Randomized clinical trial

Randomized controlled trial of adjuvant uracil–tegafur *versus* surgery alone for serosa-negative, locally advanced gastric cancer

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Background: This prospective randomized study compared the survival of patients with tumour node metastasis (TNM) stage T2 N1–2 gastric cancer treated by gastrectomy alone or gastrectomy followed by uracil–tegafur.

Methods: Patients were randomly assigned to surgery alone or to surgery and postoperative uracil–tegafur 360 mg per m^2 per day orally for 16 months. The primary endpoint was overall survival. Relapse-free survival and site of recurrence were secondary endpoints.

Results: Of 190 registered patients, 95 were randomized to each group; two patients with early cancer were subsequently excluded from the chemotherapy group. The trial was terminated before the target number of patients was reached because accrual was slower than expected. Drug-related adverse effects were mild, with no treatment-related deaths. At a median follow-up of 6·2 years, overall and relapse-free survival rates were significantly higher in the chemotherapy group (hazard ratio for overall survival 0·48, $P = 0·017$; hazard ratio for relapse-free survival 0·44, $P = 0·005$), confirming the survival benefit shown in an interim analysis performed 2 years earlier.

Conclusion: Interim and final analyses revealed a significant survival benefit for postoperative adjuvant chemotherapy with uracil–tegafur in patients with serosa-negative, node-positive gastric cancer. Registration number: NCT00152243 (http://www.clinicaltrials.gov).

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Introduction

Although recent meta-analyses have suggested that adjuvant chemotherapy provides a significant survival benefit after curative gastrectomy in patients with locally advanced gastric cancer[1–8], few individual trials have demonstrated this. Trials of adjuvant chemotherapy have suggested that future studies would require appropriate selection of the target population and intensive dosage regimens based on evidence[9]. After several multicentre clinical trials had produced negative results[10–26], the present authors designed a new dose escalation study with a simple regimen of uracil–tegafur in a well defined target population.

Most previous studies used uracil–tegafur in an adjuvant context in combination with other drugs. The daily dose was generally 300–400 mg (188–250 mg/m^2), lower than

The Editors have satisfied themselves that all authors have contributed significantly to this publication

that recommended as monotherapy, to ensure safety[25]. Studies with multiple drug regimens have generally shown negative or marginal survival benefits, although a trial in patients with moderately locally advanced gastric cancer of tumour node metastasis (TNM) stage T2 N1–2 demonstrated better survival after adjuvant chemotherapy with uracil–tegafur and mitomycin C than surgery alone[25].

In 1997, the National Surgical Adjuvant Study Group decided to perform large, simple clinical trials of uracil–tegafur monotherapy with intensive dosage regimens in breast, colorectal and gastric cancer. In accordance with the standard dose of uracil–tegafur for advanced gastric cancer[27] (response rate 27·5 per cent), 360 mg per m^2 per day was used for 5 days, followed by 2 days of rest, for 16 months. The total dose of uracil–tegafur with this regimen was almost identical to that used for conventional multiple drug regimens (210 mg/m^2 daily for 18 months). In the present study this regimen alone was used in a well defined subset of patients who had undergone curative gastrectomy.

Table 1 Characteristics of the 188 patients

	Chemotherapy ($n = 93$)	Control ($n = 95$)
Sex ratio (M : F)	70 : 23	73 : 22
Median age (years)	63	64
Depth of tumour invasion (pT2)		
Muscularis propria	49	46
Subserosa	44	49
Lymph node metastasis*		
n1	69	72
n2	24	23
Type of gastrectomy		
Total	34	26
Distal	59	67
Proximal	0	2
Lymph node dissection*		
D2	80	80
D3	7	8
D4	6	7

*Japanese Classification of Gastric Carcinoma[29].

Methods

Eligible patients with T2 N1–2 gastric cancer who had undergone curative gastrectomy and extended lymph node (D2) dissection (complete (R0) resection) were randomly assigned to control or chemotherapy groups within 6 weeks of surgery. A dynamic allocation technique (modified minimization technique) was used for randomization at a central registration centre, with N stage (N1 or N2) and institution as adjustment variables. Random allocation was strictly controlled by an independent National Surgical Adjuvant Study Group Data Centre, and institutional data monitoring was carried out to avoid investigator-related bias.

Within 6 weeks of surgery, patients allocated to the chemotherapy group received an oral daily dose of

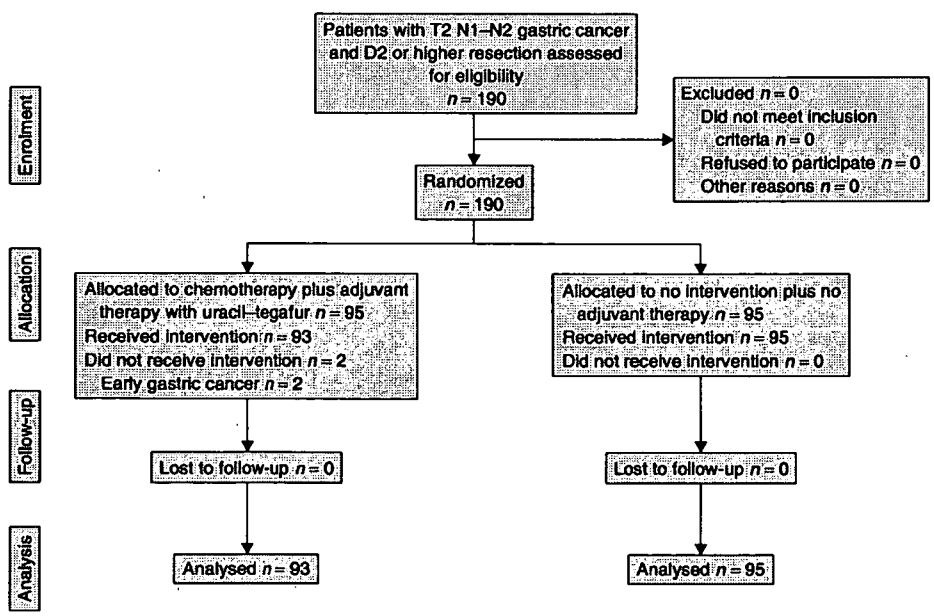

Fig. 1 CONSORT flow chart

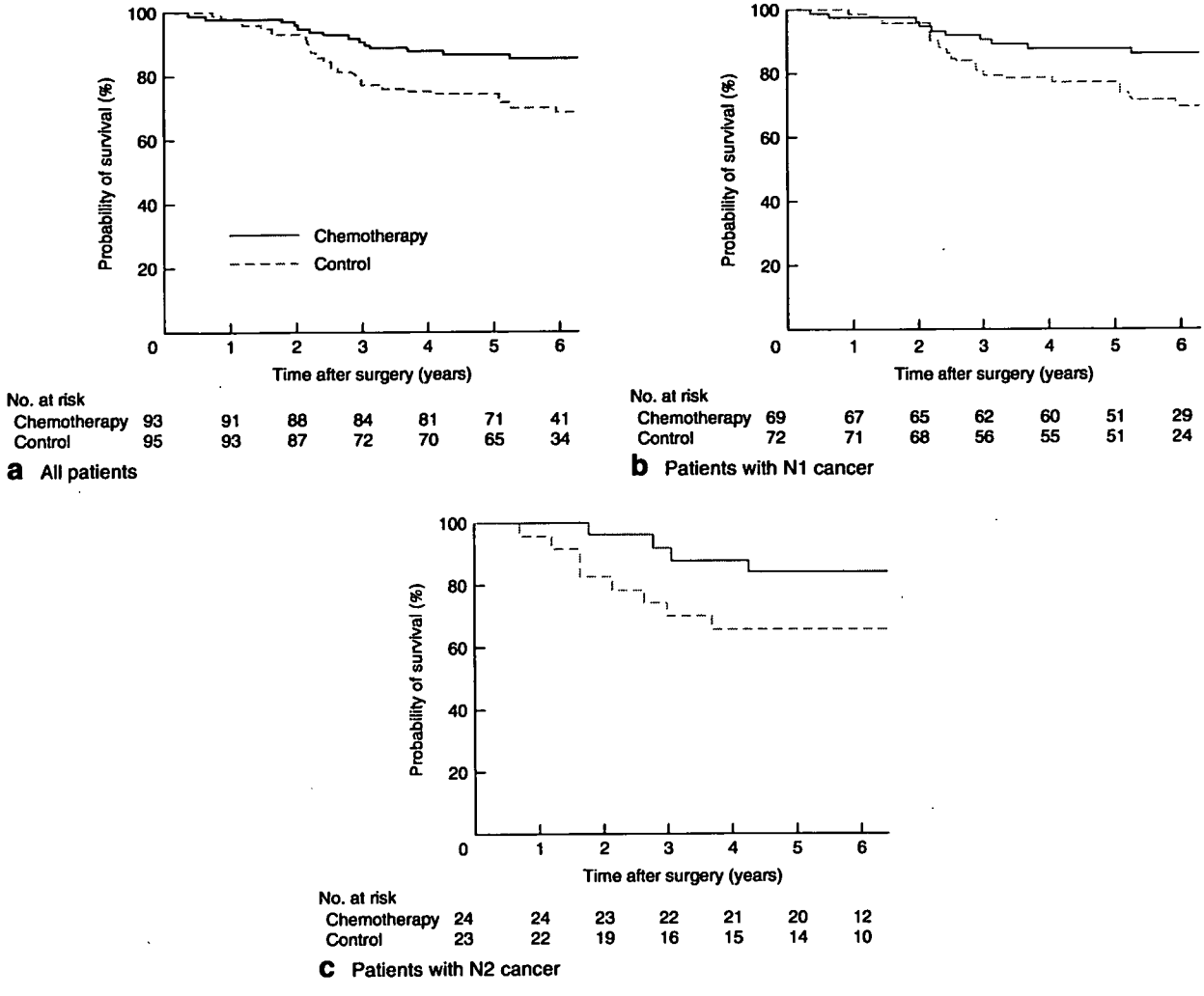

Fig. 2 Overall survival in **a** all 188 eligible patients, **b** 141 patients with N1 cancer and **c** 47 patients with N2 cancer. **a** $P = 0{\cdot}017$, **b** $P = 0{\cdot}061$, **c** $P = 0{\cdot}124$ (stratified log rank test)

uracil–tegafur of 360 mg/m^2 for 5 days every week for 16 months. Patients allocated to the control group were followed up with no adjuvant chemotherapy. Eligibility criteria included histologically proven adenocarcinoma of the stomach, curative gastrectomy with D2 or greater lymph node dissection, pathological T2 N1–2 gastric cancer, an Eastern Cooperative Oncology Group performance status of 0–2, age between 20 and 75 years, no previous chemotherapy and adequate organ function (leucocyte count over 4000 per mm^3, platelet count above 100 000 per mm^3, aspartate and alanine aminotransferase levels lower than twice the upper limit of normal (ULN) at the centre performing the test, total bilirubin concentration less than 1·5 times the ULN, blood urea nitrogen level less than 1·5 times the ULN, and creatinine concentration less than 1·5 times the ULN). Written informed consent was obtained from all patients after approval of the Institutional Review Board at each participating centre.

Statistical analysis

The primary endpoint of the trial was overall survival. Secondary endpoints were relapse-free survival and site of relapse. Overall and relapse-free survival rates were calculated using the Kaplan–Meier method. *P* values were derived with the stratified log rank test according to N stage. Hazard ratios (HRs) were calculated by Cox regression analysis using N stage as a co-variate.

Table 2 Adverse events

	Chemotherapy (n = 92)*		Control (n = 94)*	
	Grade 3†	Grade 4†	Grade 3†	Grade 4†
All events	29 of 92 (32)	1 of 92 (1)	4 of 94 (4)	0 of 94 (0)
Neutropenia	11 of 83 (13)	0 of 83 (0)	0 of 78 (0)	0 of 78 (0)
Anaemia	1 of 91 (1)	0 of 91 (0)	0 of 92 (0)	0 of 92 (0)
Raised AST level	1 of 91 (1)	0 of 91 (0)	2 of 92 (2)	0 of 92 (0)
Raised ALT level	2 of 91 (2)	0 of 91 (0)	2 of 92 (2)	0 of 92 (0)
Hyperbilirubinemia‡	8 of 89 (9)	0 of 89 (0)	2 of 90 (2)	0 of 90 (0)
Nausea/vomiting	1 of 92 (1)	0 of 92 (0)	0 of 94 (0)	0 of 94 (0)
Diarrhoea	1 of 92 (1)	1 of 92 (1)	0 of 94 (0)	0 of 94 (0)
Infection	1 of 92 (1)	0 of 92 (0)	0 of 94 (0)	0 of 94 (0)
Anorexia	6 of 92 (7)	0 of 92 (0)	0 of 94 (0)	0 of 94 (0)
Rash	1 of 92 (1)	0 of 92 (0)	0 of 94 (0)	0 of 94 (0)

Values in parentheses are percentages. *One patient excluded from chemotherapy group for refusal of drug administration, and one from control group at patient's request. †Japan Clinical Oncology Group criteria[28]. ‡More than twice the upper limit of normal. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

The 5-year overall survival rate of this patient subset (T2 N1–2) was 70 per cent in a previous study[25], and a 33 per cent reduction in the HR was expected (corresponding to a 5-year overall survival rate of 78·8 per cent). The necessary sample size was 244 patients per group, assuming a 3-year accrual period and 5-year follow-up, with a statistical power of 80 per cent to achieve a one-sided significance level of 0·050. The accrual goal was 500 patients. All analyses were based on intention-to-treat groups.

An Independent Data Monitoring Committee (IDMC) monitored the trial. Two interim analyses were originally planned, 1 and 3 years after all patients had been enrolled. Significance levels were set at 0·005 and 0·020 (one-sided) respectively. After closing the registration, the IDMC decided to undertake a single interim analysis at 2 years, owing to a lower rate of accrual than anticipated. When this interim analysis revealed a difference in survival rates between the two groups, the IDMC did not disclose this finding to investigators. Second interim and final analyses were then undertaken as originally planned at 3 and 5 years. Adverse events were evaluated using the toxicity grading criteria of the Japan Clinical Oncology Group[28].

Multivariable analysis was carried out with a Cox proportional hazards model to identify independent prognostic factors using treatment group, sex, age group, depth of invasion and extent of lymph node metastasis as explanatory variables.

Results

As accrual was slower than expected, recruitment of patients was terminated midway through the trial before the target number of patients was reached. Between June 1997 and March 2001, 190 patients were enrolled in the study, 95 randomized to the chemotherapy group and 95 to the control group. Two patients were ineligible after randomization and were excluded from the analysis because the final pathological report revealed early gastric cancer. Thus, 188 patients, 93 in the chemotherapy and 95 in the control group, were included in the intention-to-treat analysis (*Fig. 1*).

Clinical characteristics of the 188 patients are shown in *Table 1*. All major prognostic factors were similar in the two groups.

Of patients in the chemotherapy group with no recurrence, 80 per cent (73 of 91) received all scheduled doses of uracil–tegafur during the first 3 months, and 51 per cent (44 of 86) did so for 16 months. Two patients were withdrawn from treatment as a result of recurrence during the first 3 months, and seven for recurrence by 16 months.

Adverse events during follow-up are shown in *Table 2*. The main events in the chemotherapy group were bone marrow suppression (grade 3 neutropenia, 13 per cent), liver dysfunction (grade 3 hyperbilirubinaemia, 9 per cent) and gastrointestinal dysfunction (grade 3 anorexia, 7 per cent). Grade 4 diarrhoea occurred in one patient in the chemotherapy group.

At the 2-year interim analysis conducted in December 2003, both overall and relapse-free survival rates were significantly better in the chemotherapy group. The second interim analysis was conducted in November 2004 after a median follow-up of 3·8 years (3 years after registration

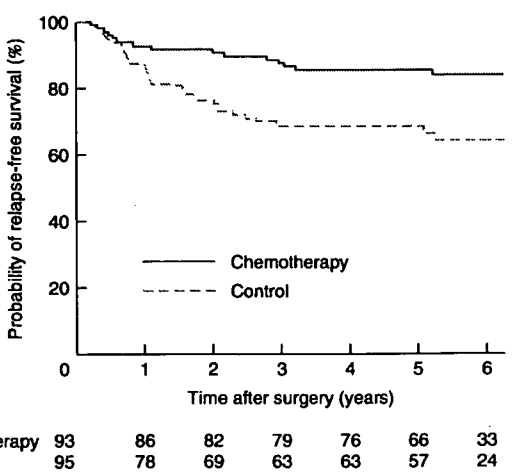

Fig. 3 Relapse-free survival in patients in the chemotherapy group compared with that in the control group. $P = 0·005$ (log rank test)

Table 3 First site of relapse

	Chemotherapy ($n = 93$)	Control ($n = 95$)	P^*
Peritoneal	4	3	0·680
Local	0	4	0·050
Haematogenous	9	14	0·290
Distant lymph nodes	2	11	0·010
Total no. of relapses	13	28	

Some patients had more than one type of recurrence. *χ^2 test.

was closed). Survival rates remained significantly better in the chemotherapy group (HR 0·46, 13 per cent difference in survival at 4 years).

These survival benefits were confirmed by the final analysis, performed after a median follow-up of 6·2 years after surgery (5 years after registration was closed). The 5-year overall survival rate was 86 per cent in the chemotherapy group and 73 per cent in the control group ($P = 0·017$) (*Fig. 2a*). The HR for overall survival in the chemotherapy group relative to the control group was 0·48 (95 per cent confidence interval (c.i.) 0·26 to 0·89). *Figs 2b* and *2c* show the results of a planned subset analysis of overall survival according to N1 (HR 0·52 (95 per cent c.i. 0·26 to 1·05); $P = 0·061$) and N2 (HR 0·40 (95 per cent c.i. 0·12 to 1·34); $P = 0·124$) status. The results of a similar analysis of 5-year relapse-free survival in chemotherapy and control groups are shown in *Fig. 3* (85 *versus* 68 per cent respectively; HR 0·44 (95 per cent c.i. 0·25 to 0·79); $P = 0·005$).

Multivariable analysis showed that treatment group ($P = 0·021$) and sex ($P = 0·032$) were significant independent prognostic factors, whereas the other three explanatory variables were not (age group, $P = 0·918$; depth of cancer invasion, $P = 0·539$; extent of lymph node metastasis, $P = 0·996$).

All causes of death included 13 recurrences in the chemotherapy group, 28 in the control group, two deaths from other cancers in the chemotherapy group, and one death unrelated to disease (traffic accident) and one for unknown reasons in the control group.

Table 3 shows the first sites of relapse in the two groups. The most common type of relapse was haematogenous metastasis to the liver. Patients in the chemotherapy group had a lower incidence of nodal metastatic recurrence.

Discussion

Both the second interim analysis after a median follow-up of 3·8 years and the final analysis after a median of 6·2 years showed a significant survival benefit for patients with T2 N1–2 gastric cancer following curative D2 gastrectomy and adjuvant chemotherapy with uracil–tegafur. Previous studies of adjuvant chemotherapy have not shown such a significant benefit[30–32].

Kato and colleagues[33] first reported the survival benefit of adjuvant uracil–tegafur alone in non-small cell lung cancer after curative surgery. Uracil–tegafur is widely used in Japan, but not in other countries. This is the first report to document a significant survival benefit for adjuvant uracil–tegafur in patients with gastric cancer.

The unexpectedly large difference in survival between the groups is a cause for concern. Such a significant finding was unexpected because the number of patients was much smaller than planned. Slow accrual might have been due partly to a lack of enthusiasm among investigators for the use of uracil–tegafur, on the basis of earlier trials. Some eligible patients might have been enrolled in other concurrent trials with similar eligibility criteria. Although some institutional selection bias may have been present, this was not reflected in the allocation of registered patients. The interim analysis unexpectedly revealed a HR of 0·46, corresponding to a 13 per cent difference in 4-year overall survival rate, at a median follow-up of 3·8 years, reaching the predefined significance level. The survival difference continued for more than 5 years after surgery and was confirmed at the final analysis, after a median follow-up of 6·2 years.

The large reductions in HR for overall and relapse-free survival may be attributable to several factors. One is the difference in the clinical stage of disease between the patients in this and earlier studies conducted by this group[25,26]. Patients in the present study had T2 N1–2 gastric cancer, whereas the authors' previous study included patients with T1 and T2 N1–2 disease. The exclusion of T1 cancer from the present study resulted in poorer 5-year overall survival in the control group than in the earlier trial, but almost no change in overall survival in the chemotherapy group, resulting in a significant survival difference. The difference in survival may therefore have been attributable to better patient selection, a higher dosage of uracil–tegafur than used in previous regimens[25] and a long duration of treatment.

A second concern was whether the survival difference actually resulted from the chemotherapy. Small numbers of patients per centre might theoretically bias the allocation of patients to treatment, but there was no evidence of this. Treatment allocation was strictly controlled by an independent data centre, minimizing the possibility of bias related to centre or investigator. The clinical characteristics of both chemotherapy and control groups were similar, and only two patients (1·1 per cent) were excluded from

analysis because of protocol violations (early cancer). The rate of compliance with treatment was 80 per cent during the first 3 months of chemotherapy and 51 per cent at the end of the study, despite the long treatment period. Lower compliance at the end of the study was due to adverse events, patient refusal or loss to follow-up. Compliance rates were consistent with those of other recent trials[33–37].

The cause of death was established in most patients. The incidence of distant lymph node relapse was significantly lower in the chemotherapy group, suggesting that after D2 dissection adjuvant chemotherapy might have inhibited the growth of minimal residual tumour in distant nodes. On subset analysis according to N1 and N2 status, the survivals of patients in the chemotherapy groups were almost identical, and the larger difference, though not statistically significant, in survival rate in patients with N2 disease might have resulted from a higher rate of residual cancer in distant nodes after D2 surgery than in those with N1 disease. No differences were observed in other types of relapse, such as liver or peritoneal metastasis. Multivariable analysis showed that treatment group and sex were significant independent prognostic factors, providing further evidence that the survival benefit was derived from adjuvant chemotherapy.

Although not widely used in Western countries until recently, adjuvant uracil–tegafur treatment appears to be effective in other cancers[34–36]. The survival benefit achieved with oral uracil–tegafur plus leucovorin is similar to that with intravenous 5-fluorouracil and leucovorin, but with less toxicity, in colorectal cancer. Adjuvant chemotherapy with uracil–tegafur alone is effective in patients with non-small cell lung[33] and rectal[38] cancer. Apart from direct cytocidal activity, low-dose chemotherapy with uracil–tegafur has been shown experimentally to have antiangiogenic effects on endothelial cells[39]. This could also influence survival.

In the present trial, the main side-effect associated with uracil–tegafur alone was moderate myelosuppression. Uracil–tegafur alone is associated with milder side-effects than when combined with leucovorin[35,36]. The advantages of survival benefit, mild toxicity and ease of administration on an outpatient basis make this an attractive approach. It was on this basis that a further large-scale clinical trial was recently undertaken in Japan using adjuvant S-1, a successor to uracil–tegafur that is anticipated to be more effective[40].

Patient selection is important in the context of adjuvant chemotherapy trials. It seems unreasonable to assume that a given regimen of adjuvant chemotherapy will be effective for all stages of disease. Conversely, selected groups of patients might benefit in terms of survival. Similarly, the quality of surgery may also be important. D2 gastrectomy for patients in the present trial carried only a small risk of stage misclassification.

Whether the present results can be extrapolated to other countries is important. Provided that D2 gastrectomy can be performed with a high level of reliability and low perioperative mortality, these results should be reproducible, because the outcomes of adjuvant chemotherapy appear to depend largely on the amount of residual tumour and the quality of surgery[41]. Macdonald and colleagues[37] in the USA reported encouraging results for adjuvant chemoradiotherapy in patients who had undergone curative gastrectomy. Their results may be representative as well as reproducible in that country, where D2 lymph node dissection is not performed routinely. Inadequate surgery might have resulted in large amounts of residual tumour in that trial. Adjuvant chemoradiotherapy may have suppressed locoregional relapse, thereby compensating for inadequate lymph node dissection. Although there is no evidence to support the superiority of D2 over D1 (limited lymph node dissection) or D0 (local) resection[42], many Japanese studies, as well as some reports from high-volume centres in Western countries, suggest that extended lymphadenectomy enhances postoperative survival[43,44]. The regimen for adjuvant therapy with uracil–tegafur might produce different outcomes under different surgical resection standards.

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Original Paper

Phase II Study of 2-Week TS1 Administration followed by 1-Week Rest for Gastric Cancer

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ABSTRACT

Background/Aims: TS-1 monotherapy with 4-week administration followed by 2-week rest is used as the community standard treatment for metastatic gastric cancer in Japan. However, according to a post-marketing survey, the percentage of patients who received three or more courses was only 44.6%; for the reasons of discontinuation due to exacerbation of symptoms or adverse reactions during the first or second course. Therefore, we conducted the phase II study of 2-weeks administration with TS-1 followed by a 1-week rest against metastatic gastric cancer, aiming for mitigation of adverse reactions without reduction of antitumor effect.

Methodology: Thirty-five patients were enrolled between 2001 and 2003 at nine institutes in Japan. One cycle of TS-1 treatment whose dosage was 80mg/m²/day consisted of administration for 2 weeks followed by a 1-week rest. The primary endpoint was overall response rate and the secondary endpoints were safety and feasibility.

Results: There were 6 PRs, 13 NCs, 11 PDs, and 5 patients were not evaluable (NE), yielding a response rate of 17%. The median survival time of all patients was 290 days. Severe adverse Grade 3 or 4 reactions were observed in 8 (23%) patients. The rate of patients who received six or more courses was 43%. The cumulative rate of the relative total administration days was 93%.

Conclusions: We concluded that the schedule of TS-1 administration for 2 weeks followed by a 1-week rest might not be superior to the conventional schedule (4 weeks on and 2 weeks off) with regard to the antitumor effect, adverse reactions and prolonged medication, although it was acceptable from the point of survival view.

KEY WORDS: TS-1; Gastric cancer; 2 weeks followed by a 1-week rest

ABBREVIATIONS: Eastern Clinical Oncology Group (ECOG); Not Evaluable (NE); Computed Tomography (CT); Body Surface Area (BSA); No Change (NC); Progressive Disease (PD)

INTRODUCTION

5-FU remains the key drug of chemotherapeutic option for metastatic gastric cancer since it was first synthesized in 1957 (1). Among a number of regimens of 5-FU devised from the pharmacokinetic studies, continuous intravenous infusion of 5-FU for 4 weeks or more, which was reported to yield higher response rates than a bolus intravenous injection (2), has been usually used for the patients with metastatic gastric cancer. However, gastrointestinal mucosal injury was identified as dose-limiting toxicity of this regimen (3). This regimen necessarily immobilizes the patients for long periods in addition to complications due to indwelling catheters.

TS-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) (4), which is composed of a mixture of tegafur (FT, a prodrug of 5-FU), Gimeracil (CDHP, a biochemical modulator which inhibits the biodegradation of 5-FU) (5), and Oteracil potacssium (Oxo, added to reduce the gastrointestinal toxicity of 5-FU) (6), was developed as an oral anticancer agent in Japan in order to improve these disadvantages of 5-FU with continuous intravenous infusion. TS-1 showed the highest response rate among many oral anticancer agents against advanced carcinomas in phase II studies (7). The response rate against metastatic gastric cancer was 43.5%, which is the highest response rate in a single anticancer agent for gastric cancer (8). Therefore, TS-1 is one of the most frequently used anticancer agent as the community standard treatment for metastatic gastric cancer in Japan. However in premarketing clinical trials (8,9) and a postmarketing survey of 3294 patients (10), in which TS-1 was orally administered at the usual dose level (80mg/m²) for 4 weeks followed by a 2-week rest (conventional schedule) for metastatic gastric cancer, the incidence of adverse reactions was 83.2% and 74.1%, respectively, and especially the latter response rate was only

Hepato-Gastroenterology 2007; 54:2167-2171

27%. The percentage of patients who received three or more courses was only 29.5%, the reasons why the discontinuation during the first or second course were mainly due to adverse reactions according to a post-marketing survey. The median time to the occurrence of the worst adverse reactions after TS-1 administration was 22 days for hematological toxicities and 15 days for diarrhea and stomatitis. Accordingly we conducted a phase II study of the new schedule of TS-1 therapy consisting of 2-week administration followed by 1-week rest (new schedule) for metastatic gastric cancer aiming at adverse reaction mitigation and prolonged medication without decreasing efficacy.

METHODOLOGY

Study Design

We conducted a multicenter phase II study that was approved by the institutional review boards of all participating hospitals and conducted in observance of the Declaration of Helsinki as well as good clinical practice guidelines. All patients provided written informed consent prior to enrollment in this study.

Patients

Thirty-five patients, enrolled between September 2001 and April 2003 at nine institutes in Japan, were required to satisfy the following eligibility criteria; 1) histologically proven gastric cancer; 2) metastatic or unresectable locally disease with one or more bidimentionally measurable target lesion documented radiographically; 3) age between 20 and 75 years; 4) Eastern Clinical Oncology Group (ECOG) scale performance status of 0, 1 or 2; 5) no prior chemotherapy or completion of adjuvant chemotherapy at least 4 weeks before entry; 6) adequate function of the bone marrow (white blood cell count ≥4,000 and <12,000 /μL platelet count ≥100x10³/μL, hemoglobin ≥8.0g/dL), liver (serum bilirubin ≤1.5mg/dL, AST/ALT level 3 x upper limit of normal (N), alkaline phosphatase level ≤2xN) and kidneys (serum creatinine ≤N); 7) normal cardiac function; 8) possibility of oral intake; no other severe medical conditions possibility of oral intake; 9) provision of give written informed consent. Exclusion criteria were as follows; 1) other active malignancy; 2) a high risk of poor outcome for concomitant nonmalignant disease (cardiac, pulmonary, renal, or hepatic disease, active uncontrolled infection, and chronic enteropathy); 3) the presence of CNS metastases 4) uncontrollable pleural effusion or ascites; 5) active gastrointestinal bleeding; 6) lactating women or those of childbearing potential. The eligibility of patients was checked once more via facsimile by the central data center (Osaka).

TABLE 1 Patient Characteristics

Patients		35
Median age, years (range)		64 (37-75)
Gender	Male	27
	Female	8
Performance status (ECOG scale)	0	13
	1	20
	2	2
Initial dose (mg/day)	80	5
	100	11
	120	19
Extent of disease	Locoregional	1
	Primary and metastatic	7
	Metastatic only	28
Evaluable sites	Primary	8
	Lymph nodes	16
	Liver	12
	Lung	3
	Peritoneum	5
	Skin	1
	Adrenal grand	1
Histopathological type	Intestinal	19
	Diffuse	16
Prior chemotherapy	Adjuvant chemotherapy	2
	No chemotherapy	33

Treatment

Before study entry, all eligible patients were required to provide a medical history and to undergo a physical examination that included assessment of weight, height, and ECOG performance status. As clinical assessment of tumor size, assay of the tumor markers CEA and CA19-9, and enhanced computed tomographic (CT) scan were also performed. After confirmation of eligibility by the central data center (Osaka), TS-1 was administered using the following method. The dosage of TS-1, which was administered orally after meals, was selected as follows: in a patient with body surface area (BSA) <1.25m², 40mg twice a day (80mg/day); BSA ≥ 1.25m² but <1.5m², 50mg twice a day (100mg/day); and BSA ≥ 1.5m², 60mg twice a day (120mg/day). One cycle of TS-1 treatment in this study consisted of administration for 2weeks followed by a 1-week rest. In patients with evidence of a grade 3 or higher toxicity, administration of TS-1 was discontinued until recovery from these adverse reactions and the dosage of restart after recovery from adverse reactions was planned to be reduced by one level (20mg/day). Treatment was suspended if the rest period was extended to over 4 weeks for adverse reactions. If a patient administered 80mg/day experienced the above toxicities, then no further treatment with more reduced dosage of TS-1 was continued.

Assessment of Response

The primary endpoint was response rate [ratio of patients attaining response (complete response - CR + partial response - PR)]. The assessment of tumor response was performed at least every 6 weeks. An independent external review committee consisting of radiologists, medical oncologists and surgeons assessed retrospectively tumor response. The antitumor effects were evaluated according to the Japanese Research Society for Gastric Cancer criteria, which was established by the WHO. This criteria was as follows: CR, eradication of all cancers and maintenance of the condition for 4 weeks or more; PR, 50% reduction in size of lesions and maintenance of the condition

for 4 weeks or more; no change (NC), less than 50% reduction in size of lesions or enlargement of lesions within 25% and maintenance of the condition for 4 weeks or more; progressive disease (PD), 25% or more enlargement of lesions or appearance of new lesions. Primary gastric lesions were evaluated by improvement of gastrographic and/or endoscopic findings.

Assessment of Feasibility

All eligible patients who had received definitive treatment were considered assessable for feasibility and toxicity. Feasibility was evaluated by the percentage of patients in this study who received six or more courses, which was equivalent to three or more courses of administration for 4 weeks followed by a 2-week rest, and by the percentage of patients who discontinue within 4th course for the reason of adverse reactions. The cumulative rate of relative total administration days was calculated by the rate between the actual total administration days and planned total administration days of TS-1. All adverse reactions experienced during the study were evaluated according to the National Cancer Institute Common Toxicity Criteria (Version 2.0) by questioning and clinical examination at least every 3 weeks during study.

Statistical Methods

The primary endpoint of this study was ORR. The number of patients to be enrolled in this study was calculated at 27, which was required for dismissing the assumption that the 95% confidence interval (CI) would be ±18%, assuming an expected response rate of 33%. Finally, we set it at 31 patients in consideration of 15% disqualified patients. Survival was estimated by the Kaplan-Meier method.

RESULTS

Patient Characteristics

Thirty-five patients were enrolled in this study between September 2001 and April 2003. The patient characteristics are summarized in **Table 1**. All 32 patients were evaluated for response and toxicity in the intent-to-treat analysis.

Adverse Reactions

Adverse reactions are summarized in **Table 2**. Main adverse reactions were hematological, gastrointestinal and cutaneous symptoms. Adverse reactions were observed in 31 patients whose percentage was 89% (95% CI: 78.0-99.1%). The severe adverse Grade 3 or 4 reactions were observed in 8 patients whose percentage was 23% (95% CI: 8.9-36.8%). All adverse reactions were reversible and there was no patient of treatment-related death.

Feasibility

The total number of treatment courses was 185 (median, 5 courses per patient; range, 1-15 courses). Total administration days of TS-1 in each patient were distributed from 6 to 210 days (median: 56 days). The cumulative rate of total administration days of TS-1 until 210 days was calculated by the Kaplan-Meier method (**Figure 1**). The rate of patients who received six or more courses (equivalent to three or more courses of administration for 4 weeks followed by a 2-week rest) was 43% (15/35). The rates of patients in whom administration was halted due to exacerbation of symptoms and adverse events were 74% (26 patients) and 26% (9 patients), respectively. The total of treatment days involving both administration period and rest period in all patients was 4026 days. If there was any interruption of TS-1 administration due to adverse reactions, 2684 days (4026 days x 14/21) were planned as the total administration days of TS-1. Actual total administration days of TS-1 in this study was 2505 days. Therefore the cumulative rate of the

TABLE 2 Adverse Reactions

Adverse reaction	Grade (No. of patients) 1	2	3	4	Overall No. (%)	Grade 3 and 4 No. (%)
Hematological						
Leucopenia	8	2	0	0	10 (29%)	0
Neutropenia	3	4	2	0	9 (26%)	2 (6%)
Anemia	10	8	1	0	19 (54%)	1 (3%)
Thrombocytopenia	2	0	1	0	3 (9%)	1 (3%)
Non-hematological						
Nausea/vomiting	9	3	1	0	13 (37%)	1 (3%)
Anorexia	10	3	2	2	17 (49%)	4 (11%)
Diarrhea	5	1	0	0	6 (17%)	0
Stomatitis	7	0	0	2	9 (26%)	2 (6%)
Fatigue	2	1	1	0	4 (11%)	1 (3%)
Cutaneous symptoms	7	1	0	0	8 (23%)	0
Headache	0	1	0	0	1 (3%)	0
Abdominal pain	1	0	0	0	1 (3%)	0
Bilirubin	1	0	0	0	1 (3%)	0
Transaminase	0	0	1	0	1 (3%)	1 (3%)

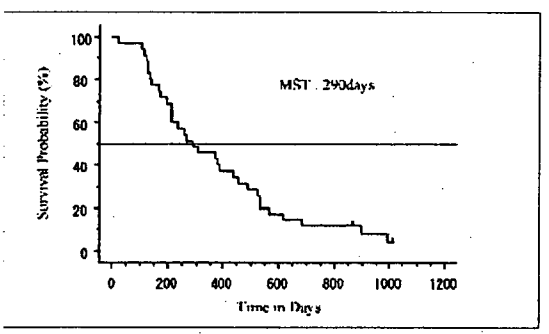

FIGURE 1
Overall survival of the 35 patients. Cumulative rate of total administration days of TS-1 by Kaplan-Meier method.

TABLE 3 Feasibility

Median treatment courses (range)	5 courses (1-15)
Total number of treatment courses	185 courses
Median administration days (range)	56 days (6-210)
Total number of administration days	2505 days
Relative total administration days	93%
Rate of patients who received six or more courses	43%
Rate of patients in whom administration was halted due to	
Exacerbation of symptoms	74%
Adverse events	26%

relative total administration days was 93% (2505/2684).

Efficacy

The responses of this study are summarized in **Table 4**. There were 6 PRs, 13 NCs, 11 PDs, and 5 patients were not evaluable (NE), yielding a response rate (RR) of 17% (6 of 35 patients; 95% CI, 7.2%-34.3%). The response rate of the patients with intestinal-type adenocarcinoma and diffuse-type adenocarcinoma were 16% and 19%, respectively. The response rate of the 33 patients without prior chemotherapy was 18% (6/33). The median response duration was 203 days (range, 53 to 235 days). The median survival time of all patients was 290 days (95% CI, 214-438) **(Figure 1)**.

DISCUSSION

Combination chemotherapy, for example DCF combination therapy (Docetaxel/CDDP/5-FU), is the one of the standard for metastatic gastric cancer in USA from the results of large scale phase III study. However this combination chemotherapy is not easily acceptable in Japan because of its high toxicities and impossibility of outpatient chemotherapy. On the other hand, Japan Clinical Oncology Group (JCOG) regards continuous intravenous infusion of 5-FU as the reference arm at present and phase III study (JCOG-9912), which inspects the superiority of CPT11+CDDP or non-numerical inferiority of TS-1 compared with continuous intravenous infusion of 5-FU as the reference arm in survival, is on-going at present in Japan. However TS-1 monotherapy is already the most frequently used regimen for metastatic gastric cancer as a community standard therapy in Japan, because of its highest response rate as a single agent among all anticancer agents for metastatic gastric cancer and its convenience as an oral agent. Three phase III trials to inspect the superiority of TS-1 combined chemotherapy with CDDP (Taiho), CPT11 (Yakuruto and Daiichi), or Docetaxel (JACCRO) in survival compared with TS-1 monotherapy as a control arm are already on-going at present in Japan. The conventional schedule of TS-1 monotherapy consists of administration of 80mg/m²/day for 4 weeks followed by a 2-week rest in one cycle and is repeated for as long as there is no exacerbation of symptoms or sever adverse events. This conventional schedule is also adopted in this clinical study described above.

TABLE 4 Response

Patients	(n)	CR	PR	NC	PD	NE	RR
Overall	35	0	6	13	11	5	17%
Metastatic site							
Lymph node	16	0	4	7	3	2	25%
Liver	12	0	0	6	6	0	0%
Lung	3	1	1	0	0	1	67%
Peritoneum	5	0	0	0	2	3	0%
Others	2	0	1	1	0	0	50%
Primary site	8	0	1	4	2	1	13%
Histological type							
Intestinal	19	0	3	9	4	3	16%
Diffuse	16	0	3	4	7	2	19%
Prior chemotherapy							
Adjuvant	2	0	0	0	1	1	0%
No chemotherapy	33	0	6	13	10	4	18%

However, the percentage of patients who received three or more courses was only 47% according to a postmarketing survey of TS-1 and TS-1 administration was halted in 33% of patients due to adverse reactions. This survey also reported that the median time to the worst toxic events was 22 days for hematological toxicities and 15 days for diarrhea and stomatitis. Therefore the new schedule of TS-1 monotherapy consisting of administration of 80mg/m²/day for 2 weeks followed by a 1-week rest was devised aiming at adverse reaction mitigation and prolonged medication. Kimura *et al.* suggested that this new schedule might mitigate adverse reactions and prolong the medication period compared with the conventional schedule for metastatic gastric cancer. However they also reported that a multicenter collaborative prospective study of this new schedule was necessary to confirm its superiority because their study involved retrospective analysis using historical controls in one institute without extramural review. Tsukuda *et al.* also reported that this new schedule seemed to be more tolerable and safer compared with the conventional schedule for adjuvant chemotherapy in advanced head and neck cancer. However, the type of cancer was different from ours and the subjects were patients receiving adjuvant chemotherapy without primary or metastatic lesion in this report. Therefore we conducted this phase II study to examine whether this new schedule might mitigate adverse reactions and prolong the medication period without decrease of its antitumor effect.

This study examined the safety and efficacy of the new schedule of TS-1. The ORR was 17% (95% CI, 7.2%-34.3%), which was the primary endpoint. Therefore, this new schedule of TS-1 administration is statistically active, but might reduce the antitumor effect compared with the conventional schedule of TS-1 administration for metastatic gastric cancer.

The incidence of adverse reactions was 89% (95% CI: 78.0x-99.1%) and that of adverse reactions at Grade 3 and 4 was 23% (95% CI: 8.9-36.8%). Judging from the fact that the incidence of adverse reactions was 78% and that of adverse reactions at Grade 3 and 4 was 20% according to a premarketing late phase II study adopting the conventional schedule of TS-1 administration, this new schedule of TS-1 administration might not reduce the toxicities compared with the conventional schedule of TS-1 administration for metastatic gastric cancer.

In this study, the rate of patients who received six or more courses (equivalent to three or more courses of the conventional schedule of TS-1) was 43% (15/35). Judging from the fact that the rate of patients who received three or more courses of the conventional schedule of TS-1 administration was 44.6% according

to a postmarketing survey, this new schedule of TS-1 administration might not unfortunately prolong medication compared with the conventional schedule of TS-1 administration for metastatic gastric cancer, nevertheless, the cumulative rate of the relative total administration days was 93% in this study.

The median survival time (MST) in our study was 290 days. Compared with 250 days (95% CI 171-376 days) reported in a premarketing late phase II study, this new schedule of TS-1 administration was acceptable from the point of survival view.

CONCLUSION

We concluded that the schedule of TS-1 administration for 2 weeks followed by a 1-week rest might not be superior to the conventional schedule (4 weeks on and 2 weeks off) with regard to the antitumor effect, adverse reactions and prolonged medication, although it was acceptable from the viewpoint of survival. Further comparative study is needed for the evaluation of this new schedule (2 weeks on and 1 week off).

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