Keywords Gastric cancer · Palliation · Chemoradiation · Local recurrence · Phase I study

Introduction

Gastric cancer is the most common malignancy in Japan and the second most frequent neoplasm in the world [1]. Although a complete surgical resection is the only curative treatment for locally advanced gastric cancer [2], some patients recur even after undergoing curative surgery. The prognosis has been reported to be 3–4 months with best supportive care and 7–10 months with chemotherapy in patients with recurrent tumors or primary advanced unresectable disease [3]. However, chemotherapy is indicated only for the patients with a good performance status and sufficient organ function, otherwise palliative treatment is considered for the patients with local symptoms or insufficient organ function. In the latter patients, chemotherapy should therefore be initiated only when these conditions are well palliated. Recently, standard chemotherapy for gastric cancer was established in Japan, based on the results of two phase III studies [4, 5]. JCOG9912 trial demonstrated the non-inferiority of S1 to 5-FU and no significant superiority of CPT-11 plus CDDP to 5-FU [4], while SPIRITS trial showed the superiority of S1 plus CDDP to S1 [5]. From these data, S1 plus CDDP has become considered the standard as first line chemotherapy.

Primary metastatic or recurrent cancers are sometimes problematic due to the local tumors which cause local symptoms such as gastrointestinal (GI) obstruction or local pain. GI obstruction causes malnutrition, and the localized pain decreases the quality of life and the performance status of the patients. To control these symptoms, chemotherapy is often insufficient, while the benefits obtained by palliative surgery do not match the surgical risk because of both the need to perform a thoracotomy for local or esophageal invasion as well as difficulties encountered in the operation itself due to adhesions after the curative D2 surgery. In Japan, although patients with local gastric tumors causing the localized symptoms are rare, these patients are difficult to treat.

Chemoradiation is another modality for the treatment of gastric cancer. Localized effects of chemoradiation therapy have been suggested in several studies in the US [6–10]. So long as chemotherapy combined with radiation, the regimen is limited for those patients. 5-FU or S1 is commonly administered in adjuvant or first line setting in Japan. Oral drug, S1 and CPT-11 are contraindicated for patients with gastrointestinal obstruction. On the other hand, paclitaxel is an attractive candidate for such patients with tumor complication due to its toxicity profiles. Also in several phase II studies of chemoradiation, paclitaxel was reported to be effective [7, 9]. The aim of this study was to evaluate the toxicities of chemoradiation therapy with paclitaxel (PTX) and cisplatin (CDDP) for localized symptoms due to unresectable primary advanced or locally recurrent gastric cancer.

Patients and methods

Selection of patients

The eligibility criteria included a histologically verified adenocarcinoma of the stomach, a gastrointestinal obstruction or localized pain due to an unresectable or locally recurrent gastric cancer located in the left upper abdomen, which is defined as the area of the abdomen on the right edge of the vertebra and above the third portion of the duodenum or left renal vein, and also as the area of the lower mediastinum within 5 cm above the esophagogastric junction, an age range from 20–80, an ECOG performance status from 0 to 1, one or no prior chemotherapy completed 3 weeks before entry, no previous chemotherapy including CDDP of more than 240 mg/m^2 or no previous combination chemotherapy of paclitaxel and cisplatin, no previous radiation therapy to the left upper abdomen, a sufficient organ function (white blood cell count $\geq$ 4,000/mm^3 and $\leq$12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin $\geq$ 8.0 g/dl, GOT $<$ 100 U/l and GPT $<$ 100 U/l, total bilirubin $<$ 2.0 mg/dl, creatinine $<$ 1.5 mg/dl, normal ECG), an estimated survival of at least for 2 months, no synchronous or metachronous malignancy in any other organs, and the patient's written informed consent. Definition of "unresectable tumor" was (1) locally unresectable M0 tumors due to severe adjacent invasion (T4), locally extensive nodal disease (bulky N), or thoracic esophageal invasion requiring thoracotomy, or (2) any M1 tumors regardless of the local resectability. The exclusion criteria included a location of the tumor which could not be detected by CT, endoscopy, or gastrointestinal imaging, a severe medical condition, a gastrointestinal obstruction requiring mechanical decompression, active bleeding from the gastrointestinal tract, a past history of allergic reactions to medicines containing the solvent, Cremophor EL, clinically apparent brain metastasis, and those in pregnancy or lactation.

Treatment schedule, starting dose, and dose-escalation schedule

On days 1, 15, and 29, paclitaxel and cisplatin was administered as a 90-min intravenous (IV) infusion followed by IV infusion of cisplatin given over 120 min in 500 ml saline. The starting doses of paclitaxel and cisplatin were 60 and

Table 1 Dose escalation schedule

Level	Paclitaxel (mg/m^2)	Cisplatin (mg/m^2)
−2	40	20
−1	50	20
1	60	20
2	70	20
3	70	25
4	80	25

20 mg/m^2, respectively (level 1). The dose-escalation schedule is presented in Table 1.

Radiation therapy

Concurrent radiation therapy was administered to the local tumor up to a dose of 45 Gy using 1.8-Gy daily fractions, 5 days per week for 5 weeks. The gross tumor volume was determined by the extent of the local tumor defined by CT, endoscopy, or gastrointestinal imaging. The planning target volume was determined by the gross tumor volume added to the volume of the margins of 0.5–2.0 cm. Radiation was delivered with at least 6 MV photons. The doses were limited to less than 36 Gy in the spinal cord and the heart. The doses were also limited as much as possible in the lung and the kidney. The radiation monitoring committee checked the local tumor detected by an upper GI series or CT scan, the treatment fields, dosimetry, and the report of the radiation therapy to evaluate the protocol compliance.

Toxicity evaluation

Toxicity was evaluated by National Cancer Institute—Common Toxicity Criteria Version 3.0 [11]. The dose limiting toxicity (DLT) was defined by grade 3 or more of non-hematological toxicities other than anorexia, nausea, vomiting, alopecia, gastrointestinal obstruction, and local pain, grade 4 of leukocytes or neutrophils, febrile neutropenia that continued for more than 4 days, grade 4 of platelets, grade 3 or more of esophagitis, ECOG performance status of 3 or 4 for more than 4 days, while withholding treatment for more than 48 days due to a delayed resolution of toxicities, and stopping the treatment due to such toxicities.

Maximum-tolerated dose and recommended dose

A schematic drawing of this phase I study is shown in Fig. 1. Three patients were assigned to each dose level. When no patient experienced DLT, the dose was escalated to the next level. When two of three patients had DLT in level 1 or level −1, the dose level was reduced to level −1 or level −2, respectively. When two of three patients had DLT in level 2 or greater, the dose level was defined as the maximum-tolerated dose (MTD). When one of three patients experienced DLT, three more patients were assigned to the same dose. When only one of six patients had DLT, the dose was escalated to the next level. When two or more of six patients experienced DLT in level 1 or level −1, the dose level was decreased to level −1 or level −2, respectively. When those patients had DLT in level 2 or greater, the dose level was defined as the MTD. The recommended dose (RD) was determined by considering the toxicity and the efficacy at each level.

Assessment of the clinical response

The clinical response was evaluated by the improvement of the grading of the GI obstruction or localized pain defined by National Cancer Institute—Common Toxicity Criteria

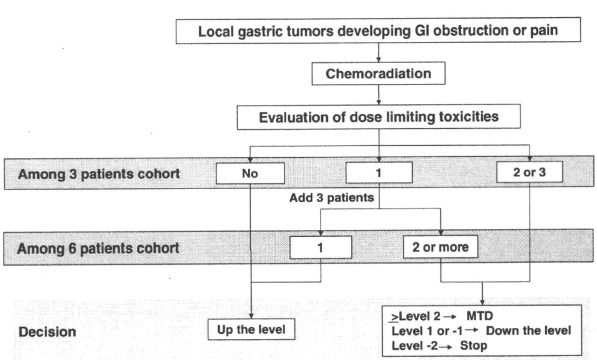

Fig. 1 Schema of this study

Version 3.0 [11]. The protocol was reviewed and approved by the local ethical committees at the each institution involved. Written informed consent was obtained before the entry of all subjects. All the data management and quality assurance were done by the ECRIN data center.

Results

Between October 2005 and May 2007, a total of nine patients were enrolled in this study. The clinical characteristics of the patients are shown in Table 2. A GI obstruction was observed in nine patients due to four primary and five recurrent tumors, and pain was present in one patient due to a primary tumor. There was no patient showing violation of the protocol and deviation in this study.

Table 2 Clinical characteristics of the patients

Total number of patients	9
Age (median, range)	72 (57–78)
Sex (male/female)	7/2
Previous treatment (yes/no)	0/9
Primary/recurrent	4/5
Unresectable factors in the primary tumor	
M	2
Bulky nodal swelling	1
T4	2
Required thoracotomy for resection	3
Macroscopic type of the primary tumor	
3	1
4	1
5	2
Histology	
Well differentiated	2
Poorly differentiated	6
Unclassified	1
Performance status	
0	5
1	4
Local symptom	
GI obstruction	9
Pain	1
Site of GI obstruction	
Cardia	4
Jejunum for esophagojejunostomty	4
Common bile duct	1
Grading of GI obstruction	
1	1
2	5
3	3
Grading of local pain	
1	1

Three patients were initially assigned to receive dose level 1. A DLT occurred in one of three patients at dose level 1, and another three patients were added to this dose cohort. Two out of six patients developed dose-limiting toxicity at dose level 1. Following the protocol, the dose level was decreased to −1. Another cohort of three patients was assigned to receive dose level −1. There was no patient showing a DLT at dose level −1. Therefore, a dose level 1 of paclitaxel 60 mg/m^2 and cisplatin 20 mg/m^2 was established as the maximum-tolerated dose. The hematological and non-hematological toxicities are shown in Tables 3 and 4.

Dose-limiting toxicity

Two patients developed dose-limiting toxicity at dose level 1. One patient required admission due to a decrease in performance status to 3 for more than 4 days caused by fatigue and anorexia of grade 3, while the other patient developed hyponatremia, esophagitis, nausea, and vomiting of grade 3 and fatigue and thrombocytopenia of grade 4. The latter patient died of DIC and pneumonia 17 days after finishing the protocol treatment. This patient was judged to have experienced treatment-related death (grade 5 of DIC and pneumonia).

Clinical response

The clinical response is shown in Table 5. After the initiation of the protocol treatment, the GI obstruction was improved in six of six patients at dose level 1 and two of three at dose level −1, while localized pain was relieved in one of one patient at dose level 1. Therefore, the clinical response was observed in eight of nine patients (89% with a 95% confidence interval from 52 to 100%).

Table 3 Hematological toxicities

	Grade					
	1	2	3	4	5	≥3
Level 1 ($n = 6$)						
Leukocytes	2	4	0	0	0	0
Neutrophils	2	2	1	0	0	1
Hemoglobin	3	2	1	0	0	1
Platelets	3	0	0	1	0	1
Level −1 ($n = 3$)						
Leukocytes	2	1	0	0	0	0
Neutrophils	1	0	0	0	0	0
Hemoglobin	2	1	0	0	0	0
Platelets	0	0	0	0	0	0

Table 4 Non-hematological toxicities

	Grade					
	1	2	3	4	5	≥3
Level 1 ($n = 6$)						
T-Bil	1	2	0	0	0	0
GOT	2	2	0	0	0	0
GPT	2	1	0	0	0	0
Creatinine	1	0	0	0	0	0
CRP	3	0	0	0	0	0
Anorexia	1	1	1	0	0	1
Nausea	0	2	1	0	0	1
Vomiting	0	1	1	0	0	1
Fever	1	0	0	0	0	0
Esophagitis	0	0	1	0	0	1
Fatigue	0	0	1	1	0	2
Pneumonia	0	0	0	0	1	1
DIC	0	0	0	0	1	1
Level −1 ($n = 3$)						
T-Bil	0	0	0	0	0	0
GOT	1	0	0	0	0	0
GPT	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0
CRP	3	0	0	0	0	0
Anorexia	1	0	0	0	0	0
Nausea	1	0	0	0	0	0
Vomiting	1	0	0	0	0	0
Fever	0	0	0	0	0	0
Esophagitis	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0
DIC	0	0	0	0	0	0

Recommended dose

Considering the toxicity and the efficacy at levels 1 and −1, the recommended dose was determined as level −1 of PTX 50 mg/m^2 and CDDP 20 mg/m^2.

Discussion

This is first Japanese trial to evaluate chemoradiation therapy for gastric cancer. Chemoradiation therapy for gastric cancer had been developed in the US because the tumors recurred mainly at the local site after curative surgeries for primary gastric cancer [12]. Recently, MacDonald et al. [6] demonstrated that adjuvant chemoradiation therapy significantly improved the overall survival by reducing the loco-regional recurrence in comparison to surgery alone in a phase III trial. Since Dutch and MRC phase III trials proved that D2 surgery could not improve the overall survival and the mortality and morbidity were high [13–16], the standard treatment for the primary resectable gastric cancer in the US has been less than D2 surgery with adjuvant chemoradiation therapy [6]. In contrast to western countries, D2 surgery is reported to be a safe procedure in Japan [17]. Although the JCOG 9501 phase III trial could not demonstrate a survival benefit of D3 surgery in comparison to D2 [18], a Taiwanese phase III trial demonstrated that D3, which was similar to the Japanese D2, could improve the survival in comparison to D1 surgery [19]. Local recurrence after D2 dissection was rare [2]. Based on these results, the standard treatment has been a D2 dissection in Japan. Therefore, chemoradiation therapy, which is another modality to control local disease, has not been developed in Japan.

Table 5 Clinical response

Level 1	Grade	
	Before	After
GI obstruction		
Case 1	3	2
Case 2	2	1
Case 3	3	0
Case 4	2	1
Case 5	2	1
Case 6	2	1
GI obstruction		
Case 1	1	1
Case 2	2	1
Case 3	3	1
Local pain		
Case 3	1	0

Although patients with local gastric tumors which cause local symptoms such as GI obstruction or local pain are rare in Japan, these patients are difficult to treat because chemotherapy is not sufficient to control the tumor-related symptoms and palliative surgery lacks the benefit to match the surgical risk due to local or thoracic invasion or postoperative adhesions. Therefore, other modalities should be developed to control these symptoms. This phase I study was conducted because there is no chemoradiation regimen validated by clinical trials in Japan.

MacDonald et al. [6] developed a chemoradiation regimen of 5-FU and LV combined with concurrent radiation of a total dose of 45 Gy for patients who underwent a curative resection for primary gastric cancer. Ajani et al. [8–10]

reported several phase II trials of chemoradiation for patients with primary gastric tumors. One regimen consisted of 5-FU and concurrent radiation of 45 Gy [8] and the other of 5-FU and paclitaxel with the same dose of radiation [9]. Safran et al. [7] also developed a chemoradiation regimen using paclitaxel and concurrent radiation of 45 Gy for patients with locally advanced or recurrent gastric cancer. In this study, the same dose of 45 Gy we used as reported in these previous studies.

Paclitaxel and cisplatin were selected as the baseline chemotherapy combined with radiation based on the following reasons. First, paclitaxel has been reported to be highly effective when combined with radiation for locally gastric tumors [7, 9]. Second, cisplatin is usually used for combination chemotherapy and up-regulates the effect of other drugs. Third, both drugs could be administered even for patients with severe GI obstruction, in contrast to the oral drug, S-1, which has been generally used as a first line treatment in Japan. Fourth, patients who are considered to be indicated for chemoradiation may sometimes have already been treated by 5-FU or S-1 before the treatment. The combination chemotherapy of paclitaxel and cisplatin has been tested for patients with metastatic gastric cancer in a recent phase I trial [20]. In that study, the recommended dose was determined to be 80 mg/m^2 paclitaxel and 25 mg/m^2 cisplatin three times weekly a month [20]. On the other hand, Safran et al. [7] reported administration of 50 mg/m^2 paclitaxel five times weekly combined with a total dose 45 Gy using 1.8 Gy daily fractions, 5 days per week for 5 weeks. Considering the total dose given in 5 weeks in these regimens and the systemic effects besides radiosensitization, an effective dose and schedule of paclitaxel and cisplatin were determined in this study.

Ideally, a phase I trial should be performed with the cohort of more than three patients at each level. However, since patients indicated for this study are extremely rare in Japan, the current phase I trial was conducted by the classical method using a cohort of three patients at each dose in 15 institutions. Of these, nine patients were recruited from six hospitals between October 2005 and May 2007. In this study, two of six patients developed dose-limiting toxicity at a dose level 1. Following the protocol, the dose level was reduced to level −1. Based on the toxicity at each level, the MTD was determined to be level 1 and RD was at level −1. Because only nine patients were examined in this study, the dose-limiting toxicities could also have been influenced by inter-patient variability and the MTD might therefore be underestimated. In this study, however, the frequency and grading of the toxicities were strikingly different between level 1 and −1. Treatment-related death was observed at dose level 1, but was not at dose level −1. Therefore, this study could suggest that level −1 was feasible. The toxicities and efficacy at dose level −1 should be re-evaluated in future phase II studies.

This study evaluated the palliative effect based on an improvement of the symptoms, which is not objective. In contrast to other clinical trials of chemotherapy to reduce the tumor in size and to prolong the survival, this treatment was designed to relieve specific symptoms. Moreover, many patients who fulfilled the eligibility in this study had no measurable lesion defined by the RECIST criteria. Therefore, the efficacy of this treatment was evaluated by the improvement of the symptoms. In this study, the palliative effect was observed in eight of nine patients, suggesting that our regimen has enough palliative effect for these patients. In the future study, this chemoradiation regimen should be evaluated by objective response such as response rate.

In conclusion, this study demonstrated that RD was determined to be a dose level −1, thus suggesting that this chemoradiation regimen may be feasible and effective for controlling the symptoms caused by the local invasion of gastric tumors.

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Conflict of interest statement None.

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微小な腹膜転移（Minimal Peritoneal Metastasis: MPM）を伴うスキルス胃癌の予後からみた外科切除の意義

吉川 貴己　青山 徹　渡辺 隆文　林 勉　尾形 高士
長 晴彦　円谷 彰　小林 理*

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Role of Surgical Resection for Scirrhous Gastric Cancer with Minimal Peritoneal Metastasis: Takaki Yoshikawa, Toru Aoyama, Takafumi Watanabe, Tsutomu Hayashi, Takashi Ogata, Haruhiko Cho, Akira Tsuburaya and Osamu Kobayashi (*Dept. of Gastrointestinal Surgery, Kanagawa Cancer Center*)

Summary

Prognosis of schirrhous gastric cancer with minimal peritoneal metastasis was poor, and the role of resection has not been clarified yet. Analysis 1: Overall survival was examined in 79 patients who underwent R0/R1 resection during 1970-1995 at Kanagawa Cancer Center (Group A), and in 47 patients who underwent R0/R1 resection and received S1 chemotherapy at the 30 hospitals of Japan Clinical Oncology Group (Group B). Hazard ratio (HR) of group B to group A was examined. HR was 0.64 at 1 year, 0.76 at 2-year, and 0.92 at 3-year. Analysis 2: HR of S1 group in SPIRITS phase III trial to FU group in JCOG 9205 phase III trial was examined. HR was 0.64 at 1 year and 0.84 at 2-year. Analysis 3: HR was compared each other including HR of ACTS-GC phase III trial. HR was ACTS<analysis 1 = analysis 2 at 1 year, and was ACTS<analysis 1<analysis 2 at 2-year. In conclusion, these results suggested that the significance of resection increased by post-operative S1 chemotherapy. Key words: Gastric cancer, Peritoneal metastasis, Surgery, Chemotherapy

要旨 微小な腹膜転移を伴うスキルス胃癌の予後は不良であり，切除の意義は明らかではない。<方法>解析1: 1970～1995年に当院でR0/R1切除した79例（A群）に対し，2001年1～12月にJCOG30施設でR0/R1切除+S-1を受けた47例（B群）のハザード比（HR）を算出した。解析2: JCOG9205-5-FU群に対するSPIRITS-S-1/CDDP（SP）群のHRを算出した。解析3: 解析1/解析2/ACTS-GCにおけるそれぞれのHRを比較した。<結果>解析1: HRは1年目0.64，2年目0.76，3年目0.92であった。解析2: HRは1年目0.64，2年目0.84であった。解析3: 1年目のHRはACTS<解析1=解析2，2年目のHRはACTS<解析1<解析2であった。<結論>HRが解析1<解析2であることから，術後S-1投与により切除の意義は増大した。

はじめに

腹膜転移を高頻度に来すスキルス胃癌の予後は不良である[1]。根治切除を行うことで予後が期待できるとする報告[1]がある一方で，外科的疾患ではないとする報告[2]もある。すでに大網などに腹膜転移を来している，少量の癌性腹水や洗浄細胞診陽性である場合などではさらに予後不良であり，切除すべきか否かも明らかではない。

一方，胃癌が治癒するためには肉眼的根治切除が必要不可欠である[3]。ACTS-GCの結果が報告されるまで，腹膜転移を有する胃癌に対しても肉眼的根治切除が追及されたが，補助化学療法の有用性が証明されていない時代においては，根治切除後に化学療法を施行しても予後は著しく不良であった[4]。腹膜転移を有する場合には，狭窄や出血などを有しない限り切除すべきではなく[4]，標準治療は化学療法とされてきた。

2007年，ACTS-GCの結果が報告され，肉眼的根治切除後Stage II/IIIの症例では，1年間のS-1を投与することで予後が有意に改善することが示された[5]。微小な腹膜転移を伴うスキルス胃癌であっても，術後S-1投与により微小転移を駆逐できれば，予後が改善する可能性がある。

* 神奈川県立がんセンター・消化器外科

連絡先: 〒241-0815 横浜市旭区中尾1-1-2 神奈川県立がんセンター・消化器外科
吉川 貴己

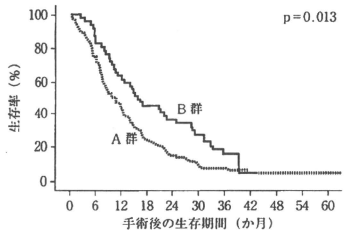

図1 微小な腹膜転移を伴うスキルス胃癌の生存曲線

本研究では，新旧時代における化学療法，切除＋化学療法のハザード比（HR）をそれぞれ比較し，切除の意義について考察した。

I. 方 法

解析1: 微小な腹膜転移（minimal peritoneal metastasis: MPM）を，胃癌取扱い規約第12版におけるP1または第13版におけるCY1と定義した。MPMを伴うが，他に遠隔転移を有しないスキルス胃癌を対象とした。S-1を含む新規抗癌剤が使用できなかった1970～1995年に，当院でR0/R1切除した79例（A群）と，新規抗癌剤を使用できた2001年1～12月にJCOG30施設でR0/R1切除＋S-1を受けた47例（B群）を対象とし，全生存曲線をKaplan-Meier法を用いて算出しlogrank検定で比較した。また，生存曲線における1年生存率，2年生存率，3年生存率を算出し，A群に対するB群のHRを算出した。

解析2: M1胃癌に対する化学療法の全生存期間として，新規抗癌剤を使用されていないJCOG9205 phase III試験[6]における5-FU群を対照とし，新規抗癌剤を使用されたSPIRITS phase III試験[7]におけるS-1/CDDP(SP)群の1年生存率，2年生存率のHRを算出した。

解析3: 解析1，解析2，ACTS-GCにおけるそれぞれのHRを比較した。

II. 結 果

解析1: A群，B群の生存曲線を図1に示す。1年生存率はA群43.0%に対しB群63.8%，2年生存率はA群15.2%に対しB群36.0%，3年生存率はA群7.0%に対しB群15.4%であった。全生存期間は，A群に比しB群で有意に良好であった（p=0.013）。A群に対するB群のHRは1年目0.64，2年目0.76，3年目0.92であった。術後経過年数とともにHRは高値となっていった。

表1 ハザード比の比較

	1年目	2年目	3年目
解析1	0.635	0.755	0.916
解析2	0.635	0.841	?
ACTS-GC	0.416	0.684	0.620

解析2: 1年生存率はJCOG9205-5-FU群28%[6]，SPIRITS-SP群54.1%[7]，2年生存率はJCOG9205-5-FU群8%[6]，SPIRITS-SP群23.6%[7]と報告されている。JCOG9205-5-FU群に対するSPIRITS-SP群のHRは1年目0.64，2年目0.84であった。経過年数とともにHRは高値となっていった。

解析3: ACTS-GC phase III試験[5]における手術単独群に対するS-1群のHRは計算すると，1年目0.42，2年目0.68，3年目0.62であった。HRは2年目以降ほぼ一定であった。HRを，解析1，解析2，ACTS-GCで比較してみる（表1）。1年目のHRは，ACTS-GC＜解析1＝解析2，2年目のHRはACTS-GC＜解析1＜解析2となっていた。

III. 考 察

解析1より，旧抗癌剤の時代に比し，S-1術後補助化学療法を使用した時代における予後は有意に改善していた。ACTS-GCではS-1術後補助化学療法によりStage II/IIIにおける有意な予後改善効果が示されたが，微小転移を伴うスキルス胃癌においてもS-1術後補助化学療法は有用であることが示唆された。

解析1と解析2のHRを比較してみると，2年目のHRが解析1＜解析2であった。化学療法の進歩によるHRよりも切除後に化学療法を加えた治療のHRが小さいことから，切除の意義は増大したと推測された。胃癌治療においては，全身療法である化学療法により微小転移を駆逐できるようになったことで切除の意義が増大し，切除の適応が拡大する可能性があるのかもしれない。ただし，今回の解析は後ろ向き解析であること，M1胃癌と微小な腹膜転移を有するスキルス胃癌とで化学療法の効果が同等であることを前提としたものであり，その解釈には限界がある。

経過年数によるHRの変化を検討してみる。ACTS-GCでは，2年目以降，HRがほぼ一定となることから，S-1による微小転移の駆逐は一時的な効果ではなかったことが示唆される。一方，解析1でのHRは，1年目＜2年目＜3年目と高くなっていた。微小な腹膜転移を伴うスキルス胃癌に対するS-1は，微小転移を一時的に抑制したにすぎない可能性がある。

本論文の要旨は第32回日本癌局所療法研究会において発表した。

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CASE REPORT

Gastrojejunostomy followed by induction chemotherapy for incurable gastric cancer with outlet obstruction

Yasuhiro Okumura, Manabu Ohashi, Souya Nunobe, Tomohiro Iwanaga, Tatsuo Kanda, Yoshiaki Iwasaki

Yasuhiro Okumura, Manabu Ohashi, Tomohiro Iwanaga, Yoshiaki Iwasaki, Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan
Souya Nunobe, Department of Gastrointestinal Surgery, Tokyo University Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Tatsuo Kanda, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan
Author contributions: Ohashi M, Nunobe S and Iwasaki Y designed the research; Okumura Y and Ohashi M wrote the paper; Iwanaga T did the clinical work; Kanda T reviewed the paper.
Correspondence to: Manabu Ohashi, MD, PhD, Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. ohamana@cick.jp
Telephone: +81-3-38232101 Fax: +81-3-38241552
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Abstract

A 72-year-old male gastric cancer patient with outlet obstruction underwent laparoscopic exploration. The examination disclosed intraperitoneal free cancer cells with no overt peritoneal, lymphatic, or hepatic metastasis. The patient underwent laparoscopy-assisted gastrojejunostomy (LAGJ) and started chemotherapy with S-1 plus cisplatin on postoperative day 13. Three course of the chemotherapy shrank the tumor markedly. Then, the patient underwent gastrectomy with a curative intent. Laparotomy revealed no intraperitoneal free cancer cells, and microscopically complete resection was achieved. The patient received S-1 chemotherapy as postoperative adjuvant treatment for 1 year, and is still alive with no evidence of peritoneal recurrence. LAGJ followed by S-1 plus cisplatin is one of the optional treatments that should be considered for patients with outlet obstruction as it may widen opportunities for potentially curative resection.

Key words: Gastric cancer; Outlet obstruction; CY1; Laparoscopy-assisted gastrojejunostomy; S-1 plus cisplatin

Peer reviewers: Giuseppe Sica, MD, PhD, Department of Surgery, University Hospital Tor Vergata, Viale Oxford 81, 00133 Rome, Italy; Dr. Abdul-Wahed Meshikhes, MD, FRCS, Chairman and Consultant Surgeon, Department of Surgery, King Fahad Specialist Hospital, Amir Bin Thabit St, Dammam, 31444, Eastern Province, Saudi Arabia

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INTRODUCTION

In gastric cancer, intraperitoneal free cancer cells, described as CY1 in the Japanese Classification of Gastric Carcinoma (JCGC), 2nd English Edition, are one of the incurable factors[1]. The term "CY1" means histologically remnant tumors and gastric cancer with CY1 is diagnosed as stage IV and associated with poor prognosis. It has been reported that the survival time of gastric cancer patients with CY1 but not with overt peritoneal and other incurable metastases (P0CY1) is almost the same as that of patients with gross peritoneal metastases[2]. However, several reports have revealed that S-1, an oral agent consisting of tegafur, gimeracil, and oteracil potassium at a molar ratio 1:0.4:1[3], might improve prognosis in gastric cancer patients with P0CY1[4,5]. Furthermore, the recent phase III clinical trial named SPIRITS trial demonstrated that S-1 plus cisplatin prolongs the survival time of patients with advanced or recurrent gastric cancer compared to S-1 alone[6].

Gastric cancer with outlet obstruction (GCOO) is a type of advanced cancer arising from the distal third of

the stomach. GCOO is associated with not only food intake inability but also metastatic disease[7]. In particular, Japanese patients with GCOO are faced with an oncology-specific issue, namely the patients cannot receive the most promising chemotherapy with S-1 plus cisplatin for incurable gastric cancer because of the inability to ingest S-1 capsules. In such patients, palliative gastrectomy is commonly selected and chemotherapy with S-1 plus cisplatin is subsequently prescribed, if possible. However, the SPIRITS trial also revealed that a considerable number of patients administering S-1 plus cisplatin suffered from severe toxic events and withdrew from the treatment[6]. Palliative gastrectomy seems to be unsuitable for inducing patients with incurable GCOO swiftly to the highly effective chemotherapy with S-1 plus cisplatin.

To solve such a practical problem, we have devised a pioneering therapeutic strategy to facilitate early induction and reliable continuation of S-1 plus cisplatin as an induction treatment for GCOO patients with P0CY1. The strategy consists of two steps. The first step is laparoscopy-assisted gastrojejunostomy (LAGJ) to allow the patient to ingest food and induce chemotherapy with S-1 plus cisplatin, the second step is gastrectomy for complete resection of the tumor and postoperative chemotherapy using S-1 alone.

Here, we present a successfully treated patient with incurable GCOO under our new therapeutic strategy.

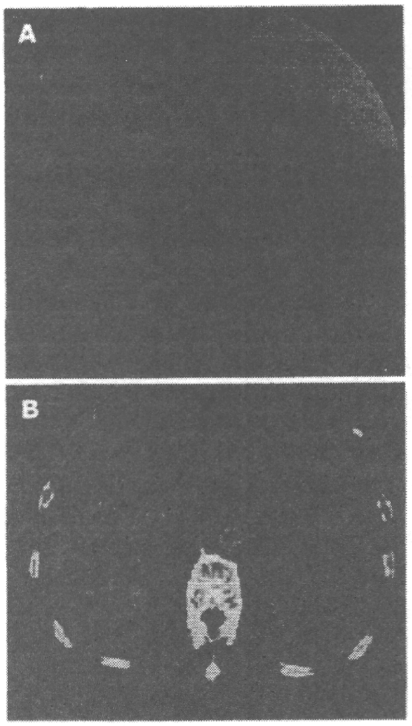

Figure 1 Gastrografin meal study revealing a tumor with ulceration at the gastric antrum, causing gastric outlet obstruction (A), and abdominal computed tomography scan showing remarkable thickness of gastric wall with no evidence of direct invasion to the pancreas head, and lymph node metastasis or distant metastasis (B).

CASE REPORT

A 72-year-old male suffering from GCOO was referred to our hospital. A gastrografin meal study revealed a type 3 tumor existing at the gastric antrum and causing gastric outlet obstruction (Figure 1A). Abdominal computed tomography scan showed neither lymph node metastasis nor distant metastasis (Figure 1B). Laboratory tests revealed that all the data were within normal limits.

Considering the high possibility of existing peritoneal metastases, we conducted laparoscopic exploration. Laparoscopic examination disclosed P0CY1, and we decided to conduct our new therapeutic strategy for GCOO with P0CY1. Laparoscopic examination was immediately converted into LAGJ with the intention of early induction of chemotherapy with S-1 plus cisplatin and the subsequent radical surgery was planned, that would enable potentially curable resection. The LAGJ was made in a Roux-en Y fashion in an antecolic manner (Figure 2A). We partitioned the stomach using a linear stapler, creating a small tunnel at the lesser curvature. Anastomosis was made between the distal stump of the proximal stomach and the jejunum. We located the partition at the upper part of the stomach, with the intent that cutting the tunnel would be a single procedure in reconstruction of the next surgery to be performed after chemotherapy (Figure 2B). The patient recovered swiftly and chemotherapy with S-1 plus cisplatin was started on postoperative day 13. The daily dose of S-1 was 120 mg/body (3 wk on and 2 wk off). Cisplatin (90 mg/body) was given intravenously on day 8 of S-1 administration. The patient received 3 cycles of the chemotherapy at the outpatient clinic without significant adverse events.

After 3 courses of the chemotherapy, examination revealed that the tumor shrank markedly although the gastric outlet obstruction still remained. The patient underwent laparotomy with a curative intent. Surgical exploration revealed that there was no metastasis to the peritoneum or the liver, and lavage cytology was negative. The tumor was excised with distal gastrectomy and D2 lymph node dissection (Figure 2C). Reconstruction was not necessary because we could retain the proximal gastrojejunostomy as a reconstruction route, which was previously made at the LAGJ.

Grossly, the resected specimen had a shallow depressed lesion at the antrum, which appeared to be only fibrosis (Figure 3). Histopathological examination revealed that the fibrotic change generated from the chemotherapy extended widely and live cancer cells were found throughout the whole gastric wall. Out of the 34 dissected lymph nodes, cancer metastasis was found in a single lymph node at station No. 7. The gastric cancer was finally diagnosed as T3, N2, H0, P0, CY0, M0, stage ⅢB, based on the JCGC, 2nd English Edition.

The patient was discharged on postoperative day 8 and underwent subsequent postoperative chemotherapy with S-1 alone for 12 mo. The patient is still alive and shows no evidence of peritoneal recurrence 20 mo after the initial surgery.

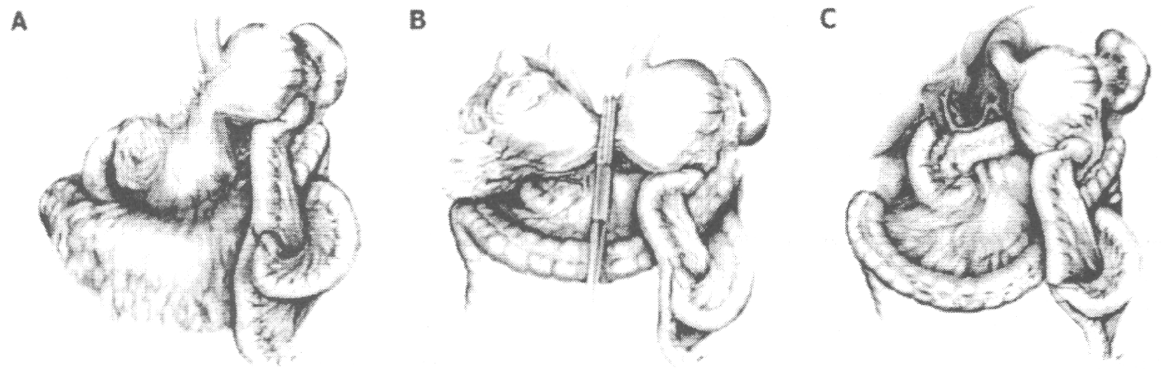

Figure 2 Laparoscopy-assisted partitioning gastrojejunostomy conducted in a Roux-en Y fashion in an antecolic manner (A), cutting the tunnel as a single procedure in reconstruction of the second surgery after chemotherapy (B), and the completely excised tumor with distal gastrectomy and D2 lymph node dissection (C).

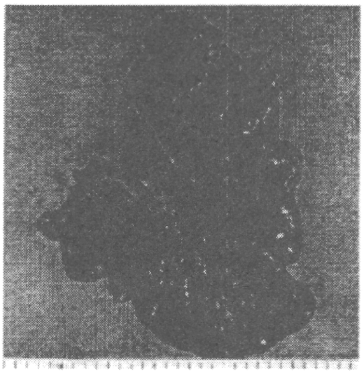

Figure 3 Resected specimen showing a grossly shallow depressed lesion as only fibrosis at the antrum with live cancer cells found in the fibrotic tissue throughout the whole gastric wall at histopathological examination.

DISCUSSION

We presented a treated patient suffering from unresectable GCOO. The patient was treated with our new therapeutic strategy for GCOO with P0CY1. He underwent LAGJ and was induced swiftly to chemotherapy with S-1 plus cisplatin as an induction treatment, followed by potentially curative gastrectomy. We reported the present case because we believe in its importance in devising a novel therapeutic strategy for GCOO with P0CY1.

In Japan, it is considered important to facilitate immediate induction and reliable continuation of S-1-based chemotherapy for the treatment of unresectable and recurrent gastric cancer. In particular, S-1 plus cisplatin, demonstrating a response rate (RR) of 54% and a median survival time (MST) of 13 mo in the SPIRITS trial[6], is recommended as the first-line chemotherapy. Recent clinical trials in other countries, such as the V325 study and the REAL-2 trial, demonstrated that RRs of docetaxel, cisplatin, and 5-fluorouracil (DCF) and epirubicin, oxaliplatin, and capecitabine (EOX) are 37.5% and 47.9%, MSTs of DCF and EOX are 9.2 and 11.2 mo, respectively[8,9]. S-1 plus cisplatin is more favorable than the other regimens tested in Western countries, and is the first choice of treatment for unresectable and recurrent gastric cancer in Japan.

There are two possible options for induction to S-1 plus cisplatin for unresectable GCOO. First, palliative gastrectomy is initially done, followed by chemotherapy with S-1 plus cisplatin. Second, methods other than gastrectomy, such as bypass surgery or metallic stent insertion to enable patients to ingest food and S-1 capsules, are performed with S-1 plus cisplatin subsequently prescribed[10,11]. There is a major problem in the first option, i.e. the feasibility of S-1 plus cisplatin after recent gastrectomy has not been established yet. S-1 plus cisplatin is a toxic regimen and the SPIRITS trial demonstrated that more than 30% of the patients assigned S-1 plus cisplatin suffered from grade 3 to 4 anorexia and myelosuppression, and withdrew from the trial because of toxic events[6]. It is possible that patients who undergo palliative gastrectomy for GCOO fail in immediate induction and reliable continuation of chemotherapy with S-1 plus cisplatin. In contrast, the second option possibly enables patients to more immediately receive chemotherapy with S-1 plus cisplatin and more reliably continue it. In the present case, we conducted LAGJ to induce immediate ingestion of food and S-1 capsules, considering that LAGJ was reported to minimally suppress the patients' immune function and enable earlier recovery of bowel movement[12]. In fact, the present patient started S-1 plus cisplatin on day 13 after LAGJ and did not suffer from severe toxicities.

In the present case, we chose S-1 plus cisplatin as the induction treatment for gastric cancer with P0CY1, and CY1 were eventually eliminated. CY1 are one of the most chemosensitive lesions among the metastases. Nakagawa *et al*[13] revealed that 61% of patients who receive preoperative chemotherapy have no free cancer cells at the time of the second surgery. Satoh *et al*[14] reported that CY1 observed by staging laparoscopy can be eliminated by preoperative chemotherapy with S-1 plus cisplatin in 7 of 10 patients. Based on these favorable data, we intended to perform curative gastrectomy for the present patient and were actually able to do so. However, whether this result contributes to survival benefits is unclear. Satoh *et al*[14] also

described that 4 of 7 responders to preoperative chemotherapy for CY1 remain free from peritoneal metastasis. Our patient presented with no signs of peritoneal recurrence even though he initially had stage IV gastric cancer. However, whether the therapeutic strategy adopted in the present case truly provides survival benefits or not, needs a longer follow-up of the patient.

Chemotherapy with S-1 plus cisplatin is suitable for gastric cancer with P0CY1. Thus, LAGJ followed by induction chemotherapy with S-1 plus cisplatin is a possible strategy if the patient has GCOO and complies strictly with the regimen.

In conclusion, LAGJ, followed by induction chemotherapy with S-1 plus cisplatin and subsequent gastrectomy with curative intent, is one of the relevant strategies for GCOO with P0CY1.

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Original article

Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002)

Taira Kinoshita[1], Mitsuru Sasako[2], Takeshi Sano[3], Hitoshi Katai[4], Hiroshi Furukawa[5], Akira Tsuburaya[6], Isao Miyashiro[7], Masahide Kaji[8], and Motoki Ninomiya[9] (on behalf of the Gastric Cancer Surgery Study Group of the Japan Clinical Oncology Group)

[1] Department of Surgical Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
[2] Department of Surgery, Hyogo College of Medicine, Kobe, Japan
[3] Department of Surgery, Cancer Institute Hospital, Tokyo, Japan
[4] Department of Surgical Oncology, National Cancer Center Hospital, Tokyo, Japan
[5] Department of Surgery, Sakai Municipal Hospital, Osaka, Japan
[6] Department of Surgical Oncology, Kanagawa Prefectural Cancer Center Hospital, Yokohama, Japan
[7] Department of Surgery, Osaka Medical Centre for Cancer and Cardiovascular Diseases, Osaka, Japan
[8] Department of Surgery, Toyama Prefectural Central Hospital, Toyama, Japan
[9] Department of Surgery, Hiroshima City Hospital, Hiroshima, Japan

Abstract

Background. **The prognosis of scirrhous gastric cancer remains poor despite extended surgery or adjuvant or neoadjuvant chemotherapy. A pilot study of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral 5-fluorouracil derivative, for neoadjuvant chemotherapy unexpectedly showed good response and a promising effect on survival. Therefore, the Japan Clinical Oncology Group conducted a phase II trial to confirm the efficacy of S-1 for neoadjuvant chemotherapy against resectable scirrhous gastric cancer.**

Methods. **Patients were eligible if they had typical scirrhous gastric cancer invading more than half of the stomach, and resectable disease confirmed by laparoscopic staging. The treatment schedule consisted of two courses (each, 4-week administration and 2-week withdrawal) of S-1 (100–120 mg/body per day), followed by radical surgery.**

Results. **Fifty-five eligible patients were registered. Three completed only one course of the neoadjuvant chemotherapy, whereas 52 completed two courses. Toxicity was acceptable, with a few grade 3 (5.5%) events, but no grade 4 adverse events. The response rate was 32.6% in 43 evaluable patients. Of the 55 patients, 2 refused operation, 1 developed lung metastasis, and 52 underwent laparotomy. The curative resection rate was 80.8%, with acceptable morbidity and no mortality. The survival curve at 2 years' follow up showed a better survival rate than that of the historical controls, but did not reach the expected survival rate.**

Conclusion. **S-1 neoadjuvant chemotherapy appeared feasible and showed positive effects against scirrhous gastric cancer; however, the survival rate with S-1 did not reach the expected rate required when selecting an agent for a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy against scirrhous gastric cancer.**

Offprint requests to: T. Kinoshita

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Key words Scirrhous gastric cancer · Neoadjuvant chemotherapy · S-1

Introduction

Scirrhous gastric cancer, also known as linitis plastica or Borrmann type 4, is a special type of stomach cancer known for its very poor prognosis. It is very difficult to identify this cancer in its early stage, and even aggressive surgical procedures and adjuvant chemotherapies have not considerably improved the survival rate in patients with this neoplasia. Owing to its low incidence, only a few drug trials against this neoplasia have been conducted thus far. On the other hand, several studies of neoadjuvant chemotherapy against scirrhous gastric cancer have suggested the efficacy of such treatment [1–4]. However, all these studies involved a small sample size and they usually did not determine the survival benefits of such treatment. Furthermore, a phase II trial of sequential high-dose methotrexate and fluorouracil combined with doxorubicin (FAMTX) for neoadjuvant chemotherapy has shown moderate toxicity and no survival benefits [5]. Interestingly, S-1, which is a dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine, has shown the highest response rate among many oral anticancer agents against unresectable advanced gastric cancer in early and late phase II trials [6–8]. In these late phase II trials, S-1 showed a 33% response rate against scirrhous gastric cancer. Because of the reported promising effects of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer in a previous pilot study [9], the Japan Clinical Oncology Group

(JCOG) decided to conduct a phase II trial to determine survival benefits of S-1 treatment.

Patients, materials and methods

Patient eligibility

Patient eligibility required the fulfillment of the following criteria: histologically confirmed gastric adenocarcinoma; potentially resectable laparoscopy-confirmed typical scirrhous gastric cancer (without definitive ulceration) that invaded more than half of the stomach; received no prior treatment; 70 years or younger; Eastern Cooperative Oncology Group performance status of 0 or 1; and oral intake possible. Patients also had to have adequate organ functions (creatinine clearance, ≥50 ml/min; blood urea creatinine, within the institutional limit; GOT and GPT, within twice the institutional limit; leukocytes, 3500/mm^3≤ leukocyte <12000/mm^3; hemoglobin, ≥9.0 g/dl; thrombocytes, ≥100000/mm^3; total bilirubin, within twice the institutional limit; and normal electrocardiogram).

Diagnostic and staging procedures included physical examination, barium gastrography, endoscopy, chest X-ray, abdominal computed tomography (CT) scan, and laparoscopy with cytological examination of peritoneal washing of the Douglas pouch. Patients with positive cytology on peritoneal washing and potentially resectable disease without visible peritoneal dissemination were also included in the study.

This study was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

Treatment schedule

Chemotherapy consisted of two courses (4-week administration and 2-week withdrawal) of S-1 at 100–120 mg/body per day. After two courses of neoadjuvant chemotherapy, patients were reevaluated for the presence of potentially resectable disease and those who were positive underwent laparotomy. Because two patients underwent endoscopic examination after one course of chemotherapy and stopped chemotherapy due to progressive disease, the treatment protocol was revised such that the evaluation of the effect of neoadjuvant chemotherapy should be carried out only after two courses and only by fluoroscopic examination. If indicated, patients received curative or palliative resection or exploratory laparotomy within 14 days after completing the second course of adjuvant chemotherapy. Patients with curative resection were followed up without any adjuvant chemotherapy every 3 months until cancer relapse.

Evaluation of response and toxicity

Potentially resectable scirrhous gastric cancer usually shows no measurable lesions, except for primary foci. We decided to evaluate the response of only primary foci following chemotherapy. Because it is very difficult to evaluate the response of the primary foci using the Response Evaluation Criteria in Solid Tumors criteria, we used a National Institutes of Health (NIH) image to calculate the barium-filling area or whole stomach on a double-contrast fluoroscopic examination study, as well as to compare the area before and after chemotherapy. Responses were classified as partial response (PR), more than 50% increase in the area after chemotherapy; stable disease (SD), 0 to less than 50% increase in the area; and progressive disease (PD), any decrease in the area and the appearance of new lesions. National Cancer Institute Common Toxicity Criteria ver2.0 were employed for determining chemotherapy toxicity.

Pathological assessment was performed to evaluate disease extent, resection margins, and response to chemotherapy as evidenced by the presence of necrotic and cancer cells. The pathological response to chemotherapy was classified according to the following criteria provided by the Japanese Gastric Cancer Association [10]: grade 0, absence of necrosis or degeneration; grade 1a, necrosis or degeneration is observed in less than one-third of the tumor; grade 1b, less than two-thirds and more than one-third of the tumor show necrosis or degeneration; grade 2, more than two-thirds of the tumor shows necrosis or degeneration; grade 3, all tumors show necrosis or degeneration.

Historical controls

Because we applied laparoscopic staging to exclude patients with visible peritoneal dissemination, it was very difficult to find good historical controls. Laparoscopic staging had gained popularity at the commencement of this trial; however, we had no identical historical controls. The historical controls consisted of 241 patients who had the same lesions as those described in the eligibility criteria for this study, and who had no visible peritoneal dissemination at laparotomy without laparoscopic staging, and had been treated at the participating institution during 1991–1993. Data for the historical controls were as follows: 2-year survival rate, 45%; curative resection rate, 90.3%; 30-day operative mortality rate, 1.2%; and in-hospital mortality rate, 3.5%.

Statistical considerations

The primary endpoint of this study was the 2-year survival rate. Fifty-five patients were required to be registered on the basis of the expectation that the 2-year survival rate of those receiving this neoadjuvant chemo-

therapy would be 60% (15% higher than that of the historical controls), allowing 10% of ineligible patients. Survival time was calculated from the initial date of the initiation of neoadjuvant chemotherapy to the date of death or the last follow-up date. Survival data were analyzed according to the method of Kaplan and Meier and then compared with the data of the historical controls.

Results

Patient accrual

From March 14, 2001, to February 4, 2003, 55 patients were enrolled in the study from 15 institutions. The mean age was 56 years (range, 31–70 years).

Neoadjuvant chemotherapy

The patients were composed of 26 male and 29 female patients. The scheduled two courses of neoadjuvant chemotherapy were performed in 52 patients. The remaining 3 patients received one course, because 2 of the 3 patients were judged to have PD by endoscopic evaluation after one course before the revision of the protocol, and 1 patient was found to have advanced bile duct carcinoma after one course of chemotherapy. These 3 patients received curative resection after one course of neoadjuvant chemotherapy. There was no chemotherapy-induced grade 4 adverse reaction in the cohort. Only 3 patients developed grade 3 adverse reactions (Table 1).

As mentioned earlier, the effect of adjuvant chemotherapy was evaluated from the change in the barium-filling area before and after the chemotherapy, as calculated from the NIH images. Among the 43 patients whose fluoroscopic films could be evaluated, 14 patients (32.6%) showed more than 1.5 times enlargement of the stomach (PR); 13 patients showed SD (30.2%), and 16 patients showed PD (37.2%).

Table 1. Adverse reactions

	Grade				%	
	0	1–2	3	4	Grade 4	Total
T. Bil	32	23	0	0	0	55
WBC	42	13	0	0	0	55
Neutrophils	42	12	1	0	0	55
ALT	43	11	2	0	0	55
AST	45	9	0	0	0	55
Hb	48	7	0	0	0	55
Nausea/vomiting	36	19	0	0	0	55
Pigmentation	44	11	0	0	0	55
Anorexia	45	10	0	0	0	55
Diarrhea	45	10	0	0	0	55
Stomatitis	45	10	0	0	0	55
General fatigue	46	9	0	0	0	55

Only three patients developed grade 3 adverse reactions, and they recovered by withdrawal of S-1

T. Bil, serum total bilirubin; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin

Operation

Among the 55 patients, 3 did not undergo operation, because of the refusal of 2 and because the other patient was found to have pulmonary metastases. Fifty-two patients underwent laparotomy, including the 3 patients who received one course of the neoadjuvant chemotherapy. Among the 52 patients, 6 patients did not undergo resection (5, peritoneal dissemination; 1, unresectable invasion of the duodenum and pancreatic head). Ten patients underwent palliative resection of the main tumor (2, peritoneal dissemination; 6, positive cytological examination of abdominal washing; 1, unresectable tumor with severe invasion to the retroperitoneum; 1, widespread lymph node metastases). The other 36 patients underwent curative total gastrectomy with various combined organ resections (25, spleen; 1, distal pancreas + spleen; 5, gallbladder; 2, left adrenal gland; 2, transverse colon; 1, pancreatic head and duodenum). Among the 36 patients, only 1 had D1 lymph node dissection and the remaining 35 had D2 or more lymph node dissection.

The mean operation time for curative resection was 214 min (range, 130–460 min) and that for noncurative resection was 295 min (range, 150–401 min). The mean blood loss for curative resection was 586 ml (range, 30–1815 ml) and that for noncurative resection was 872 ml (range, 230–2100 ml).

Among the 46 patients who underwent resection, postoperative complications were observed in 11 patients (23.9%). Overall, there was no mortality and there were no serious complications. The actual complications were as follows: wound infection, deep vein thrombosis, pancreatic fistula, anastomotic ulcer, pneumonia, pulmonary embolism, sepsis, abdominal abscess, liver function disorder, and mycotic uveitis.

Changes in the T, P, and CY (cytological examination of the abdominal washing) factors before and after neoadjuvant chemotherapy are shown in Tables 2 and 3. With regard to the T factor, a response was observed in 14 patients; however, cancer progression was observed in 8 patients. In regard to the P and CY factors, a response (PR) was observed in only 2 patients; however, 10 showed progressive disease (PD). The other 40 patients showed stable disease (SD).

The pathological therapeutic effects of neoadjuvant chemotherapy were evaluated according the grading described by the Japanese classification of gastric carci-

noma [10] general rules for gastric cancer study: grade 0, 12 patients (26.1%); grade 1a, 19 patients (41.3%); grade 1b, 4 patients (8.7%), and grade 2, 11 patients (23.9%).

At the time of the scheduled analyses (March 2005), 10 patients were still alive without recurrence, 13 were alive with recurrence, and 32 had already passed away. The modes of recurrence were as follows: peritoneal, 17 patients; retroperitoneal, 2 patients; local, 1 patient; lymph node, 1 patient.

Table 2. Changes in T factors before and after chemotherapy

Laparoscopic T		Pathological T
T2:7		T2:11
T3:39	Chemotherapy	T3:37
T4:5		T4:4
Tx:1		

Progression, 8 patients; downstage, 14 patients
Tx, T unknown

Table 3. Changes in P and CY factors before and after chemotherapy

No change or progression (SD and PD)	
P0, CY0→P0, CY0	37 (SD)
P0, CY0→P0, CY1	2 (PD)
P0, CY1→P0, CY1	3 (SD)
P0, CY0→P1	4 (PD)
P0, CY1→P1	4 (PD)
Downstage (PR)	
P0, CY1→P0, CY0	2 (PR)

The survival curves of all patients (n = 55) and the historical controls are shown in Fig. 1. The survival curve of the study arm was better than that of the historical controls; however, the survival rate did not reach the expected rate (2-year survival rate: 59% vs 60%).

With regard to the secondary endpoints, the response rate to the neoadjuvant chemotherapy was 32.6%. The rate of postoperative complications was 23.9%, as against 25.7% in the historical controls. The in-hospital mortality rate was 0% as against 3.5% in the historical controls. The curative resection rate was 80.8%, as against 90.3% in the historical controls.

Discussion

Despite recent advances in chemotherapy and extended surgery, the treatment outcomes of scirrhous gastric cancer, also known as diffuse gastric cancer, linitis plastica, or Borrmann type 4 in the West, have remained very poor because of the aggressive biological behavior of this tumor. Because of failure to improve survival even with aggressive postoperative chemotherapy, neoadjuvant chemotherapy has been applied to patients with resectable or unresectable scirrhous gastric cancer.

To date, the efficacy of neoadjuvant chemotherapy against scirrhous gastric cancer remains to be established because of the lack of well-validated phase II and phase III studies. The first phase II neoadjuvant chemotherapy trial was reported by Takahashi et al., using FAMTX [5]. In their trial, neoadjuvant chemotherapy was shown to be seemingly feasible against scirrhous

Fig. 1. Survival curves of all patients (n = 55) and the historical controls (n = 241)

gastric cancer, producing a higher resectability rate without any increase in morbidity rate. However, an interim analysis of the 2-year survival rate in 20 patients enrolled in the trial showed no improvement over the survival rate of the historical controls. Myelosuppression was the major cytotoxic effect of the FAMTX regimen, and grade 3 or 4 neutropenia was observed in 14 out of the 20 patients (70%). Eleven of these 14 patients required granulocyte colony-stimulating factor support. The overall response rate was 15% (3 PRs in 20 patients). Eighteen resected specimens showed only marginal histological effects (grades 0-Ib). For these reasons, Takahashi and co-workers discontinued the trial.

Because S-1 showed promising effects when used for neoadjuvant chemotherapy against scirrhous gastric cancer in a pilot study [9], we decided to conduct a phase II trial of S-1 to determine its beneficial effects on survival. Because of the difficulty in excluding patients with peritoneal dissemination by conventional diagnostic imaging procedures such as CT scan and the use of barium enema, we performed laparoscopic examination to identify and exclude patients with peritoneal dissemination.

At the time of starting the phase II trial, laparoscopic examination for cancer staging was still not a common procedure. Thus, we need to standardize this technique using a video for the quality control of the procedure. Regarding the historical controls, it was not possible to submit patients without peritoneal dissemination to laparoscopic examination, for the same reason. Data for previous patients with the same eligibility criteria and without peritoneal dissemination, confirmed by laparotomy, were collected from the participating institutions. Thus, in the present study, the control group was not identical to the study group.

Neoadjuvant chemotherapy using S-1 was safe and feasible when compared with other toxic combination chemotherapies. Only a few grade 3 and no grade 4 adverse reactions resulting from cytotoxicity were observed, and no specific morbidity and no increases in morbidity and mortality rates were seen when compared with the data in the historical controls.

Patients with positive cytological examination results were included in this phase II trial. This is the reason why we expected the S-1 neoadjuvant chemotherapy to produce negative cytological examination results. However, the results of the trial, in terms of cytological findings, were not very promising. Without considering the cytological examination results, it can be observed that although there was no significant difference in the curative resection rate between the study group and the historical control group, the curative resection rate in the study group was lower than the expected rate.

From the viewpoint of the pathological therapeutic effects of chemotherapy, S-1 neoadjuvant chemotherapy showed a much better therapeutic effect than FAMTX.

The survival rate of our study group showed a better curve than that of the historical controls; however, it did not reach the expected rate ($P = 0.245$). On the other hand, combination chemotherapy using S-1 and cisplatin (CDDP) showed a markedly high response rate (76%) in a phase II trial. Therefore, this combination can be considered more promising than S-1 monotherapy for neoadjuvant chemotherapy against scirrhous gastric cancer. The JCOG has also completed the accrual of patients evaluated in the phase II trial of neoadjuvant chemotherapy using the above S-1 and CDDP regimen for resectable scirrhous and more-than-8-cm giant type 3 gastric cancer. Because of the superiority of this regimen over S-1 monotherapy in terms of the response rate and pathological therapeutic effects, the JCOG group has already started a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy using S-1 + CDDP as against extended surgery in patients with scirrhous or large type 3 gastric cancer.

In summary, neoadjuvant chemotherapy using S-1 against potentially resectable scirrhous gastric cancer appears feasible and effective; however, in the present phase II trial, the survival rate of the patients did not reach the expected rate. On the other hand, an S-1 + CDDP regimen is now being tested in a phase III trial by the JCOG group as a more promising neoadjuvant regimen.

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Talaporfin-mediated photodynamic therapy for peritoneal metastasis of gastric cancer in an *in vivo* mouse model: Drug distribution and efficacy studies

KENTARO KISHI[1], MASAHIKO YANO[1], MASAHIRO INOUE[2], ISAO MIYASHIRO[1], MASAAKI MOTOORI[1], KOJI TANAKA[1], KUNIHITO GOTO[1], HIDETOSHI EGUCHI[1], SHINGO NOURA[1], TERUMASA YAMADA[1], MASAYUKI OHUE[1], HIROAKI OHIGASHI[1] and OSAMU ISHIKAWA[1]

Departments of [1]Surgery and [2]Biochemistry, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

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Abstract. Photodynamic therapy (PDT) is a potential treatment for the peritoneal dissemination of gastric cancer, because its cytotoxicity is limited to superficial lesions. We examined the accumulation of talaporfin in peritoneal metastatic nodules and determined the optimal laser condition for these nodules. We also evaluated the pathological response after therapy. We created a peritoneal metastasis model in nude mice using the MKN-45 EGFP cell line. We evaluated the accumulation of talaporfin in peritoneal metastatic nodules and normal organs by spectrophotometric analysis 2-8 h after i.p. talaporfin. To determine optimal PDT conditions, we treated metastatic nodules and the small intestine using multiple laser doses (2, 5, and 10 J/cm^2, respectively). Accumulation of talaporfin was detected in metastatic nodules in higher intensities than in the small intestine. The fluorescent intensity of the peritoneal metastatic nodules gradually decreased dependent on the time interval between the laser treatment and talaporfin administration. Fluorescent intensity in the small intestine decreased more than in the metastatic nodules. The pathological response rates by dose were 52.5% at 2 J/cm^2, 43.2% at 5 J/cm^2, and 64.4% at 10 J/cm^2, respectively, when the laser treatment was used 2 h after talaporfin administration, whereas at 4 h, they were 20.8, 25.5, and 26.2%, respectively. Finally, the recommended treatment conditions were considered to be a 2 J/cm^2 laser dose and a 4-h interval in terms of toxicity. Talaporfin-mediated PDT may be an effective treatment modality for patients with advanced gastric adenocarcinoma and metastatic peritoneal nodules.

Correspondence to: Dr Kentaro Kishi, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinariku, Osaka, Osaka 537-8511, Japan
E-mail: kisi-ke@mc.pref.osaka.jp

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Introduction

Gastric cancer remains a worldwide health problem, accounting for 10% of all new cancer diagnoses and 12% of all cancer-related deaths. Diagnosis of gastric cancer is often made when the disease is advanced and unresectable (1). In Japan, a nation-wide screening program has resulted in early diagnosis and prompt surgical intervention and has thus improved the prognosis of patients with primary gastric cancer, resulting in a 5-year over all survival rate of 68.2% (2). However, the prognosis of patients with advanced gastric cancer remains poor, with 5-year survival rates of 43.5% for stage III cancer and 9.9% for stage IV cancer.

Peritoneal dissemination is one of the most common recurrence patterns after radical resection of advanced gastric cancer; it is observed in 25.6% of patients with serosa-positive gastric cancer (2). Peritoneal dissemination is thought to be caused by micrometastatic nodules on peritoneal surfaces or floating cancer cells in the abdominal cavity that were not detected at the time of surgery. If peritoneal recurrence rates can be reduced, the prognosis of advanced gastric cancer will be dramatically improved.

To date, many clinical trials aimed at decreasing peritoneal recurrences have been conducted. These trials have studied such treatment modalities as systemic adjuvant chemotherapy (3-8), intraperitoneal chemoperfusion with or without hyperthermia (9) and chemoradiotherapy (10,11). Although several meta-analyses showed a marginally significant benefit of some of the above therapies, no single randomized clinical trial has demonstrated a significant survival benefit. It is therefore widely thought that there is currently no standard effective therapy for preventing peritoneal recurrence of gastric cancer.

In photodynamic therapy (PDT), a systemically administered photosensitizing agent is activated by laser light of a specific wavelength delivered by an optical fiber. Light-activated photosensitizer molecules react with endogenous oxygen, resulting in the generation of singlet oxygen, which initiates a series of intracellular events that result in the destruction of target tissues while avoiding significant side effects in the patient. With respect to side-effect profiles