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ORIGINAL ARTICLE

Phase I study of neoadjuvant chemoradiotherapy with S-1 and oxaliplatin in patients with locally advanced gastric cancer

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Abstract
Purpose The aim of this phase I study was to investigate the optimal dose of S-1 and oxaliplatin with concurrent radiotherapy in a preoperative setting for locally advanced gastric cancer.
Patients and methods Twelve patients with histologically confirmed clinical stage T2N+ or T3–T4 gastric adenocarcinoma received dose level −1 (oral S-1 at 60 mg/m^2/day + oxaliplatin 40 mg/m^2 intravenously on days 1, 8, 15 and 22) or dose level 1 (S-1 80 mg/m^2/day + oxaliplatin 40 mg/m^2), with concurrent radiotherapy at daily fractions of 1.8 Gy 5 days per week, to a total dose of 41.4 Gy. Surgical resection, including D2 dissection, was performed within 4 weeks after the last day of chemotherapy.
Results Chemoradiotherapy was generally well tolerated, with the most common dose-related grade 1 or 2 adverse events being anemia, nausea, vomiting, anorexia and abdominal pain. Two DLTs (prolonged thrombocytopenia and stomach perforation) were observed at dose level 1 ($n = 6$) and resulted in dose de-escalation to level −1. The recommended dose for future study is dose level −1, at which 1 of 6 patients developed grade 3 vomiting and anorexia. R0 resection was possible in 11 patients. Pathologic down-staging was observed in 6 patients, including one complete response. No clinically relevant postoperative complications occurred.
Conclusions The activity of preoperative concurrent chemoradiotherapy with S-1 (60 mg/m^2/day for 28 consecutive days) and oxaliplatin (40 mg/m^2 on days 1, 8, 15 and 22) will be explored more extensively in a phase II study in patients with locally advanced GC.

Keywords Stomach neoplasm · Preoperative · Chemotherapy · Radiotherapy · Concurrent

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Introduction

Gastric cancer (GC) is the most frequently occurring malignancy in Korea [1] and is one of the main causes of cancer death. Most patients with early-stage disease undergo curative resection. However, more than half of these patients will recur and develop metastatic disease [2].

Postoperative adjuvant therapy significantly reduces the risk of relapse in patients with locally advanced GC who have undergone potentially R0 resection [3]. However, many patients do not qualify for this strategy because the rate of R0 resection is often less than 50% in the community [4–6].

Subsequently, the preoperative treatment was proposed to overcome the poor R0 resection rates and high locoregional relapse rates. In a randomized trial comparing perioperative chemotherapy given before and after radical surgery with surgery alone [7], a perioperative chemotherapy regimen of epirubicin, cisplatin and 5-fluorouracil (ECF) decreased tumor size and stage. Similarly, increased R0 resection rate was reported in a randomized trial comparing preoperative chemotherapy with surgery alone [8]. However, the latter trial failed to demonstrate a survival benefit with preoperative chemotherapy. Ideally, a successful preoperative treatment should increase R0 resection rate and substantially reduce locoregional relapse. In reflection of high locoregional relapse in gastric cancer following curative resection, the preoperative strategy with concurrent chemoradiotherapy could be considered as a reasonable treatment strategy [9]. Previous studies have demonstrated acceptable tolerability of preoperative chemoradiotherapy in GC patients [3, 10, 11]. Moreover, several phase II studies revealed that preoperative chemoradiotherapy strategy resulted in substantial pathologic response and thus prolonged survival time in locally advanced GC [12, 13].

This phase I study was designed to determine the dose-limiting toxicity (DLT) of S-1 and oxaliplatin given concurrently with radiotherapy and to define the recommended dose (RD) for subsequent phase II study. Although in advanced disease the combination of fluoropyrimidines and platinum is considered as a standard chemotherapy [14], S-1 and oxaliplatin combination has not been investigated with concurrent radiotherapy for patients with GC. The dose of oxaliplatin was gradually escalated with fixed doses of radiation and S-1 chemotherapy in this phase I trial.

Patients and methods

Patients

Patients were eligible for inclusion in this single-center, phase I dose-escalating study if they were $\geq$18 years of age, had weight loss of <5% over the 3 months before registration, had an Eastern Cooperative Oncology Group performance status of 0–1, had a histologically confirmed, previously untreated, locally advanced (i.e., clinical stage T2N+, T3–T4 and/or N+, according to the American Joint Committee on cancer TNM system 6th edition) adenocarcinoma arising from the stomach or gastroesophageal junction and adequate organ (hematologic, renal and hepatic) function. Only GC patients without definite evidence of distant metastases were eligible to enter the study. Exclusion criteria included any prior chemotherapy or abdominal irradiation, a PS of two or more, second primary malignancy or significant co morbidities. The present study was conducted in accordance with the declaration of Helsinki. All patients gave their written informed consent after having informed of the purpose and investigational nature of the study. The institutional review board of Samsung Medical Center (Seoul, Korea) reviewed and approved the protocol (NCT# 01106066).

Study procedures

The primary goal of the study was to determine the maximum-tolerated dose (MTD) of oral S-1 and intravenous oxaliplatin when given concurrently with preoperative radiotherapy in patients who have locally advanced GC. The regimen defined using the MTD of oxaliplatin could then be used in a subsequent phase II trial. Patients were to undergo a baseline evaluation and staging of their tumors. In addition to staging by computed tomography (CT) and a chest X-ray, an endoscopic ultrasound (EUS) of the stomach and a general laparoscopic survey of the abdominal cavity were performed before study entry. The histological confirmation of suspected peritoneal lesions was performed during the diagnostic laparoscopy. All staging procedures were to be carried out within 4 weeks of study registration.

Eligible patients were treated with a four-week course of preoperative chemoradiotherapy. From day 1, they received radiotherapy in the amount of 1.8 Gy per day, for a total of 41.4 Gy (23 fractions). Radiation fields included the stomach and regional lymph nodes, as determined using a 3D conformal technique. CT-based simulation and dosimetry were used to ensure adequate coverage of the primary tumor. Concurrently with radiotherapy, S-1 was given orally twice a day throughout the four-week course of treatment, including weekends, and oxaliplatin was administered intravenously on the first day of 4 consecutive weeks.

Within 4–8 weeks after the completion of chemoradiotherapy, a total or subtotal gastrectomy with D2 lymph node dissection was performed. Reconstruction of the gastrointestinal passage was performed according to institutional guidelines. To determine the efficacy of the protocol therapy, a standard pathologic analysis was performed on all surgical specimens. In all cases, the postoperative TNM status was obtained. A pathologically complete response was defined as the absence of any residual tumor in the surgical specimens (ypT0N0).

Strict quality control measures for treatments were implemented and monitored. All patients received the standard radiotherapy regimen and surgery a priori as defined in the study protocol. After the completion of the planned surgery, postoperative adjuvant chemotherapy was recommended and the subsequent treatments and eventual outcomes were recorded. Postoperative morbidity was assessed up to 30 days post-surgery.

A traditional phase I methodology was employed in assessing dose-limiting toxicity (DLT) and MTD. Chemotherapy consisted of S-1 given orally at 80 mg/m^2/day and oxaliplatin given by intravenous infusion on days 1, 8, 15 and 22. Initially, four escalating dose levels of oxaliplatin were planned. The starting dose of oxaliplatin was 40 mg/m^2, with escalation planned to 50, 60 and 70 mg/m^2. A minimum of three patients assessable for toxicity were to be treated at each dose level. Toxicity was assessed until 4 weeks post-completion of radiotherapy—8 weeks in total. The next dose level was not available for recruitment until toxicity data were available for the entire 8-week period for all patients at a particular dose level. If a DLT was not observed among the first three patients treated at a given dose level, then the dose was escalated. If one of three patients experienced a DLT, then an additional three patients were treated at that dose level. In the absence of further DLT, the dose was escalated. The highest dose level at which zero of three or one of six patients developed DLT was considered the MTD. It was the intention of the investigators to use the chemoradiotherapy regimen at the MTD in a subsequent phase II trial for an expanded number of patients. No intra-patient dose escalation was allowed.

Toxicity and dose modification

Toxicity was graded according to the National Cancer Institute criteria (CTCAE v3). DLTs included grade 4 neutropenia or thrombocytopenia of more than 7 days in duration. Febrile neutropenia lasting for longer than 3 days and requiring antibiotics was also classified as a hematologic DLT. Non-hematologic DLTs included all grade 3 or 4 non-hematologic toxicities, except for grade 3 diarrhea, nausea or vomiting responsive to medical therapy. Delay in treatment for more than two weeks due to toxicity or prolonged toxicity despite dose modification or interruption were also considered dose-limiting. In the cases in which toxicities were not defined in the protocol, but were considered by investigators to be severe enough (i.e., perforation, bleeding, etc.), the study committee could decide that the toxicity was equivalent to DLT.

Chemotherapy dose modification was planned for both hematologic and non-hematologic toxicity. In cases of DLT, treatment was discontinued until the patient's recovery to grade 0 or 1 and restarted at the next lower dose level and/or modified as appropriate to the toxicity. If a patient experienced grade 3 or higher toxicity, chemotherapy was withheld until recovery. Radiotherapy was also temporarily withheld when a patient experienced DLT.

Results

Of the 31 patients assessed for eligibility between March 2009 and November 2010, 15 were found to be eligible after baseline screening procedures, including EUS and laparoscopic survey. Sixteen patients were ineligible due to following reasons: laparoscopically proven peritoneal seeding ($n = 5$), intestinal obstruction ($n = 1$), laparoscopically detected paraaortic lymph node involvement ($n = 1$), unexpected tumor bleeding ($n = 1$) and advanced stage ($n = 8$). Of the 15 eligible patients, three patients were excluded from the present analyses due to consent withdrawal ($n = 2$) and death by car accident ($n = 1$), before the commencement of therapy. The consort diagram of patients through the study is shown in Fig. 1. Among the 12 evaluable patients, most had a PS of 0 (Table 1).

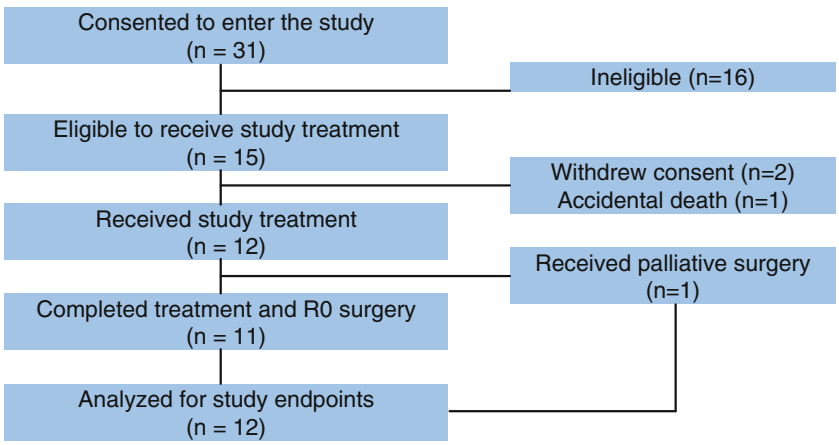

Fig. 1 Consort diagram of patients

Table 1 Baseline characteristics of patients

Characteristics	Number of patients (%)
Age, years	
Median	56
Range	39–76
Gender	
Male	9 (95)
Female	3 (25)
Performance status	
0	9 (75%)
1	3 (25)
Differentiation	
Well	1 (8)
Moderate	1 (8)
Poorly	5 (42)
Signet ring cell	5 (42)
Lauren classification	
Intestinal	5 (42)
Diffuse	6 (50)
Mixed	1 (8)
Tumor location	
Gastroesophageal junction	1 (8)
Body of stomach	1 (8)
Antrum	10 (83)
Clinical stages	
T2N1	1 (8)
T3N1	3 (25)
T2N2	2 (17)
T4aN1	1 (8)
T3N2	4 (33)
T4bN1	1 (8)

Details of toxicity in the two dose levels are shown in Table 2. The most common adverse event of all grades was anemia, followed by nausea, vomiting, anorexia and abdominal pain. At least 90% of the dose intensities of S-1 and oxaliplatin, calculated in terms of the mean percentage of the total intended dose that could be delivered at each dose level, were achieved. At the two dose levels, 96% of the intended dose of radiotherapy was delivered.

During dose level 1, two patients experienced DLT. One patient developed grade 2 thrombocytopenia and failed to recover his platelet count after 2 weeks. No further chemotherapy was given, although he went on to complete his radiotherapy after a 7-day delay, with a subsequent slow platelet recovery over the following 4 weeks. There was uncertainty as to the nature of this episode, particularly in view of the fact that he did not show other anticipated treatment-related toxicities (anorexia, neutropenia or bleeding episodes). Another dose level 1 patient developed gastric perforation during the last week of chemoradiotherapy and underwent an emergency operation. Despite its not being defined in the protocol, the investigators decided it was equivalent to a DLT. Then, the study protocol was amended, and further dose escalation was not pursued. Instead, the dose of S-1 was decreased to 60 mg/m^2/day, because the DLT was not thought to be related to oxaliplatin (dose level −1).

At dose level −1, one of the first three patients developed grade 3 anorexia and vomiting, despite appropriate supportive care. Thus, three additional patients were added on this dose level, with no further DLTs. After a review of the data by the investigators, dose level −1 was chosen as the revised recommended dose at which to include further patients.

Surgery was performed on all 12 patients. The median time between the last dose of chemoradiotherapy and surgery was 28 days, with a range of 2–33 days. One dose level 1 patient, who developed gastric perforation and received palliative subtotal gastrectomy as mentioned above, was found to have peritoneal dissemination. R0 resection with D2 lymph node dissection was successful in the remaining 11 patients. Ten patients underwent a subtotal gastrectomy and one a total gastrectomy. Postoperatively, the median inpatient stay was 11 days, with a range of 6–18 days. No patients died during study period or within 30 days post-surgery. There was no wound infection or anastomotic wound dehiscences.

Of the 12 resected specimens, one showed a complete response (ypT0N0) and five showed significant down-staging (Table 3). T down-staging (ypT0) was achieved in two patients at each dose level. One and three patients given dose level 1 and dose level −1, respectively, achieved N down-staging (ypN0).

Discussion

This phase I study testing preoperative concurrent chemoradiotherapy in patients with locally advanced GC determined the RDs of S-1 60 mg/m^2/day on days 1–28 and oxaliplatin 40 mg/m^2 on days 1, 8, 15 and 22. The toxicity profile of chemoradiotherapy was similar to that observed in postoperative chemoradiotherapy trials [3, 11]. Among the 12 patients who underwent surgery, one patient had a path CR and 5 patients achieved significant down-staging. These findings suggest that preoperative chemoradiotherapy may have a role in the treatment of locally advanced GC, although further studies are needed to more precisely assess its activity and toxicity.

In clinical settings, surgical resection remains the primary treatment option for patients with localized GC. Survival can be improved with the application of effective

Table 2 Worst grade toxicities per patient according to dose levels

CTCAE grade	Dose level 1 ($n = 6$)				Dose level −1 ($n = 6$)			
	1	2	3	4	1	2	3	4
Hematologic	–	–	–	–	–	–	–	–
Anemia	5	–	–	–	5	1	–	–
Leukopenia	1	1	–	–	2	2	–	–
Thrombocytopenia	2	1	–	–		1	–	–
Non-hematologic								
Nausea	4	1	–	–	3	3	–	–
Vomiting	3	1	–	–	3	1	1	–
Anorexia	4	2	–	–	3	2	1	–
Stomatitis	3	1	–	–	3	–	–	–
Diarrhea	1	1	–	–	1	1	–	–
Abdominal pain	5	1	–	–	6	–	–	–
Neuropathy	1	1	–	–	3	1	–	–
Fatigue	3	1	–	–	2	1	–	–
Hyperpigmentation	4	–	–	–	5	–	–	–
Hand–foot reaction	2	–	–	–	2	–	–	–
Dizziness	1	–	–	–	–	–	–	–
Dysphagia	1	1	–	–	2	–	–	–
Constipation	–	1	–	–	2	1	–	–

Table 3 Pretreatment clinical staging compared with pathologic staging

Clinical staging	Pathologic staging				
	T0	T1	T2	T3	T4
T2	–	2	1	–	–
T3	3	2	1	1	–
T4	1	–	–	–	1
	N0	N1	N2		
N1	3	1	2	–	–
N2	1	1	4	–	–

postoperative treatments, including chemoradiotherapy [3]. Chemotherapy, given preoperatively and/or postoperatively [7, 15], has shown a survival benefit when compared with surgery alone and is considered another standard of care in patients with locally advanced GC. These trials have triggered us to interrogate the necessity of radiotherapy as a component of gastric cancer treatment. However, the postoperative strategy can only be applied to patients with an R0 resection, and the quality of surgery is frequently suboptimal (i.e., there is a low rate of D2 lymph node dissection). It is currently unclear whether the addition of radiotherapy to preoperative treatment is beneficial in terms of locoregional control and survival.

Among studies testing preoperative therapy in GC, the present one is unique in using EUS and diagnostic laparoscopy as screening and staging procedures. EUS has been known to be accurate in determining the depth of tumor invasion [16]. Additionally, laparoscopic staging has a theoretical advantage in selecting patients with potentially resectable disease [17], specifically when detection of occult peritoneal dissemination is important.

In line with previous studies on preoperative chemoradiotherapy in GC [9, 12, 13], the predominant adverse events in this study were anemia, anorexia, nausea and vomiting. No patients developed grade 3 or 4 hematologic toxicity at the two dose levels tested. The patient who developed gastric perforation during the last week of therapy showed signs of rapid tumor shrinkage. Although multiple peritoneal nodules were found at surgery, it is noteworthy that the primary tumor had regressed to ypT0. In studies by Ajani et al. [12, 13], patients received up to two cycles of induction chemotherapy, followed by concurrent chemoradiotherapy. Complete pathological response rates and R0 resection rates of 26–30 and 70–77% were reported, respectively. Our study differs from those in delivering a lower dose of radiotherapy. In addition, we omitted induction chemotherapy, because long duration of the induction therapy resulting in the delay of optimal surgery may contribute to tumor growth and metastases.

When considering preoperative treatments, adverse events expressed both during chemoradiotherapy and also

as postoperative morbidity are important. Within the limitations of a small sample size, we observed no deaths or clinically significant postoperative morbidity in the present study. Except for one patient with peritoneal disease, R0 resection and D2 lymph node dissection were performed without prolonged or complicated wound problems.

In conclusion, a complex preoperative strategy requiring EUS and diagnostic laparoscopy as part of the initial staging, followed by concurrent chemoradiotherapy with S-1 and oxaliplatin, can be successfully performed. The safety and efficacy of this regimen (S-1 60 mg/m^2/day for 28 days + oxaliplatin 40 mg/m^2 on days 1, 8, 15 and 22, with concurrent radiotherapy at 41.4 Gy) will be tested in a phase II study with a larger numbers of patients.

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