# Phase I study of S-1 and biweekly docetaxel combination chemotherapy for advanced and recurrent gastric cancer

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**Abstract.** A phase I study of S-1 and biweekly docetaxel (DOC) combination therapy was conducted to determine the maximum tolerated dose (MTD) and pharmacokinetic parameters. Fourteen patients with advanced or recurrent gastric cancer were analyzed. The treatment consisted of S-1 [body surface area (BSA) <1.25 $m^2$:80 mg/day, 1.25≤ BSA <1.50 $m^2$: 100 mg/day, 1.50 $m^2$≤ BSA; 120 mg/day, orally, day 1-14) and DOC (30-40 mg/$m^2$/day, intravenously, day 1 and 15], which were repeated as often as possible every four weeks. Pharmacokinetic analysis was done at DOC 40 mg/$m^2$/day. Initially, patients were administered S-1 and 40 mg/$m^2$/day of DOC, and DOC 40 mg/$m^2$/day was considered as MTD. In detail, one patient developed neutropenia (grade 4, G4), and two other patients had no day 15 DOC administration because of neutropenia (grade 3, G3). When S-1 and 35 mg/$m^2$/day of DOC were administered to three patients, no adverse reactions were noted. In six patients treated with S-1 and 30 mg/$m^2$/day of DOC, one patient developed neutropenia (G4), and another patient developed diarrhea (G3) and anorexia (G3). The rest of this cohort showed no adverse reactions. Although 5-fluorouracil and gimeracil concentrations remained high under impaired renal function, no pharmacokinetic interactions appeared between S-1 and DOC under normal renal function. The dose limiting toxicity of a combination of S-1 and biweekly DOC was leukopenia and neutropenia. The recommended dose for this combination in phase II study is DOC 35 mg/$m^2$/day.

## Introduction

S-1 is a novel oral anticancer drug, which was developed based on the biochemical modulation of tegafur (FT) by 5-chloro-2,4-dihydroxypyridine (gimeracil, CDHP) and potassium oxonate (oteracil, oxo) in a molar ratio of 1:0.4:1 (1-3). FT is a prodrug of 5-fluorouracil (5-FU), an active drug against various forms of gastrointestinal malignancy. 5-FU is degraded to α-fluoro-ß-alanine by dihydropyrimidine dehydrogenase (DPD), which is produced in various organs, including tumor tissue. CDHP strongly inhibits DPD, which results in a prolonged increased concentration of 5-FU in the plasma (4). Oxo inhibits phosphorylation of 5-FU to 5-fluorouridine-5'-monophosphate (5). As oxo is distributed in the gastrointestinal tract after oral administration, it possibly decreases 5-FU-induced gastrointestinal tract toxicity (5). Thus, S-1 was designed both to increase antitumor activity and to reduce drug-induced adverse gastrointestinal adverse reaction.

Independent phase II studies of S-1, including gastric cancer patients without prior chemotherapy, give an excellent response rate and survival (6-8). The response rate using S-1 alone is comparable to or better than the response rate in combination studies such as FAMTX or ECF, which has been mainly used in Europe or the United States (9-12). S-1 has been in common use in clinical practice since March 1999 in Japan against advanced and recurrent gastric cancer. Clinical information on this drug has accumulated. We previously summarized recent clinical data of 29 patients with advanced or recurrent gastric cancer and, as expected, a high response rate and good survival were confirmed in patients without prior chemotherapy (13). However, in patients who had received chemotherapy, the response rate was 12.5%. Today, S-1 is a main drug for the treatment of advanced or recurrent gastric cancer, especially in first-line chemotherapy. However, the questions arise as to which is the best chemotherapy regimen for second-line chemotherapy, and whether combination therapy of S-1 is superior to S-1 monotherapy. Thus, a new combination therapy of S-1 is worth exploring.

Docetaxel (DOC) is a semi-synthetic taxane prepared from a non-cytotoxic precursor extracted from the needles of the European yew tree *Taxus baccata*. Docetaxel accelerates microtubule assembly from tubulin, and blocks depolymerization of microtubules. Stable microtubules result in cell death. As a single agent, taxanes are currently the most widely administered agents for metastatic breast cancer after anthracycline treatment (14). DOC is also active against gastric cancer. Independent

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Table I. Patient characteristics (n=14).

| Covariate | | No. of patients |
|---|---|---|
| Gender | | |
| Male | | 13 |
| Female | | 1 |
| Age (years old) | | 58 (41-72) |
| Performance status | | |
| 0 | | 10 |
| 1 | | 4 |
| Type of disease | | |
| Recurrence | | 7 |
| Inoperable | | 3 |
| Postoperation with residual tumor | | 4 |
| Histological type | | |
| Differentiated | | 6 |
| Undifferentiated | | 8 |
| Treatment course | 24 courses | [1-4 courses for each pt] |
| Level 1 (n=5) | 9 courses | [1-4 courses for each pt] |
| Level 0 (n=3) | 7 courses | [1-4 courses for each pt] |
| Level -1 (n=6) | 8 courses | [1-2 courses for each pt] |
| Calculated creatinine clearance (ml/min) | 81.3 | (33.9-129.8) |

pt, patient.

Table II. Hematological toxicity.

| | NCI-CTC grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | % grade ≥3 |
| Level 1 (n=5) | | | | | |
| Leukopenia | 1 | 1 | 1 | 1 | 40 |
| Neutropenia | | | 2 | 1 | 60 |
| Anemia | | 3 | 1 | | 20 |
| Thrombocytopenia | 1 | | | | 0 |
| Level 0 (n=3) | | | | | |
| Leukopenia | | 1 | | | 0 |
| Neutropenia | | 1 | | | 0 |
| Anemia | | 1 | | | 0 |
| Thrombocytopenia | | | | | 0 |
| Level -1 (n=6) | | | | | |
| Leukopenia | 1 | 1 | 3 | | 50 |
| Neutropenia | | 1 | 2 | 1 | 50 |
| Anemia | | 4 | | | 0 |
| Thrombocytopenia | | | | | 0 |

NCI-CTC grade, National Cancer Institute-Common Toxicity Criteria grade.

phase II studies in Japan showed that the response rate is 23.7% (15,16).

Recent reports of docetaxel-based combination therapy showed high response rates as a first line for gastric cancer patients (17,18). We focused on DOC as a candidate for combination therapy with S-1, and we made a phase I study of S-1 and biweekly DOC combination therapy, to find the maximum tolerated dose (MTD) and recommended dose in a phase II clinical trial.

## Patients and methods

*Eligibility*. Patients with advanced or recurrent gastric cancer were eligible for this study. This study started after obtaining approval from the institutional review board. Disease characteristics included the following criteria: i) histologically or cytologically proved gastric cancer, ii) measurable or evaluable lesions, iii) no prior chemotherapy (history of postoperative adjuvant chemotherapy was allowed), and iv) adjuvant therapy (including chemotherapy and immunotherapy) must be finished at least four weeks before the combination therapy starts. Patient characteristics included the following criteria: i) age of ≥20 and <75 years, ii) an Eastern Cooperative Oncology Group performance status of ≤2, iii) adequate hematopoietic function (4000/mm$^3$≤ white blood cell ≤12000/mm$^3$, neutrocyte, ≥2000/ mm$^3$, platelet ≥10x10$^4$/mm$^3$, hemoglobin ≥9.0 g/dl), iv) adequate hepatic function [total bilirubin ≤1.5 mg/dl, transaminase ≤2 times institutional normal upper limit (if caused by liver metastases, transaminase ≥2 times may be allowed based on the doctor's judgement)], v) serum creatinine ≤ institutional normal upper limit, blood urea nitrogen ≤25 mg/dl, vi) adequate cardiac function, vii) neither brain metastases nor history of brain metastases, and viii) before treatment, written informed consent must be obtained from the patients. As complimentary data about renal function, creatinine clearance was calculated based on a formula described elsewhere (19).

From March 2001 to June 2003, 17 patients were enrolled in this study. Three patients were excluded because 1 of them showed marked disease progression before initiation of the treatment and 2 of them took half of the indicated dose of S-1 during the treatment. Thus, a total of 14 patients were evaluated.

*Dose and drug administration*. S-1 was administered orally in the morning and evening on days 1-14 according to the body surface area (BSA); BSA <1.25 m$^2$; 80 mg/day, 1.25≤ BSA <1.50 m$^2$; 100 mg/day, 1.50 m$^2$≤ BSA; 120 mg/day). DOC was diluted in normal saline and was administered with an infusion pump for 1 h on days 1 and 15. As a premedication, 8 mg of dexamethasone was administered intravenously, 0.5 h before; and 4 mg orally, 12, 24, 36 and 48 h after the start of DOC administration. One course was 28 days, and was repeated as often as possible. Treatment continued unless disease progressed, unacceptable toxicity occurred or the patient refused further treatment. The dose of DOC started at

Table III. Non-hematological toxicity

| | NCI-CTC grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | % grade ≥3 |
| Level 1 (n=5) | | | | | |
| Anorexia | 1 | | 1 | | 20 |
| Diarrhea | | | 1 | | 20 |
| General fatigue | 1 | | | | 0 |
| Skin eruption | 1 | | | | 0 |
| Level 0 (n=3) | | | | | |
| Anorexia | 1 | | | | 0 |
| Nausea, vomiting | 1 | | | | 0 |
| Stomatitis | 1 | | | | 0 |
| General fatigue | 1 | | | | 0 |
| Alopecia | 1 | | | | 0 |
| Level -1 (n=6) | | | | | |
| Anorexia | 2 | | 1 | | 16.7 |
| Diarrhea | 1 | 1 | | 1 | 16.7 |
| Stomatitis | 1 | | | | 0 |
| General fatigue | 2 | 1 | | | 0 |
| Alopecia | 4 | | | | - |
| Headache | 2 | | | | 0 |
| Abdominal pain | | 1 | | | 0 |

NCI-CTC grade, National Cancer Institute-Common Toxicity Criteria grade.

40 mg/m$^2$ (Level 1). Doses of 35 mg/m$^2$ (Level 0) and 30 mg/m$^2$ (Level -1) were also evaluated because the dose limiting toxicity (DLT) was at Level 1.

*DLT, MTD and dose escalation schedule*. Toxicity was evaluated according to the National Cancer Institute (NCI) common toxicity criteria. The DLT was defined as: i) grade 4 leukopenia or neutropenia lasting longer than three days despite the use of granulocyte-colony stimulating factor (G-CSF), ii) grade 3 neutropenia with a fever of >38˚C lasting longer than three days despite the use of G-CSF, iii) grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding tendency, and iv) grade 3-4 non-hematological toxicity except nausea, vomiting or alopecia.

In an initial study, three patients at one dose level were evaluated: i) the dose was defined as MTD when all patients developed DLT; ii) when one or two of three patients developed DLT, three other patients were enrolled; iii) when more than three of six patients developed DLT, the dose was defined as MTD; iv) when fewer than two of six patients developed DLT, the dose was increased to the next step.

*Pharmacokinetic study design*. Pharmacokinetic study was conducted for three patients on the first day of treatment at dose level 1 (S-1 at the fixed dose described above, and DOC 40 mg/m$^2$). S-1 and DOC administration started simultaneously, and heparinized blood samples to test for 5-FU, FT, CDHP and oxo were taken from the patients before and 1, 2, 4 and 8 h after administration. Heparinized blood samples to test for DOC were taken before and 0.5, 1, 1.5, 2, 3, 4, 5 and 8 h after administration. Immediately, the blood samples were cooled in ice and then centrifuged at 3000 round per minute for 15 min, and the separated serums were stored at -80˚C until assay. The plasma levels of FT, 5-FU, CDHP, oxo and DOC concentration were measured as described elsewhere (20,21). WinNonlin ver.3.0 (Phasight Co.) software was used to calculate the pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration-versus-time curve from time zero to infinity (AUC 0-∞), and plasma elimination half-life (T 1/2).

Independently from this phase I study, three patients with advanced or recurrent gastric cancer were treated with docetaxel monotherapy biweekly (40 mg/m$^2$). After informed consent was obtained, blood samples were taken at the same times as used in the phase I study. The plasma docetaxel concentration was measured by using the same method.

## Results

*Patients characteristics, toxicity and DLT*. Table I lists patient characteristics. The performance status was 0 in 10 patients, and the median age was 58 years old. Twenty four courses were conducted, with a mean of 1.7 courses for each patient (range 1-4 courses). The creatinine clearance was >50 ml/min except for patient 1 in the pharmacokinetic study. Tables II and III list hematological and non-hematological toxicity profiles.

This study started with a cohort of three patients at DOC dose 40 mg/m$^2$ (Level I). Leukopenia and neutropenia were found as DLT, and Level 1 (40 mg/m$^2$) as MTD. In detail, one patient developed grade 4 neutropenia and another patient could not receive day 15 DOC administration due to prolonged grade 3 leukopenia and neutropenia; the third patient developed no adverse reactions. Two additional patients were enrolled in Level 1; one of these patients also could not receive day 15 DOC administration because of grade 3 neutropenia.

In the second step, we evaluated the DOC dose at 30 mg/m$^2$ (Level -1) as the safety of the registered patients was the highest priority. Among the first three patients in this cohort, one patient completed two courses of treatment, one patient developed grade 4 leukopenia and neutropenia and the third patient discontinued treatment because this patient developed grade 3 anorexia and grade 3 diarrhea. As the latter two patients were considered to show DLT, an additional three patients were enrolled in this cohort. Two of these patients developed grade 3 leukopenia and neutropenia, and the third patient developed grade 2 diarrhea, abdominal pain and grade 1 headache: no DLT appeared during the treatment. Thus, 30 mg/m$^2$ (Level -1) was not considered as DLT.

In the third step, three patients received S-1 and DOC 35 mg/m$^2$ (Level 0), to confirm if DOC at 30 mg/m$^2$ (Level -1) or DOC at 35 mg/m$^2$ (Level 0) can be a recommended dose. Although grade 2 leukopenia, neutropenia and anemia developed in 1 patient, grade 3 and 4 hematological toxicity were not noted. When considering non-hematological toxicity, only grade 1 anorexia, nausea, vomiting, stomatitis, general

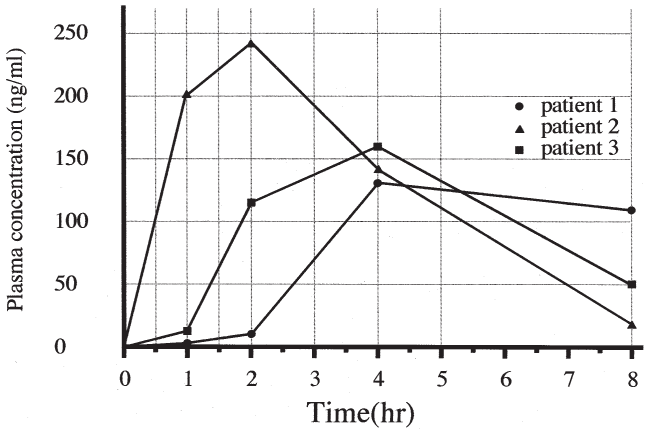


Figure 1. Plasma 5-fluorouracil concentration after administration of combined S-1 and docetaxel (DOC) (S-1, 50 mg/body, orally; DOC, 40 mg/m$^2$, 1 h infusion, intravenously).

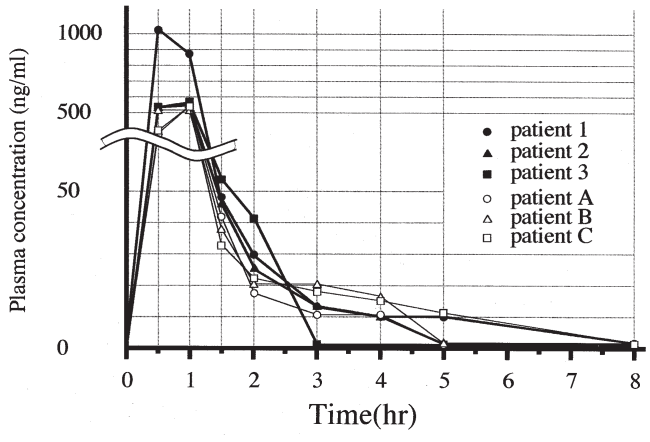


Figure 2. Plasma docetaxel (DOC) concentration after administration of DOC alone or DOC and S-1 combination. (S-1, 50 mg/body, orally; DOC, 40 mg/m$^2$, 1 h infusion, intravenously). Patients 1-3 were treated with a combination of S-1 and DOC, whereas patients A-C were treated with DOC monotherapy.

fatigue and alopecia were noted. Thus, DOC at 35 mg/m$^2$ (Level 0) was considered a recommended dose.

*Pharmacokinetics*. A pharmacokinetic study was conducted with three patients on the first day of treatment at dose level 1 (S-1 orally at the dose stated in the Patients and methods section, and DOC at 40 mg/m$^2$ intravenously for 1 h). Fig. 1 shows 5-FU concentrations in combined therapy (patients 1-3). Fig. 2 shows DOC concentrations in patients treated with combined therapy (patients 1-3), as well as in patients treated with DOC at 40 mg/m$^2$ monotherapy (patients A-C). Table IV shows the Cmax, Tmax, AUC 0-∞ and T1/2. Although the Cmax of 5-FU was from 132.6 to 244.4 ng/ml, the 5-FU concentration was maximum at 2-4 h after administration. One patient with impaired renal function (patient 1) showed a prolonged 5-FU concentration plateau and a longer half-life of 5-FU.

In terms of DOC pharmacokinetics, plasma DOC concentration in the Level 1 combination therapy group was maximum at 0.5-1 h after the start of administration (i.e., 0.5 h before or at the end of administration), and then decreased rapidly. The change in plasma DOC concentration in the DOC monotherapy group showed the same pharmacokinetic profile.

Table IV. Pharmacokinetic parameters after administration of S-1 and DOC (40 mg/m$^2$) combination therapy (patients 1-3) and DOC monotherapy (patients A-C).

| | Cmax (ng/ml) | Tmax (h) | AUC 0-∞ (ng. h/ml) | T 1/2 (h) |
|---|---|---|---|---|
| 5-FU | | | | |
| Patient 1 | 132.6 | 4 | 2737 | 13.6 |
| Patient 2 | 244.4 | 2 | 1072 | 1.31 |
| Patient 3 | 158.0 | 4 | 941 | 2.42 |
| FT | | | | |
| Patient 1 | 3235.1 | 4 | 33295 | 5.99 |
| Patient 2 | 2008.6 | 1 | 10610 | 3.91 |
| Patient 3 | 1859.8 | 2 | 16658 | 6.88 |
| CDHP | | | | |
| Patient 1 | 294.3 | 4 | 2054 | 3.89 |
| Patient 2 | 428.6 | 1 | 1380 | 2.10 |
| Patient 3 | 259.4 | 2 | 1559 | 3.30 |
| Oxo | | | | |
| Patient 1 | 71.7 | 4 | 506 | 3.59 |
| Patient 2 | 112.8 | 1 | 495 | 2.50 |
| Patient 3 | 38.3 | 2 | 771 | 13.6 |
| DOC | | | | |
| Patient 1 | 1030 | 0.5 | 1055.6 | 1.87 |
| Patient 2 | 554 | 1 | 625.4 | 1.53 |
| Patient 3 | 569 | 1 | 660.0 | 1.18 |
| DOC | | | | |
| Patient A | 544 | 1 | 490.7 | 1.85 |
| Patient B | 510 | 0.5 | 655.3 | 3.22 |
| Patient C | 517 | 1 | 533.2 | 2.99 |

Cmax, maximum plasma concentration; Tmax, time to maximum plasma concentration; AUC 0-∞, area under the plasma concentration-versus-time curve from time zero to infinity; T1/2, plasma elimination half-life.

## Discussion

In Japan, gastric cancer still remains most frequent malignancy. Despite of the advance in early detection of this disease and surgical improvement, the survival of patients with recurrent and advanced gastric cancer is unsatisfactory. The Japan Gastric Cancer Association issued the first edition of gastric cancer treatment guidelines in March 2001 to provide a common basis of understanding of the extent of disease and selection of proper treatment (22). This guideline did not mention particular regimen of chemotherapy for advanced and recurrent gastric cancer, but it stated that 5-FU and cisplatin may be important drugs. Thus, the standard regimen has not been established.

S-1 is synthesized in Japan and has been a key drug in the treatment of advanced and recurrent gastric cancer in Japan because of a high response rate (7,8,13). In this study, we investigated the safety and pharmacokinetic profiles of a combination therapy of S-1 and biweekly DOC. As a monotherapy, the DLT of DOC is leukopenia and neutropenia (15,16). Although, in patients in Europe and in the United States, the DLT of S-1 is diarrhea (23), the DLT of S-1 in Japanese patients is mainly haematological and stomatitis and diarrhea is mild (6-8). As expected, in the S-1 and biweekly DOC regimen, the DLT was leukopenia and neutropenia in this study. Although the toxicity profile of both drugs is similar in Japanese patients, we thought it rational to examine this combination for the following reasons: i) the mechanism of antitumor activity of S-1 and DOC is completely different, ii) DOC is beneficial for gastric cancer patients who have been previously treated and for patients as a first-line therapy (15,16), and iii) the resistance of 5-FU is overcome by DOC *in vitro* (24). Our previous *in vivo* therapeutic experiment that used gastric cancer xenografts showed that S-1 (day 1-14 administration) and DOC (day 1 or day 8 intravenous administration) were synergistic (25), although schedule dependency between paclitaxel and 5-fluorouracil *in vitro* has been reported (26). Thus, we scheduled days 1-14 of administration with S-1 with days 1 and 15 of administration with DOC.

The combination therapy of DOC and continuous 5-FU has showed no pharmacokinetic interaction between the two drugs (27,28). As the pharmacokinetics of S-1 is similar to that of continuous 5-FU intravenous infusion (29), S-1 may not interact with DOC unless the 5-FU concentration remains the same as expected. One study showed that pharmacokinetic parameters of 5-FU in Japanese patients were Cmax, 128.5 ng/ml; Tmax, 3.5 h; AUC 0-14, 724 ng.h/ml; and T1/2, 1.9 h (29). In our study, the AUC of 5-FU in patients 2 and 3 were similar to these data. Patient 1, which developed grade 4 leukopenia and neutropenia, showed a larger AUC 0-$\infty$ of 5-FU and CDHP. The calculated creatinine clearance was 33.9 ml/min. The different pharmacokinetic profile may be partly explained by impaired renal function. CDHP, excreted in the kidney, inhibits DPD, the catabolic enzyme of 5-FU, and results in a prolonged and higher 5-FU concentration in the plasma. Impaired renal function is directly connected to an elevated level of CDHP, which results in a prolonged plasma 5-FU plateau level. The results of a postmarketing survey of S-1 in Japan support this hypothesis (30). This survey monitored the toxicity profile and estimated creatinine clearance and showed that patients with a lower creatinine clearance frequently experience severe adverse reactions. In terms of DOC, hepatic metabolism and biliary excretion is the major pathway of DOC elimination (31). Our data showed that the plasma concentration of DOC is maximum just after drug administration, and the same pharmacokinetic profiles were confirmed with or without combination with S-1.

In conclusion, patients should be strictly screened for impaired renal function based on creatinine clearance. Although careful blood count monitoring should be used, a combination therapy of S-1 and biweekly DOC is worth investigating. The recommended dose for this combination is 35 mg/m$^2$/day DOC on days 1 and 15.

## References


1. Takechi T, Nakano K, Uchida J, Mita A, Toko K, Takeda S, Unemi N and Shirasaka T: Antitumor activity and low intestinal toxicity of S-1, a new formulation of tegafur, in experimental tumor models in rats. Cancer Chemother Pharmacol 39: 205-211, 1997.
2. Fukushima M, Shimamoto Y, Kato T, Uchida J, Yonekura R, Ohshimo H and Shirasaka T: Antitumor activity and toxicity of S-1, an oral combination of tegafur and two biochemical modulators, compared with continuous infusion of 5-fluorouracil. Anticancer Drugs 9: 817-823, 1998.
3. Fukushima M, Satake H, Uchida J, Shimamoto Y, Kato T, Takechi T, Okabe H, Fujioka A, Nakano K, Ohshimo H, Takeda S and Shirasaka T: Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluoruoracil on human tumor xenografts. Int J Oncol 13: 693-698, 1998.
4. Tatsumi K, Fukushima M, Shirasaka T and Fujii S: Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. Jpn J Cancer Res 78: 748-755, 1987.
5. Shirasaka T, Shimamoto Y and Fukushima M: Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 53: 4004-4009, 1993.
6. Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y and Taguchi T: 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, 1999.
7. Koizumi W, Kurihara M, Nakano S and Hasegawa K: Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. Oncology 58: 191-197, 2000.
8. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y and Taguchi T: 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, 1998.
9. Wils JA, Klein HO, Wagener DJ, Bleiberg H, Reis H, Korsten F, Conroy T, Fickers M, Leyvraz S, Buyse M and Duez N for the European Organization for Research and Treatment of Cancer, Gastrointestinal Tract Cooperative Group: Sequential high-dose methotrexate and fluorouracil combined with doxorubicin - a step ahead in the treatment of advanced gastric cancer: a trial of the EORTC Gastrointestinal Tract Cooperative Group. J Clin Oncol 9: 827-831, 1991.
10. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A and Meehan M: Randomized trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15: 261-267, 1997.
11. Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, Joffe JK, Mackean M, Mansi J, Leahy M, Hill A, Oates J, Rao S, Nicolson M and Hickish T: Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 80: 269-272, 1999.
12. Kelsen D, Atiq OT, Saltz L, Niedzwiecki D, Ginn D, Chapman D, Heelan R, Lightdale C, Vinciguerra V and Brennan M: FAMTX versus etoposide, doxorubicin and cisplatin: a random assignment trial in gastric cancer. J Clin Oncol 10: 541-548, 1992.
13. Takahashi I, Kakeji Y, Emi Y, Sakurai M, Yonemura Y, Kimura Y and Maehara Y: S-1 in the treatment of advanced and recurrent gastric cancer: current status and future prospects. Gastric cancer 6 (suppl 1): S28-S33, 2003.
14. Valero V, Holmes FA, Walters RS, Theriault RL, Esparza L, Fraschini G, Fonseca GA, Bellet RE, Buzdar AU and Hortobagyi GN: Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. J Clin Oncol 13: 2886-2894, 1995.
15. Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J and Hirabayashi N: Late phase II clinical study of RP56976 (Docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese cooperative study group trial (group A). Jpn J Cancer Chemother 25: 1915-1924, 1998.
16. Mai M, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, Hirabayashi N, Taguchi T and Furue H: A late phase II clinical study of RP56976 (docetaxel) in patients with advanced or recurrent gastric cancer: a cooperative study group trial (group B). Jpn J Cancer Chemother 26: 487-496, 1999.

17. Park YH, Ryoo BY, Choi SJ and Kim HT: A phase II study of capecitabine and docetaxel combination chemotherapy in patients with advanced gastric cancer. Br J Cancer 90: 1329-1333, 2004.
18. Roth AD and Ajani J: Docetaxel-based chemotherapy in the treatment of gastric cancer. Ann Oncol 14 (suppl 2): ii41-ii44, 2003.
19. Cockcroft DW and Gault MH: Prediction of clearance from serum creatinine. Nephron 16: 31-41, 1976.
20. Matsushima E, Yoshida K, Kitamura R and Yoshida K: Determination of S-1 (combined drug of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate) and 5-fluorouracil in human plasma and urine using high-performance liquid chromatography and gas chromatography-negative ion chemical ionization mass spectrometry. J Chromatogr 691: 95-100, 1997.
21. Vergniol JC, Bruno R, Montay G and Frydman A: Determination of taxotere in human plasma by a semi-automated high-performance liquid chromatographic method. J Chromatogr 582: 273-278, 1992.
22. Nakajima T: Gastric cancer treatment guidelines in Japan. Gastric Cancer 5: 1-5, 2002.
23. Hoff PM, Saad ED, Ajani JA, Lassere Y, Wenske C, Medgyesy D, Dwivedy S, Russo M and Pazdur R: Phase I study with pharmacokinetics of S-1 on an oral daily schedule for 28 days in patients with solid tumors. Clin Cancer Res 9: 134-142, 2003.
24. Hill BT, Whelan RD, Shellard SA, McClean S and Hosking LK: Differential tumor cell lines and certain drug resistant sublines *in vitro*. Invest New Drugs 12: 169-182, 1994.
25. Takahashi I, Emi Y, Kakeji Y, Uchida J, Fukushima M and Maehara Y: Increased antitumor activity in combined treatment TS-1 and docetaxel - a preclinical study using gastric cancer xenografts. Oncology 68: 130-137, 2005.
26. Grem JL, Nguyen D, Monahan BP, Kao V and Geoffroy FJ: Sequence-dependent antagonism between fluorouracil and paclitaxel in human breast cancer cells. Biochem Pharmacol 58: 477-486, 1999.
27. Lortholary A, Maillard P, Delva R, Boisdron-Celle M, Perard D, Vernillet L, Besenval M and Gamelin E: Docetaxel in combination with 5-fluorouracil in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy: a phase I, dose-finding study. Eur J Cancer 36: 1773-1780, 2000.
28. Ando M, Watanabe T, Sasaki Y, Ying DF, Omuro Y, Katsumata N, Narabayashi M, Tokue Y, Fujii H, Igarashi T, Wakita H, Ohtsu T, Itoh K, Adachi I and Taguchi T: A phase I trial of docetaxel and 5-day continuous infusion of 5-fluorouracil in patients with advanced or recurrent breast cancer. Br J Cancer 77: 1937-1943, 1998.
29. Hirata K, Horikoshi N, Aiba K, Okazaki M, Denno R, Sasaki K, Nakano Y, Ishizuka H, Yamada Y, Uno S, Taguchi T and Shirasaka T: Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. Clin Cancer Res 5: 2000-2005, 1999.
30. Nagashima F, Ohtsu A, Yoshida S and Ito K: Japanese nationwide post-marketing survey of S-1 in patients with advanced gastric cancer. Gastric Cancer 8: 6-11, 2005.
31. Marre F, Sanderink GJ, De Sousa G, Gaillard C, Martinet M and Rahmani R: Hepatic biotransformation of docetaxel (taxotere) *in vitro*: involvement of the CYP3A subfamily in humans. Cancer Res 56: 1296-1302, 1996.