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ORIGINAL PAPER

Validity of neoadjuvant chemotherapy with docetaxel, cisplatin, and S-1 for resectable locally advanced gastric cancer

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Abstract Gastrectomy with D2 lymphadenectomy plus postoperative chemotherapy is the standard treatment for resectable locally advanced gastric cancer in Japan. However, the prognosis of patients with serosa-positive tumors remains unsatisfactory because of peritoneal recurrence. This study aimed to investigate the validity of neoadjuvant therapy with docetaxel, cisplatin, and S-1 (DCS) in patients with locally advanced gastric cancer. Thirty patients with locally advanced gastric cancer underwent neoadjuvant DCS therapy at Dokkyo Medical University Hospital between June 2013 and October 2015. Gastrectomy and D2 lymphadenectomy were performed after two cycles of preoperative DCS therapy. The clinical responses of the primary gastric tumors based on endoscopic findings were partial response in 17 patients (57%) and stable disease in 13 patients (43%). Analysis of pathological response in the primary gastric lesions showed grade 1a in five patients (17%), grade 1b in nine patients (30%), grade 2 in 11 patients (37%), and grade 3 in five patients (17%). Twenty-four patients (80%) remained alive after a median follow-up period of 31 months. The 2- and 3-year overall survival rates in all patients were 89 and 70%, respectively. The 2-year overall survival rate in pathological responders (grade 1b-3) was 96%, compared with 50% in pathological non-responders (grade 1a) ($P = 0.00187$). Pathological responders had a significantly higher survival rate than non-responders. These results indicate that neoadjuvant DCS therapy may improve the prognosis in patients with serosa-positive locally advanced gastric cancer.

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Introduction

Established gastric cancer screening programs allow cancers to be detected at relatively early stages, and patients with early gastric cancer now represent more than half of all gastric cancer patients in Japan [1]. However, gastric cancer remains the second leading cause of cancer-related deaths worldwide [2, 3] and is especially prevalent in Eastern Asia [4]. Gastrectomy with D2 lymphadenectomy plus adjuvant chemotherapy is the standard treatment for resectable locally advanced gastric cancer in Asia [5, 6], with postoperative S-1 chemotherapy for 1 year in Japan [5]. However, the prognosis of patients with stage III disease and serosa-positive tumors remains unsatisfactory, highlighting the need for improved therapeutic strategies [7].

Other approaches to the treatment for advanced gastric cancer have been established in Western countries; perioperative (pre- or postoperative) chemotherapy is a standard treatment in Europe [8–10], while perioperative chemoradiation is often used in the USA [11]. Preoperative chemotherapy has potential benefits, including tumor reduction, eliminating micrometastasis, increasing surgical curability by down-staging of the tumor, and improving compliance with postoperative chemotherapy [12]. Several phase II trials have revealed the safety and feasibility of preoperative chemotherapies such as S-1 plus cisplatin, S-1 plus docetaxel, and paclitaxel plus cisplatin [13–16]. However, recent phase II trials of a triplet regimen consisting of docetaxel, cisplatin, and S-1 (DCS) in patients with unresectable or recurrent gastric cancer have reported very high response rates and longer survival [17, 18].

Although this triplet regimen is expected to improve the prognosis of patients with advanced gastric cancer in Japan, the efficacy and safety of DCS in a neoadjuvant setting have not yet been established.

In this study, we investigated the validity of neoadjuvant DCS therapy in patients with serosa-positive locally advanced gastric cancer.

Patients and methods

Patients

The study included 30 patients with locally advanced gastric cancer who were examined at the First Department of Surgery, Dokkyo Medical University Hospital, between June 2013 and October 2015, and who gave informed consent to undergo neoadjuvant DCS therapy rather than adjuvant chemotherapy following gastrectomy. The eligibility criteria were as follows: (1) histologically confirmed gastric adenocarcinoma; (2) clinically diagnosed with tumor penetrating the serosa (T4); (3) no previous chemotherapy or radiotherapy; (4) no distant metastasis such as non-regional lymph node, liver, lung, or bone; (5) no ascites; (6) Eastern Cooperative Oncology Group performance status 0–1; and (7) aged 20–74 years. Clinical evaluation was performed by upper gastrointestinal endoscopy, computed tomography (CT), endoscopic ultrasound, barium enema, and positron emission tomography. Tumor-node-metastasis (TNM) factor and disease staging were determined according to the Japanese Classification of Gastric Carcinoma 3rd English edition [19]. The study protocol was approved by the institutional review board of our hospital, and written informed consent was obtained from all patients.

Treatment

S-1 80 mg/m^2/day was administered orally twice daily on days 1–14 of a 4-week cycle. Docetaxel 35 mg/m^2 and cisplatin 35 mg/m^2 were given as an intravenous infusion on days 1 and 15 of each cycle with hydration. This regimen was performed for two cycles every 4 weeks, if there was no unacceptable toxicity. Upper gastrointestinal endoscopy and CT were carried out after neoadjuvant chemotherapy, to assess the resectability of the tumors. Total gastrectomy or distal gastrectomy with D2 lymphadenectomy was performed, depending on the tumor location, between 3 and 4 weeks after the last preoperative chemotherapy. Patients, except those with stage IV gastric cancer, received postoperative chemotherapy with S-1 at a dose of 80 mg/m^2/day for 1 year. Patients with stage IV gastric cancer received doublet chemotherapy including S-1.

Clinical response and pathological assessment

Patients with measurable or non-measurable lesions examined by CT were reevaluated using the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) [20] before surgery. The clinical response of the primary gastric tumor was evaluated based on endoscopic findings and pathological response in resected specimens according to the Japanese Classification of Gastric Carcinoma Criteria [19]. Tumors were graded as 0–3 based on the degree of necrosis or disappearance of the tumor in relation to the estimated total amount of tumor. In this study, patients classified as grade 0 and 1a were regarded as non-responders, and those with grades 1b, 2, and 3 were regarded as responders. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Surgical complications were assessed according to the Clavien–Dindo classification [21].

Statistical analysis

Overall survival (OS) was defined as the duration from the date of initial DCS therapy to the date of death by any cause. Survival curves were evaluated according to the Kaplan–Meier method, and differences between the two groups were analyzed using log-rank tests. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

A total of 30 patients were enrolled between May 2011 and October 2015. Their characteristics are shown in Table 1. Histologically, 18 patients (60%) had undifferentiated adenocarcinomas and 12 patients had differentiated adenocarcinomas. Most tumors were macroscopic type 3 (76.7%). All patients were diagnosed with tumors penetrating the serosa by endoscopic ultrasound and abdominal CT. Twenty-six patients (86.7%) were cT4a (serosa: SE), and four (13.3%) were cT4b (adjacent structures: SI). Eighteen patients (60%) had regional lymph node metastasis, and 20 patients (66.7%) had cStage III gastric cancer.

Neoadjuvant chemotherapy and clinical response

A total of 29 patients (97%) received two cycles of DCS therapy according to the protocol despite dose reduction in eight patients (27%). Preoperative chemotherapy was stopped after one cycle because of severe adverse events in only one patient. The clinical response of the primary

Table 1 Patient characteristics ($n = 30$)

	Number of patients (%)
Age (years)[a]	63 (38–74)
Gender	
Male	22 (73.3)
Female	8 (26.7)
Performance status (ECOG)	
0	24 (80)
1	6 (20)
Histological type	
Differentiated	12 (40)
Undifferentiated	18 (60)
Macroscopic type	
Type 1	1 (3.3)
Type 2	1 (3.3)
Type 3	23 (76.7)
Type 4	4 (13.3)
Type 5	1 (3.3)
Depth of tumor invasion	
cT4a (SE)	26 (86.7)
cT4b (SI)	4 (13.3)
LN metastasis	
cN0	12 (40)
cN1	11 (36.7)
cN2	5 (16.7)
cN3	2 (6.7)
cStage	
IIB	10 (33.3)
IIIA	10 (33.3)
IIIB	7 (23.3)
IIIC	3 (10)

[a] Values are median and range

gastric tumor based on endoscopic findings was partial response (PR) in 17 patients (57%) and stable disease (SD) in 13 patients (43%). Among the 30 patients, six had target lesions in regional lymph nodes that could be evaluated by RECIST. The best overall response to neoadjuvant chemotherapy was PR in these six patients with target lesions and non-CR/non-progressive disease (PD) in the other 24 patients without target lesions. No patient experienced PD during neoadjuvant chemotherapy.

Adverse events

All adverse events are shown in Table 2. The most common grade 3 or 4 hematological toxicities were neutropenia (53%) and leukocytopenia (30%). Febrile neutropenia occurred in six patients (20%), including in four patients in the first cycle and two patients in the second cycle. Most patients recovered in a few days with administration of granulocyte-colony stimulating factor and appropriate antibiotics. DCS chemotherapy was discontinued in one patient because of grade 4 febrile neutropenia and grade 4 hypotension. The most frequent grade 3 or 4 non-hematological toxicities were anorexia (30%), nausea (10%), diarrhea (10%), and mucositis (10%). There were no treatment-related deaths.

Surgery and postoperative complications

The surgical outcomes are summarized in Table 3. Gastrectomy with lymphadenectomy was performed according to the Japanese Gastric Cancer Treatment guidelines [22]. Total gastrectomy with splenectomy was performed for complete resection of splenic hilar lymph nodes (No. 10), when the adenocarcinoma was located along the greater curvature of the upper stomach. Combined resection of the transverse colon was performed in one patient because of direct invasion by the primary tumor. R0 resection was achieved in 28 patients (93%) and R2 resection in two patients (7%) with peritoneal dissemination. Postoperative complications were observed in five patients (17%), all of whom recovered with conservative treatment. Pancreatic fistulas occurred in two of the eight patients (25%) who underwent splenectomy. Hospitalization was prolonged because of anorexia following healing of the pancreatic fistula in one patient (101 days), and the median postoperative hospital stay was 15 days.

Efficacy

The tumor classifications after neoadjuvant chemotherapy are shown in Table 4. Clinically, tumor down-staging was observed in 18 patients (60%), and no patient had PD. According to the pathological classification, 18 patients (60%) showed down-staging, whereas seven (23%) were evaluated with more advanced staging. Peritoneal metastasis was found in two patients who were finally diagnosed as Stage IV. Analysis of the pathological responses in the primary gastric lesions of the 30 patients showed grade 1a in five patients (17%), grade 1b in nine patients (30%), grade 2 in 11 patients (37%), and grade 3 in five patients (17%).

Survival analysis

The median follow-up period was 33 months, after which 24 patients (80%) remained alive. Tumor recurrence occurred in six patients after 13 months (range 5–23 months), including recurrence in the peritoneum in three patients, and in the pericardium, lymph node, and

Table 2 Adverse events associated with neoadjuvant DCS therapy

Adverse event (NCI-CTC)	G1 (Number of patients)	G2	G3	G4	Overall (%)	G 3/4 (%)
Leukocytopenia	3	9	7	2	70	30
Neutropenia	1	3	11	5	67	53
Febrile neutropenia	–	–	5	1	20	20
Anemia	9	7	2	0	60	7
Thrombocytopenia	0	1	0	0	3	0
Anorexia	5	1	9	0	50	30
Nausea	0	2	3	0	17	10
Vomiting	2	2	0	0	13	0
Diarrhea	4	2	3	0	30	10
Constipation	14	0	0	0	47	0
Hiccups	1	5	0	0	20	0
Abdominal pain	1	0	2	0	10	7
Dysgeusia	3	0	0	0	10	0
Mucositis	0	0	3	0	10	10
Pancreatitis	0	1	0	0	3	0
Myocardial infarction	0	0	0	1	3	3
Hypotension	0	0	0	1	3	3
Depressed level of consciousness	0	1	0	0	3	0

Table 3 Surgical outcomes

	Number of patients (%)
Surgical procedure	
Total gastrectomy	22 (73)
Distal gastrectomy	8 (27)
Lymph node dissection	
D2-No. 10	11 (37)
D2	15 (50)
D2+	4 (13)
Combined organ resection	
Spleen	8 (27)
Transverse colon	1 (3)
Residual tumor	
R0	28 (93)
R2	2 (7)
Operation time (min)[a]	256 (175–351)
Blood loss (g)[a]	470 (17–1775)
Complication	
Pancreatic fistula G3	2 (7)
Wound infection G1	2 (7)
Anastomotic stenosis G2	1 (3)
Postoperative hospital stay (day)[a]	15 (10–101)

[a] Values are median and range

brain in one patient each. These patients received second-line chemotherapy. The OS curves of all patients are shown in Fig. 1a. The 2- and 3-year OS rates were 89 and 70%, respectively. There was a significant difference in OS between pathological responders (grade 1b-3) and non-responders (grade 1a) (Fig. 1b). The 2-year OS rate in the pathological responders was 96%, compared with 50% in the pathological non-responders ($P = 0.00187$). The 3-year OS rate was 100% for grade 3, 88% for grade 2, 67% for grade 1b, and 0% for grade 1a ($P = 0.0149$) (Fig. 1c).

Discussion

The results of the present study indicated that neoadjuvant DCS therapy may improve the prognosis in patients with serosa-positive locally advanced gastric cancer. However, the results also suggested that careful management of adverse events was crucial. Both the safety and efficacy of this treatment strategy need to be confirmed before it can be considered as a standard treatment option.

The V325 phase III trial demonstrated that response rates and survival in patients with advanced gastric cancer were improved by the addition of docetaxel to cisplatin and fluorouracil in a first-line setting [23], since when the DCS regimen has recently been attempted in the preoperative setting in Japan [24, 25]. The present study of neoadjuvant DCS therapy demonstrated a clinical response rate of 57% and pathological response rate of 83%. Previous studies similarly reported that neoadjuvant DCS had a higher pathological response rate (71.2–87.5%) compared with a doublet regimen (14.5–51%) [24, 25]. Furthermore,

Table 4 Tumor classification after neoadjuvant DCS therapy

	Clinical classification (yc)[a]	Pathological classification (yp)[a]
Depth of tumor invasion		
T0	0	5
T2 (MP)	0	5
T3 (SS)	8	9
T4a (SE)	21	11
T4b (SI)	1	0
LN metastasis		
N0	24	16
N1	1	3
N2	5	5
N3	0	6
Peritoneal metastasis		
P0	30	28
P1	0	2
Stage		
0	0	4
IB	0	5
IIA	7	4
IIB	16	4
IIIA	2	3
IIIB	5	4
IIIC	0	4
IV	0	2

The clinical classification following preoperative treatment is designated ycTNM and the pathological classification ypTNM

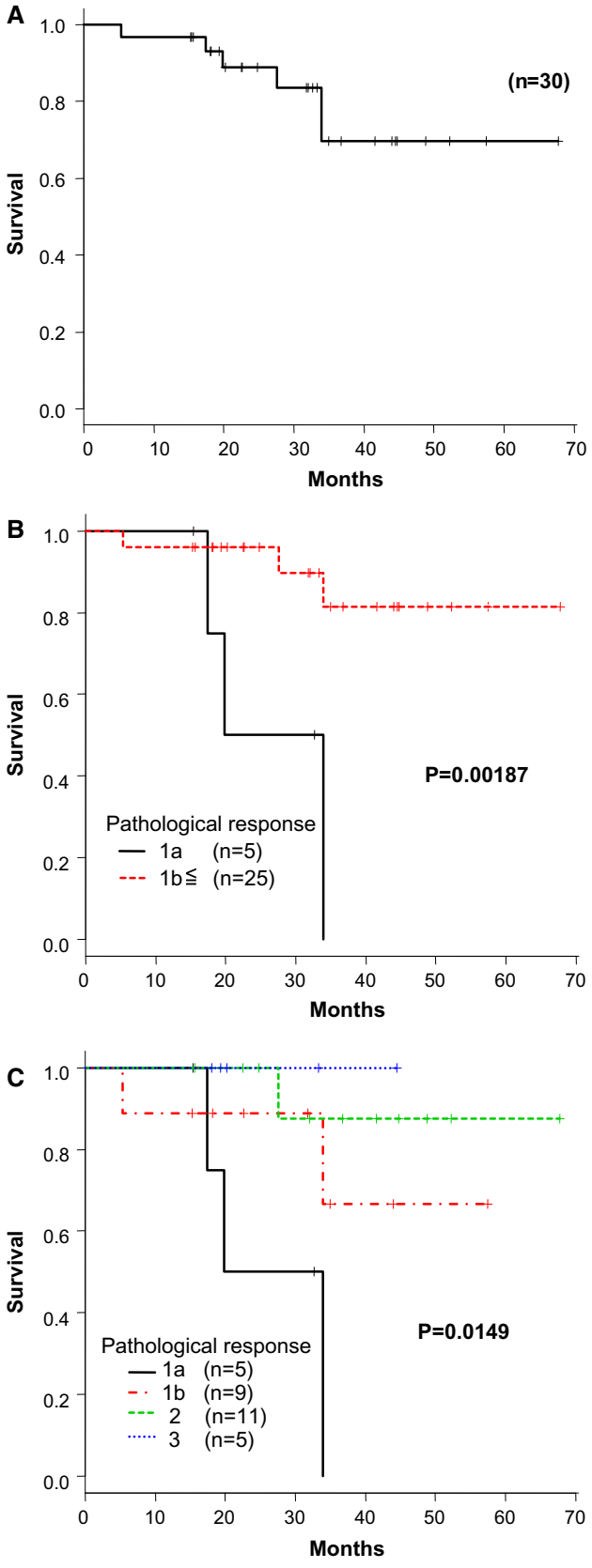
[a] According to the Japanese Classification of Gastric Carcinoma 3rd English edition

neoadjuvant DCS therapy demonstrated excellent 3-year OS (88%) in patients with locally advanced gastric cancer with staging laparoscopy [25]. Similarly, in our study without staging laparoscopy, relatively few cases (20%) were diagnosed with tumor recurrence within 3 years. However, a previous report of systemic DCS in patients with marginally resectable gastric cancer showed insufficient efficacy for reducing peritoneal recurrence; the peritoneal recurrence rate in patients with Borrmann type 4 or type 3 tumors reached 50% [26]. However, the peritoneal recurrence rate in the current study, which included 90% of patients with Borrmann type 4 or type 3 tumors, was only 10% including two cases with stage IV. Our results thus indicated that neoadjuvant DCS therapy may be an effective treatment for locally advanced gastric cancer, without peritoneal dissemination.

Most physicians are nervous about the severe toxicity of the triplet regimen, and many patients who undergo neoadjuvant DCS therapy experience grade 3 or higher adverse events [24, 25]. Close monitoring and appropriate treatment are particularly necessary for the management of hematological adverse events such as neutropenia (25–53%), leukocytopenia (16.9–30%), and febrile neutropenia (6.3–20%). Although gastrectomy following chemotherapy was possible in all our patients, candidates for neoadjuvant DCS therapy should be selected cautiously based on the patient's physical condition.

Some surgeons believe that preoperative chemotherapy can lead to postoperative complications after gastrectomy with D2 lymphadenectomy, and the reported incidence of postoperative complications after neoadjuvant DCS therapy ranged from 18.6 to 31.3% [24, 25]. The postoperative morbidity rate in the present study was 17%, and the most frequent grade 3 complication was pancreatic fistula (7%). This result is consistent with previous reports of the incidence of complications (17.9–29.4%) in patients who underwent D2 gastrectomy without preoperative chemotherapy [27, 28]. Several studies suggested that postoperative complications were not increased in the presence of neoadjuvant chemotherapy [24, 29, 30]. Although pancreatic fistulas were often observed in patients who underwent gastrectomy with bursectomy following neoadjuvant chemotherapy [30], our study revealed a correlation with splenectomy.

The main disadvantage of neoadjuvant chemotherapy is the potential loss of cancer resectability as a result of



◀**Fig. 1** **a** Kaplan–Meier analysis of overall survival (OS) in all patients who underwent neoadjuvant DCS chemotherapy. **b** OS in pathological responders (≥grade 1b) and non-responders (grade 1a). **c** OS according to pathological response

disease progression during preoperative chemotherapy. Although no patient in the current study experienced clinical PD during neoadjuvant chemotherapy, peritoneal dissemination was observed in two patients (7%) during gastrectomy. However, we did not use staging diagnostic laparoscopy to identify peritoneal dissemination, which may therefore already have existed at the time of diagnosis. Laparoscopy thus appears to be necessary to determine the stage of disease and duration of chemotherapy in patients with serosa-positive locally advanced gastric cancer.

Conclusion

The results of this study confirmed that neoadjuvant DCS therapy was effective in patients with serosa-positive locally advanced gastric cancer who underwent subsequent D2 gastrectomy. However, further investigations are required to confirm the validity of neoadjuvant DCS therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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