (<50,000/mm^3), total bilirubin >2.0 mg/ml, or transaminase levels higher than 5 times the upper limit of normal developed, chemotherapy was withheld until recovery. In patients who had grades 3 or 4 hematologic or nonhematologic toxicity, the GEM dose was reduced by 20% for all subsequent courses.

Assessments

All patients underwent computed tomography after every 2 cycles of chemotherapy, and tumor response was evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumors). Toxicity was evaluated with the National Cancer Institute - Common Toxicity Criteria (CTC ver. 3.0). Patients were regularly interviewed to assess signs and symptoms such as pain, nausea, vomiting, mucositis, general fatigue, diarrhea, asthenia, and body weight loss.

Statistical analysis

Overall survival and median survival time were estimated by the Kaplan-Meier method and compared using the log-rank test. Patients' characteristics, toxic effects, and laboratory values were compared between patients receiving GEM+S-1 and those receiving GEM alone using the χ^2 and Fisher's *t*-tests.

P values of <0.05 were considered as statistically significant.

Results

Patient characteristics

A total of 96 patients with locally advanced or metastatic pancreatic cancer received GEM+S-1 from 2003 through 2009, and 66 patients received GEM alone from 2001 through 2007. Their clinical characteristics are shown in Table 1. In the GEM+S-1 group, 29 patients had locally advanced cancer and 67 had metastatic cancer. In the GEM-alone group, 19 patients had locally advanced cancer and 47 had metastatic cancer. Sites of metastases (GEM+S-1 vs. GEM alone) were the liver (46 cases vs. 26 cases), lymph nodes (24 cases vs. 22 cases), ascites (11 cases vs. 9 cases), lung (11 cases vs. 2 cases), and bone (3 cases vs. 2 cases) (Sites were overlapping). Most patients had a Karnofsky performance status of 80% to 100% in both groups, indicating good general condition. There were no significant differences in clinical characteristics between the GEM+S-1 group and the GEM-alone group.

Table 1. Patient characteristics

Characteristics	GEM+S-1 (n = 96)		GEM alone (n = 66)		P
	No.	%	No.	%	
Sex					NS
Male	44	45.8	35	53.0	
Female	52	54.2	31	47.0	
Age (years)					NS
Mean	65.6		66.7		
SD	8.7		8.8		
Range	41-83		42-83		
Karnofsky performance status					NS
100	37	38.5	14	21.2	
90	48	50.0	37	56.1	
80	11	11.5	13	19.7	
70	0	0.0	2	3.0	
Disease extent					NS
Locally advanced	29	30.2	19	28.8	
Metastatic	67	69.8	47	71.2	
Site of metastatic disease					NS
Liver	46	48.0	26	39.4	
Lymphnode	24	25.0	22	33.3	
Ascites	11	11.5	9	13.6	
Lung	11	11.5	2	3.0	
Bone	3	3.1	2	3.0	

Table 2. Treatment and efficacy results

	GEM+S-1 (n = 96)	GEM alone (n = 66)
No. of cycles		
median	12.0	7.0
range	2-22	2-22
Tumor response, %		
CR	0	0
PR	36.5	7.6
SD	47.9	53.0
PD	15.6	39.4
Overall survival time		
median, month	16.2	7.8
Survival rate, %		
6-month	80.2	66.3
1-year	56.8	29.7
2-year	25.2	8.1

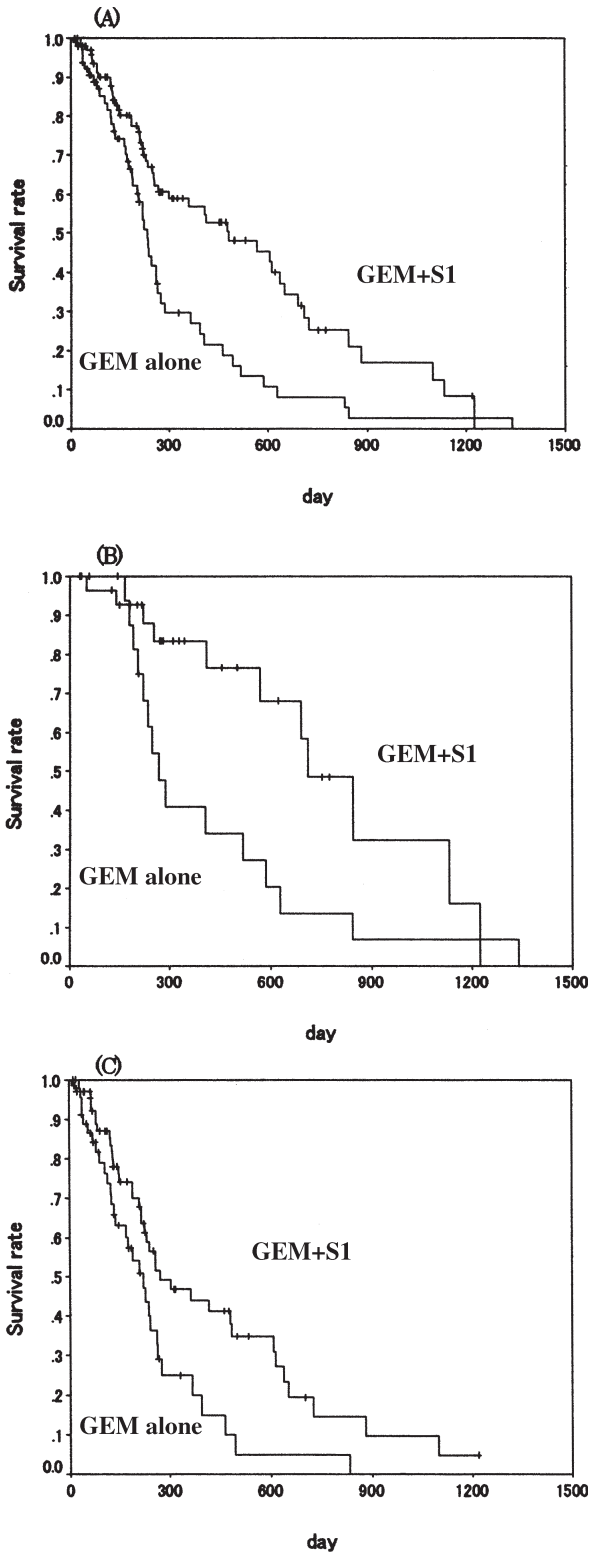

Figure 1. (**A**) Kaplan-Meier survival curves for the overall study group, (**B**) Patients with locally advanced pancreatic cancer, (**C**) Patients with metastatic pancreatic cancer. There were statistical significances (**A**, P = 0.008; **B**, P = 0.003; **C**, P = 0.008).

Treatments and efficacy

The median number of treatment cycles was 12.0 in the GEM+S-1 group (range, 2-22) and 7.0 in the GEM-alone group (range, 2-22). The responses of the patients are shown in Table 2. The overall response rate was 36.5% in the GEM+S-1 group and 7.6% in the GEM-alone group (P = 0.00028), and there were no complete responses in either group. Kaplan-Meier survival curves are shown in Figure 1A. The median survival time was 16.2 months in the GEM+S-1 group and 7.8 months in the GEM-alone group, and the 1-year survival rate was 56.8% in the GEM+S-1 group and 29.7% in the GEM-alone group (both, P = 0.008).

Kaplan-Meier survival curves for the patients with locally advanced pancreatic cancer are shown in Figure 1B. In the patients with locally advanced pancreatic cancer, the median survival time was 23.7 months (95% confidence interval [CI], 18.1-29.3) in the GEM+S-1 group and 8.9 months (95% CI, 7.2-10.7) in the GEM-alone group, and the 1-year survival rate was 83.5% in the GEM+S-1 group and 34.2% in the GEM-alone group (both groups, P = 0.003). In the patients with metastatic pancreatic cancer, the median survival time was 9.0 months (95% CI, 4.3-13.7) in the GEM+S-1 group and 8.2 months (95% CI, 5.9-10.5) in the GEM-alone group, and the 1-year survival rate was 44.0% in the GEM+S-1 group and 24.9% in the GEM-alone group (both groups, P = 0.008) (Figure 1C). There were cases of discontinued treatment because of cerebrovascular infarction in 1 patient in the GEM+S-1 group and in 2 patients in the GEM-alone group.

Toxicity

Treatment-related adverse events are summarized in Table 3. The incidences of grades 3 or 4 leukopenia, neutropenia, anemia, and thrombocytopenia were, respectively, 25.0%, 26.0%, 15.6%, and 7.3% in the GEM+S-1 group, and 22.7%, 39.4%, 4.5%, and 15.2% in the GEM-alone group (anemia, P < 0.05; others, P > 0.05). Most of these events were well tolerated, and there were no severe complications. Grades 3 or 4 nonhematologic toxicities (GEM+S-1 vs. GEM alone) were nausea (1.0% vs. 4.5%), vomiting (0.0% vs. 3.0%), anorexia (3.1% vs. 10.6%), and general fatigue (13.5% vs. 0.0%). These effects were tolerable and reversible. Treatment was discontinued because of cerebrovascular infarction in 1 patient in the GEM+S-1 group and 2 patients in the GEM-alone group.

Table 3. Treatment related toxicity (grades 3 and 4)

Adverse Event	GEM+S-1 (n = 96)		GEM alone (n = 66)		P
	No.	%	No.	%	
Leucopenia	24	25.0	15	22.7	NS
Neutropenia	25	26.0	26	39.4	NS
Anemia	15	15.6	3	4.5	<0.05
Thrombocytepenia	7	7.3	10	15.2	NS
Nausea	1	1.0	3	4.5	NS
Vomitting	0	0	2	3.0	NS
Anorexia	3	3.0	7	10.6	NS
General fatigue	13	13.5	0	0	<0.05

Discussion

Until the 1990s, chemotherapy was largely ineffective against locally advanced or metastatic pancreatic cancer. Since the introduction of GEM, however, chemotherapy was confirmed to prolong survival. The standard regimen for locally advanced or metastatic pancreatic cancer has been single-agent GEM. However, the overall response remained unsatisfactory, with low survival rates and short median survival times. Various regimens for GEM-based combination chemotherapy have, therefore, been studied in an effort to improve response and outcomes.

5-FU had been the mainstay of chemotherapy for pancreatic cancer until GEM became available, but 5-FU in combination with GEM did not improve the median survival of patients with advanced pancreatic cancer as compared with single-agent GEM.[2] Erlotinib is the only agent that was statistically shown to provide an additional survival benefit as compared with GEM alone in patients with advanced pancreatic cancer.[9] However, the benefit in terms of overall survival was only 2 weeks. Therefore, new GEM-based combination regimens are being investigated to improve clinical benefits for patients with pancreatic cancer.

S-1 is an oral fluorinated pyrimidine preparation that has produced moderate-to-high response rates in patients with gastric cancer, colorectal cancer, and biliary cancer.[12,13] An early phase II study of S-1 in patients with metastatic pancreatic cancer reported a response rate of 21.1% with a median survival time of 5.6 months.[16] In a late phase II study, the response rate was 37.5% with a median survival of 9.2 months.[17]

Recently, several studies have assessed combinations of GEM and S-1 in patients with locally advanced or metastatic pancreatic cancer.[18-23] One phase II trial of oral S-1 combined with GEM in metastatic pancreatic cancer obtained a median survival time of 12.5 months (95% CI, 5.9-19.1) and a 1-year survival rate of 54%

(95% CI, 36-72). In that study, S-1 (30 mg/m^2 twice daily) was given orally for 14 consecutive days, and GEM (1,000 mg/m^2) was given on days 8 and 15 of a 21-day cycle.[18] Grades 3 or 4 toxic effects were leukopenia (33%), neutropenia (55%), anemia (9%), thrombocytopenia (15%), anorexia (6%), fever (9%), and interstitial pneumonia (6%). Another phase II trial reported a median survival time of 7.89 months (95% CI, 5.96-9.82) in patients with locally advanced or metastatic pancreatic cancer who received S-1 (40 mg/m^2 orally twice daily on days 1-14 of a 21-day cycle) plus GEM (1,250 mg/m^2 on days 1 and 8), repeated every 3 weeks.[20] The major toxicities were grades 3 or 4 neutropenia (28.1%), grades 3 or 4 thrombocytopenia (15.6%), and grade 3 diarrhea (15.6%). Oh et al. performed a multicenter phase II study of GEM+S-1 combination chemotherapy in patients with unresectable pancreatic cancer.[23] The median survival time was 8.4 months (95% CI, 5.7-11.1), and the 1-year survival rate was 34% (95% CI, 19%-49%). The regimen used was GEM 1,000 mg/m^2 on days 1 and 8 plus S-1 40 mg/m^2 given orally twice daily on days 1 to 14 of a 21-day repeated cycle. The major grades 3 or 4 hematologic toxicities were neutropenia (39.5%), leukopenia (15.8%), thrombocytopenia (2.6%), and anemia (7.9%), and the major grades 3 or 4 nonhematologic toxicities included anorexia (10.5%), stomatitis (2.6%), rash (7.9%), fatigue (7.9%), and hyperbilirubinemia (5.3%). These studies used similar regimens and obtained comparable median survival times and 1-year survival rates. Toxicities were consistently mild and tolerable.

In the present study, the overall median survival time was 16.2 months (95% CI, 8.7-23.6), and the 1-year survival rate was 56.8% in the GEM+S-1 group, which were significantly better than the results in the GEM-alone group (P = 0.008). The incidences of grades 3 or 4 leukopenia, neutropenia, anemia, and thrombocytopenia were 25.0%, 26.0%, 15.6%, and 7.3%, respectively; and most of these events were tolerable, with no severe complications. Grades 3 or 4 nonhematologic toxicities were nausea (1.0%), anorexia (3.1%), and general fatigue (13.5%). These adverse effects were also tolerable and reversible.

Our regimen in the GEM+S-1 group differed from those used in previous studies, i.e., regimens in previous studies were that GEM 1,000-1,250 mg/m^2 was given intravenously on days 1 and 8 or on days 8 and 15, and S-1 30-40 mg/m^2 twice daily was given orally on days 1 to 14 of a 21-day cycle.[19,20-23] On the other hand, our regimen was that GEM 1,000 mg/m^2 was given intravenously on days 1 and 15 and S-1 40 mg/m^2 twice daily was given orally on days 1 to 7 and days 15 to 21 of a 28-day cycle. In this regimen, GEM was given biweekly, not weekly, and patients had S-1 free time for 1 week after S-1 was given. We therefore considered our regimen was more eligible and tolerable for patients, and they could receive the chemotherapy continuously and achieved a higher level of efficacy as a result.

This cycle can be broken down into two, 2-week cycles, during which the same treatment is given. These 2-week cycles are easy for patients to understand and facilitate the design of the treatment plans.

In conclusion, the survival of patients who received the regimen described in the present study of GEM+S-1 combination chemotherapy was significantly longer than that of patients who received GEM alone. Further randomized controlled studies are warranted to confirm these results showing that the GEM+S-1 regimen was feasible and well tolerated in patients with locally advanced or metastatic pancreatic cancer.

References

1. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403-13.
2. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002; 20: 3270-5.
3. Bramhall SR, Schulz J, Nemunaitis J, et al. A double-blind placebo-controlled, randomized study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* 2002; 87: 161-7.
4. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002; 94: 902-10
5. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004; 22: 3776-83.

6. Oettle H, Richards D, Ramanathan RK, et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol* 2005; 16: 1639-45.
7. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005: 23: 3509-16.
8. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006; 24: 3946-52.
9. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; 25: 1960-6.
10. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007; 25: 2212-7.
11. Bernhard J, Dietrich D, Scheithauer W, et al. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial-SAKK 44/00-CECOG/PAN.1.3.001. *J Clin Oncol* 2008; 26: 3695-701.
12. Shirasaka T, Shimamato Y, Ohshimo H, et al. 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* 1996; 7: 548-57.
13. Takechi T, Nakano K, Uchida J, et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother Pharmacol* 1997; 39: 205-11.
14. Tatsumi K, Fukushima M, Shirasaka T, et al. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res* 1987; 78: 748-55.
15. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993; 53: 4004-9.
16. Ueno H, Okusaka T, Ikeda M, et al. An early phase II study of S-1 in patients with metastatic pancreatic cancer. *Oncology* 2005; 68: 171-8.
17. Okusaka T, Funakoshi A, Furuse J, et al. A late phase II study of S-1 for metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2008; 61: 615-21.
18. Nakamura K, Yamaguchi T, Ishihara T, et al. Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. *Br J Cancer* 2006; 94: 1575-9.
19. Lee GW, Kim HJ, Ju JH, et al. Phase II trial of S-1 in combination with gemcitabine for chemo-naïe patients with locally advanced or metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2009; 64: 707-13.
20. Ueno H, Okusaka T, Ikeda M, et al. A phase I study of combination chemotherapy with gemcitabine and oral S-1 for advanced pancreatic cancer. *Oncology* 2005; 69: 421-7.
21. Nakamura K, Yamaguchi T, Ishihara T, et al. Phase I trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. *Br J Cancer* 2005; 92: 2134-9.
22. Kim MK, Lee KH, Jang BI, et al. S-1 and gemcitabine as an outpatient-based regimen in patients with advanced or metastatic pancreatic cancer. *Jpn J Clin Oncol* 2009; 39: 49-53.
23. Oh DY, Cha Y, Choi IS, et al. A multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer. *Cancer Chemother Pharmacol* 2010: 65: 527-36.