

A pilot clinical study of a combination of docetaxel and doxifluridine for the treatment of advanced/recurrent gastric cancer with prior chemotherapy

Research Article

Hajime Kase*, Naoyasu Saito, Natsuki Tokura, Naohiro Washizawa, Makoto Kikuchi and Kazuo Kobayashi

The First Department of Surgery, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan

*Correspondence: Hajime Kase, The First Department of Surgery, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan; Telephone: +81-3-3762-4151; Fax: +81-3-3298-4348; e-mail: hajimejij@aol.com

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Abbreviations: best supportive care, (BSC); cisplatin, (CDDP); confidence interval, [CI]; docetaxel, (TXT); doxifluridine, (5'-DFUR); granulocyte colony stimulating factor, (G-CSF); Methotrexate, (MTX); National Cancer Institute common toxicity criteria version 2, (NCI-CTC ver.2); partial response, (PR); performance status, (PS); platelet-derived endothelial cell growth factor, (PD-ECGF); progression of disease, (PD); proximal margin, (PM); stabilization of the disease, (SD); thymidine phosphorylase, (dThdPase)

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Summary

A pilot study was conducted to assess the activity and tolerability of a combination chemotherapy regimen of docetaxel (TXT) and doxifluridine (5'-DFUR) in patients with advanced/recurrent gastric cancer. Eligibility criteria for patients included the following: (1) histologically proven gastric cancer, (2) performance status of 2 or less, (3) age 75 years or younger, (4) one or more prior chemotherapy regimens, (5) adequate bone marrow, liver, renal, and cardiac functions, and (6) provision of written informed consent. The treatment consisted of TXT (60 mg/m²) on Day 1 and 5'-DFUR (600 mg/day) on Days 1 to 21, repeated every 4 weeks. Objective responses to chemotherapy in measurable or evaluable lesions were evaluated using standard World Health Organization criteria. Nine patients were enrolled in the study. The antitumor effect was evaluated in 8 of the 9 patients, excluding 1 patient who had no evaluable lesion. The overall response rate was 37.5% (3 of 8 patients, 95% confidence interval [CI], 8.5% to 75.5%) and the disease control rate (partial response and stabilization of disease) was 87.5% (7 of 8 patients, 95% CI, 47.4% to 99.7%). The median survival time was 531 days (19.0 months) for all patients. Grade 3 leukopenia was observed in 1 patient (11.1%), but grade 3 or 4 diarrhea, which is commonly encountered in patients undergoing chemotherapy, was not observed. Other adverse reactions were mild. No treatment-related deaths occurred. This combination chemotherapy regimen was active and well tolerated. The results suggest that this combination therapy is an appropriate regimen for future Phase 2 trials.

I. Introduction

In recent years, the survival rate for gastric cancer has been dramatically improved by early detection and curative surgery. However, the prognosis for patients with unresectable advanced/recurrent gastric cancer is still poor. Some randomized studies (Murad et al, 1993; Glimelius et al, 1994; Pyrhonen et al, 1995) have reported that the median survival time of patients with advanced/recurrent gastric cancer is 6 to 9 months in those who received chemotherapy and about 3 months in those

who received the best supportive care (BSC). In most of the chemotherapy regimens for the treatment of advanced/recurrent gastric cancer in Japan, 5-FU is used as the base therapy and is combined with cisplatin (CDDP), with the response rate being reported to be 34.3 to 65.9% (Sasaki et al, 1997; Kusaba et al, 1999; Tsuji et al, 1999; Saji et al, 2002). However, the prognosis is poor in the case of gastric cancer for which the first-line chemotherapy is ineffective and no active second-line

therapy has been established. Therefore, the establishment of an effective second-line therapy is required.

Docetaxel (TXT) is a taxoid that possesses an antitumor effect and is extracted from the needle leaves of the European yew tree (*Taxus baccata*). TXT exerts its antitumor activity by promoting the polymerization of microtubule proteins and inhibiting mitosis (Diaz and Andreu, 1993). In cases of gastric cancer, TXT has been shown to exhibit antitumor activity and has been used clinically. However, the efficacy of TXT as a monotherapy is insufficient, with the response rate being about 20% (Taguchi et al, 1998; Mai et al, 1999). Therefore, it is necessary to use TXT in combination with a drug with which a synergistic effect can be expected. However, in gastric cancer, there has been only one case report on a drug that showed efficacy in such a combination regimen (Sato et al, 2002), although a few clinical studies have been performed in the past. Therefore, the present study was conducted as a pilot study to confirm the activity and tolerability of the combination regimen of TXT and 5'-DFUR in the treatment of gastric cancer.

II. Materials and methods

A. Eligibility criteria

Patients registered for the present study were required to satisfy the following eligibility criteria: 1) presenting with resected but non-cured or recurrent histologically proven gastric cancer; 2) a performance status (PS) of 2 or less on the scale of the Eastern Clinical Oncology Group; 3) aged 75 years or younger; 4) one or more prior chemotherapy regimens which were completed at least 4 weeks before registration; 5) normal (adequate) bone marrow function (white blood cell count 4,000/ μ L, absolute neutrophil count 2,000/ μ L, platelet count 10,000/ μ L), liver function (serum bilirubin level 2.0mg/dL, serum transaminase level 3-fold the normal limit), renal function (serum creatinine level 1.5mg/dL, blood urea nitrogen level 25mg/dL, creatinine clearance 50ml/min); 6) normal cardiac function; 7) absence of any other medical condition; 8) absence of any other active tumor; and 9) provision of written informed consent before commencement of the study.

B. Treatment schedule

On Day 1, TXT (60 mg/m²) was administered by intravenous injection over a period of more than 1 hour. On Day 1 to Day 21, doxifluridine (5'-DFUR) was administered orally at 600 mg/day. This therapy was repeated every 4 weeks as long as there was no progression of disease (PD), no refusal by a patient to continue the study or no unacceptable adverse reactions. In the event of the occurrence of any of the following in patients at the start of the subsequent treatment cycle, the administration of TXT and 5'-DFUR was to be postponed until the resolution of the adverse reaction: Leukopenia, neutropenia or thrombocytopenia of Grade 2 or higher; or diarrhea or infections of Grade 1 or higher. If the start of the next administration was delayed 1 week or more due to these adverse reactions, the therapy was to be discontinued. In the event of Grade 3 or 4 hematological adverse reactions or diarrhea, the administration of TXT and 5'-DFUR was to be suspended temporarily. After resolution of these reactions, the therapy was to be resumed with a reduction in the dose of TXT of 20%. Granisetron was routinely used before administration of TXT. No restriction was placed on the supportive care to be provided in the event of the occurrence of serious adverse events, including the use of

granulocyte colony stimulating factor (G-CSF) and anti-diarrheal drugs.

C. Evaluation

Objective responses to chemotherapy in measurable or evaluable lesions were evaluated using standard World Health Organization criteria. A survival curve was generated using the Kaplan-Meier method. For the evaluation of adverse reactions, the National Cancer Institute common toxicity criteria version 2 (NCI-CTC ver.2) was applied.

III. Results

A. Patient characteristics

Nine patients with gastric cancer were registered from June 2000 to June 2001 and evaluated for treatment response and adverse events. However, Patient No. 5, who was a resected but non-cured case judged positive for cancer infiltration at the resection margin [proximal margin (PM): +] after surgery, was not evaluated for treatment response because no evaluable lesion was detected on the CT image. Table 1 shows patient demographics. The age range of the patients at the start of treatment was 51 to 74 years (median: 66 years), and the number of males and females was 8 and 1, respectively. All of these patients were rated as 0 or 1 for PS. Histologically, poorly differentiated adenocarcinoma was observed in 4 patients (44.4%), tubular adenocarcinoma and mucinous adenocarcinoma in 2 patients (22.2%) each, and papillary adenocarcinoma in 1 patient (11.1%). The metastatic lesions in patients who had evaluable metastatic lesions were located in the liver (3 patients: 33.3%), lymph nodes (3 patients: 33.3%) and peritoneum (4 patients: 44.4%). The response of these patients to chemotherapy prior to registration in the present study was progression of the disease (PD) (Table 1). In addition, all patients underwent a cisplatin (CDDP) +5-fluorouracil (5-FU) regimen, and 5 underwent 2 regimens as prior therapy.

B. Response and survival

Of 8 patients who had measurable or evaluable lesions, 3 patients were rated as exhibiting a partial response (PR), 4 patients as exhibiting stabilization of the disease (SD), and 1 patient as exhibiting progression of the disease (PD). Thus, the response rate was 37.5% (3 of 8 patients; 95% CI: 8.5% to 75.5%). The disease control rate (partial response and stabilization of disease) was 87.5% (7 of 8 patients; 95% CI: 47.4% to 99.7%). The response rates in patients who had metastatic lesions in the liver, lymph nodes and peritoneum were 33.3% (1 of 3 patients), 66.6% (2 of 3 patients) and 25% (1 of 4 patients), respectively (Table 2). The median survival time was 531 days for all patients, and the 1-year survival rate was 66.7% (Figure 1).

C. Adverse reactions

The total number of treatment cycles was 107 (median: 10 cycles per patient; range: 4 to 18 cycles). Adverse reactions observed with this regimen are summarized in Table 3. Grade 3 leukopenia was observed in 1 patient (11.1%) and was resolved quickly by a single

Table 1. Patient demographics

Patient No.	Sex	Age	Site evaluated	Histological type	number of course	survival days	response	Previous tretment
1	m	64	Lymph node	por 1	18	840	SD	FP, MTX+5-FU
2	f	62	Lymph node/peritoneum	tub 2	10	385	PR	FP
3	m	51	Lymph node	por 2	16	827	PR	FP (NAC), MTX+5-FU
4	m	72	Peritoneum	por 2	9	300	SD	FP
5	m	60	None	muc	16	757	NE	FP (NAC)
6	m	74	Peritoneum	por 2	4	124	PD	FP
7	m	66	Liver metastatic lesion/peritoneum	tub 2	8	294	SD	FP (NAC), 5-FU (HAI)
8	m	70	Liver metastatic lesion	muc	10	1011	PR	FP, MTX+5-FU, 5-FU (HAI)
9	m	71	Liver metastatic lesion	pap	16	531	SD	FP, 5-FU (HAI)

HAI: hepatic arterial infusion chemotherapy
 NAC: neoadjuvant chemotherapy
 FP: 5-FU plus cisplatin
 NE: not evaluated

Table 2. Response rate

Response rates

CR	PR	SD	PD	Total
	3	4	1	8

The degree classified by part for the response rate

	CR	PR	SD	PD	Total
Liver		1	2		3
Lymph nodes		2	1		3
Peritoneum		1	2	1	4

administration of G-CSF. Other hematological adverse reactions were mild.

The most frequently observed non-hematological adverse reactions were alopecia (100%) and nail changes (88.9%). However, these reactions were rated as lower than Grade 3 and the patients were eligible to continue the study. Although diarrhea was observed in 4 patients (44.4%), it was rated as Grade 1 in all cases, and therefore there was no dose reduction or prolongation or cessation of treatment due to diarrhea. The diarrhea in these patients was resolved by the use of loperamide or other appropriate antidiarrheal drugs. Other non-hematological adverse reactions were mild. There was no cessation of treatment due to adverse reactions and no treatment-related deaths.

D. Dosage adjustments

The patient who developed Grade 3 leukopenia was eligible to continue the treatment after reducing the dose of TXT by 20%. There was no case in which the treatment was delayed due to adverse reactions. Thus, all patients

were able to receive the treatment on an outpatient basis as scheduled.

E. Case report

The CT images (T3, N3, H1, P0, Cy0, Stage IV, and pap) of Patient No. 8 with multiple liver metastatic tumors, who was rated as exhibiting PD after prior therapy with CDDP+5-FU, Methotrexate (MTX)+5-FU and 5-FU (hepatic arterial infusion), are shown. After administration of TXT+5'-DFUR, the liver metastatic lesion shrunk, and a PR was attained on the 4th treatment cycle (**Figure 2**).

IV. Discussion

The present pilot study was conducted to assess the antitumor effect and tolerability of a combination chemotherapy regimen of docetaxel (TXT) and doxifluridine (5'-DFUR) in patients with advanced/recurrent gastric cancer who failed to respond to

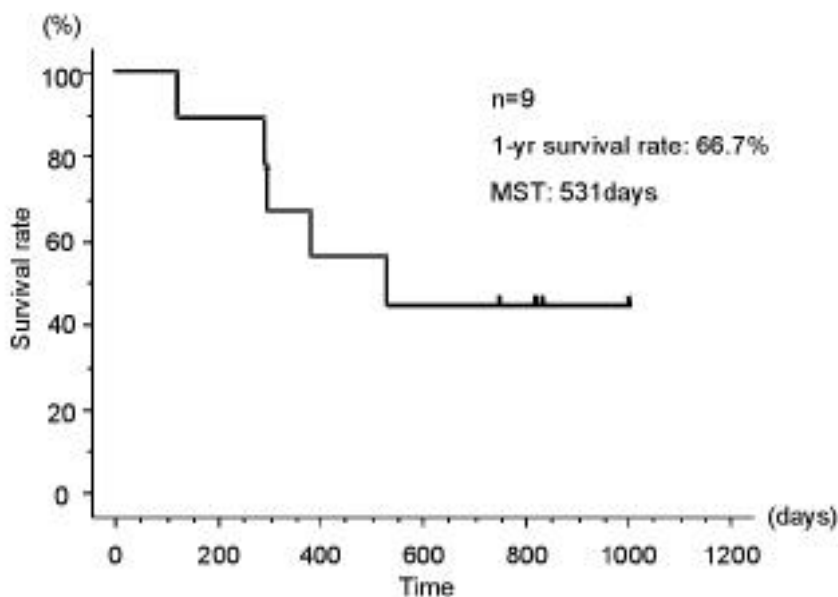


Figure 1. The survival rate of all the patients (n=9)

Table 3. Adverse reactions*

Adverse event	NCI-CTC Grade (no of patients)				Grade3 and 4 (%)
	1	2	3	4	
Leukopenia	1	2	1	-	44.4
Neutropenia	-	3	-	-	33.3
Edema	1	2	-	-	22.2
Fervescence	2	-	-	-	22.2
Alopecia	4	5	-	-	100
Changes in nails	6	2	-	-	88.9
Skin	6	-	-	-	44.4
Anorexia	3	-	-	-	33.3
Diarrhea	4	-	-	-	44.4
Nausea/ vomiting	2	-	-	-	22.2

* NCI-CTC version 2

prior therapy. Patients with gastric cancer who fail to respond to the first-line chemotherapy regimen and for whom no second-line therapy has been established generally have a poor prognosis. In the present study, TXT was selected because it is an anti-cancer agent possessing a completely new mechanism of action, and because it is reported to have little cross-tolerance to currently used anti-cancer agents. In addition, 5'-DFUR was selected (Sawada et al, 1998) because it has been clinically demonstrated to produce a synergistic effect when used concomitantly with TXT in other cancers such as breast cancer.

The most likely mechanism by which the synergistic effect is produced is that TXT upregulates thymidine phosphorylase (dThdPase), an enzyme responsible for the metabolism of 5'-DFUR. dThdPase has been shown to exist more abundantly in tumor tissues than in normal tissues and has recently been found (Furukawa et al, 1992) to be identical to Platelet-derived endothelial cell growth factor (PD-ECGF), which is involved in neovascularization. 5'-DFUR is an intermediate metabolite of capecitabine, which is used globally for the treatment of large intestine cancer and breast cancer. 5'-DFUR is a pro-drug that exerts its action following conversion to 5-FU by dThdPase, and its efficacy and

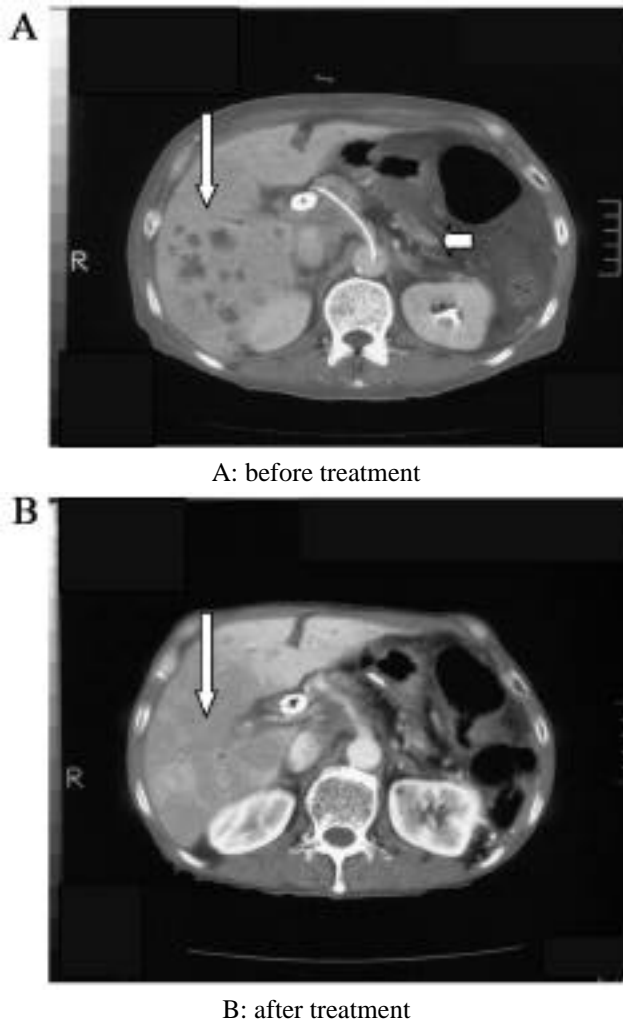


Figure 2. The CT images of Patient No. 8 before and after the treatment with TXT+5'-DFUR. the solid vertical arrow indicates a stent in common bile duct, and the horizontal arrow indicates an obstructed infusion catheter.

—▶ : Stent in common bile duct

◀ : Obstructed infusion catheter

safety in the treatment of solid cancers including gastric cancer have been recognized in Japan, Korea, and Italy, among other countries.

Recent basic studies (Endo et al, 1999; Sato et al, 2002) have reported that several types of anticancer agent, including TXT, specifically upregulate dThdPase in tumor tissues, and that concomitant use of these agents with 5'-DFUR/capecitabine can produce a synergistic effect. O'Shaughnessy et al, (2002) conducted a clinical study to compare TXT and TXT/capecitabine, and demonstrated the usefulness of the TXT/capecitabine combination regimen, with the response rate being 30% and 42%, and the MST being 11.5M and 14.5M, respectively.

In Japan, Tominaga et al, (2001) conducted a Phase I study of the combination regimen of TXT and 5'-DFUR in advanced/recurrent breast cancer, and reported a synergistic effect with the combination regimen, with the response rate being 58.3%. However, although there are clinical reports on the combination regimen of TXT and 5'-DFUR in breast cancer, there is only one clinical case

report (Sato et al, 2002) on this combination regimen in gastric cancer. Therefore, the present study was necessary to confirm the activity and tolerability of the combination regimen of TXT and 5'-DFUR in gastric cancer.

The overall response rate in the combination regimen was 37.5% (3 of 8 patients), and the disease control rate (partial response and stabilization of disease) was 87.5% (7 of 8 patients; 95% CI: 47.4% to 99.7%). In particular, 2 of 4 patients rated as exhibiting SD maintained this status for more than 6 months. In 3 patients with multiple liver metastatic tumors for whom hepatectomy was not applicable, the hepatic artery infusion therapy had to be discontinued because of catheter obstruction. Following treatment with the combination regimen, one of the 3 patients was rated as exhibiting a PR, and the remaining 2 patients were rated as exhibiting SD. Their survival times were also prolonged to 294 days, 1011 days and 531 days. This result suggests that the combination regimen is effective in patients for whom hepatic artery infusion therapy is not suitable. Two Japanese clinical studies (Taguchi et al, 1998; Mai et al, 1999) of TXT in the second-line management of advanced/recurrent gastric cancer reported the response rate of TXT monotherapy at 60 mg/m² to be 20% and 22%, respectively. In a Phase II clinical study (Taguchi et al, 1985) of 5'-DFUR, the response rate was reported to be about 15.8%. Taking these data into consideration, the results from our study suggest that TXT and 5'-DFUR used in combination may produce a synergistic antitumor effect.

In this study, the median survival time was 531 days. Thus, since the survival time was prolonged in these patients with advanced/recurrent gastric cancer who had undergone prior therapy, this combination regimen is considered to give a survival benefit.

The adverse event with the highest incidence in this regimen was nail changes, such as perionychia, nail deformation and onychoptosis. In Phase II clinical studies (Taguchi et al, 1998; Mai et al, 1999) where TXT monotherapy at 60 mg/m² was administered every 3 to 4 weeks to patients with gastric cancer, the subjective and objective adverse events observed included no adverse events related to nails. The incidence of adverse events related to nails was also low among the adverse events observed with 5'-DFUR. Therefore, the nail changes were considered to be adverse events specific to the concomitant use of TXT and 5'-DFUR. In the most serious case, a subungual abscess accompanied by pain was observed, followed by nail avulsion, but none of the changes resulted in cessation of treatment. For the resolution of these adverse events, it was necessary to use analgesics and antibiotics, and such treatment from the early stage following the onset of the adverse events was effective.

The dose of 5'-DFUR was determined based on the Phase I study of Tominaga et al, (2001). However, in that study, one case of non-hematotoxic nausea/vomiting of Grade 2 and two cases of stomatitis of Grade 2 were observed, whose relation with the test drug was not completely ruled out. Therefore, the dose was set at 600 mg/day that is 25% lower than the usual dose of 800 mg/day, in order to reduce the incidence of adverse event

such as diarrhea, since it was to be used in combination with TXT in gastric cancer treatment. Another consideration in setting the dose was that, by reducing the dose level used in the present study by 20 %, the chemotherapeutic dosage and administration could be performed on an outpatient basis. As a result, although the incidence of diarrhea is usually high among the adverse events observed with 5'-DFUR, diarrhea of Grade 1 was observed only in 4 patients in the present study. Therefore, the occurrence of diarrhea is not problematic, and the patients were able to continue the treatment. The incidence (11.1%) of leukopenia of Grade 3 or higher was relatively low and the condition was improved quickly following treatment with G-CSF. There was no case of infection. The leukopenia and neutropenia observed in the present study did not result in postponement or cessation of the subsequent treatment cycle with TXT and 5'-DFUR, and there were no treatment-related deaths. Thus, the adverse reactions observed in the present study were controllable, and all patients were able to receive the chemotherapy on an outpatient basis.

In conclusion, because the efficacy of the combination regimen is high and adverse reactions to it are controllable, it was considered to be a useful therapy because it can be administered safely on an outpatient basis over a prolonged period of time to patients with advanced/recurrent gastric cancer who have undergone prior therapy. The combination regimen is considered to have a high potential for clinical use and merits investigation in further clinical studies.

References

- Diaz JF and Andreu JM (1993) Assembly of purified GOT-tubulin into microtubules induced by taxol and taxotere, reversibility, ligand stoichiometry and competition. **Biochemistry** 32, 2747-2755.
- Endo M, Shinbori N, Fukase Y, Sawada N, Ishikawa T, Ishituka T, and Tanaka Y (1999) Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5'-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. **Int J Cancer** 83, 127-134.
- Furukawa T, Yoshimura A, Sumizawa T, Haraguchi M, Akiyama S, Fukui K, Ishizawa M, and Yamada Y (1992) Angiogenic factor. **Nature** 356, 668.
- Glimelius B, Hoffman K, Haglund V, Nyren O and Sjoden PO (1994) Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. **Ann Oncol** 5, 189-190.
- Kusaba H, Mitsugi K, Nakano S, and Saijou N (1999) Problems and prospects for combined chemotherapy with 5-fluorouracil and low-dose cisplatin. **Jpn J Cancer Chemother** 26, 1575-1580.
- Mai M, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, Hirabayashi N, Taguchi T, and Furue H (1999) A late phase II clinical study of RP56976 (Docetaxel) in patients with advanced/recurrent gastric cancer, A Japanese cooperative study group trial (Group B). **Jpn J Cancer Chemother** 26, 487-496.
- Murad AM, Santiago FF, Petroiam A, Rocha PRS, Roderigues MAG and Rausch M (1993) Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. **Cancer** 72, 37-41.
- O'shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, and Leonard R (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer, phase III trial results. **J Clin Oncol** 20, 2812-2823.
- Pyrhonen S, Kuritunen T, Nyandoto P and Kouri M (1995) Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. **Br J Cancer** 71, 587-91.
- Saji S, Toge T, Kurosu Y, Hirata K, Gochi A, Tominaga S, and Inokuchi (2002) Interim report of JFMC study no. 23--phase III randomized clinical trial on the effectiveness of low-dose cisplatin plus 5-FU as a postoperative adjuvant chemotherapy for advanced gastric cancer. **Jpn J Cancer Chemother** 29, 2499-2507.
- Sasaki K, Hirata K, Denno R, Oikawa I, Mukaidani M, Hiraie K (1997) Combination chemotherapy of continuous infusion 5-fluorouracil and low-dose cisplatin in advanced gastrointestinal and lung adenocarcinoma. **Jpn J Cancer Chemother** 24, 959-964.
- Sato A, Shimada K, Nakamachi M, Ushio J, Yamamoto W, Kurihara M and Matsukawa M (2002) Effectiveness of doxifluridine (5'-DFUR)/doxitaaxel against advanced/recurrent gastric cancer showing resistance to various anticancer drug regimens. **Gastric Cancer** 5, 233-236.
- Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, and Ishituka H (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. **Clin Cancer Res** 4, 1013-1019.
- Taguchi T, Sakai K, Terasawa T, Irie K, Yamamoto M, Kawahara T, Satomi T, Tomita K, Yamaguchi A et al. (1985) Phase II study of 5'-DFUR (5'-deoxy-5-fluorouridine) by the Cooperative Study Group. **Jpn J Cancer Chemother** 12, 2179-2184.
- Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, and Hirabayashi N (1998) 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.
- Tominaga K, Nishimura R, Aoyama H, Iwase H, Mitsuyama S., Asaga T, and Kimura M (2001) A phase I study of docetaxel (TXT) and doxifluridine (5'-DFUR) combination therapy in patients with advanced and recurrent breast cancer. **Jpn J Cancer Chemother** 28, 965-972.
- Tsuji A, Morita S, Horimi T, Takazaki M, Takahashi I, and Shirasaka T (1999) Chemotherapy with low-dose CDDP and continuous 5-FU for the treatment of advanced gastric cancers. **Jpn J Cancer Chemother** 26, 933-938.



Dr. Hajime Kase