Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin and S-1 in gastric cancer patients with para-aortic lymph node metastases

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We performed preoperative chemotherapy with combined docetaxel, cisplatin and S-1 (DCS therapy) for treatment of advanced gastric cancer with para-aortic lymph node metastases. The aim of this study was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities. Furthermore, we evaluated the feasibility of DCS therapy in a preoperative setting, and also examined the pathological response. Fifteen patients received intravenous docetaxel and cisplatin (30, 35 or 40 mg/m^2, each dose escalation was reciprocal) on days 1 and 15 and oral S-1 (40 mg/m^2 twice daily) on days 1–14 every 4 weeks. After one cycle of chemotherapy, toxicities were evaluated and after two cycles of chemotherapy, patients who were judged to be candidates for curative resection underwent gastrectomy with D2 lymphadenectomy plus para-aortic lymph node dissection. The MTD of this combination was presumed to be at dose level 3 (docetaxel 40 mg/m^2 and cisplatin 35 mg/m^2). The dose-limiting toxicities were grade 4 neutropenia in one patient, grade 3 febrile neutropenia in two patients and grade 3 diarrhoea in two patients. Thirteen of the 15 patients received complete resection and there was no operation-related death. Good pathological responses were observed in 12 cases with lesions in the lymph nodes (complete response, $n=4$; partial response, $n=8$) and 11 patients with primary stomach lesions (complete response, $n=2$; partial response, $n=9$). This preoperative DCS therapy was considered feasible and provided a high pathological response rate in gastric cancer patients with para-aortic lymph node metastases. *Anti-Cancer Drugs* 20:752–756 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Gastric cancer is still one of the leading causes of cancer death in east Asia and eastern Europe. Recent improvements and chemotherapy have considerably improved the prognosis of gastric cancer. However, the prognosis of unresectable cancer remains poor. These unresectable cancers consist of haematological metastases, peritoneal metastases and distant lymph node metastases, such as para-aortic lymph node metastases. More than 20% of patients with advanced gastric cancer develop para-aortic lymph node metastasis [1]. These cases should be considered as systemic disease because the prognoses are quite poor even after D2 lymphadenectomy plus para-aortic lymph node dissection (PAND) alone [2–4]. These observations indicate that multimodality therapies are needed as novel approaches to improve the treatment outcome.

Preoperative chemotherapy is a promising strategy of multimodality therapy. The potential benefits of preoperative chemotherapy include increasing the likelihood of curative resection by downstaging the tumour, eliminating micrometastases and determining whether the tumour is sensitive to chemotherapy. A pathological complete response (pCR) to preoperative chemotherapy may be a surrogate for longer survival [5], but this beneficial effect remains to be established. Therefore, a powerful new preoperative chemotherapy regimen is required.

S-1 is a new oral anticancer drug that was developed based on the biochemical modulation of tegafur, which is a prodrug of 5-fluorouracil, by 5-chloro-2,4-dihydroxypyridine and potassium oxonate to increase antitumor activity and reduce gastrointestinal adverse reaction [6,7]. Phase II studies of S-1 have indicated response rates of 44–54% in patients with advanced gastric cancer [8,9], and combinations with cisplatin or docetaxel have shown higher overall response rates [10,11].

There have been two earlier reports of docetaxel, cisplatin and S-1 combination chemotherapy (DCS therapy) [12,13]. The potential for DCS therapy as

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a useful regimen for unresectable gastric cancer was supported by these studies, which showed high response rates. However, it is controversial whether these regimens are safe and effective in a preoperative setting. To our knowledge, this is the first report evaluating the feasibility of preoperative DCS therapy and safety in surgery consisting of gastrectomy with D2 lymphadenectomy plus PAND for unresectable gastric cancer with para-aortic lymph node metastases.

Patients and methods

Eligibility

Patients fulfilling the following criteria were enrolled in this study: (i) histologically confirmed gastric adenocarcinoma; (ii) presence of para-aortic lymph node metastases [detection of two or more enlarged lymph nodes > 10 mm by computed tomography (CT)]; (iii) absence of peritoneal metastasis confirmed by staging laparoscopy; (iv) age of 18–75 years; (v) Eastern Cooperative Oncology Group performance status of 0–1; (vi) no prior chemotherapy or radiotherapy; (vii) normal organ functions, including bone marrow, heart, lung, liver and kidney; (viii) no other malignancies; and (ix) written informed consent. The study protocol was approved by the Institutional Review Board of Kanazawa University Hospital, Kanazawa, Japan. Before entry into the study, all patients underwent the following investigations: chest radiography, gastrointestinal fibrescopy, gastrointestinal barium radiography and spiral CT of the chest and abdomen.

Treatment

Patients received two cycles of preoperative chemotherapy, consisting of docetaxel as a 1-h intravenous infusion on days 1 and 15, cisplatin as a 2-h intravenous infusion on days 1 and 15 with hyperhydration and S-1 [orally 40 mg/m^2 twice daily (b.i.d.)] on days 1–14 every 4 weeks. Prophylactic administration of antiemetic medication (5-HT3 antagonist plus corticosteroid) at a standard dose was routinely used to prevent gastrointestinal symptoms and anaphylactic reaction. Sequential escalating doses of docetaxel with cisplatin were tested as outlined in Table 1. The dose of docetaxel was escalated in increments of 5 mg/m^2 from 35 to 40 mg/m^2 and the dose of cisplatin was also escalated from 30 to 35 mg/m^2 (each dose escalation was reciprocal). At least three assessable patients were treated at each dose level, and assessment of the dose-limiting toxicities (DLTs) was made only in the first treatment cycle. If one or two of three patients at a dose level experienced DLT, then three additional patients were treated at that dose level. If at least three of six patients had DLT, the dose level was defined as the maximum tolerated dose (MTD). The recommended dose (RD) was that immediately below the MTD. DLT was defined as grade 4 neutropenia lasting for more than 3 days, or grade 3/4 febrile neutropenia, grade 4 thrombocytopenia, or grade 3 nonhaematological toxicity excluding nausea/vomiting. During treatment, physical examinations, complete blood counts and serum chemical examination were performed at least biweekly, that is, before drip infusion of docetaxel and cisplatin on days 1 and 15 in each cycle. If the neutrophil count was less than 1000/ml, the platelet count was less than 70 000/ml or $\geq$ grade 2 nonhaematological toxicity other than nausea/vomiting and alopecia occurred, subsequent chemotherapy was delayed until these adverse events had subsided. If DLTs occurred, the dose was reduced to immediately below this level. Even if there were no significant toxicities in the first cycle, dose escalation was prohibited in the second cycle. Toxicity was measured by the Common Toxicity Criteria of the National Cancer Institute, Version 2.0.

Table 1 Dose escalation schedule

Level	Docetaxel (mg/m^2)	Cisplatin (mg/m^2)	S-1 (mg/m^2)
0	30	30	80
1	35	30	80
2	35	35	80
3	40	35	80

Evaluation of the disease

CT scan and gastrointestinal fibrescopy were performed in each cycle. The objective response to chemotherapy in measurable and primary lesions was evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumours) in metastatic lesions and according to the Japanese Research Society for Gastric Cancer criteria in primary lesion [14].

Surgery

After two cycles of DCS therapy, conventional examinations, such as a CT scan of the whole abdomen and chest, and endoscopy of the upper gastrointestinal tract, were carried out to assess the resectability of the tumours. Surgery was performed at least 4 weeks after the second cycle in patients who were judged to be candidates for curative resection. The type of operation depended on the location and extent of the primary lesion, but the resection lines had to be at least 3 cm from the edge of the macroscopic tumour. *En bloc* resection of adjacent organs was performed when their involvement was suspected. D2 lymphadenectomy plus PAND was routinely performed as described earlier [1,15].

Pathological examination of surgical specimens

All resected specimens were examined by pathologists and the pathological response to chemotherapy was evaluated according to the criteria of the Japanese Research Society for Gastric Cancer [14]. According to the amount of necrosis or disappearance of the tumour in the estimated total amount of the lesion, grade 0–3 were provided. That was, grade 0, neither necrosis nor cellular or structural change could be seen throughout the lesion; grade 1a, necrosis or disappearance of the tumour was

present in less than one-third of the whole lesion, or only cellular or structural changes were visible amounts; grade 1b, necrosis or disappearance of the tumor was present in no more than two-thirds of the whole lesion; grade 2, necrosis or disappearance of the tumour was present in more than two-thirds of the whole lesion, but viable tumour cells were still remaining; grade 3, the whole lesion fell into necrosis and/or was replaced by fibrosis, with or without granulomatous changes. No viable tumour cells were observed. In this study, patients showing grades 0 and 1a were considered as pathological nonresponders and those showing grades 1b, 2 and 3 were considered as pathological responders.

Results

Patient characteristics

Between November 2007 and December 2008, 15 patients were enrolled in this study. Their characteristics are summarized in Table 2. The patients consisted of 11 men and four women, with a median age of 63 years (range 48–72 years). The Eastern Cooperative Oncology Group performance status was 0 in 12 patients and 1 in three patients. Histologically, nine patients had intestinal type and six had diffuse type. All 15 patients had paraaortic lymph node metastases, and distant metastases other than lymph node metastases were found in the livers of three patients.

Toxicity

All patients evaluable for toxicity and adverse effects during the first cycle are summarized in Tables 3 and 4. The main toxicities were nausea, diarrhoea, leucopenia and neutropenia. No patients experienced more than grade 2 liver or renal dysfunction.

The first cohort of three patients was enrolled at dose level 1, and no DLTs were observed. During dose escalation, two patients at dose level 2 experienced DLTs (grade 3 diarrhoea and grade 3 gastrointestinal bleeding). Therefore, three additional patients were enrolled at dose level 2 and none of the three had more than grade 3 toxicity. In the first three enrolled patients at dose level 3, one patient had grade 3 diarrhoea and febrile neutropenia, and three additional patients were enrolled at dose level 3. Two of the three patients at dose level 3 experienced $\geq$ grade 3 toxicities; one had grade 4 leucopenia and neutropenia, and the other had grade 3 febrile neutropenia. Owing to these results, no additional patients were enrolled at dose level 3 and MTD was determined at dose level 3. Dose level 2 was declared the RD. There were no cases of treatment-related death.

Table 2 Patient characteristics

Patient number	15
Sex	
Male/female	11/4
Age (median) (years)	48–72 (63)
PS (ECOG)	
0/1/2	12/3/0
Histological type	
Intestinal/diffuse	9/6
Target lesion	
Primary tumour	15
Lymph node	15
Liver	3

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 3 Haematological toxicities

NCI-CTC grade	1	2	3	4	% of grade 3/4
Level 1 (n=3)					
Anaemia	1	0	0	0	0
Leucocytopenia	1	0	0	0	0
Neutropenia	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0
Level 2 (n=6)					
Anaemia	1	0	1	0	16
Leucocytopenia	2	1	0	0	0
Neutropenia	1	1	0	0	0
Thrombocytopenia	1	0	0	0	0
Level 3 (n=6)					
Anaemia	1	0	1	0	16
Leucocytopenia	2	1	2	1	50
Neutropenia	2	1	2	1	50
Thrombocytopenia	1	0	0	0	0

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

Table 4 Nonhaematological toxicities

NCI-CTC grade	1	2	3	4	% of grade 2–4
Level 1 (n=3)					
Nausea/vomiting	1	0	0	0	0
Diarrhoea	1	0	0	0	0
GI bleeding	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0
Level 2 (n=6)					
Nausea/vomiting	1	2	1	0	50
Diarrhoea	1	1	1	0	33
GI bleeding	0	0	1	0	16
Febrile neutropenia	0	0	0	0	0
Level 3 (n=6)					
Nausea/vomiting	2	2	1	0	50
Diarrhoea	1	1	1	0	33
GI bleeding	0	0	0	0	0
Febrile neutropenia	0	0	2	0	33

GI, gastrointestinal.

Clinical response

As per the protocol, patients who received two cycles of chemotherapy were evaluable for clinical response. Two patients at dose level 3 were not evaluated because they received only one cycle of chemotherapy as a result of toxicity. Clinical responses are summarized in Table 5. The response rates according to site were as follows: primary lesion, 76.9% (10 of 13); lymph node metastases, 76.9% (10 of 13); and liver metastases, 100% (three of three). The overall response rate was 76.9% and the disease control rate was 100%.

Table 5 Clinical response

Lesion	No. of patients	CR	PR	SD	PD	RR	DCR
Primary	13	0	10	3	0	76.9	100
Lymph node	13	0	10	3	0	76.9	100
Liver	3	0	3	0	0	100	100
Overall	13	0	10	3	0	76.9	100

CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

Table 6 Pathological response of resected specimens

Grade	3	2	1b	1a	0	Response rate[a] (%)
Primary lesion	2	8	1	2	0	84.6
Lymph node	4	5	3	1	0	91.5
Liver	1	1	0	0	0	100

[a]Grades 0 and 1a were considered as pathological nonresponder and grades 1b, 2 and 3 were considered as pathological responder.

Surgery and pathological examination

Thirteen of the 15 patients underwent surgery; six had total gastrectomy, four had subtotal gastrectomy, two had proximal gastrectomy and one had oesophagogastrectomy. All of the patients who underwent surgery had D2 lymphadenectomy plus PAND. The median number of dissected lymph nodes was 34 (range 17–81) in total and 9 (range 3–31) in the para-aortic region. Of the three patients with hepatic metastases, two had partial hepatectomy and one had radio-frequency ablation. An R0 resection was achieved in 12 patients with the exception of one patient with hepatic radio-frequency ablation (92%; this was 80% of the initial 15 patients). Major surgery-related complications developed in three patients (23% of 13 patients) as follows: two had a pancreatic fistula and one had anastomotic leakage. The minor complications, such as malaise, diarrhoea and lymphorrhoea were relatively frequent. All of the patients with complications were treated successfully.

Pathological findings of surgically resected specimens are listed in Table 6. There were two pCRs among the primary lesions. The grades of pathological effect of chemotherapy were grade 1a in two patients, grade 1b in one patient, grade 2 in eight patients and grade 3 in two patients. Pathological examination of the dissected lymph nodes showed no viable cancer cells in four patients, and all of metastatic lymph nodes including the para-aortic lymph nodes showed necrosis with fibrosis. One of two patients who underwent partial hepatectomy also had no cancer cells in the residual tumour and showed only necrotic tissue and granulation.

Discussion

We performed a phase I study of docetaxel, cisplatin and S-1 as preoperative chemotherapy for 15 unresectable gastric cancer patients with para-aortic lymph node metastases. There have been few studies of the use of these three agents in unresectable gastric cancer. Takayama *et al.* [12] defined the RD with docetaxel 60 mg/m^2 triweekly, cisplatin 60 mg/m^2 triweekly and S-1 40 mg/m^2 b.i.d. during 2 weeks. The response rate was 88.2%, but a high incidence of grade 3–4 neutropenia (66.7%) was also observed. This regimen was considered unsuitable for preoperative chemotherapy because the risk of surgery-related complications seemed to increase. Nakayama *et al.* [13] also defined the RD of docetaxel 40 mg/m^2 every 4 weeks, cisplatin 70 mg/m^2 every 4 weeks and S-1 40 mg/m^2 b.i.d. during 2 weeks. None of 13 patients showed CR and the response rate was relatively low (69.2%). Treatment schedules remain a central issue in the search for a balance between a good response rate and low toxicity. Therefore, docetaxel and cisplatin were administered biweekly in our study with anticipation of both decreased toxicity and increased response. DLT consisted of neutropenia and diarrhoea at a dose of 40 mg/m^2 of docetaxel, and the RD was determined to be docetaxel 35 mg/m^2, cisplatin 35 mg/m^2 and S-1 40 mg/m^2 b.i.d. Our regimen showed a high clinical response ratio (77.0%) and a very high disease control ratio (100%) despite the low incidence of grades 3–4 neutropenia (23.1%). The incidences of toxicities in this study were clearly lower than for the two other DCS regimens, while capable of achieving high-dose intensity. These results suggest that this biweekly schedule of docetaxel and cisplatin is also suitable for use on an outpatient basis, in contrast to the two other DCS regimens that require hospital admission.

In this study, we selected patients with para-aortic lymph node metastases detected as two or more enlarged (>10 mm) lymph nodes by spiral CT. For these unresectable gastric cancer patients, gastrectomy not with D2 lymphadenectomy but with D2 lymphadenectomy plus PAND was performed after two cycles of preoperative DCS therapy. D2 lymphadenectomy plus PAND is thought to be associated with high rates of both mortality and morbidity. However, a randomized controlled trial in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND for curable gastric cancer (JCOG9501) showed no statistically significantly differences in either mortality or morbidity between the two groups [16]. That is, D2 lymphadenectomy plus PAND may be relatively safe treatment by experienced surgeons. In fact, we found major surgery-related complications in 23% of cases, which was relatively low considering that D2 lymphadenectomy plus PAND had been performed after chemotherapy. Hard and fibrous tissue in the tumour site owing to the effects of chemotherapy made surgery more difficult. However, this was not associated with increased incidence of postoperative complications.

With regard to antitumour activity, the pathological response rates were 84.6% in the primary lesion, 91.5% in lymph nodes and 100% in the liver. In two studies of DCS therapy, pCR was achieved in only one case, whereas we confirmed four cases of pCR in which the tumour cells disappeared and all dissected lymph nodes showed necrosis and fibrosis. Although our study population consisted of only 15 patients, these antitumour activities were superior to those reported earlier.

Our DCS therapy including biweekly docetaxel and cisplatin was well tolerated with minimal toxicity and high rate of pathological response in comparison with the results obtained with two other DCS regimens. Preoperative chemotherapy with biweekly docetaxel and cisplatin plus concurrent S-1 is a feasible and effective treatment schedule that leads to rapid shrinkage of the primary lesion and metastatic lesions, and in combination with D2 lymphadenectomy plus PAND may be a promising strategy for unresectable gastric cancer with para-aortic lymph node metastases. However, the number of patients included in this study was small, and further evaluations are required in larger patient populations. Therefore, a multi-institutional phase II trial of preoperative chemotherapy is currently being started using this regimen in patients with para-aortic lymph node metastases by the Japan Clinical Oncology Group.

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References

1 Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, *et al.* Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy-Japan Clinical Oncology Froup study 9501. *J Clin Oncol* 2004; **22**:2767–2773.

2 Yonemura Y, Katayama K, Kamata T, Fushida S, Segawa M, Ooyama S, *et al.* Surgical treatment of advanced gastric cancer with metastasis in para-aortic lymph node. *Int Surg* 1991; **76**:222–225.

3 Isozaki H, Okajima K, Fujii K, Nomura E, Izumi N, Mabuchi H, *et al.* Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. *Hepatogastroenterology* 1999; **46**:549–554.

4 Kunisaki C, Shimada H, Yamaoka H, Wakasugi J, Takahashi M, Akiyama H, *et al.* Significance of para-aortic lymph node dissection in advanced gastric cancer. *Hepatogastroenterology* 1999; **46**:2635–2642.

5 Nakajima T, Ohta K, Ishihara S, Oyama S, Nishi M, Ohashi Y, *et al.* Combined intensive chemotherapy and radical surgery for incurable gastric cancer. *Ann Surg Oncol* 1997; **4**:203–208.

6 Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, *et al.* Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 1996; **7**:548–557.

7 Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxanic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993; **53**:4004–4009.

8 Sugimachi K, Maehara Y. The S-1 gastrointestinal cancer study group: an early phase II study of oral S-1, a newly developed 5-fluorouracil delivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999; **57**:202–210.

9 Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1M tegaful-0.4M gimestat-1M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34**:1715–1720.

10 Lenz HJ, Lee FC, Haller DG, Singh D, Benson AB 3rd, Strumberg D, *et al.* Extended safety and efficacy data on S-1 plus cisplatin in patients with untreated, advanced gastric carcinoma in a multicenter phase II study. *Cancer* 2007; **109**:33–40.

11 Yoshida K, Ninomiya M, Takakura N, Hirabayashi N, Takiyama W, Sato Y, *et al.* Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. *Clin Cancer Res* 2006; **12**:3042–3047.

12 Takayama T, Sato Y, Sagawa T, Okamoto T, Nagashima H, Takahashi Y, *et al.* Phase I study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. *Br J Cancer* 2007; **97**:851–856.

13 Nakayama N, Koizumi W, Sasaki T, Higuchi K, Tanabe S, Nishimura K, *et al.* A multicenter phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). *Oncology* 2008; **75**:1–7.

14 Japanese Research Society for Gastric Cancer. Response assessment of chemotherapy and radiotherapy for gastric carcinoma part IV. In: Nishi M, Omori Y, Miwa K, editors. *Japanese classification gastric carcinoma*. 1st ed. Tokyo: Kanehara; 1995. pp. 89–100.

15 Yoshikawa T, Sasako M, Sano T, Nashimoto A, Kurita A, Tsujinaka T, *et al.* Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from results prospective randomized controlled trial. *Br J Surg* 2006; **93**:1526–1529.

16 Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, *et al.* D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; **359**:453–462.