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Clinical Trial Notes

Phase II Trial of Preoperative Chemotherapy with Docetaxel, Cisplatin and S-1 for T4 Locally Advanced Gastric Cancer

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The standard treatment for T4 locally advanced gastric cancer is gastrectomy with D2 lymph node dissection followed by adjuvant chemotherapy with S-1 for 12 months; however, prognostic outcome in Stage IIIb has been insufficient. It is expected that survival is improved by preoperative treatment with a triplet regimen of docetaxel, cisplatin and S-1 (divided DCS therapy). A multicenter Phase II study has been conducted to evaluate the safety and efficacy of two courses of preoperative chemotherapy followed by gastrectomy. Fifty-five patients are required for this study. The primary endpoint of the study is pathological response rate of primary lesions. Secondary endpoints are overall survival, disease-free survival, R0 resection rate and adverse events.

INTRODUCTION

The standard approach for locally advanced gastric cancer is to achieve R0 resection. Although gastrectomy with D2 lymph node dissection, the so-called extended dissection in western countries, has been undergone, peritoneal metastases (relapse) has been found frequently in T4 gastric cancer. In order to decrease incidence of relapse after R0 resection, postoperative adjuvant chemotherapy is recommended. Recent study, Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC), demonstrated that S-1 is an effective adjuvant treatment for East Asian patients who have undergone D2 dissection for locally advance gastric cancer (1). According to the subgroup analysis of ACTS-GC, there is no prognostic difference between the patients with and without S-1 in Stage IIIb. More intensive regimen, such as S-1 plus cisplatin which has demonstrated a significant higher response rate and longer survival than S-1 alone in SPIRITS trials (2), is needed for Stage IIIb consisting mostly of T4 gastric cancer, while S-1 plus cisplatin should reveal low compliance and high adverse events after gastrectomy (3, 4).

On the other hand, the potential benefits of preoperative chemotherapy include increasing the likelihood of curative resection by down-staging of the tumor, eliminating micrometastases and improving compliance against chemotherapy by avoiding surgery-related gastrointestinal symptoms. Although MAGIC trial demonstrated that preoperative chemotherapy achieved down-staging and revealed longer survival than surgery alone, 5 years survival rate of surgery alone in Japanese intergroup studies is ~70% which is superior to the result of preoperative chemotherapy in MAGIC trial (5). It is reason why that Japanese standard surgery for locally advanced gastric cancer is gastrectomy with D2 lymph node dissection, while D1 dissection is standard in Western Europe.

S-1/CDDP regimen (where CDDP is cisplatin) has now become one of the Japanese standards for unresectable or recurrent gastric cancer, because S-1 plus cisplatin has demonstrated significant higher response rate and longer survival than S-1 alone in the SPIRITS trial. In a preoperative setting, phase II study of S-1 plus cisplatin for the patients

with locally advanced gastric cancer (JCOG0210) showed 48% of pathological response rate (pRR) in the primary lesion (6). Some reports described that a pRR to preoperative chemotherapy may be a surrogate for longer survival (7), but the efficacy of S-1 plus cisplatin is not sufficient in the view point of the pRR. Therefore, the combination chemotherapy consisting of docetaxel, cisplatin and S-1 (DCS therapy) has been anticipated as a more powerful regimen of preoperative setting for locally advanced gastric cancer.

We have already described the feasibility and efficacy of preoperative chemotherapy using DCS therapy in gastric cancer patients with para-aortic lymph node metastases (8). Fifteen patients received intravenous docetaxel and cisplatin (30, 35 or 40 mg/m^2, each dose escalation was reciprocal) on Day 1, and 15 and S-1 (40 mg/m^2 twice daily) on Day 1−14 every 4 weeks. Dose-limiting toxicities were neutropenia, febrile neutropenia and diarrhea. Recommended dose of this combination was presumed to be 35 mg/m^2 of docetaxel and 35 mg/m^2 of cisplatin. pRRs were 85% in primary lesions and 92% in lymph node metastases after two cycles of chemotherapy. These results were considered expectable for locally advanced gastric cancer.

In the present study, we hypothesize that preoperative chemotherapy combining DCS in T4 locally advanced gastric cancer would induce a 70% of pRR. The aim of this Phase II study was to evaluate the feasibility and efficacy of this regimen and to select a candidate for an experimental arm in the next Phase III trial.

PROTOCOL DESIGN OF THE STUDY

Purpose

The aim of this study was to evaluate the safety and efficacy of preoperative chemotherapy with DCS for the treatment of patients with locally advanced gastric cancer.

Study Setting

The study is a multi-institutional prospective Phase II trial, in which participating institutions included 25 specialized centers as of 2011.

Endpoint

The primary endpoint is pRR of the primary lesion. Secondary endpoints are overall survival, disease-free survival, R0 resection rate and adverse events defined by Common Terminology Criteria for Adverse Events version 3.0.

Eligibility Criteria

The primary tumor is staged according to the third English edition of the Japanese Classification of Gastric Carcinoma (9).

Inclusion Criteria

Prior to enrollment in this study, patients must fulfill all of the following criteria: histologically confirmed gastric adenocarcinoma; T4 carcinoma that is staged according to the third English edition of the Japanese Classification of Gastric Carcinoma, without distant metastases evident on chest, abdominal and pelvic computed tomography (CT) and staging laparoscopy; the length of esophageal invasion $\leq$3 cm; age 20−75 years; Eastern Cooperative Oncology Group performance status of 0−1; no prior chemotherapy or radiotherapy; no major surgical procedure; no apparent bleeding from primary lesion; fair oral intake; adequate hematological, liver and renal functions; written informed consent.

Exclusion Criteria

Patients are excluded for any of the following reasons: apparent infection; serious co-morbidities such as cardiovascular disease, pulmonary fibrosis or intestinal pneumonia, bleeding tendency, uncontrolled hypertension, poorly controlled diabetes mellitus or another serious medical condition; a synchronous or metachronous active malignancy; central nervous system disorder; a previous history of severe drug-induced allergy; pregnancy or breastfeeding.

Treatment Methods

The experimental treatment consists of two phases: preoperative chemotherapy and surgical resection.

Chemotherapy

Preoperative chemotherapy consisted of docetaxel 35 mg/m^2 as a 1-h intravenous infusion on Days 1 and 15, cisplatin 35 mg/m^2 as a 2-h intravenous infusion on Days 1 and 15 with hyperhydration and S-1, which is administered orally at a dose of 80 mg/m^2/day divided into two split daily dose for 14 days followed by 14 days of rest. This regimen performed two cycles every 4 weeks.

Surgery

After two cycle 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 tumors. Surgery was performed between 4 and 8 weeks after the completion of chemotherapy. The type of operation depended on the location and extent of the primary lesion, but the resection lines had to be at least 5 cm from the edge of the macroscopic tumor. En bloc resection of adjacent organs was performed when their involvement was suspected. D2 lymphadenectomy was routinely performed as described earlier and if necessary, para-aortic lymphadenectomy was also permitted.

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 (9). Lesions were graded according to the amount of viable tumor cells of the tumor as follows: Grade 0, no evidence of effect; Grade 1a, viable tumor cells occupy more than two-thirds of the tumorous area; Grade 1b, viable tumor cells remain in more than one-third but less than two-thirds of the tumorous area; Grade 2, viable tumor cells remain in less than one-third of the tumorous area; Grade 3, no viable tumor cells remain. In this study, patients showing Grades 0 and 1a were regarded as pathological non-responders and those showing Grades 1b, 2 and 3 were regarded as pathological responders.

Follow-up

S-1 80 mg/m^2/day as adjuvant chemotherapy is allowed after R0 resection for 1 year, if possible. For patients with consequent R1–2 resection or non-resection, subsequent therapy is not stipulated and is decided by each clinician.

STUDY DESIGN AND STATISTICAL METHODS

This trial determined the efficacy and safety of combined treatment of preoperative chemotherapy followed by surgery for locally advanced gastric cancer. In JCOG0210 study, pRR of patients with preoperative chemotherapy consisting of S-1 and cisplatin followed by gastrectomy was 48%. Regarding the regimen in this study, triplet regimen is more powerful than doublet regimen in JCOG0210. Therefore, the primary hypothesis was that a 70% pRR would be achievable using this regimen but a pRR of $<$50% would not be desirable. In this Phase II trial, the planned sample size was 50 patients, which was calculated by Southwest Oncology Group's two-stage attained design based on a target pRR of 70% and a minimum pRR of 50%, with an a error of 0.05 and a,b error of 0.2. Assuming a dropout or ineligibility rate of $\sim$10%, the target number of enrolled patients was determined to be 55 patients.

UMIN REGISTRATION OF THE PROTOCOL

The study protocol was registered to the UMIN Clinical Trials Registry (UMIN000001858) on 1 July 2009.

PARTICIPATING INSTITUTIONS

Surgery departments of the following 25 centers from north to south of Japan were participating in the trial:

Hirosaki University Hospital, Yamagata Prefectural Central Hospital, Higashiohmiya General Hospital, Tokyo Women's Medical University Hospital, Tokyo Metropolitan Cancer Center Komagome Hospital, IUHW Mita Hospital, Niigata Cancer Center Hospital, Niigata City General Hospital, Niigata University Medical and Dental Hospital, Saiseikai Daini Niigata Hospital, Nagaoka Central General Hospital, Toyama Prefectural Central Hospital, Kanazawa University Hospital, Fukui University Hospital, Hiratsuka City Hospital, Gunma Prefectural Center Hospital, Saitama Medical Center, Kyoto Prefectural University Hospital, Gifu City Hospital, Kinki University Hospital, Osaka Medical Center Hospital, Hiroshima City Hospital, Hiroshima Red Cross Hospital, Shikoku Cancer Center Hospital, Kagawa University Hospital, Ehime University Hospital, Nanpu Hospital.

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Conflict of interest statement

None declared.

References

1. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810–20.
2. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215–21.
3. Kodera Y, Ishiyama A, Yoshikawa T, Kinosita T, Ito S, Yokoyama H, et al. A feasibility study of postoperative chemotherapy with S-1 and cisplatin (CDDP) for gastric carcinoma (CCOG0703). *Gastric Cancer* 2010;13:197–203.
4. Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, et al. Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. *Cancer Chemother Pharmacol* 2011;1423–8.
5. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
6. Fujitani K, Sasako M, Iwasaki Y, Yoshimura K, Sano T, Nashimoto A, et al. A phase II study of preoperative chemotherapy (CX) with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancer: JCOG0210. In: Proceedings of the 43th ASCO Meeting (Abstr 4609), Chicago, 1–5 June, 2007.
7. Kurokawa Y, Sasako M, Ando N, Sano T, Igaki H, Iwasaki Y, et al. Validity of response criteria in neoadjuvant chemotherapy against gastric and esophageal cancer: correlative analyses of multicenter JCOG trials. In: Proceedings of the 45th ASCO Meeting (Abstr 11), Orland, 29 May–2 June, 2009.
8. Fushida S, Fujimura T, Oyama K, Yagi Y, Kinoshita J, Ohta T. Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin and S-1 in gastric cancer patients with para-aortic lymph node metastases. *Anticancer Drugs* 2009;20:752–6.
9. Japanese Gastric Cancer Association. *Japanese Classification of Gastric Carcinoma*, 3rd English edition. *Gastric Cancer* 2011;14:101–12.