TS-1 as first-line therapy for gastric linitis plastica: historical control study

Tohru Sasaki, Wasaburo Koizumi, Satoshi Tanabe, Katsuhiko Higuchi, Norisuke Nakayama and Katsunori Saigenji

Gastric linitis plastica (LP) is usually found as an advanced gastric cancer and has a poor prognosis. No sufficiently effective chemotherapy has been reported. In recent years, TS-1 has yielded a high response rate for advanced gastric cancers and favorable treatment results have also been suggested for gastric LP. We retrospectively compared and discussed anti-tumor effects and survival time for 62 consecutive patients with unresectable gastric LP who underwent chemotherapy at Kitasato University East Hospital between November 1995 and December 2002. They were divided into two groups: 19 patients given chemotherapy including TS-1 as first-line therapy (TS-1 group), and 43 patients given chemotherapy mainly with 5-fluorouracil, cisplatin, methotrexate and mitomycin C (non-TS-1 group). The overall response was 57.9% [95% confidence interval (CI) 35.7–80.1%] in the TS-1 group, which was significantly greater than the 27.9% (95% CI 14.5–41.3%) of the non-TS-1 group ($P < 0.01$). The median survival time was 402 days (95% CI 251–553 days) in the TS-1 group, which was also significantly longer than the non-TS-1 group (213 days, 95% CI 165–261 days, $P < 0.01$). Neutropenia and febrile neutropenia of grade 3 or higher were observed in 21.1 and 5.2%, respectively, in the TS-1 group, which were lower than the values of 37.2 and 20.9% in the non-TS-1 group. We conclude that greater anti-tumor effects and longer survival time can be expected from chemotherapy including TS-1 for gastric LP compared with conventional chemotherapy. *Anti-Cancer Drugs* 17:581–586 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, **17**:581–586

Keywords: gastric cancer, linitis plastica, TS-1

Department of Gastroenterology, Kitasato University East Hospital, Kanagawa, Japan.

Correspondence to T. Sasaki, Department of Gastroenterology, Kitasato University East Hospital, Asamizodai 2-1-1, Sagamihara, Kanagawa 228-8520, Japan.
Tel: +81 042 748 9111; fax: +81 042 740 1881;
e-mail: tohrus@kitasato-u.ac.jp

Received 4 September 2005 **Accepted** 16 January 2006

Introduction

The term linitis plastica (LP) was first used by Brinton in 1865 [1], and later defined as a diffuse type of gastric cancer with a tendency to grow invasively and not form marginal ridges [2,3]. In most cases, LP is poorly differentiated and originates in the gastric fundal gland area, showing mainly extensive submucosal invasion without forming obvious concavities or recesses [3], and forming a 'leather bottle'-like appearance or giant folded walls. Marked lymph node metastasis, peritoneal metastasis and direct invasion into the gastrointestinal tract are present in many LP patients [4], but imaging diagnosis and histological diagnosis by biopsy are difficult, and it is often found as an advanced cancer with peritoneal metastasis at diagnosis. In the US, the diffuse type, especially the signet ring cell subtype gastric cancer, has tended to become more prevalent [5].

LP has a poor prognosis compared with other advanced cancers [6] and the 5-year survival rate is only 10–20% even in cases which are surgically treated [7]. Surgical treatment is often only palliative [4]. Yoshikawa, *et al.* reported that out of 223 cases, curative resections were performed in 65 cases and non-curative resections in 117 cases, with median survival times (MSTs) of 727 and 272 days, respectively, but the MST in the inoperable cases was 88 days [8]. In a report examining the efficacy of surgical treatments in 86 cases of LP by Hamy *et al.*, the 1-year survival rate was 50% and the 5-year survival rate was 10%, which suggested that satisfactory treatment results were not obtained [9]. With the extended operations (complete removal of top-left peritoneal viscera + Appleby surgery) advocated by Furukawa *et al.*, the 5-year survival rates at stage III and IV of LP were 40 and 5%, respectively, which did not lead to an obvious improvement in prognosis compared with the 5-year survival rates of 20 and 3% with traditional surgery [10]. Thus, LP is considered to be a clinical condition with a very poor prognosis among advanced cancers and not only surgical treatment, but also chemotherapy is considered to be important. Although there are few reports examining the efficacy of chemotherapy only for LP, in cases where 5-fluorouracil (5-FU) + cisplatin were administered as neoadjuvant chemotherapy [11] and surgical resection was performed later, gastric LP had a significantly poor prognosis compared with non-gastric LP, and the overall MST was approximately 6 months, while it was 16 months for non-gastric LP [12].

0959-4973

In a phase II study of 5-FU + cisplatin for advanced gastric cancer, the overall MST was approximately 9 months, while it was less than 6 months for LP [13]. In recent years, many new anti-tumor drugs have been developed. TS-1 is an oral fluorinated pyrimidine drug, and showed high response rates (35–53.6%) and high usefulness as monotherapy in phase I and II studies [14–17]. The report of Koizumi *et al.* indicated that TS-1 shows a high response rate (52.0%) for poorly differentiated adenocarcinomas [17], suggesting the efficacy of TS-1 for LP, which in most cases is a poorly differentiated adenocarcinoma. In this study, we compare LP cases in which chemotherapy including TS-1 was given as first-line therapy with LP cases given conventional chemotherapy as control and discuss the efficacy of TS-1 for LP.

Methods

Patient eligibility

The subjects were LP patients consecutively given chemotherapy at Kitasato University East Hospital between November 1995 and December 2002, meeting the following eligibility criteria: unresectable gastric LP (a diffuse type of gastric cancer [2,3]) identified as adenocarcinoma histologically, no prior treatment, 0–2 Eastern Clinical Oncology Group (ECOG) performance status (PS), sufficient organ function, oral intake possible and informed consent obtained.

Treatment methods

TS-1 group

We administered the dosage of TS-1 as approved in Japan. We calculated the dosages from the body surface area, and administered 80 mg/day to patients with areas of 1.25 m^2 or less, 100 mg/day to patients with areas of 1.25–1.5 m^2 and 120 mg/day to patients with areas of more than 1.5 m^2, divided into two daily doses. The course consisted of a 4-week administration period and a 2-week washout period, and treatment was repeated as long as progressive disease (PD) or serious adverse events did not occur. When we began to employ chemotherapy using cisplatin in combination with TS-1 from 2000, we administered the above doses of TS-1 for 3 weeks with a washout period of 2 weeks and cisplatin was administered once at a dose of 60 mg/m^2 on day 8.

Non-TS-1 group

As a control to compare the curative effects, LP patients given chemotherapy at the same time satisfying the above eligibility criteria were used as control cases. However, since TS-1 was marketed in 1999, the control cases included many cases before marketing of TS-1. Treatments included chemotherapy with 5-FU alone (F group; continuous 5-FU 800 mg/m^2, days 1–5), with methotrexate (MTX) + 5-FU + cisplatin (MFP group; bolus MTX 30 mg/m^2 and 5-FU 600 mg/m^2, days 1 and 8, and continuous low-dose cisplatin 6 mg/m^2, days 1–14) or with 5-FU + cisplatin + mitomycin C (MMC) (FMP group; continuous 5-FU 600 mg/m^2, days 1–5, MMC 6 mg/m^2, day 6, and cisplatin 60 mg/m^2, day 7 [18]) as first-line therapy. We determined the dosages and dosing periods based on protocols approved in Japan.

Evaluation

We determined the effects using computerized tomography (CT), gastroscopy and gastrography before and after treatment in all cases. We determined the curative effects based on the WHO standards [19] for metastatic foci. We also evaluated primary foci based on the General Rules for Gastric Cancer Studies of the Japanese Research Society for Gastric Cancer [20], because some cases of LP have no measurable lesion and so it is necessary to evaluate the primary foci for the determination of response in LP cases. With respect to ascites, we classified patients in whom ascites disappeared on CT as a 'partial response (PR)', patients with no marked change as 'no change (NC)' and patients who became worse as 'progressive disease (PD)'. We classified adverse events according to the 'Criteria for the evaluation of clinical effects of solid cancer chemotherapy' [21] prepared by the Japan Society for Cancer Chemotherapy based on the WHO standards [19].

Statistical

We compared patient characteristics using the χ^2-test. For MST and time to progression (TTP), we calculated cumulative survival curves by the Kaplan–Meier method and compared result by the generalized Wilcoxon test.

Results

Patient characteristics (Table 1)

Nineteen patients given chemotherapy including TS-1 as the first-line therapy (TS-1 group), included 11 men and eight women, and the median age was 60 years (range 27–74). The 43 controls (non-TS-1 group) consisted of 21 men and 22 women with a median age of 60 years (range 19–77). No significant difference was observed between the two groups. The PS was 0 in 11 cases, 1 in six cases and 2 in two cases in the TS-1 group, while the respective numbers were 14, 20 and nine in the non-TS-1 group. Although there were biases in the cases with worse PS in the non-TS-1 group compared with the TS-1 group, there was no significant difference between the two groups. In the TS-1 group, the histological types were diffuse type in 17 cases and intestinal type in two cases; in the non-TS-1 group, there were 41 and two cases, respectively. In both groups, most of them were diffuse type, but some intestinal cases were included. In patients with difficulty in eating due to pyloric obstruction, gastrojejunostomy was performed before chemotherapy to enable oral intake. There were two such cases in the TS-1 group and five in the non-TS-1 group.

Table 1 Patient characteristics

	TS-1	Non-TS-1	*P*
No. of patients (November 1995–December 2002)	19	43	
Sex (M/F)	11/8	21/22	0.97
Median age [years (range)]	60 (27–74)	60 (19–77)	0.37
PS (ECOG)			0.22
0	11	14	
1	6	20	
2	2	9	
Histological type			0.21
intestinal	2	2	
diffuse	17	41	
gastrojejunostomy	2	5	0.81
Chemotherapy	TS-1 alone 8 plus COOP 11	5-FU 4 FMP 14 MFP 25	

Table 2 Overall response

	TS-1		Non TS-1	
	CR/PR/NC/PD/NE	RR (95% CI)	CR/PR/NC/PD/NE	RR (95% CI)
Overall[a]	0/11/8/0/0	57.9 (35.7–80.1)	0/12/22/9/0	27.9 (14.5–41.3)
Target site				
primary	0/9/10/0/0	47.4	0/9/28/2/4	20.9
liver	0/1/0/0/0	100	0/3/1/0/0	75.0
lymph nodes	0/5/5/0/0	50.0	1/8/7/2/0	50.0
Ascites	0/4/4/0/0	50.0	0/3/15/4/0	13.6

NE, not evaluable; RR, response rate.
[a]$P < 0.01$.

Table 3 Adverse events

	TS-1		Non-TS-1	
	Total (%)	Grade ≤ 3 (%)	Total (%)	Grade ≤ 3 (%)
Hematological toxicities				
neutropenia	16 (84.2)	4 (21.1)	37 (86.0)	16 (37.2)
febrile neutropenia		1 (5.2)		9 (20.9)
anemia	11 (57.9)	1 (5.2)	33 (76.7)	2 (4.7)
thrombocytopenia	3 (15.8)	0 (0)	25 (58.1)	2 (4.7)
Non-hematological toxities				
Laboratory data				
AST	1 (5.2)	0 (0)	11 (25.6)	1 (2.3)
ALT	2 (10.5)	1 (5.2)	11 (25.6)	1 (2.3)
ALP	2 (10.5)	1 (0)	11 (25.6)	0 (0)
T.Bill	2 (10.5)	1 (0)	2 (4.7)	0 (0)
Cr	3 (15.8)	0 (0)	8 (18.6)	0 (0)
Others				
diarrhea	4 (21.1)	1 (5.2)	6 (14.0)	0 (0)
stomatitis	4 (21.1)	0 (0)	1 (4.7)	0 (0)
anorexia	7 (36.8)	1 (5.2)	12 (27.9)	0 (0)
nausea	8 (42.1)	0 (0)	23 (53.5)	0 (0)
pigmentation	3 (15.8)	0 (0)	2 (4.7)	0 (0)
eruption	2 (10.5)	0 (0)	5 (11.6)	0 (0)
hand–foot syndrome	0 (0)	0 (0)	1 (4.7)	0 (0)

In the TS-1 group, cisplatin was used in combination with TS-1 from 2000. Eight cases out of 19 cases were treated with TS-1 alone and 11 cases by a combination with cisplatin. In the non-TS-1 group, four cases were in the F group, 25 cases in the MFP group and 14 cases in the FMP group.

Response (Table 2)

The overall response in the TS-1 group was 57.9% [95% confidence interval (CI) 35.7–80.1%], which was higher than the 27.9% (95% CI 14.5–41.3%) in the non-TS-1 group ($P < 0.01$). The response rates by target site in the TS-1 group were 47.4, 100, 50.0 and 50.0% for primary foci, metastasis in the liver, lymph node metastasis and cancerous ascites, respectively, and 20.9, 75.0, 50.0 and 13.6%, respectively, in the non-TS-1 group.

Adverse events (Table 3)

As hematological toxicity, neutropenia was observed in 84.2% in the TS-1 group and 86.0% in the non-TS-1 group. Serious adverse events of grade 3 or more for neutropenia and febrile neutropenia were observed in 21.1 and 5.2% of the TS-1 group, and 37.2 and 20.9%, respectively, of the non-TS-1 group, showing fewer adverse events in the TS-1 group. There was no discontinuation of TS-1 due to hematological toxicity. Anemia and thrombocytopenia were observed in 57.9 and 15.8%, respectively, of the TS-1 group, and in 76.7 and 58.1%, respectively, of the non-TS-1 group. The only serious adverse events of grade 3 or more were anemia in one case in the TS-1 group and two cases in the non-TS-1 group.

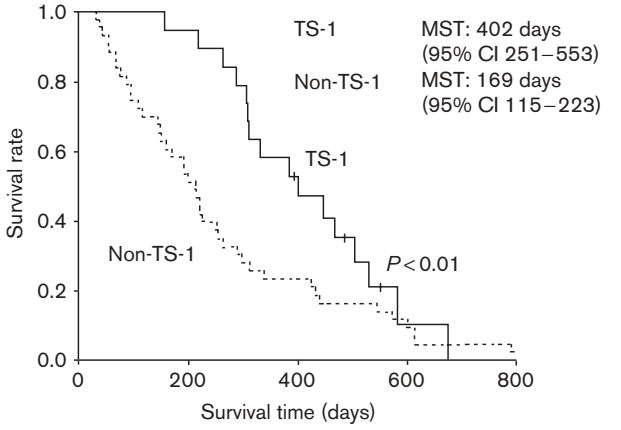
Non-hematological toxicity included hepatic dysfunction (increase in AST and increase in ALT) in a few cases in the TS-1 group (5.2 and 10.5%) and in 25.6% each in the non-TS-1 group. The hepatic dysfunction was improved by the discontinuation of drugs. Diarrhea and stomatitis, which are characteristic of 5-FU-type drugs, were each observed in 21.1% of the TS-1 group, and in 14.0 and 4.7%, respectively, of the non-TS-1 group. Serious diarrhea of grade 3 was observed in one case in the TS-1 group, but the symptoms were improved by the discontinuation of the drug and responded to medical treatment. Anorexia and nausea were observed at comparatively high percentages, 36.8 and 42.1%, respectively, of the TS-1 group, and in 27.9% and 53.5%, respectively, of the non-TS-1 group. Hand–foot syndrome was observed in one case in the non-TS-1 group, but the symptoms were mild. There were two cases of discontinuation of TS-1 due to adverse events in the TS-1 group (one case of drug-induced eruption and one case of diarrhea). There was no toxic death in any group.

Survival (Fig. 1)

With respect to overall survival, MST was 402 days (95% CI 251–553 days) in the TS-1 group, which was significantly longer than the 213 days (95% CI 165–261 days) in the non-TS-1 group ($P < 0.01$).

The 1-year survival rate was 52.6% in the TS-1 group and 23.2% in the non-TS-1 group. The TTP was 155 days

Fig. 1



Overall survival.

(95% CI 91–219 days) in the TS-1 group and 112 days (95% CI 53–148 days) in the non-TS-1 group ($P = 0.054$).

Discussion

We set out to determine whether TS-1 could show greater anti-tumor effect and longer survival in gastric LP compared with conventional chemotherapy. Chemotherapy for LP has consisted of the same regimens as many other unresectable advanced gastric cancers, but curative effects have not been satisfactory. Chemotherapy for conventional advanced cancers has been performed mainly using cytostatic drugs, such as 5-FU, cisplatin, MMC, MTX and doxorubicin, alone or in combination, and by administering them i.v. [22]. The response rates for monotherapy, however, were low (15–30%) [23–27] and although comparatively high response rates (40–73%) for combination therapy (FAM, FAMTX, FP and ECF) were reported [28–31], the MST remained at 5.5–10.6 months. Serious adverse events including myelosupression were observed and there has been no report showing efficacy for LP. In Japan, alternating treatment with MTX and 5-FU (MF) based on biochemical modulation was reported to be effective for poorly differentiated cancers in a phase II study [32]. Since Konishi *et al.* reported that the response rate of MF for poorly differentiated patients was 32.1% [33], MF has been mainly given for LP in our institution.

In recent years, new cytostatic drugs, such as irinotecan (CPT-11) [34], paclitaxel [35], docetaxel, oxaliplatin, capecitabine [36] and TS-1, have become available. TS-1, in particular, is suggested to be effective in poorly differentiated cases [17] and since it was reported that when TS-1 was used as a neoadjuvant chemotherapeutic agent for LP, curative resection was possible in three out of five cases (60%) [37].

TS-1 is an oral dihydropyrimidine dehydrogenase (DPD)-inhibiting fluoropyrimidine, which inhibits DPD, a metabolic enzyme of 5-FU, and maintains high 5-FU concentrations in tumor and blood [38,39]. In TS-1, 5-2,4-dihydroxypyrimidine (CHDP), a reversible competitive inhibitor of DPD, and oteracil potassium (Oxo), which reduces gastrointestinal disorders caused by 5-FU, are present in a molar ratio of FT:CDHP:Oxo = 1:0.4:1 to tegafur (FT), the pro-drug of 5-FU, with a remarkable oral absorption [14]. It is reported that TS-1 retains a high efficacy even in gastric cancer cell lines with high DPD activity, by the concomitant use of DPD [40]. In a study on 41 patients with gastric cancer administered TS-1, the MST of 18 DPD-positive cases was 338 days and that of 23 DPD-negative cases was 207 days ($P = 0.206$), which shows TS-1 was effective regardless of DPD activity [41]. In another report, although involving few patients, TS-1 showed efficacy in gastric cancer cases with high DPD activity [42]. The possibility that DPD activity is comparatively high in LP cases can be considered as a reason for the higher response rate and longer survival time in the TS-1 group. Although no conclusion on the relationship between TS activity or DPD activity of gastric cancer and curative effects and prognosis by 5-FU have been obtained [43], it is reported that DPD activity differs in differentiated and poorly differentiated adenocarcinomas, suggesting higher DPD activity in poorly differentiated adenocarcinoma [44]. The possibility of high DPD activity and poor prognosis was also suggested for poorly differentiated colorectal adenocarcinoma [45].

Measurements of TS and DPD activities in normal tissues and tumor tissues in LP and further investigations of sensitivity to TS-1 and survival time are required in the future. Another hypothesis is longer exposure to chemotherapy with oral continuous chemotherapy versus sequential chemotherapy. However, the infusional 5-FU regimens or capecitabine (used in a western standard ECF or ECX regimen) are also potentially active.

In this study, objective responses were not reviewed by an external expert committee and the interpretation of response is usually difficult for LP. Although the difference was not significant, worse PS in the non-TS-1 group was observed. In addition, the TS-1 group consisted of two regimens (TS-1 alone and in combination with cisplatin) because higher curative effects with a response rate of 73% was suggested in a phase II study during this investigation [46]. Therefore, the overall response rate and MST may be overestimated because of these potential biases.

In Japan, studies comparing 5-FU alone, CPT-11 + cisplatin and TS-1 alone TS-1 alone and 5-FU + leucovorin, TS-1 alone and TS-1 + irinotecan, TS-1 alone and TS-1 + taxotere, and TS-1 alone and TS-1 + cisplatin are

in progress as phase III studies, and TS-1 alone or combination therapies with TS-1 may become standard treatments for unresectable advanced gastric cancers depending on the results. Higher anti-tumor effects and longer survival time are also expected with chemotherapy including TS-1 for gastric LP with a poor prognosis compared with conventional chemotherapy. It is necessary to conduct a prospective randomized study of TS-1 for LP and to determine the most effective first-line therapy for LP in the future.

Conclusion

TS-1 as first-line chemotherapy for gastric LP showed an overall response of 57.9% and a median survival time of 402 days, which were significantly greater and longer compared with 27.9% and 213 days in conventional chemotherapy. Furthermore, adverse events were fewer in TS-1-treated patients. Although several potential biases were considered, greater anti-tumor effects and longer survival time can be anticipated from chemotherapy including TS-1 for gastric LP compared with conventional chemotherapy.

Acknowledgments

The authors are indebted to Professor J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this manuscript.

References

1 Barwick KW. Linitis plastica: one disease or more? *J Clin Gastroenterol* 1982; **4**:70–72.
2 Lauren P. The two main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**:31–49.
3 Ming SC. Gastric carcinoma: a pathobiological classification. *Cancer* 1977; **39**:2475–2485.
4 Aranha GV, Georgen R. Gastric linitis plastica is not a surgical disease. *Surgery* 1989; **106**:758–62; discussion 762–763.
5 Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973–2000: increase in the signet ring cell type. *Arch Pathol Lab Med* 2004; **128**:765–770.
6 Yokota T, Teshima S, Saito T, Kikuchi S, Kunii Y, Yamauchi H. Borrmann's type IV gastric cancer: clinicopathologic analysis. *Can J Surg* 1999; **42**:371–376.
7 Bollschweiler E, Boettcher K, Hoelscher AH, Sasako M, Kinoshita T, Maruyama K, *et al.* Is the prognosis for Japanese and German patients with gastric cancer really different? *Cancer* 1993; **71**:2918–2925.
8 Yoshikawa T, Tsuburaya A, Kobayashi O, Sairenji M, Motohashi H, Noguchi Y. Should scirrhous gastric carcinoma be treated surgically? Clinical experiences with 233 cases and a retrospective analysis of prognosticators. *Hepatogastroenterology* 2001; **48**:1509–1512.
9 Hamy A, Letessier E, Bizouarn P, Paineau J, Aillet G, Mirallie E, *et al.* Study of survival and prognostic factors in patients undergoing resection for gastric linitis plastica: a review of 86 cases. *Int Surg* 1999; **84**:337–343.
10 Furukawa H, Hiratsuka M, Iwanaga T, Imaoka S, Ishikawa O, Kabuto T, *et al.* Extended surgery – left upper abdominal exenteration plus Appleby's method – for type 4 gastric carcinoma. *Ann Surg Oncol* 1997; **4**:209–214.
11 Rougier P, Lasser P, Ducreux M, Mahjoubi M, Bognel C, Elias D. Preoperative chemotherapy of locally advanced gastric cancer. *Ann Oncol* 1994; **5**(**Suppl 3**):59–68.
12 Rougier P, Mahjoubi M, Lasser P, Ducreux M, Oliveira J, Ychou M, *et al.* Neoadjuvant chemotherapy in locally advanced gastric carcinoma – a phase II trial with combined continuous intravenous 5-fluorouracil and bolus cisplatinum. *Eur J Cancer* 1994; **30A**:1269–1275.
13 Rougier P, Ducreux M, Mahjoubi M, Pignon JP, Bellefqih S, Oliveira J, *et al.* Efficacy of combined 5-fluorouracil and cisplatinum in advanced gastric carcinomas. A phase II trial with prognostic factor analysis. *Eur J Cancer* 1994; **30A**:1263–129.
14 Taguchi T, Inuyama Y, Kanamaru R, Hasegawa K, Akazawa S, Niitani H, *et al.* Phase I study of S-1. S-1 Study Group. *Gan To Kagaku Ryoho* 1997; **24**:2253–2264.
15 Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y, *et al.* An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. The S-1 Gastrointestinal Cancer Study Group. *Oncology* 1999; **57**:202–210.
16 Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, 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* 1998; **34**:1715–1720.
17 Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. *Oncology* 2000; **58**:191–197.
18 Koizumi W, Tanabe S, Kurihara M, Kondou I, Yamazaki I, Saigenji K. Pilot study of combined treatment with continuous infusion of 5-fluorouracil, mitomycin C, and cisplatin (FMP) in patients with inoperable advanced gastric cancer. *Oncol Rep* 1999; **6**:643–646.
19 WHO.*Handbook for reporting results of cancer treatment*. Geneva: WHO; 1979.
20 Japanese Research Society for Gastric Cancer. *Japanese classification of gastric carcinoma*. Tokyo: Kanehara; 1995.
21 Japanese Society for Cancer Therapy. Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. *J Jpn Soc Cancer Chemother* 1993; **28**:101–130.
22 Ajani JA, Ota DM, Jackson DE. Current strategies in the management of locoregional and metastatic gastric carcinoma. *Cancer* 1991; **67**(**1 Suppl**):260–265.
23 Moynihan T, Hansen R, Anderson T, Quebbeman E, Beatty P, Ausman R, *et al.* Continuous 5-fluorouracil infusion in advanced gastric carcinoma. *Am J Clin Oncol* 1988; **11**:461–464.
24 Kaufman S. 5-Fluorouracil in the treatment of gastrointestinal neoplasia. *N Engl J Med* 1973; **288**:199–201.
25 Schein PS, Macdonald JS, Hoth D, Wooley PV. Mitomycin C: experience in the United States, with emphasis on gastric cancer. *Cancer Chemother Pharmacol* 1978; **1**:73–75.
26 Moertel CG, Lavin PT. Phase II–III chemotherapy studies in advanced gastric cancer. Eastern Cooperative Oncology Group. *Cancer Treat Rep* 1979; **63**:1863–1869.
27 Lacave AJ, Wils J, Diaz-Rubio E, Clavel M, Planting A, Bleiberg H, *et al.* *cis*-Platinum as second-line chemotherapy in advanced gastric adenocarcinoma. A phase II study of the EORTC Gastrointestinal Tract Cancer Cooperative Group. *Eur J Cancer Clin Oncol* 1985; **21**: 1321–1324.
28 MacDonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, *et al.* 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980; **93**: 533–536.
29 Wils J, Bleiberg H, Dalesio O, Duez N, Blijham G, Planting A, *et al.* An EORTC Gastrointestinal Group evaluation of the combination of sequential methotrexate and 5-fluorouracil, combined with adriamycin in advanced measurable gastric cancer. *J Clin Oncol* 1986; **4**:1799–1803.
30 Lacave AJ, Baron FJ, Anton LM, Estrada E, De Sande LM, Palacio I, *et al.* Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. *Ann Oncol* 1991; **2**:751–754.
31 Findlay M, Cunningham D, Norman A, Mansi J, Nicolson M, Hickish T, *et al.* A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). *Ann Oncol* 1994; **5**:609–616.
32 Murakami M, Ota K, Miyazaki T, Niitsu Y, Wakui A, Yokoyama M, *et al.* Sequential methotrexate-5-fluorouracil (MTX-5-FU) treatment of patients with advanced gastric and colorectal cancer. Sequential Methotrexate-5-FU Study Group. *Gan To Kagaku Ryoho* 1987; **14**:2482–2490.
33 Konishi T, Hiraishi M, Mafune K, Miyama T, Hirata T, Mori K, *et al.* Therapeutic efficacy and toxicity of sequential methotrexate and 5-fluorouracil in gastric cancer. *Anticancer Res* 1994; **14**(**3B**):1277–1279.
34 Koizumi W, Kurihara M, Satoh A, Takiuchi H, Tanabe S, Shimada K, *et al.* Phase 1/11 study of bi-weekly irinotecan plus cisplatin in the treatment of advanced gastric cancer. *Anticancer Res* 2005; **25**(**2B**):1257–1262.

35 Ohtsu A, Boku N, Tamura F, Muro K, Shimada Y, Saigenji K, *et al.* An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. *Am J Clin Oncol* 1998; **21**:416–419.
36 Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, *et al.* Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol* 2005; **23**: 5660–5667.
37 Kinoshita T, Konishi M, Nakagohri T, Inoue K, Oda T, Takahashi S, *et al.* Neoadjuvant chemotherapy with S-1 for scirrhous gastric cancer: a pilot study. *Gastric Cancer* 2003; **6**(**Suppl 1**):40–44.
38 Diasio RB. Oral DPD-inhibitory fluoropyrimidine drugs. *Oncology (Huntingt)* 2000; **14**(**10 Suppl 9**):19–23.
39 Schmoll HJ. Dihydropyrimidine dehydrogenase inhibition as a strategy for the oral administration of 5-fluorouracil: utility in the treatment of advanced colorectal cancer. *Anticancer Drugs* 2003; **14**:695–702.
40 Fujiwara H, Terashima M, Irinoda T, Takagane A, Abe K, Nakaya T, *et al.* Superior antitumour activity of S-1 in tumours with a high dihydropyrimidine dehydrogenase activity. *Eur J Cancer* 2003; **39**:2387–2394.
41 Miyamoto S, Boku N, Ohtsu A, Yoshida S, Ochiai A, Okabe H, *et al.* Clinical implications of immunoreactivity of thymidylate synthase and dihydropyrimidine dehydrogenase in gastric cancer treated with oral fluoropyrimidine (S-1). Study Group of S-1 for Gastric Cancer. *Int J Oncol* 2000; **17**:653–658.
42 Usuki H, Ishimura K, Yachida S, Hagiike M, Okano K, Izuishi K, *et al.* Dihydropyrimidine dehydrogenase (DPD) activity in gastric cancer tissue and effect of DPD inhibitory fluoropyrimidines. *Gastric Cancer* 2003; **6**(**Suppl 1**):66–70.
43 Miyamoto S, Ochiai A, Boku N, Ohtsu A, Tahara M, Yoshida S, *et al.* Discrepancies between the gene expression, protein expression, and enzymatic activity of thymidylate synthase and dihydropyrimidine dehydrogenase in human gastrointestinal cancers and adjacent normal mucosa. *Int J Oncol* 2001; **18**:705–713.
44 Nakata B, Muguruma K, Yamagata S, Yukimoto K, Maeda K, Nishiguchi Y, *et al.* Differences in dihydropyrimidine dehydrogenase activities between gastric and colorectal cancer. *Dig Dis Sci* 2004; **49**:60–64.
45 Ochiai T, Sugitani M, Nishimura K, Noguchi H, Watanabe T, Sengoku H, *et al.* Correlation between clinical pathophysiologic factors and expression of orotate phosphoribosyl transferase (OPRT), thymidylate synthase (TS), and dihydropyrimidine dehydrogenase (DPD) in colorectal cancer. *Gan To Kagaku Ryoho* 2002; **29**:413–420.
46 Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, *et al.* Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2003; **89**:2207–2212.