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ORIGINAL ARTICLE

A phase I study of palliative chemoradiation therapy with paclitaxel and cisplatin for local symptoms due to an unresectable primary advanced or locally recurrent gastric adenocarcinoma

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Abstract
Purpose To establish the maximum tolerated dose and dose-limiting toxicity of chemoradiation with paclitaxel (PTX) and cisplatin (CDDP) for patients with local symptoms due to unresectable primary advanced or locally recurrent gastric adenocarcinoma located at left-upper abdomen.
Methods Chemotherapy consisted of PTX at escalating doses of 40–80 mg/m^2 per day and CDDP at escalating doses of 20–25 mg/m^2 per day on days 1, 15, and 29. Concurrent radiation was administered up to a dose of 45 Gy for 5 weeks.
Results A total of nine patients were enrolled, of which six were into level 1 (PTX 60 mg/m^2 and CDDP 20 mg/m^2) and three into level −1 (PTX 50 mg/m^2 and CDDP 20 mg/m^2). At level 1, one patient developed grade 3 fatigue, and the other experienced grade 5 DIC, grade 5 pneumonia, grade 4 thrombocytopenia, grade 3 hyponatremia, and grade 3 esophagitis as dose-limiting toxicities. A palliative effect was observed in eight of nine patients; six of six patients at level 1 and two of three at level −1.
Conclusion PTX 50 mg/m^2 and CDDP 20 mg/m^2 given biweekly with concurrent radiation therapy of 45 Gy were well tolerated.

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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

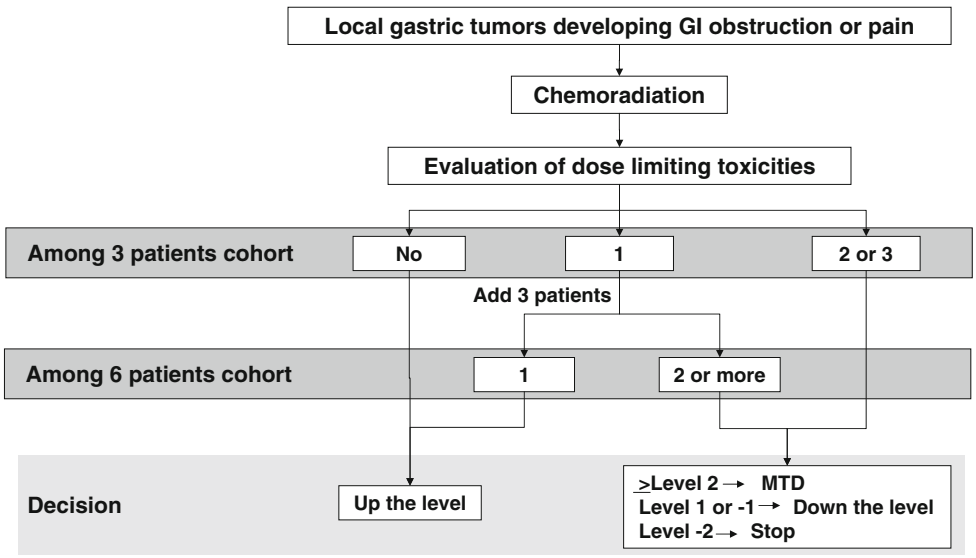

Fig. 1 Schema of this study

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.

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.

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

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

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

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.

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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