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Preoperative Chemotherapy with S-1 and Cisplatin for Highly Advanced Gastric Cancer

ATSUSHI NASHIMOTO, HIROSHI YABUSAKI, SATORU NAKAGAWA, YASUGIRO TAKII, YOSHIAKI TSUCHIYA and TANAKA OTSUO

Department of Surgery, Niigata Cancer Center Hospital, 2-15-3, Kawagishi-cho, Chuo-ku, Niigata 951-8566, Japan

Abstract. *Feasibility and efficacy of S-1 and cisplatin followed by surgery was evaluated, and factors contributing to survival benefit were analyzed. Patients and Methods: In total, 120 consecutive patients with highly advanced gastric cancer were treated with S-1 (80 mg/m^2 for 21 consecutive days) and cisplatin (50 mg/m^2 on day 8). Results: The response rate was 62.5% overall, and 75.7% for these with metastatic lymph nodes. Grade 3/4 adverse events were less than 10%. The median survival time was 41.9 months among 93 patients whose primary lesion was resected. Liver metastasis, R2 resection, poor performance status and lack of response were identified as independent risk factors by a multivariate analysis. Conclusion: Preoperative chemotherapy with S-1 and cisplatin was effective. The results show the need for different approaches in the treatment of patients with metastases and these without.*

The only curative treatment for gastric adenocarcinoma is R0 resection, arguably accompanied by D2 lymph node dissection according to the Guidelines of the Japanese Gastric Cancer Association (JGCA) (1). Local control is considered an essential component of the treatment for gastric carcinoma, and extended lymphadenectomy can accomplish this task safely in experienced hands (2). The prognosis for stage III/IV advanced gastric cancer (AGC) remains unsatisfactory, however, and further improvement in surgical technique is unlikely to lead to notable progress in the outcome (3-4). Hence the development of an effective multimodal strategy has been sought after by various study groups.

Correspondence to: Atsushi Nashimoto, MD, Ph.D., Department of Surgery, Niigata Cancer Center Hospital, 2-15-3, Kawagishi-cho, Chuo-ku, Niigata 951-8566, Japan. Tel: +81 252665111, Fax: +81 252333849, e-mail: nasimoto@niigata-cc.jp

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A recent meta-analysis performed in the West showed that combination regimens achieve better survival outcomes than those with 5-fluorouracil (5-FU) monotherapy and that regimens containing 5-FU, anthracyclines and cisplatin (CDDP) are the most effective (5). A perioperative chemotherapy using this triplet was actually found to improve survival of potentially curable AGC significantly when compared with treatment by surgery alone (6). Downstaging and eradication of micrometastases through the preoperative chemotherapy component may have had a particularly important role in such a strategy. In Japan, postoperative adjuvant chemotherapy by S-1, a dehydropyrimidine dehydrogenase-inhibiting 5-FU derivative, was found to improve survival of patients with curatively resected stage II/III gastric cancer. Addition of adequate preoperative therapy to this strategy may enhance the survival of patients with resectable AGC, while downstaging through preoperative chemotherapy may provide patients with more advanced cancer some chance for cure. One candidate for use is intensive preoperative chemotherapy under such circumstances would be a combination of S-1 and CDDP, which led to a response rate of 54% and median survival time of 13 months among patients with unresectable gastric cancer in a phase III trial (7). This combination was also shown to be feasible as a preoperative induction therapy in a case series involving a smaller number of patients (8).

In the current study, 120 consecutive AGC patients who were treated with S-1/CDDP therapy prior to surgery were retrospectively analyzed to assess the efficacy and safety of this combination as a preoperative therapy and to identify the subset of patients who may benefit from this strategy.

Patients and Methods

Patients. The files for one hundred and twenty consecutive patients with primary AGC who were treated preoperatively by a combination of S-1 and CDDP between October 2000 and December 2005 were retrieved from the prospective database of Niigata Cancer Center according to the following criteria: histologically confirmed adenocarcinoma of the stomach; clinically diagnosed as locally

advanced T3/T4-stage disease or metastatic disease; evaluable lesions on computed tomography (CT) scan, at upper gastrointestinal series and/or upper digestive endoscopies; age less than 75 years; ECOG performance status between 0 and 2; no prior chemotherapy or radiotherapy; sufficient organ functions represented by leukocyte count of more than 3,000/mm^3, platelets more than 10×10^4/mm^3, GOT/GPT less than 2 times the upper limit of normal range (ULN), total bilirubin less than 2.0 mg/dl, BUN and creatinine less than the ULN; no serious co-morbidities; no concurrent active malignancy; no serious psychosomatic disorder; and provision of written informed consent. Staging laparoscopy was performed only for patients with linitis plastica or those with macroscopically type 3 cancer with preoperatively estimated diameter of >8 cm. Cytological examination of the peritoneal washes was performed at the time of staging laparoscopy, but the result was used only as a reference, and detection of cancer cells in this examination did not preclude patients from receiving preoperative chemotherapy followed by surgery.

Treatment schedule. All patients received systemic chemotherapy consisting of S-1 and CDDP. S-1 was orally administered at a dose of 80 mg/m^2 for 21 consecutive days, followed by 14 days of rest. With the intent to deliver the treatment on an outpatient basis, the dose of CDDP was modified from the original version by Koizumi *et al.* in which 60 mg/m^2 had been administered. CDDP was administered intravenously on day 8 at a dose of 50 mg/m^2. The treatment was repeated every 5 weeks. Patient status was evaluated after each course of the treatment. Toxicity was assessed using the National Cancer Institute-Common Toxicity Criteria version 3.0. The response of measurable lesions was evaluated according to the RECIST criteria. The primary lesion, when not considered as measurable by the RECIST criteria, was assessed according to the Japan Gastric Cancer Association (JGCA) clinical criteria for response assessment of chemotherapy and radiotherapy. The assessment was based on shrinkage and morphological change of the primary tumor as evaluated by barium contrast study and/or endoscopic examinations (9).

Patients with locally advanced cancer were treated by chemotherapy until primary cancer or massive nodal metastases responded and resection with curative intent was deemed possible. Patients with metastatic cancer (those with hepatic or peritoneal metastases) were treated until metastatic lesions achieved complete response by CT or became co-resectable. Patients who remained with clear evidence of unresectable disease and those who did not respond to the chemotherapy were discouraged from receiving surgery. Surgery with intent to cure was performed at least 3 weeks after the final cycle. Most patients were treated by S-1 monotherapy as an adjuvant therapy after surgery. Treatments after R2 resection or at detection of recurrent disease were decided at the discretion of each physician.

Study design and statistical analysis. Median survival time (MST) was calculated from the initiation of chemotherapy to death or the day when the patient was last interviewed. Survival curves were calculated by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate analyses using Cox's proportional hazards model was performed to identify independent prognostic factors. All statistical calculations were performed using statistical analysis system (SAS) version 8.2 (IBM, North Caroline, USA) and a value of $p<0.05$ was considered as statistically significant.

Results

Patient demographics. Characteristics of the 120 patients are shown in Table I. There were 75 men and 45 women with a median age of 61 years (range 29 to 83 years). There were 44 patients with linitis plastic type cancer (36.7%). Non-curative factors included liver metastasis in 8 patients, peritoneal dissemination in 30, involvement of abdominal para-aortic lymph nodes in 34 and locally advanced and potentially unresectable gastric cancer in 12. The pretreatment clinical stage (c-stage) was diagnosed according to the classification of JGCA, which was based on the findings of CT, upper GI series, endoscopy, and staging laparoscopy. Preoperative stages were decided according to the JGCA staging system (c-stage II: 1 case; c-stage III: 33 cases; c-stage IV:86 cases). Distribution of the c-stage IV factors was as follows: metastasis to the paraaortic nodes in 34 cases, cT4N2 in 12 cases, hepatic metastasis in 8 cases, peritoneal dissemination in 30 cases, and other distant metastasis in 4 cases.

Proportion of the treatment performed at outpatient clinic. The median number of administered courses was 3 (range: 1-7), and the proportion of care given in the outpatient setting was 86%. Forty-seven patients who underwent staging laparoscopy were admitted for the procedure and given the first course of chemotherapy during the same stay in the hospital. Of the 73 remaining patients, 22 managed to receive chemotherapy entirely on an outpatient clinic basis. However, the rest of the patients needed admission for hydration and antiemetic therapy during administration of CDDP.

Surgery. After chemotherapy, 27 patients failed to be treated by surgery, mostly because of persistence of metastatic disease through imaging studies. The remaining 93 patients underwent surgery and gastrectomy was performed in all patients. The overall resection rate was 77.5%. The surgical procedure was total gastrectomy in 57 patients and distal gastrectomy in 36 patients. R0 resection was possible in 68 patients (73.1% of all patients who underwent surgery), of whom 25 received combined resection of the involved adjacent organs and 14 underwent extended lymph node dissection including of the para-aortic lymph nodes. Of those who underwent surgery, there were 59 males and 34 females, with a median age of 61 years (range: 29 to 77 years) (Table II). The median hospital stay was 18 days. The median duration of surgery was 195 minutes and the median blood loss was 225 ml. The distribution of postoperative c-stage was as follows; 26 patients in c-stage I/II, 26 in c-stage III, and 41 in c-stage IV. R0 resection was successfully performed in 68 (73.1%) patients. Downstaging was obtained in 32 (34.4%) patients.

Clinical response to chemotherapy. The objective response of the evaluable lesions is shown in Table III. The overall

Table I. *Patient characteristics (N=120).*

Variable		No. of cases
Age, years median (range)	61.0 (29-83)	
Gender	Male/female	75/45
Performance status	0/1/2	80/26/14
Location	L/M/U/LMU	18/33/37/32
T stage	T3/T4	108/12
Metastasis		
Lymph node	N3/N1,2/N0/?	34/72/5/9
Liver	H0/H1	112/8
Peritoneum	P0/P1	90/30
Gross type	Type 2, 3/type 4	76/44
Histological type	Diff./undiff.	44/76
Clinical stage	II,III/IV	34/86

? unknown; L, lower; M, middle; U, upper.

Table II. *Patient characteristics of resected cases.*

Variable		No. of cases
Gender	Male/female	59/34
Age, years	median (range)	61.0 (29-77)
Hospital stay (days)	median (range)	18 (13-198)
Duration of operation (min)	median (range)	195 (90-367)
Bleeding vol. (ml)	median (range)	225 (20-1510)
Surgical procedure	DGR/TGR	36/57
LN dissection	D1/D2/D3	16/63/14
Depth of tumor invasion (T)	T1,2/T3/T4	11/57/25
Lymph node metastasis (N)	N0,N1/N2/N3	42/34/17
Pathological stage	I-II/III/IV	26 /26 /41
Curability	CA, CB/CC	68/25
Histological effect (Grade)	1a /1b/2/3	46/28/18/1

N=93; resection rate 77.5%. DGR, distal gastrectomy; TGR, total gastrectomy; D1, dissection of all the group 1 nodes; D2, dissection of all the group 1 and 2 nodes; D3, dissection of all the group 1, group 2 and group 3 nodes; CA, no residual disease with high probability of cure; CB, no residual disease but not fulfilling criteria for CA; CC, definite residual disease; Grade, grading due to the proportion of degeneration area in the tumor by the Japanese Classification of Gastric Carcinoma; (1a, the proportion of degeneration area in the tumor is less than 1/3; 1b, 1/3-2/3; 2, more than 2/3; 3, no viable tumor cell).

Table III. *Response.*

	No. of cases	CR	PR	NC	PD	ORR (%)
Overall	120	1	74	42	3	62.5
Primary lesion	120	2	72	45	1	61.7
Metastatic lesions						
Lymph nodes	74	4	52	18	0	75.7
Liver	7	1	1	5	0	28.6
Peritoneum	*21	0	5	14	2	23.8
Other	**4	0	0	3	1	0.0

*CY1→CY0 (9 cases); **lung and pleura, ovary ×3. CY, peritoneal cytology; CY0, benign and/or indeterminate cells on peritoneal cytology; CY1, cancer cells on peritoneal cytology.

Table IV. *Toxicity.*

	NCI-CTC Grade					
	1	2	3	4	Overall (%)	Grade 3/4 (%)
Hematological						
Leucopenia	24	27	1	0	43.3	0.8
Neutropenia	27	31	9	0	55.8	7.5
Anemia	35	36	7	1	65.0	6.7
Thrombocytopenia	36	8	5	3	40.8	6.7
Creatinine	11	0	0	0	9.2	0.0
Total bilirubin	3	3	0	0	5.0	0.0
GOT/GPT	12	5	0	0	15.3	0.0
Non-hematological						
Anorexia	51	23	7	0	67.5	5.8
Nausea	51	14	3	0	56.7	2.5
Vomiting	18	6	0	0	20.0	0.0
Diarrhea	18	1	2	0	17.5	1.7
Constipation	2	1	0	0	2.5	0.0
Stomatitis	23	3	0	0	21.7	0.0
Taste disturbance	30	2	0	0	26.7	0.0
Hand-foot skin reaction	16	0	0	0	13.3	0.0
Pigmentation	47	5	0	0	43.3	0.0
Nail changes	30	0	0	0	25.0	0.0
Alopecia	10	0	0	0	8.3	0.0
General fatigue	26	7	1	0	28.3	0.8
Gastric ulcer	0	0	1	1	1.7	1.7

response rate (ORR) was 62.5% (95% confidence interval (CI): 53.8-71.2%). There were 75 responders (one complete response (CR) and 74 partial responses (PR)), when the response to the primary lesion was disregarded. Response rate for regional/para-aortic lymph nodes, primary gastric tumor (assessed based on JGCA clinical criteria for response assessment of chemotherapy and radiotherapy), liver metastases and peritoneal metastases was 75.7% (56/74), 61.7% (74/120), 28.6% (2/7) and 23.8% (5/21), respectively. Twenty-five other patients (42.4%) had stable disease (SD), and only 2 patients had progressive disease (PD). Pathologic CR of the metastatic lymph nodes, including para-aortic lymph nodes, was confirmed after surgery in 4 patients. Of the 75 responders, residual tumor was completely resected in 51 (68.0%). Out of the 47 patients who underwent staging laparoscopy, 31 were found to have peritoneal metastasis; of these, complete remission of the peritoneal disease was confirmed at surgery in 9 (29.0%).

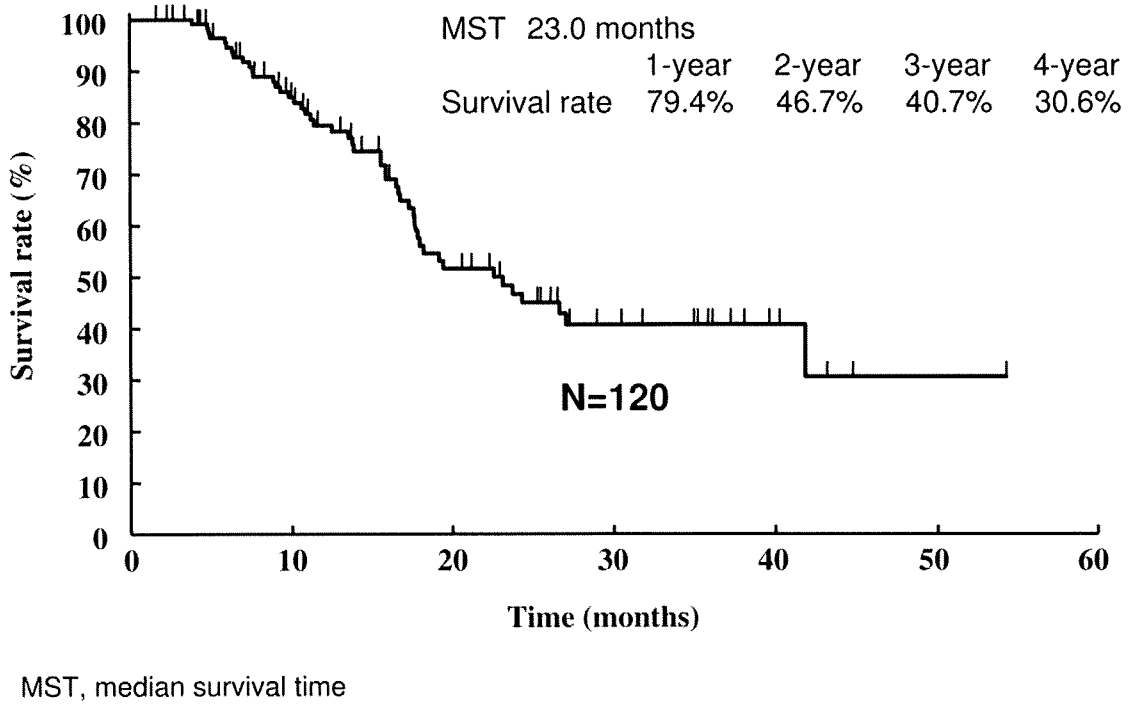

Figure 1. *Cumulative probability of overall survival as estimated by the Kaplan-Meier method in 120 patients. The median survival time was 23.0 months, and a 4-year survival rate was 30.6%.*

Toxicity. The adverse reactions during 308 cycles of S-1/CDDP regimen were evaluated according to NCI-CTC grade (Table IV). The most frequent toxicities of S-1/CDDP were myelosuppression and gastrointestinal symptoms. The incidence of notable adverse events were 55.8% for neutropenia, 43.3% for leukocytopenia, 65.0% for anemia 65.0%, 40.8% for thrombocytopenia, 67.5% for anorexia, 56.7% for nausea, respectively. However the incidence of grade 3/4 toxicity was infrequent: neutropenia 7.5%, leucopenia 0.8%, anemia 6.7%, thrombocytopenia 6.7%, anorexia 5.8% and nausea 2.5%. The preoperative chemotherapy was generally well tolerated. There was no surgical mortality, and postoperative surgical morbidity was remarkably low at 17.2%.

Survival and analysis of prognostic factors. The median survival time of patients overall was 23.0 months, with a 4-year survival rate of 30.6% (Figure 1). The median survival time of patients who went on to receive surgery was 41.9 months (95% CI: 31.9-51.9 months) and the 3-year survival rate was 51.2% (95% CI: 37.4-64.9%) (Figure 2). There was a statistically significant difference in survival between these patients and these who failed to receive gastrectomy.

For all patients, response to chemotherapy, location of the tumor, resectability of the primary lesion, liver metastasis, and peritoneal metastasis were predictive of the overall survival (Table V). In the multivariate analysis, response to chemotherapy, peritoneal metastasis and hepatic metastasis were the only independently prognostic factors (Table VI).

For the patients who were treated by gastrectomy, curability of surgery, response to the chemotherapy, hepatic metastasis, peritoneal metastasis, the extent of lymph node dissection, N category, and performance status were identified as significant prognostic determinants (Table VII). Of these, hepatic metastasis, curability of surgery, performance status and response to the chemotherapy were identified as independent prognostic factors (Table VIII).

Discussion

Gastric carcinoma remains a major health problem worldwide, primarily because it is often diagnosed at an advanced stage. In addition, it often relapses even after a potentially curative resection, and multimodal treatments have been sought after by various study groups to combat residual micrometastases. One of the consequences is that postoperative chemoradiation was found to significantly improve outcome of curatively resected patients and has become a standard of care in North America (10-11). There is a suspicion, however, that radiation as a local therapy may have compensated for poor local control due to suboptimal surgery, and the Japanese surgeons remained confident that extended nodal dissection precludes the need for adjuvant

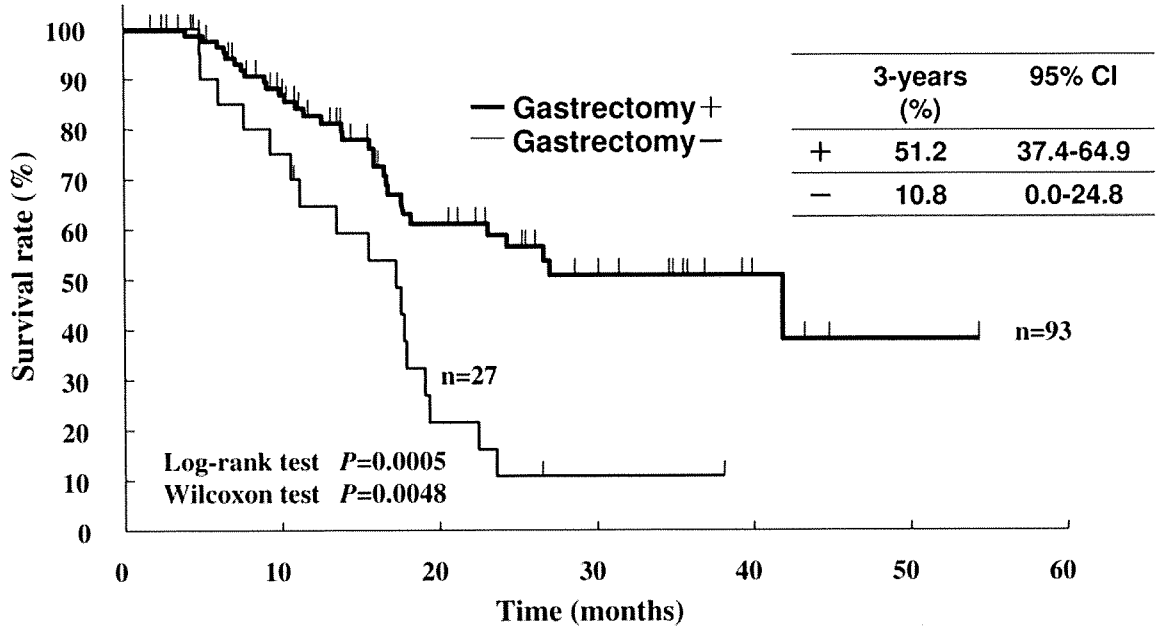

Figure 2. *Cumulative probability of survival in the gastrectomy group (93 patients) and the non-gastrectomy group (27 patients) as estimated by the Kaplan-Meier method. A 3-year survival rate of the former and the latter was 51.2% and 10.8%, respectively. There was a statistically significant difference.*

treatment focused around the gastric bed. However, the Japanese experts felt promise when S-1, a novel oral fluoropyrimidine derivative, became available. This drug achieved a response rate of more than 40% when used as a single agent (12-13), while the response rate rose to 50-75% when used in combination with CDDP (12), irinotecan (14-15), docetaxel (17-18), and paclitaxel (19-20). Their expectations were met when an interim analysis of a pivotal phase III study revealed that postoperative adjuvant chemotherapy with single agent S-1 significantly improved survival of stage II-III gastric cancer patients when compared with surgery alone (21).

Gastrectomy causes various gastrointestinal symptoms and nutritional deficits, and additive toxicity through postoperative chemotherapy could be a substantial burden for the patients. More than 10% of the Japanese patients in the aforementioned phase III trial had actually failed to continue with oral S-1 at three month postoperatively. Post-gastrectomy deterioration of compliance regarding chemotherapy was also observed in the British MAGIC trial, in which 88% of patients received preoperative chemotherapy whereas only 55% tolerated the same therapy postoperatively (6). Thus, there is a rationale for delivery of a somewhat toxic but effective chemotherapy preoperatively, and neoadjuvant chemotherapy is a promising option for resectable AGC. In addition, the indication for preoperative chemotherapy could be extended to include AGC with synchronous metastases, provided the metastatic lesions are co-resectable or become resectable after chemotherapy.

Table V. *Univariate analysis of 120 patients with primary AGC who were treated preoperatively by a combination of S-1 and CDDP (log-rank test).*

Variable		*P*-value
Response due to JCGC	(PR/NC,PD)	<0.0001
Location	(L,M,U/LMU)	0.0068
Surgery	(+/–)	0.0005
Liver metastasis	(H0/H1)	<0.0001
Peritoneal metastasis	(P0/P1)	0.0002
Gender	(Female/male)	0.1521
Histological type	(Diff./undiff.)	0.3697
Gross type	(Type 2,3/type 4)	0.0815
T stage	(T1, T2/T3, T4)	0.0826
Lymph node metastasis	(N0, N1/N2, N3)	0.4623
Age	(≤59 *vs.* 60+)	0.6489
PS	(0/1, 2)	0.1154

JCGC, Japanese classification of gastric cancer; PR, partial response; NC, no change; PD, progressive disease; PS, performance status according to the WHO criteria.

Although chemotherapy is the standard of care for metastatic gastric cancer, it does not cure the disease. One can argue therefore that surgery remains an option as a part of multimodal therapy for patients with resectable metastases. When such is the case, preoperative chemotherapy provides useful information as regards drug sensitivity and biology of

Table VI. *Multivariate analysis of 120 patients with primary AGC who were treated preoperatively by a combination of S-1 and CDDP. Cox's proportional hazard model (SAS ver. 8.2, score method).*

Variable	Hazard ratio	95% Confidence limits	*P*-value
Liver metastasis (H0/H1)	8.142	(1.446-5.586)	<0.0001
Response (CR,PR/NC,PD)	2.842	(1.300-5.149)	0.0025
Peritoneal metastasis (P0/P1)	2.587	(3.459-19.162)	0.0068

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table VII. *Univariate analysis of 93 patients underwent gastrectomy after chemotherapy (log-rank test).*

Variable		*P*-value
Curability	(CA,CB/CC)	<0.0001
Liver metastasis	(H0/H1)	0.0001
Response	(PR/NC,PD)	0.0026
Peritoneal metastasis	(P0/P1)	0.0119
LN dissection	(D1/D2,3)	0.0164
Lymph node metastasis	(N0,1/N2,3)	0.0251
PS	(0/1,2)	0.0352
Gender	(Male/female)	0.0781
Location	(LMU/L,M,U)	0.1020
Age	(<59 *vs.* 60+)	0.2040
Gross type	(Type 2,3/type 4)	0.2577
cT stage	(T1,2/T3,4)	0.5851
Histological type	(Diff./undiff.)	0.9282

CA, no residual disease with high probability of cure; CB, no residual disease but not fulfilling criteria for CA; CC, definite residual disease; D1, dissection of all the group 1 nodes; D2, dissection of all the group 1 and 2 nodes; D3, dissection of all the group 1, group 2 and group 3 nodes.

Table VIII. *Multivariate analysis of 93 patients underwent gastrectomy after chemotherapy. Cox's proportional hazard model. (SAS ver. 8.2, score method).*

Variables	Hazard ratio	95% confidence limits	*P*-value
fH (0/1)	6.308	(2.145-18.553)	0.0008
Curability (A,B/C)	3.608	(1.610-8.085)	0.0018
PS (0/1,2)	2.856	(1.308-6.234)	0.0084
Response (CR,PR/NC,PD)	2.585	(1.155-5.787)	0.0209

CA, no residual disease with high probability of cure; CB, no residual disease but not fulfilling criteria for CA; CC, definite residual disease; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

cancer, besides the potential to downstage the disease, and prevents futile surgery for cancer that is destined for rapid progression. In either of the settings, efficacy along with safety of preoperative chemotherapy and its influence on surgery that follows need to be addressed.

Chemotherapeutic regimens with high response rates are required to achieve downstaging along with eradication of micrometastases whilst preventing disease progression. In due course, a combination of S-1 and CDDP has become acknowledged in Japan as a candidate for neoadjuvant chemotherapy owing to its remarkable response rate, in excess of 70%, and this is the regimen with which the authors chose to treat AGC patients preoperatively. A combination of S-1 and CDDP was first established by Koizumi *et al.*, by which 60 mg/m^2 of CDDP was to be administered on day 8 of a 5-week course. Administration at this dosage was feared to cause nausea and potential damage to renal function, and patients usually had to be admitted for a few days for continuous intravenous infusion along with extensive use of antiemetics. To lower the risk of organ dysfunction prior to surgery and in an attempt to deliver all the drugs on an outpatient basis, we modified the dose of CDDP to 50 mg/m^2. Consequently, CDDP was delivered entirely on the outpatient basis in 22 out of 73 patients, but admission was still necessary for all remaining patients. Response rate for the nodal metastases was satisfactory at over 70%, but those for other metastatic lesions were substantially lower. Given that the number of beds available for preoperative chemotherapy is limited, establishment of a modified regimen with further dose reduction, perhaps through an increase in the number of intravenous deliveries per cycle to preserve the dose intensity, may be warranted.

Response to the chemotherapy is undoubtedly a valuable parameter in deciding whether or not to proceed to surgery for metastatic cancer. When chemotherapy is performed in the neoadjuvant setting, however, cancer is usually resectable before the treatment. The response will then have to be evaluated even more cautiously and diligently to avoid delay in surgery when the cancer is not responding to the chemotherapy. When the tumor is not accompanied by distant metastasis or bulky lymphadenopathy, the primary lesion would be the only target for evaluating response. In addition, shrinkage of the primary may allow surgeons to avoid total gastrectomy in cases of advanced cancer of the distal or mid-portion of the stomach. Thus, the Authors insisted on assessing response in the primary lesion according to the Japanese criteria, although these lesions are not considered as measurable by the RECIST criteria. Marked response to the primary was observed in 61.7% of the patients.

In the current population of advanced/metastatic cancer, the R0 resection rate among those who eventually underwent surgery was unexpectedly high at 73.1%. The MST was 23

months overall and 42 months among those who underwent surgery. The combination of S-1 and CDDP thus provided promising survival data with a favorable toxicity profile with no treatment-related deaths. Multivariate analysis of all patients identified peritoneal metastasis and hepatic metastasis as independent prognostic factors in all patients. Of patients with metastatic cancer, only those with hepatic metastasis that responded to chemotherapy went on to receive surgery. Nevertheless, hepatic metastasis remained an independent prognostic factor among those who underwent surgery. These results confirm that the outcome of patients with metastatic cancer is quite different from those with locally advanced cancer (those who undergo so-called neoadjuvant chemotherapy). In future, these two groups of patients should thus be treated by different strategies and analyzed independently.

Conclusion

S-1/CDDP at a reduced dose was safe and feasible when given preoperatively, without notable influence over the surgical morbidity. It remained effective against the primary tumor and nodal metastases. The survival benefit of cytoreductive surgery in metastatic cancer that responds to such chemotherapy needs to be addressed by a randomized trial, while another trial is needed to confirm its benefit in the neoadjuvant setting for locally advanced cancer.

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Original article

Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer

T. Yoshikawa[1], M. Sasako[2], S. Yamamoto[3], T. Sano[4], H. Imamura[5], K. Fujitani[6], H. Oshita[7], S. Ito[8], Y. Kawashima[9] and N. Fukushima[10]

[1]Department of Gastrointestinal Surgery, Kanagawa Cancer Centre, Yokohama, [2]Department of Surgery, Hyogo College of Medicine, Nishinomiya, [3]Statistics and Epidemiology Section, Cancer Information Services and Surveillance Division, Centre for Cancer Control and Information Services, National Cancer Centre, Tokyo, [4]Gastric Surgery Division, National Cancer Centre Hospital, Tokyo, [5]Department of Surgery, Sakai Municipal Hospital, Sakai, [6]Department of Surgery, National Hospital Organization Osaka Medical Centre, Osaka, [7]Department of Surgery, Gifu Municipal Hospital, Gifu, [8]Department of Gastrointestinal Surgery, Aichi Cancer Centre Hospital, Nagoya, [9]Division of Gastroenterological Surgery, Saitama Cancer Centre, Saitama, and [10]Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan

Correspondence to: Dr T. Yoshikawa, Department of Gastrointestinal Surgery, 1-1-2 Nakao, Asahi-Ku, Yokohama 241-0815, Japan (e-mail: yoshikawat@kcch.jp)

Background: Locally advanced gastric cancer with extensive lymph node metastasis is usually considered unresectable and so treated by chemotherapy. This trial explored the safety and efficacy of preoperative chemotherapy followed by extended surgery in the management of locally advanced gastric adenocarcinoma.

Methods: Patients with gastric cancer with extensive lymph node metastasis received two or three 28-day cycles of induction chemotherapy with irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent gastrectomy with curative intent with D2 plus para-aortic lymphadenectomy. Primary endpoints were 3-year overall survival and incidence of treatment-related death.

Results: The study was terminated because of three treatment-related deaths when 55 patients had been enrolled (mortality rate above 5 per cent). Two deaths were due to myelosuppression and one to postoperative complications. Clinical response and R0 resection rates were 55 and 65 per cent respectively. The pathological response rate was 15 per cent. Median overall survival was 14·6 months and the 3-year survival rate 27 per cent.

Conclusion: This multimodal treatment of locally advanced gastric cancer provides reasonable 3-year survival compared with historical data, but at a considerable cost in terms of morbidity and mortality.

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Introduction

Macroscopically complete tumour removal is a prerequisite to cure gastric cancer[1,2]. Japanese surgeons have explored the benefits and disadvantages of para-aortic nodal dissection for locally advanced tumours with nodal metastases[3–6]. The Japanese Gastric Cancer Association (JGCA) defines para-aortic lymph nodes as being regional lymph node stations (JGCA-N3)[7]. Tumours with bulky nodal metastases surrounding the coeliac artery and its branches (JGCA-bulky N2) are usually considered unresectable. The prognosis of patients with JGCA-N3 or JGCA-bulky N2 is extremely poor even when the entire tumour and lymph nodes can be resected with curative intent. Further, complete resection of these tumours often requires combined organ resection, such as distal pancreatectomy, resulting in major surgical complications[8]. Even after this surgery with curative intent, most tumours recur, suggesting that distant micrometastases were already present.

In contrast to the Japanese staging system, the tumour node metastasis (TNM) staging of the International Union Against Cancer (UICC) defines para-aortic metastases as

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

distant metastases[9]. In Western countries, tumours with JGCA-N3 or JGCA-bulky N2 are therefore regarded as unresectable disease that warrants palliative chemotherapy. These patients rarely survive for more than 3 years when they receive chemotherapy alone or when surgery is followed by postoperative chemotherapy. To improve this dismal prognosis, a different strategy should be developed.

Preoperative chemotherapy has some theoretical benefits in these patients in comparison with postoperative chemotherapy. First, extended surgery can be performed easily and safely because the chemotherapy usually leads to shrinkage of lymph nodes, increasing the likelihood of R0 resection. Second, more intensive chemotherapy is possible with high compliance. Third, distant micrometastases can be treated early, before local therapy has begun. Recently, the effectiveness of a regimen of preoperative and postoperative epirubicin, cisplatin and infused fluorouracil for less advanced disease was suggested[10]. Combined chemotherapy using irinotecan hydrochloride plus cisplatin is also an attractive regimen for preoperative chemotherapy. In a phase II trial using this regimen in patients with metastatic gastric cancer, a response rate of 48 per cent and acceptable toxicity were reported[11].

The present study was conducted to evaluate the efficacy and safety of preoperative chemotherapy with irinotecan plus cisplatin followed by gastrectomy with D2 plus para-aortic nodal dissection for locally advanced gastric cancer with extensive lymph node metastases.

Methods

The study was conducted as a prospective multi-institutional phase II trial between 2000 and 2003 involving the 21 institutions of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with locally advanced gastric cancer presenting at their institution were considered for participation in the study. The absence of peritoneal dissemination was confirmed by laparoscopy before entry into the study.

Eligibility criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; para-aortic nodal metastases and/or bulky N2 cancers confirmed by contrast-enhanced computed tomography (CT) (definitions in *Fig. 1*); no metastases outside the para-aortic region, as confirmed by contrast-enhanced CT; no peritoneal or pleural effusion; no

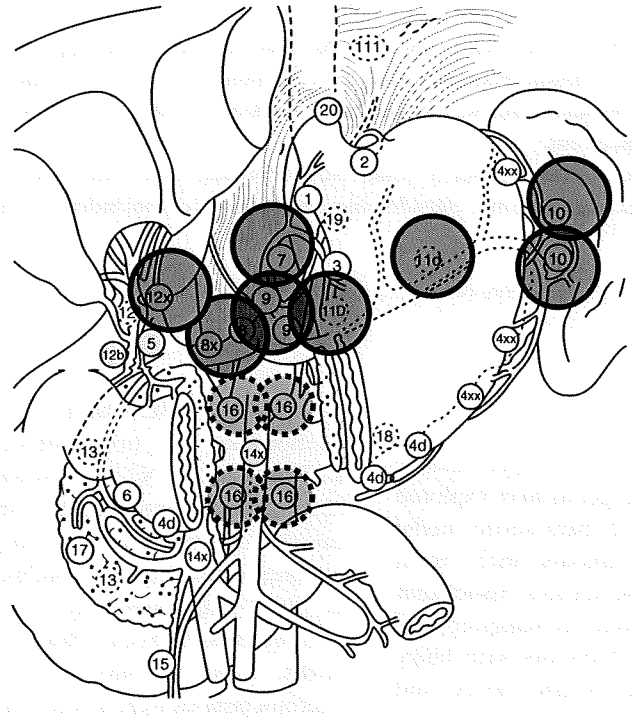

Fig. 1 Definitions of bulky N2 and para-aortic nodal metastases. Bulky N2 (in solid circles): at least one node of 3 cm or more in diameter, or at least three consecutive nodes each of diameter 1·5 cm or more, along the coeliac, splenic, common or proper hepatic arteries. Para-aortic nodes (in dashed circles): at least one node of 1 cm or more in diameter around the abdominal aorta

clinically apparent brain or bone metastases; no peritoneal metastases and negative cytology at laparoscopy; non-scirrhous type macroscopically; 20–70 years of age; Eastern Cooperative Oncology Group performance status 0 or 1; no previous chemotherapy or radiotherapy. In addition, patients had to have no signs of organ failure, as assessed by a white blood cell (WBC) count minimum of 4000/mm^3 and maximum of 12 000/mm^3, platelet count of 100 000/mm^3 or above, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than three times the upper limit of normal, total bilirubin 1·5 mg/dl or less, creatinine 1·2 mg/dl or less and creatinine clearance 60 ml/min or above, and haemoglobin 9·0 g/dl or more. There had to be no ischaemic change or ventricular arrhythmia on exercise electrocardiography, a forced expiratory volume in 1 s of 50 per cent or more, arterial partial pressure of oxygen (PaO_2) of 70 mmHg or above, and indocyanine green test in 15 min of 10 per cent or less in cases of liver dysfunction, negative serology for viral hepatitis and no past history of hepatitis. All patients gave written informed consent.

Exclusion criteria included: active gastrointestinal bleeding, infection, watery diarrhoea, synchronous or metachronous (within 10 years) malignancy other than carcinoma *in situ*, pregnancy or lactation, treatment with a major tranquillizer, lung fibrosis or interstitial pneumonitis, and bowel obstruction. Patients with allergic reactions to iodine were excluded because contrast-enhanced CT could not be performed. All patients were registered centrally at the JCOG Data Centre, where data management, central monitoring and statistical analysis were conducted. For quality assurance, a site visit audit was performed by the JCOG Audit Committee.

Preoperative chemotherapy

Irinotecan 70 mg/m^2 was administered on days 1 and 15 and cisplatin 80 mg/m^2 was given on day 1 as one course, repeated every 4 weeks[11]. If the patient had a WBC of 4000/mm^3 or less, platelet count of 10 000/mm^3 or lower, diarrhoea of grade 1 or above (increase of four or more stools per day over pretreatment), an episode of infection or abnormal serum creatinine concentration, administration of irinotecan and/or cisplatin was postponed until recovery. If recovery did not occur within 2 weeks, chemotherapy was stopped. On day 15 of each course, if the patient had an adverse event the second administration of irinotecan was postponed, and was not given if the adverse event was still observed on day 22. If the patient had haematological adverse events of grade 4 (haemoglobin level less than 6·5 g/dl, leucocyte count below 1000/mm^3, neutrophil count less than 500/mm^3, or platelet count below 25 000/mm^3), diarrhoea of grade 3 or higher (increase of more than seven stools per day or incontinence, or need for parenteral support for dehydration), or if the second administration of irinotecan was not given in the last course, the next dose of irinotecan was reduced to 60 mg/m^2. If the patient had a serum creatinine level of 1·2–1·5 mg/dl, the next dose of cisplatin was reduced to 60 mg/m^2. If serum creatinine was 1·5 mg/dl or above, initiation of the next course was delayed.

Some 7–13 days after the second administration of irinotecan in each course, resectability was evaluated based on CT findings by the Response Evaluation Criteria in Solid Tumours (RECIST)[12]. If curative resection was considered possible after the second course, the patient had surgery immediately. If curative resection was considered difficult, a further course of chemotherapy was added before surgery.

Surgery

Resection criteria included: R0 resection deemed possible by gastrectomy with D2 plus para-aortic nodal dissection, and no evidence of organ failure as assessed by a WBC count greater than 3000/mm^3 and less than 12 000/mm^3, platelet count above 100 000/mm^3, AST and ALT levels less than three times the upper limit of normal, total bilirubin less than 1·5 mg/dl, creatinine below 1·5 mg/dl and creatinine clearance above 50 ml/min, and PaO_2 greater than 70 mmHg. Eligible patients were operated on 3–6 weeks after chemotherapy.

After laparotomy, resectability was again evaluated and, if intraperitoneal wash cytology was negative, R0 resection was attempted by gastrectomy with D2 plus para-aortic nodal dissection, as described previously[13]. If necessary, D2 plus para-aortic nodal dissection was combined with splenectomy and/or distal pancreatectomy.

The treatment protocol was completed when a patient had received two or three courses of preoperative chemotherapy and had undergone R0 resection by gastrectomy with D2 plus para-aortic nodal dissection (*Fig. 2*). After completion of the protocol, no further treatment was given until tumour recurrence.

Quality control of surgery

During the recruitment period, participating surgeons and data centre representatives met three times per year to monitor the study. At each meeting, videos of various surgical procedures, including nodal dissection, were presented by several participating institutions,

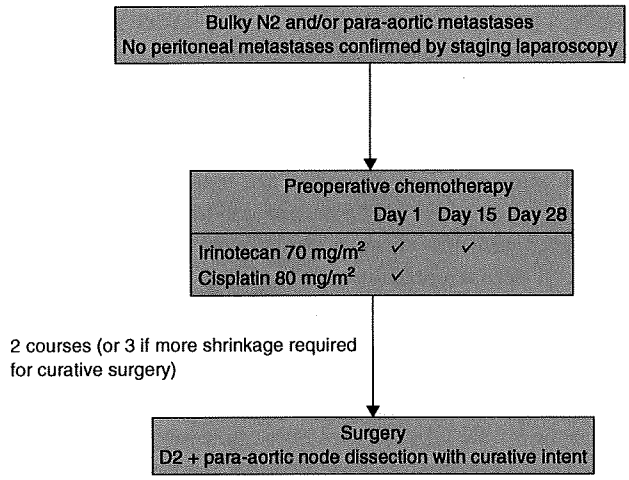

Fig. 2 Study outline

and technical details were discussed for critique. To assess compliance with lymphadenectomy, the number of dissected nodes was recorded.

Objectives and evaluation

Primary endpoints were overall survival and incidence of treatment-related death. Secondary endpoints were number of R0 resections, response to chemotherapy, chemotherapy-related toxicity and surgical complications. Clinical response was evaluated by RECIST[12], based on CT with a central review. Surgical specimens were evaluated pathologically and graded according to the proportion of tumour affected by degeneration or necrosis[14]: grade 0, no part of tumour affected; grade 1a, less than one-third affected; grade 1b, between one-third and two-thirds affected; grade 2, between two-thirds and entire tumour affected; and grade 3, no residual tumour. A pathological response was defined as one-third or more of the tumour affected (grade 1b, 2 or 3). Adverse events during chemotherapy were evaluated by the National Cancer Institute – Common Toxicity Criteria version 2.0[15].

Statistical analysis

For sample size calculation, treatment was considered effective if the lower limit of the 95 per cent confidence interval (c.i.) for 3-year survival exceeded 15 per cent. In terms of feasibility and efficiency, sample size was determined as 60 with a 3-year entry and 3-year follow-up period. In this setting, the exact binomial lower confidence limit for a 3-year overall survival rate of 30 per cent (18 of 60) was 18·9 per cent and that for 25 per cent (15 of 60) was 14·8 per cent. This was considered sufficiently precise to make inferences based on 3-year survival. Hence, the sample size was calculated as 60.

The survival curve was estimated using the Kaplan–Meier method; 95 per cent c.i. were calculated with the Greenwood formula[16]. Treatment was considered safe if point estimates of treatment-related death did not exceed 5 per cent. The stopping rule for safety was prespecified so that the study would be terminated when treatment-related death had been observed in three patients (treatment-related death exceeding 5 per cent). Statistical analysis was performed with SAS® version 8.2 (SAS Institute, Cary, North Carolina, USA). This phase II trial was approved by the JCOG Protocol Review Committee and institutional review board of each institution involved.

Results

Between August 2000 and May 2003, 55 patients were entered into the study and underwent preoperative chemotherapy. All patients were followed for more than 3 years after registration. When 55 patients had been registered, three were judged as treatment-related deaths by the JCOG data and safety monitoring committee, and the study was terminated according to the stopping rules. Thus, the treatment-related death rate was 5 (95 per cent c.i. 1 to 15) per cent. *Table 1* shows patient demographics and tumour characteristics. A flow diagram from chemotherapy to surgery is shown in *Fig. 3*. The clinical response rate for all eligible patients was 55 (95 per cent c.i. 41 to 68) per cent (30 of 55 patients) (*Fig. 3*).

Table 1 Demographics and tumour characteristics in 55 eligible patients

Median (range) age (years)	63 (46–70)
Sex ratio (M : F)	42 : 13
ECOG performance status	
0	47
1	8
Histology	
Differentiated	30
Undifferentiated	25
Nodal status	
Para-aortic nodes and bulky N2	19
Only para-aortic nodes	11
Only bulky N2	25

ECOG, Eastern Cooperative Oncology Group.

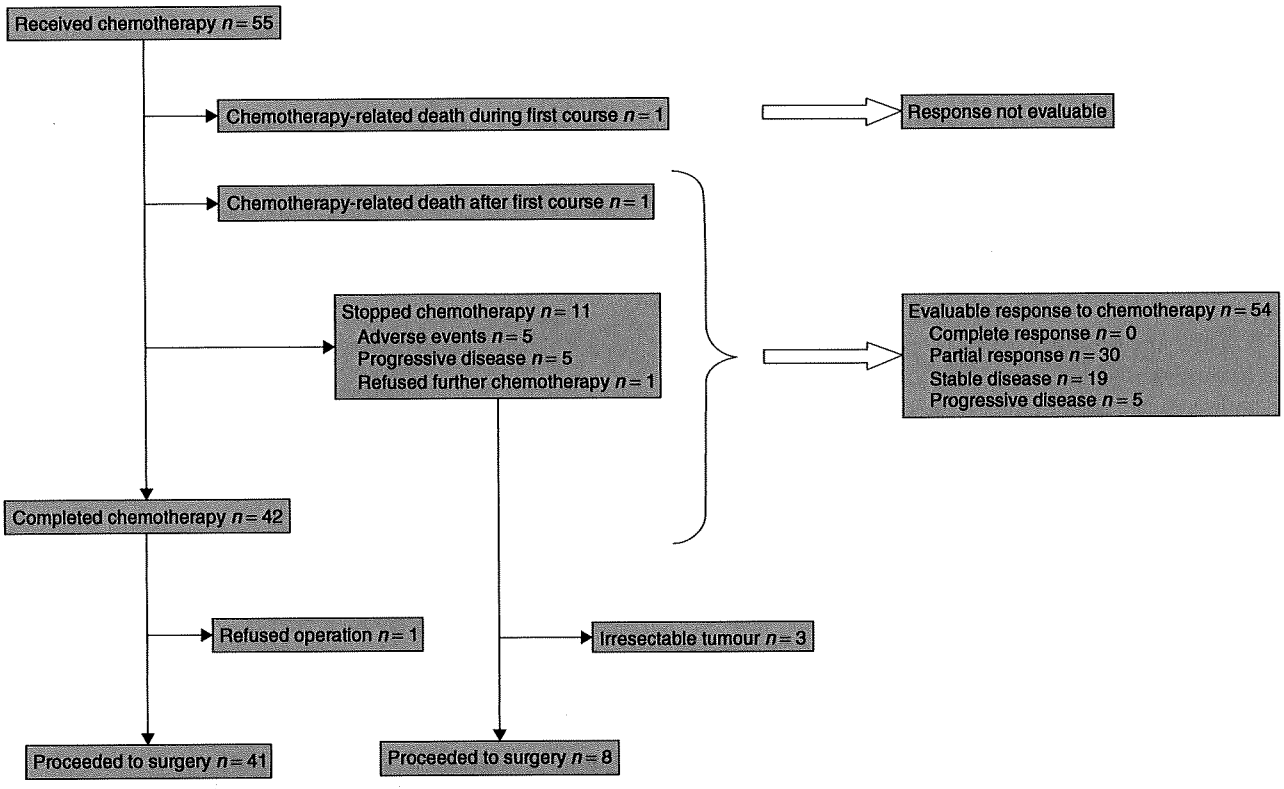

Fig. 3 Flow diagram from chemotherapy to surgery in 55 eligible patients

Table 2 Details of 49 patients who underwent surgery

	No. of patients
Peritoneal cytology	
Negative	45
Positive	4
Type of resection	
Total gastrectomy	32
Distal gastrectomy	15
Bypass	1
Exploratory laparotomy	1
Dissection of nodes along splenic artery	
With splenectomy and distal pancreatectomy	14
With splenectomy	16
Without splenectomy	13
No nodal dissection	6†
Operating time (min)*	370 (40–930)
Blood loss (ml)*	1050 (0–5650)
Blood transfusion	34
No. of para-aortic nodes dissected*	26 (0–86)
No. of nodes dissected*	87 (45–179)

*Values are median (range). †Exploratory laparotomy in one patient, bypass in one, palliative resection in one and non-curative resection in three patients.

Table 3 Pathological findings in resected patients

	No. of patients (n = 47)
Depth of tumour invasion	
T1	3
T2	18
T3	19
T4	6
Unknown	1*
JGCA, nodal status	
N0	1
N1	7
N2	9
N3	30
JGCA, pathological response	
Grade 0	6
Grade 1a	33
Grade 1b	2
Grade 2	5
Grade 3	1

*Not evaluable as no residual cancer cells. JGCA, Japanese Gastric Cancer Association.

Surgical findings and surgical pathology

Forty-nine patients proceeded to surgery (*Table 2*). Resection with curative intent was undertaken in 46 patients. One patient had only exploratory laparotomy because of peritoneal metastases, one underwent gastrojejunostomy, and one required palliative resection to stop bleeding from the primary tumour. Of the 46 patients who had resection with curative intent, R0 resection was performed in 36, R1 in four (positive surgical margin, three; positive peritoneal cytology, one) and R2 in six with unresectable tumours (*Table 3*). Thus, the proportion of R0 resections in the 55 eligible patients was 65 (95 per cent c.i. 51 to 78) per cent.

The pathological response rate in resected patients was 15 (95 per cent c.i. 7 to 27) per cent.

Adverse events from chemotherapy

Toxicity of grade 3 or above included leucopenia (31 per cent), neutropenia (55 per cent), anaemia (24 per cent), febrile neutropenia (16 per cent), nausea (36 per cent), vomiting (13 per cent) and diarrhoea (5 per cent). Two patients died from myelosuppression after the initial chemotherapy course, giving a chemotherapy-related mortality rate of 4 per cent (two of 55 patients).

Surgical complications

Surgical complications are shown in *Table 4*. One (2 per cent) of 49 patients died from multiple organ failure 3 days after thoracoabdominal surgery for oesophageal invasion in addition to a total gastrectomy with pancreaticosplenectomy.

Overall survival

The 3-year survival rate was 27 (95 per cent c.i. 15 to 39) per cent, and thus the lower limit of the 95 per cent c.i. was higher than the prespecified threshold (*Fig. 4*). Median survival was 14·6 (95 per cent c.i. 10·1 to 24·1) months.

Table 4 Surgical complications in the 49 operated patients

	No. of patients
Leakage	1 (2)
Pancreatic fistula	6 (12)
Abdominal abscess	2 (4)
Pneumonia	2 (4)
Ileus	0 (0)
Wound infection	2 (4)
Stenosis of anastomosis	1 (2)
Cardiac failure	1 (2)
Renal dysfunction	1 (2)
Other	6 (12)

Values in parentheses are percentages.

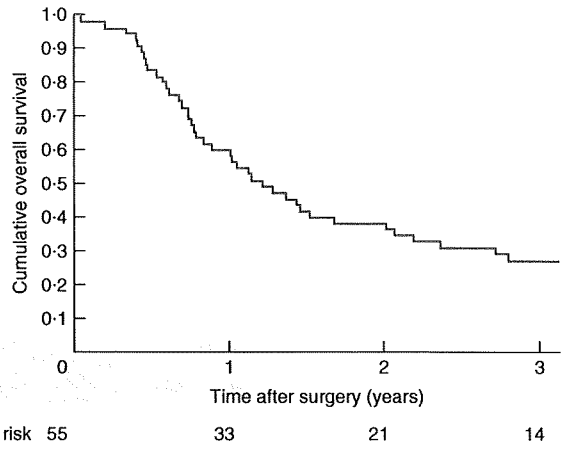

Fig. 4 Kaplan–Meier overall survival curve for the 55 eligible patients

Discussion

This multi-institutional phase II prospective trial of neoadjuvant chemotherapy in locally advanced gastric cancer with extensive lymph node metastases showed that multimodality treatment can achieve a high 3-year survival rate of 27 per cent. Usually these patients rarely survive for more than 3 years when treated by chemotherapy alone or by surgery followed by postoperative chemotherapy. Thus, the protocol treatment was effective for these patients, but was achieved at the cost of considerable morbidity and mortality, and the study had to be stopped prematurely because of treatment-related deaths.

The combination chemotherapy of irinotecan plus cisplatin was chosen because it had achieved a high response rate of 59 per cent in a previous phase II study of chemotherapy-naive patients with metastatic gastric cancer[11]. At the start of the present study in 2000, this was considered to be the most effective and promising regimen for gastric cancer. In Japan, based on these data, a phase III trial was initiated to determine the superiority of irinotecan plus cisplatin compared with 5-fluorouracil (5-FU) alone for metastatic gastric cancer[17]. In the present study, the clinical response to preoperative chemotherapy was 55 per cent, comparable with previous results using this regimen in patients with metastatic gastric cancer[11]. Although the above-mentioned Japanese phase III trial (JCOG 9912) did not demonstrate superiority for this regimen compared with 5-FU alone, a subset analysis for tumours with target lesion defined by RECIST

showed that combination chemotherapy of irinotecan plus cisplatin gave a median survival of 12·1 months, which was significantly longer than for 5-FU alone[17]. This suggested that irinotecan plus cisplatin was especially active against tumours forming bulky masses[17]. In contrast to the impressive clinical response of metastatic nodes, the pathological response in the primary tumours was relatively low in the present study. In gastric cancer, the pathological response rate is usually less than 20 per cent for any chemotherapeutic regimen, suggesting the importance of appropriate local control by surgery. The relatively good overall survival at 3 years in the present study appears to be due to the effects of neoadjuvant chemotherapy in two ways: downstaging of lymph node metastases, which enabled R0 resection in 65 per cent of patients, and good control of micrometastases.

Treatment-related death was observed in 5 per cent of patients in this study, indicating that this treatment protocol is hazardous. Of three patients, two died from chemotherapy-induced myelosuppression. Neutropenia and diarrhoea were the major toxicities of this regimen, as reported previously[11,17]. Compared with these trials, toxicity in the present study was relatively low, but the mortality rate was high. In two treatment-related deaths from chemotherapy, severe myelosuppression appeared immediately after the first administration of irinotecan plus cisplatin. Boku and colleagues[17] observed severe diarrhoea only during the first course of the same regimen in patients with unresectable gastric cancer. Noda and co-workers[18] reported on the efficacy of combination therapy with irinotecan plus cisplatin for small cell lung cancer, using a different schedule and dosage than those in the present study. They observed treatment-related deaths in three patients (4 per cent) during the first or second cycle of chemotherapy. Taken together, all of these results indicate that severe haematological toxicity and diarrhoea should be managed carefully, especially during the initial cycles of chemotherapy.

Recently, genetic polymorphism of UTG1A1, which is involved in glucuronidation of SN-38 or is an active metabolite of irinotecan, has been reported to be associated with irinotecan toxicity[19,20]. Polymorphisms of UGT have also recently been suggested as a risk factor for irinotecan-induced neutropenia[21]. These factors might have been involved in the treatment-related deaths observed in the present study, although genetic analysis was not performed. Patient risk may be reduced not only by careful management of myelosuppression, but possibly also by patient selection based on genetic analysis. However, further studies are needed to confirm this. Because the combination chemotherapy regimen employed in this study is difficult to manage in terms of toxicity, a new phase II study has been initiated to evaluate a preoperative S-1 (oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine and potassium oxonate) plus cisplatin regimen, which is considered less toxic for patients with extensive nodal metastases. S-1 and cisplatin showed a high response rate of over 50 per cent with mild toxicity in recent trials of patients with metastatic gastric cancer[22,23].

The operative mortality rate in this study was 2 per cent. In the JCOG 9501 trial, which compared D2 with D2 plus para-aortic nodal dissection, the mortality rate was 0·8 per cent for D2 plus para-aortic nodal dissection[13], whereas in the JCOG 9502 trial, which compared an abdominal approach with a left thoracoabdominal approach for gastric tumours invading the oesophagus, mortality rates were 0 and 4 per cent respectively[24]. Thus, the thoracoabdominal approach was the more hazardous of the two procedures. Because the influence of preoperative chemotherapy on surgery is unclear, patients who require such an extensive thoracoabdominal operation should probably be excluded from future studies.

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The authors declare no conflict of interest.

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A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study)

Y. Kodera [a,*], S. Ito [b], Y. Mochizuki [b], K. Kondo [c], K. Koshikawa [d], N. Suzuki [e], H. Kojima [f], T. Kojima [f], T. Matsui [f], T. Takase [g], K. Tsuboi [h], M. Fujiwara [a], A. Nakao [a] for Chubu Clinical Oncology Group

[a] *Department of Surgery II, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan*
[b] *Department of Gastroenterological Surgery, Aichi Cancer Center Chuo Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan*
[c] *Department of Surgery, Nagoya Medical Center, 4-1-1, Sannomaru, Naka-ku, Nagoya, Aichi 460-0001, Japan*
[d] *Department of Surgery, Komaki Municipal Hospital, 1-20, Jobushi, Komaki, Aichi 485-5820, Japan*
[e] *Department of Surgery, Aichi Koseiren Atsumi Hospital, 1-1, Akaishi, Kobe-cho, Tahara, Aichi 441-3415, Japan*
[f] *Department of Surgery, Aichi Cancer Center Aichi Hospital, 18 Ketsumachi Aza Kuriyado, Okazaki, Aichi 444-0011, Japan*
[g] *Department of Surgery, Aichi Koseiren Kainan Hospital, 396 Minami Honda, Maegasu-cho, Yatomi, Aichi 498-8502, Japan*
[h] *Department of Surgery, Koritsu Tosei Hospital, 160 Nishi Oiwake-cho, Seto, Aichi 489-8642, Japan*

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Abstract

Background: Patients with gastric cancer who have positive cytologic results for cancer cells in peritoneal washings (CY1) have poor outcomes, even in the absence of other distant metastases. A standard treatment for such patients remains to be established.
Methods: We conducted a phase II trial with the 2-year survival rate as the primary endpoint. Patients who had gastric cancer with CY1 status but no other residual disease received postoperative chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) at a daily dose of 80 mg/m^2 for 4 weeks, followed by 2 weeks of rest. This cycle was continued until disease progression or intolerable adverse events. D2 dissection was the recommended surgical procedure; splenectomy could be omitted at the discretion of the surgeon. Accrual of 50 patients was planned, and a 2-year survival rate of more than 36% was needed to exceed the historical control.
Results: Forty-eight patients were enrolled, among whom 47 were assessable for survival and 46 for adverse reactions. Median overall survival was 705 days, and progression-free survival was 376 days. The 2-year survival rate was 47%. Median time to treatment failure was 288 days. Neutropenia was the commonest ≥grade 3 toxicity (6 patients), and anorexia was the most frequent ≥grade 2 non-hematologic toxicity (10 patients).
Conclusions: Gastrectomy followed by S-1 monotherapy resulted in survival that surpassed historical data and can serve as an active control treatment for future trials in patients who have gastric cancer with CY1 status in the Far East.

Keywords: Gastric cancer; S-1; Cytologic examination; Peritoneal carcinomatosis

Introduction

Despite the declining incidence in Western Europe[1] and the United States,[2] gastric carcinoma remains the second most common cause of cancer-related death worldwide, with over 600 000 deaths per year.[3] Peritoneal carcinomatosis is a major pattern of disease recurrence after D2 dissection, a standard procedure in the Far East that presumably improves locoregional control.[4,5] Similar problems could also develop in the United States if a strategy of D1 dissection followed by chemoradiation is found to achieve good local control.[6] Peritoneal metastasis is generally considered to arise from free cancer cells shed from the serosal surface of locally advanced gastric cancer. Such cells, if present, can be detected by cytologic examination of peritoneal washings,[7] a standard diagnostic procedure performed for accurate staging in all patients with advanced

* Corresponding author. Tel.: +81 52 744 2250; fax: +81 52 744 2255.
E-mail address: ykodera@med.nagoya-u.ac.jp (Y. Kodera).

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gastric cancer who undergo surgery in Japan. Positive cytologic results for cancer cells indicate a very high risk of peritoneal carcinomatosis. The Japanese Classification of Gastric Carcinoma classifies positive cytologic results as CY1 status. Patients with CY1 status are automatically considered to have Stage IV disease, and surgery is classified as curability C, i.e., noncurative resection.[8] The prognostic significance of positive cytologic results of peritoneal washings has also been acknowledged in Europe,[9] and more recently, in the United States.[10]

Currently, there is no standard treatment for patients found to have CY1 status after surgery. Surgeons in Japan encounter this situation rather frequently, because preoperative evaluation with the cytologic examination in addition to staging laparoscopy[11] remains an option, not a standard of care for the patients with locally advanced cancer. Hence, results of the cytologic examination are often obtained only after the surgery. Since gross peritoneal carcinomatosis indicates incurable disease, early treatment with anticancer drugs is usually recommended in addition to surgery for CY1 disease. S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) has had response rates of >40% in phase II trials[12,13] and good tolerability in patients with gastric cancer when given within 2–6 weeks after surgery.[14] A pivotal phase III trial conducted in Japan has shown that S-1 is effective in a postoperative adjuvant setting in patients with stages II and III gastric cancer.[15] These promising results have led to the increased use of S-1 for postoperative treatment in patients with CY1 disease. In the present study, patients who underwent R1 resection and had microscopic evidence of residual disease only in the form of free cancer cells in the abdominal cavity postoperatively received oral S-1. Our main objective was to evaluate the 2-year survival rate as compared with a historical control.

Patients and methods

Patient eligibility

Eligible patients had to meet all of the following criteria: (i) a confirmed diagnosis of gastric adenocarcinoma and an age of less than 80 years; (ii) gastrectomy with systemic lymphadenectomy, preferably with D2 dissection, performed; (iii) no distant metastasis with the exception of minimal peritoneal deposits that were completely resected; (iv) no prior treatment besides surgery; and (v) positive cytologic results for cancer cells on examination of peritoneal washings (CY1). Cytologic examination was performed as recommended by the Japanese Classification of Gastric Carcinoma,[8] i.e., 100 mL of saline was introduced into the pouch of Douglas, stirred gently, and aspirated. Direct washing of the serosa of the stomach or of the upper abdominal cavity was not performed. The specimens were examined by board-certified pathologists after conventional Papanicolaou and Giemsa staining. It was not mandatory to obtain the results of cytologic examinations during surgery. The interval from surgery to the start of therapy was not to exceed 6 weeks. Other eligibility criteria included a Cooperative Oncology Group performance status of 0–2, and adequate organ functions, defined as total neutrophil count $\geq 3000/mm^3$, platelet count $\geq 100\,000/mm^3$, hemoglobin ≥ 8.0 g/dL, serum creatinine within the normal range according to the criteria of the hospital where the test was performed, total serum bilirubin <1.5 mg/dL, and serum aspartate aminotransferase and alanine aminotransferase <2.5 times the upper limit of normal. Patients with other active malignancies or uncontrolled concomitant diseases were excluded. Written informed consent was obtained from all participants after they had received a full explanation of the nature of the study. The study was approved by the institutional review board of Nagoya University Hospital and all other hospitals belonging to the Chubu Clinical Oncology Group that participated in this multicenter trial.

Pretreatment evaluation, treatment plan, and dose attenuation

At baseline, a complete medical history was taken, and a physical examination was performed. Laboratory assessment at baseline included blood cell counts, serum chemistry profiles, serum tumor markers (carcinoembryonic antigen, CA19-9), and urinalysis. Patients also underwent a baseline electrocardiographic examination and computed tomography (CT) scans of the chest, abdomen and pelvis.

Patients received S-1 at an oral dose of 40 mg per square meter of body-surface area twice daily for 4 weeks, followed by 2 weeks without chemotherapy. Patients with a body-surface area of less than 1.25 m^2 received 80 mg daily; those with a body-surface area of 1.25 m^2 to less than 1.5 m^2 received 100 mg daily; and those with a body surface area of 1.5 m^2 or greater received 120 mg daily. This 6-week cycle was repeated in an outpatient setting under medical supervision until disease progression, unacceptable adverse events, or the patient's withdrawal of consent. If the patients had either ≥grade 3 hematologic toxicity or ≥grade 2 non-hematologic toxicity, the daily dose of S-1 was decreased from 120 mg to 100 mg, from 100 mg to 80 mg, or from 80 mg to 50 mg. If adverse events tended to occur during the third or fourth week of S-1 treatment, the schedule could be modified to a 3-week cycle, in which patients were given S-1 for 2 weeks followed by 1 week of rest.

Disease status was assessed once every 3 months on the basis of serum tumor markers and at least once every 6 months by CT scanning. Adverse events were monitored by interviews, blood chemical profiles, and blood cell counts once every 2 weeks. All toxic effects were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2.0).

Biostatistics

Data on 30 consecutive patients with gastric cancer who underwent surgery from 1995 to 1999 and had positive cytologic results of peritoneal washings (CY1) as the sole cause of noncurative resection were retrospectively retrieved from the database of Aichi Cancer Center Hospital, a high-volume center in the Aichi district of Japan. Survival data were analyzed for these patients to provide a historical control. The 2-year survival rate of this cohort was 13.3% (90% confidence interval, 3.1–23.5%). The 2-year survival rate of patients with advanced/metastatic gastric cancer who were given single-agent S-1 at National Cancer Center East (a high-volume center that participated in late phase II trials of S-1 before the drug became available to community hospitals) was 36%. On the basis of these data, we assumed that the 2-year survival rate of our series would be 36% and expected that the lower limit of the 90% confidence interval would exceed 23.5% (i.e., the upper limit of the 90% confidence interval for the historical control) to calculate the required number of patients. We estimated that 50 patients would have to be enrolled to achieve a 2-year survival rate of 36% (18/50) with a 90% confidence interval of 24.8–47.3% and designated the 2-year overall survival rate as the primary endpoint of this study. The secondary endpoints were safety and the time to treatment failure. Survival analyses were carried out with the Kaplan–Meier method.

Results

Patient population

Forty-eight patients were enrolled between February 2002 and July 2006. The demographic and clinicopathologic characteristics of the patients are shown in Table 1. One of the patients was mistakenly enrolled despite having no cytologic evidence of cancer cells in peritoneal washings (CY0). This patient was ineligible and excluded from further analysis. Resections were classified as palliative (R1) according to the results of cytologic examination of peritoneal washings in all but one patient who had a positive resection margin on microscopic examination of the resected specimen in addition to the CY1 status. This patient was included in the survival analysis; it was assumed at the time that CY1 would be a stronger prognostic determinant than a positive resection margin. The patient died 561 days after surgery. Another patient who died of myocardial infarction 5 days after starting treatment with S-1 was included in the analysis of survival but not of adverse events; this death was considered unlikely to have been treatment-related.

Of the 47 eligible patients, 7 patients had peritoneal deposits, which were co-resected at surgery (Table 1). Seven patients were intraoperatively confirmed to have invasion to adjacent organs (T4), and 38 others had serosal invasion.

Table 1
Patient demographics ($n = 47$).

	No.	%
Age, years		
Mean (range)	63 (39–79)	
Gender		
Female	15	32
Male	32	68
ECOG Performance Status		
0	35	74
1	12	26
2	0	0
pT categories		
1	2	4
2	2	4
3	37	79
4	6	13
pN categories		
0	5	11
1	11	23
2	25	53
3	6	13
Peritoneal deposits		
No	40	85
Yes	7	15
Histological type		
Undifferentiated	25	53
Differentiated	18	38
Mucinous	4	9
Surgery		
Total gastrectomy	19	41
Distal gastrectomy	27	57
Pancreaticoduodenectomy	1	2
Nodal dissection		
D0	1	2
D1	13	28
D2	31	66
D3	2	4

All but five patients were confirmed to have nodal involvement on pathological examination; six patients had metastasis to the paraaortic lymph nodes.

Responses and survival

Owing to the unique eligibility criteria, objective response was not assessable in any patient. Overall survival and progression-free survival are shown in Fig. 1. Median overall survival time was 705 days, and progression-free survival time was 376 days. The 2-year survival rate was 47% (90% confidence interval, 34.8–58.8%). The lower limit of the 90% confidence interval exceeded the upper limit of the confidence interval for the historical control (23.5%). The most frequent pattern of disease recurrence was peritoneal carcinomatosis, occurring in 26 patients. Other patterns of recurrence were hepatic in 4 patients, lymphatic in 4, locoregional in 2, pulmonary in 1, and osseous in 1. Median survival after confirmation of recurrence was 183 days. Median time to treatment failure was 288 days (Fig. 2). There was no difference in survival between the 7 patients with visible peritoneal

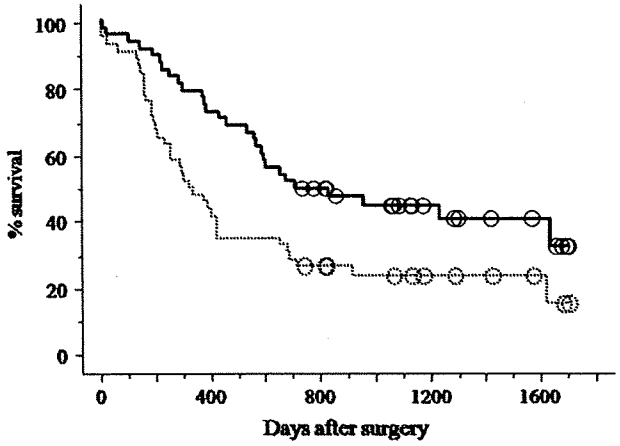

Figure 1. Overall survival (solid line) and progression-free survival (dotted line) of patients with gastric cancer who had free cancer cells in the peritoneal cavity and underwent surgery followed by S-1 monotherapy. Median survival was 705 days with a 2-year survival rate of 47%. Progression-free survival was 376 days.

deposits in addition to positive cytologic results and the other 40 patients with only positive cytologic results.

Compliance, dose intensity, and toxicity

Two patients did not start chemotherapy within 6 weeks after surgery because of surgical complications; however, treatment was eventually started in all enrolled patients. S-1 monotherapy was terminated within 1 year because of toxicity in seven patients. In four of these patients, S-1 was withdrawn within the first 6-week cycle. The dose of S-1 had to be reduced by one level in 7 of the 40 patients who tolerated treatment. The treatment schedule was switched to a 3-week cycle in two of the seven patients who underwent dose reduction and in one other patient. Treatment was generally well tolerated. The toxicity profile is shown in Table 2. Grade IV toxicity occurred in only one patient, who was among the four patients who discontinued therapy during the first cycle. Neutropenia was the most common grade III toxicity, and anorexia and nausea were the commonest reasons for drug withdrawal.

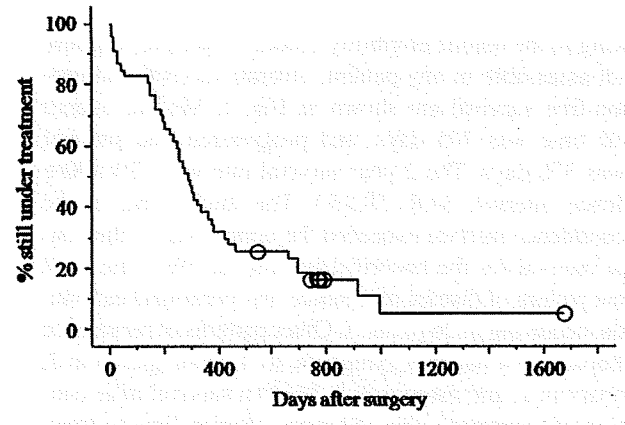

Figure 2. Time to treatment failure in patients with gastric cancer who had free cancer cells in the peritoneal cavity and underwent surgery followed by S-1 monotherapy. Median time to treatment failure was 288 days.

Table 2
Adverse events in postoperative S-1 monotherapy ($n = 46$).

	No. of patients			% ≥Grade 3
	Grade 2	Grade 3	Grade 4	
Leukocytopenia	15	1	0	2
Neutropenia	12	6	0	13
Anemia	20	3	0	7
Thrombocytopenia	1	0	0	0
	No. of patients			% ≥Grade 2
	Grade 2	Grade 3	Grade 4	
Anorexia	7	3	1	24
Nausea	4	4	0	17
Vomiting	2	0	0	4
Stomatitis	6	0	0	13
Diarrhea	8	0	0	17
AST/APT	2	2	0	9
Bilirubin	3	6	0	20
Creatinine	1	0	0	2
Pigmentation	9	0	0	20
Eruption	5	1	0	13
General malaises	1	3	0	9

Discussion

S-1 as a logical candidate for treatment of CY-1 stage gastric cancer

CY1-stage disease has not been studied extensively in clinical trials, despite the clear prognostic value of cytologic examination.[7] The main reason for the paucity of studies has been the lack of measurable lesions and consequent difficulty in evaluating treatment response. The optimal treatment strategy for patients who have gastric cancer with CY1 status thus remains to be defined. S-1 is an oral fluoropyrimidine that has had very high response rates when given as a single agent in the Far East.[12,13] The efficacy and safety profile of S-1 after gastrectomy have been evaluated in a pivotal phase III trial in Japan.[15] In that trial, postoperative adjuvant chemotherapy with S-1 was also suggested to reduce the incidence of peritoneal recurrence.[15] We have previously studied the activity of S-1 in an *in vivo* model of peritoneal metastasis and reported that S-1 given early after the dissemination of gastric cancer cells may be effective.[16] S-1 monotherapy may therefore be a useful treatment option for patients with CY1 status in community hospitals. Clinical data supporting its efficacy in this subgroup of patients had been lacking, however, and a prospective study was awaited.

Difficulties in designing a clinical trial for CY1 stage cancer

Since patients with CY1 status have no measurable lesions, the endpoint of a clinical trial had to be survival time. Ideally, a randomized controlled study comparing S-1