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Original article

Retrospective analysis of 45 consecutive patients with advanced gastric cancer treated with neoadjuvant chemotherapy using an S-1/CDDP combination

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Abstract

Background. **Standard treatment for highly advanced gastric cancer (AGC) has not been established yet. Neoadjuvant chemotherapy (NAC) represents a promising approach, which may improve the prognosis of AGC. In this study, we analyzed the feasibility and efficacy of NAC with S-1 (TS-1)/cisplatin CDDP in order to design appropriate clinical trials for AGC.**

Methods. **Results for a series of 45 consecutive patients with AGC treated with S-1/CDDP induction chemotherapy since January 2002 were analyzed retrospectively.**

Results. **The primary tumor was resected in 36 of the 45 patients (resectability, 80.0%). Progression of the disease during chemotherapy was observed in 1 patient only (2.2%). No treatment-related deaths occurred, and serious adverse effects (grade 3–4) were noted in only 2.2% of the patients. The overall median survival time was 1.82 years. Especially noteworthy is that, in patients with highly advanced disease (pretreatment [c]-stage IV; $n = 27$), resectability was 66.7% and curative (R0) resection was possible in 10 patients. The median survival times for c-stage IV patients who had total, curative, and noncurative resections were 20.8, 22.3 and 12.6 months, respectively. R0 resection was possible for all c-stage III patients ($n = 17$), with a 2-year overall survival of 90.9%. The downstaging rate was 55.6% (20/36), resulting in a significantly improved prognosis for the downstaged patients ($P = 0.012$).**

Conclusion. **Induction chemotherapy using S-1/CDDP for AGC appears to be a safe and promising treatment. We have therefore started two independent multiinstitutional clinical trials to evaluate the efficacy of this treatment.**

Key words Gastric cancer · Neoadjuvant chemotherapy · S-1/CDDP

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Introduction

Gastric cancer remains one of the world's most commonly diagnosed cancers [1]. Although the incidence of gastric cancer is declining in Western countries, there has been a significant increase in the incidence of proximal cardia and gastroesophageal cancer in the past two decades [2]. The majority of patients presenting with regional or distant disease have a 5-year survival, ranging from 35% for stage II to less than 5% for stage IV [3].

The principal treatment for gastric adenocarcinoma is surgery, even though high recurrence rates after curative resection are the rule. MacDonald et al. [4] reported the results of Intergroup Trial 0116, which showed that postoperative chemoradiation significantly improved the overall survival of patients with advanced gastric cancer (AGC). It should be noted, however, that R0 resection was mandatory in this trial, although the R0 resection rate for AGC in the United States can be as low as around 30% [5]. In Japan, a nationwide surveillance program and standardized D2 nodal dissection have resulted in a 5-year survival rate of over 70% for stage I/II gastric cancer. However, the prognosis for stage III/IV AGC remains poor [6]. Hence, improvements in the R0 resection rate and overall survival rate for AGC through the development of a novel multimodal strategy are urgently needed.

The neoadjuvant approach has the potential to help overcome problems such as low RO resection rate and poor prognosis in the treatment of AGC, and various neoadjuvant trials have been conducted [7–22]. Although evidence of the survival benefits of a neoadjuvant approach has not been established yet, the MAGIC (ISRCTN 93793971) trial has demonstrated that perioperative chemotherapy produced significantly longer disease-free and overall survival compared with

these parameters in patients receiving surgery alone [17]. Essential factors for a successful induction chemotherapy regimen are high efficacy and good feasibility. In this respect, S-1/cisplatin (CDDP) can be considered one of the best regimens for induction chemotherapy, because a response rate of 74% was established in a phase I/II study, in conjunction with acceptable levels of toxicity [23]. Because neoadjuvant chemotherapy (NAC) is a complex multimodal treatment consisting of induction chemotherapy and surgery, it is difficult to design relevant clinical trials without having assessed of preliminary clinical experience. The aim of our study was to delineate an optimal protocol for NAC by means of retrospective analyses of the feasibility and efficacy of induction S-1/CDDP chemotherapy for AGC, especially with regard to patient selection, induction chemotherapy cycles, and surgical procedure.

Patients and methods

Patients

Between January 2002 and October 2004, a cohort of 45 patients with AGC (stage II, $n = 1$; stage III, $n = 17$; stage IV, $n = 27$), treated with S-1/CDDP induction chemotherapy at Kyoto University Hospital, Shimane Prefectural Central Hospital, and Tazuke Kofukai Kitano Hospital, was enrolled in this study. All patients had histologically proven gastric adenocarcinoma, without prior treatment. Pretreatment staging was based on past history and the findings obtained from physical examination, chest X-ray examination, upper endoscopy, and abdominal helical computed tomography (CT). Laparoscopic staging was encouraged but not mandated. Eligibility for this study was as follows: (1) stage II/III/IV gastric cancer, staged according to the Japanese Gastric Cancer Association (JGCA) staging system. For pretreatment (c)-stage IV, locally advanced gastric cancer, without massive ascites due to peritoneal dissemination or distant metastasis, was included; (2) performance status (PS) of 1 or less based on the Eastern Cooperative Oncology Group (ECOG) criteria; (3) adequate bone marrow function (white blood cell count > 3000 cells/ml, platelet count > 100000 cells/ml), normal renal function (serum creatinine level < 1.2 mg/dl or creatinine clearance > 50 ml/dl), and normal liver function (serum transaminase level less than double the normal upper limit). Written informed consent was obtained for all patients.

Induction chemotherapy

S-1 was given orally, at 80 mg/m^2, for 21 consecutive days; 60 mg/m^2 of CDDP was diluted in 400 ml physiological saline and administered as a 120-min i.v. infusion on day 8, together with standard premedications and hydration. Patient status was evaluated after every course. The first 15 patients were treated with a single-cycle administration protocol and the remaining 30 with a two-cycle protocol. If there were no signs of disease progression, the second cycle of the two-cycle protocol was started 14 days after the final oral administration of S-1 in the first cycle [23].

Surgery and postoperative chemotherapy

A radical operation was performed 3 to 6 weeks after the final oral administration of S-1. The type of surgery depended on the location and extent of the primary cancer. For distal cancers, a subtotal gastrectomy was considered adequate, with total gastrectomy performed at the discretion of the surgeon. Total gastrectomy was performed for all proximal cancers, with en-bloc resection of adjacent organs when their involvement was suspected. The spleen was removed and the pancreas tail was preserved whenever possible. D2 nodal dissection, based on the classification of the JGCA, was also attempted [24]. A curative (R0) resection was defined as the en-bloc removal of a tumor together with the lymph nodes and the omentum, leaving the proximal and distal margins disease-free. S-1, at 80 mg/m^2, was administered postoperatively, orally, for 14 consecutive days. The adjuvant chemotherapy was repeated every 21 days and discontinued 1 year after the operation if no recurrence had been observed.

Patient evaluation

The pretreatment stage (c-stage) was diagnosed according to the JGCA staging system [24] and was based on the combined results of helical CT, upper endoscopy, and laparoscopy. The toxicity of the induction chemotherapy was assessed based on the National Cancer Institute Common Toxicity Criteria, version 2, and evaluation of the PS of the patients was based on the ECOG criteria.

Tumor response was determined according to the classification of the Japanese Research Society for Gastric Cancer, and was based on tumor volume, as estimated on X-ray or CT scan images [25]. A complete response (CR) was defined as the disappearance of all evidence of cancer, and a partial response (PR) as more than a 50% reduction in tumor volume without any evidence of new lesions. No change (NC) was defined as either less than 50% reduction, or less than 25% increase without any new lesions, or the deterioration of clinical cancer-related symptoms and the absence of measurable lesions. Progressive disease (PD) was defined as a more than 25% increase in a solitary lesion, the appearance of new lesions, or the deterioration of

clinical cancer-related symptoms and the absence of measurable lesions. The survival period was calculated from the start of outpatient sequential chemotherapy to death or the latest follow-up day. The duration of progression-free survival was defined as the period from the start of the treatment to the first day when PD was noted.

Patients underwent follow-up examinations, carried out by surgical oncology staff members, every 3 to 4 months after completion of the therapy, and CT scans of the abdomen and pelvis were routinely obtained every 3 to 4 months. The site of the first recurrence was documented on the basis of relevant imaging, with additional therapy after recurrence administered at the discretion of the oncology clinicians.

Statistical analysis

Survival was calculated, by the Kaplan-Meier method, from the initial date of treatment to the occurrence of an event or to the date of the most recent follow-up visit. The log-rank test was used for univariate analysis and a value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient demographics are outlined in Table 1. The 45 enrolled patients comprised 32 men and 13 women, with a median age of 64 years. Diagnosis of the pretreatment stage was based on the combined results of helical CT, upper endoscopy, and laparoscopy, in accordance with the JGCA staging system [24] (c-stage II, $n = 1$; c-stage III, $n = 17$; c-stage IV, $n = 27$). Distribution of the c-stage IV factors was: c-N3, $n = 5$; c-T4N2, $n = 4$; liver metastasis, $n = 1$; peritoneal seeding, $n = 14$; more than two c-stage IV factors, $n = 3$.

Clinical response and toxicity of induction chemotherapy

Lesions measurable on CT were observed in 23 of the 45 patients (lymph node metastasis in 22 patients and liver metastasis in 1), and 10 of these patients (43.5%; 95% confidence interval (CI), 23.2% to 63.7%) displayed a major response (0, CR; 10, PR). Pretreatment laparoscopic examination in 28 patients identified histologically proven peritoneal seeding in 10 of the patients, 7 (70%) of whom showed complete remission (CR) of peritoneal seeding at the time of operation. Progressive disease (PD) was observed in only 1 patient (2.2%) during induction chemotherapy. A summary of the toxicity of the induction chemotherapy (Table 2) shows that no grade 4 adverse effects were observed, and that the incidence of grade 3/4 neutropenia was 2.2%. One patient suffered ischemic heart attack during the hydration stage of CDDP administration, but there were no treatment-related deaths.

Table 1. Patient characteristics

Parameter	$n = 45$
Median age	64 Years
Range	47–80 Years
Sex	
Male/Female	32/13
Histology	
Diffuse	22
Intestinal	22
Unknown	1
Clinical JGCA stage	
c-Stage II	1
c-Stage IIIA	12
c-Stage IIIB	5
c-Stage IV	27

Table 2. Toxicity of induction chemotherapy

		Toxicity grade (NCI-CTC)			
$n = 45$	Total (%)	1/2	3	4	Grade 3/4 (%)
Leukopenia	29.3	11	1	0	2.2
Neutropenia	22	8	1	0	2.2
Thrombocytopenia	2.4	1	0	0	0
Anemia	9.8	4	0	0	0
Nausea	24.4	10	0	0	0
Vomiting	4.9	2	0	0	0
T-Bil	9.8	4	0	0	0
Cardiovascular	2.4	0	1	0	2.2

Table 3. Surgical outcomes

	n	Operation	Downstaging	R0 resection
c-Stage II	1	1	0	1
c-Stage III	17	17	10	17
c-Stage IV	27	18	10	10

Table 4. Distribution of pretreatment and postoperative stages

	Pretreatment stage	Postoperative stage
Stage IA	0	3
Stage IB	0	5
Stage II	1	8
Stage IIIA	12	7
Stage IIIB	5	5
Stage IV	18	8

Surgical outcomes

Surgical outcomes are summarized in Table 3. R0 resection was successfully performed for all 18 patients with c-stage II/III gastric cancer. Of the 27 patients with c-stage IV gastric cancer, 9 were assessed as incurable after induction chemotherapy (NC in 8 and PD in 1). The other 18 c-stage IV patients underwent surgery, and R0 resection was accomplished in 10. Downstaging was observed in 20 patients (10 each in c-stage, III and IV).

As shown in Table 4, none of the 36 patients resected showed pretreatment c-stage I and 1 (2.7%) showed pretreatment c-stage II, while 8 patients each showed pathological Stages I and II (44.4% of the 36 resected patients). The distribution of downstaging factors was: N factor, $n = 11$; T factor, $n = 12$; P/Cy factor, $n = 7$; and H factor, none. The surgical morbidity rate was 25.6% and the mortality rate was zero.

Survival

The overall survival curve for the 45 patients (Fig. 1) shows that the median survival time was 1.82 years. The survival curves for the operated patients are shown in Fig. 2. For c-stage III patients, the 2-year overall survival rate was 90.9%, while for the c-stage IV patients, the 1-year overall survival rate was 81.3% and the median survival time was 1.86 years. As shown in Fig. 3, the prognosis for the downstaged patients was significantly better than that for those who did not achieve downstaging ($P = 0.012$). Grade 2 pathological response was observed in 9 patients, and grade 3 in one patient. The 2-year overall survival of these 10 patients was 80%.

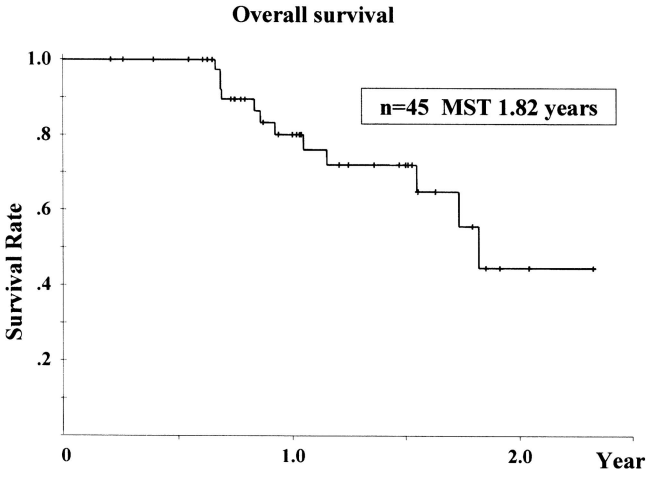

Fig. 1. Overall survival of 45 consecutive patients treated with S-1 (TS-1)/cisplatin (CDDP) prior to surgery. *MST*, median survival time

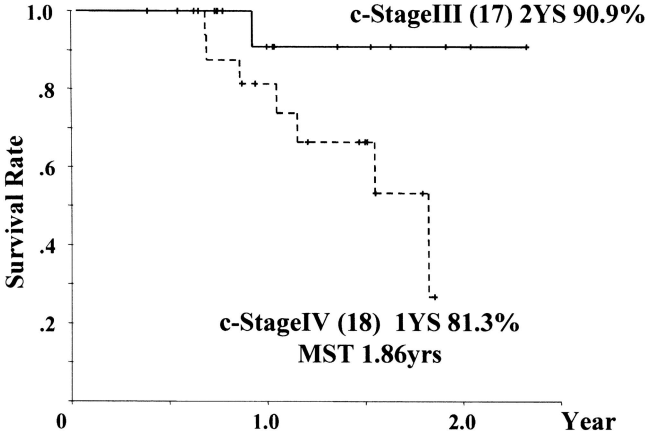

Fig. 2. Overall survival for all operated patients according to pretreatment clinical stage (*c*). *2YS*, 2-year overall survival rate; *1YS*, 1-year overall survival rate

Discussion

The poor outcome associated with surgery alone for locally advanced gastric cancer has prompted many investigators to look for additional therapeutic modalities for this disease. Several metaanalyses have found significant but minor survival benefits associated with postoperative adjuvant chemotherapy for gastric cancer [26–28]. Thus far, however, no randomized controlled trials have been conducted to determine whether standard regimens involving adjuvant chemotherapy have significant survival benefits. However, a neoadjuvant approach using preoperative chemotherapy is attractive for a number of reasons, including good compliance of patients preoperatively, improvement of surgical curability as a result of downstaging, and the sparing of

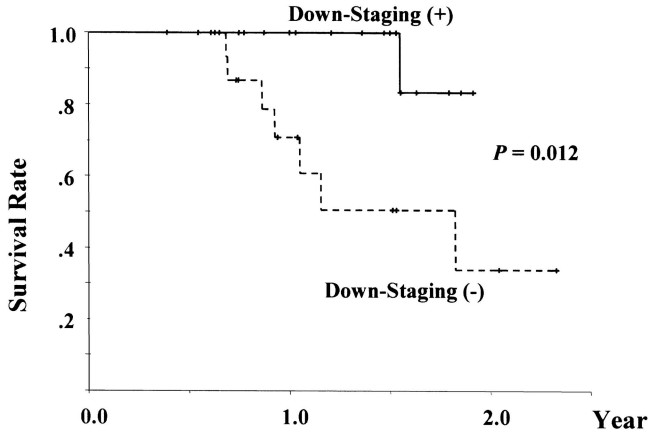

Fig. 3. Survival curves for patients who achieved downstaging and those who did not

Table 5. Summary of clinical trials

	Category 1	Category 2
Eligibility	Resectable (stages II–IV)	Unresectable (stage IV)
Number of trials	11	5
Phase II/III	9/2	4/1
Response rate	35.3%	42.6%
PD rate	12.2%	19.3%
MST	22.8 Months	12.2 Months
Resection rate	89.4%	49.3%
Curability (R0 rate)	70%	37%
MST after R0 resection	33.7 Months	21.2 Months
Preop. laparoscopy	3 Trials	1 Trial

induction chemotherapy in patients with biologically aggressive disease. The outcomes of recent clinical trials of neoadjuvant chemotherapy [7–22], summarized in Table 5, show that, while trials for unresectable disease (category 2) showed a poor prognosis, favorable prognoses were observed after R0 resection for both resectable and unresectable patients. In most previous trials, staging laparoscopy was not mandatory. Compared with the latest chemotherapy protocols, the responses and downstaging rates for induction chemotherapy in previous neoadjuvant chemotherapy (NAC) trials were relatively low. These results indicate the overriding importance of two issues for clinical trials of NAC: the selection of an appropriate patient group by means of precise preoperative staging, and the employment of a feasible and highly effective chemotherapy regimen.

Our study showed better prognosis for c-stage III than for c-stage IV patients. Potentially curative advanced gastric cancer (AGC) would thus be a promising target for NAC. For an accurate evaluation of the efficacy of NAC, c-stage III patients should therefore be distinguished from c-stage IV patients, and these two categories should be assessed separately in two independent clinical trials. The accuracy of the preoperative stage diagnosis of the patients analyzed in our study was mainly due to a combination of findings obtained with helical CT and laparoscopy [29,30]. Because peritoneal seeding is one of the most important prognostic factors for AGC, confirmation of such seeding is crucial for predicting the efficacy of NAC. While it is difficult to detect peritoneal seeding with conventional imaging modalities, direct exploration of the abdominal cavity by means of laparoscopy provides accurate information, not only on peritoneal seeding for cytological evaluation but also on the depth of the primary tumor. Of our 28 patients who had pretreatment laparoscopy, peritoneal seeding was detected in 10, 7 of whom (70%) showed CR of peritoneal seeding at the time of the operation. Of these 7 patients, recurrence was observed in 5 (peritoneal recurrence in 3; lymph node and liver metastasis, in 1 patient each). Because there is, as yet, no conclusive evidence as to whether such CR as a result of chemotherapy in gastric cancer has a beneficial impact on survival, pretreatment laparoscopy should be mandatory in clinical trials of NAC for AGC.

High efficacy and good feasibility are essential requirements for NAC regimens. A 74% response rate with S-1/CDDP has been reported in AGC [23] and a relatively high response rate, of 43.5%, was observed in our study. The short-term prognosis (2-year overall survival rate of 90.9% for c-stage III and 1-year overall survival rate of 81.3% for c-stage IV) in this study was better than the findings for our historical controls (corresponding rates of 68.7% and 57.6%). Compared with previous studies [7–22], both the R0 resection and downstaging rates in our study were remarkably high. Furthermore, the rate of disease progression was 2.2%, which was low compared with that reported in previous studies (Table 5). The pathological CR rate in this study was relatively low compared with those for other cancers, including breast cancer, ovarian cancer, and bladder cancer. The high pathological CR rate attained with NAC has led to better prognosis in those cancers [31–33]. On the other hand, the pathological CR rate for ECF (epirubicin, CDDP, and 5-fluorouracil), used for AGC in the MAGIC trial, was also very low [8]. However, the present trial clearly demonstrated a survival benefit for the perioperative chemotherapy arm. Taken together, these findings suggest that, in spite of the low pathological CR rate, S-1/CDDP can be expected to become one of the most effective and suitable regimens for neoadjuvant therapy for gastric cancer.

In regard to the number of cycles of our induction chemotherapy, a PR was observed after the two-cycle protocol in most of the patients, while it took approximately 6 months until PD with S-1/CDDP, which

correspond to those for a four-cycle protocol. The median time to PR and the median overall duration of response in responders of S-1/CDDP were 29 days (range, 24–64 days), and 162 days (range, 63–244 days), respectively [23]. Because R0 resection can be achieved for stage III AGC without preoperative treatment, we decided on two treatment cycles for the clinical trials as described below.

Although the extent of lymph node dissection was left to the surgeon's discretion in several major clinical trials in Western countries [4,17], it would be preferable for surgical procedures to be standardized for a more accurate evaluation of the efficacy of neoadjuvant treatment. Our results indicate that S-1/CDDP induction chemotherapy does not appear to have any negative effect on operative morbidity or mortality after D2 lymph node dissection; therefore, we adopted this as the standard surgical procedure for our clinical trials.

S-1 alone was administered postoperatively in the present study, because, in our preliminary trial, postoperatively, a single cycle of S-1/CDDP could not be completed in five consecutive patients, because of severe fatigue (data not shown). Although feasibility analysis of this adjuvant chemotherapy has not been completed, compliance with postoperative S-1 administration was good in most patients in the present study. Postoperative deterioration of compliance with chemotherapy was observed in the MAGIC trial, in which preoperative chemotherapy was successfully administered to 88% of the patients, while the same regimen was administered to only 55% of patients postoperatively. Poor compliance with intensive chemotherapy immediately after surgery should be taken into consideration as part of the treatment of gastric cancer. Thus far, there is no evidence of a survival benefit for postoperative S-1 administration in patients with AGC. In future randomized control studies to evaluate the survival benefits of NAC, researchers should therefore pay attention to whether or not the control arm includes postoperative chemotherapy.

In conclusion, induction chemotherapy with S-1/CDDP resulted in a high success rate for R0 resection of stage IV disease, a high downstaging rate, and low toxicity, thus leading to good short-term prognosis. However, further carefully designed clinical trials are needed, with longer overall survival as the primary endpoint. To this end, we have started two clinical trials. One feature of these trials is the separate evaluation of the efficacy of two-cycle S-1/CDDP treatment for c-stage III and c-stage IV patients, accomplished by using the JGCA staging system combined with accurate preoperative diagnosis, based on the results of helical CT and laparoscopic examinations. The eligibility criteria for the phase III trial (KYUH-UHA-GC04-03, NCT00182611, http://cancer.gov/clinicaltrials) are curable T3/4 and/or N2 but not stage IV gastric cancer, staged by means of laparoscopy and helical CT. Stage IV gastric cancer is the target of the other trial, which has been designed as a phase II study and is registered at the website of the National Cancer Institute (KYUH-UHA-GC03-01, NCT00088816, http://cancer.gov/clinicaltrials).

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