

Clinical Trial Notes

A Phase I/II Trial of Radiotherapy Concurrent with TS-1 Plus Cisplatin in Patients with Clinically Resectable Type 4 or Large Type 3 Gastric Cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group OGSG1205

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A Phase I/II trial of radiotherapy administered concurrently with TS-1 plus cisplatin has been initiated in Japanese patients with clinical resectable type 4 or large type 3 gastric cancer. The aim of this trial is to determine the recommended dose of TS-1 and cisplatin combined with radiotherapy at a fixed dose in the Phase I study, and to evaluate the efficacy and safety in the Phase II study. The primary endpoint for Phase II is the pathological complete response rate, assessed using surgically resected specimens. Secondary endpoints are the response rate, progression-free survival, overall survival, operation transitional rate, R0 resection rate, rate of treatment completion, rate of down-staging and rates of postoperative complications and adverse events. In Phase II, a total of 30 patients will be enrolled in the Osaka Gastrointestinal Cancer Chemotherapy Study Group trial over a period of 6 years.

Key words: GI-stomach-radoncol – GI-stomach-surg – clinical trial-trial design

INTRODUCTION

In Japan, classification of gastric carcinoma as defined by the Japanese Gastric Cancer Association indicates Borrmann type IV carcinoma as being type 4 (1). In English literature, the terms *linitis plastica* (2) and scirrhous carcinoma (3) have been used for similar macroscopic types of lesion. The type 4 gastric adenocarcinoma, defined as infiltrative, may occur in the stomach diffusely or in a localized fashion, in accordance with the extent of gastric involvement (4). Some studies have demonstrated its association with the macroscopic type 4 gastric cancer (GC), and it has shown a

poor prognosis (5,6). Thus, despite advances in the treatment of GC, the surgical results for type 4 GC remain poor, with lower rates of curative resection and survival (5,6).

To improve the prognosis of type 4 GC, Furukawa et al. performed left upper abdominal exenteration and Appleby's method for type 4 GC. They reported that, in Stage IV cases, there was no difference in the survival rates over 3 years between the extended resection group and the normal resection group. However, there was a significant difference in survival benefit between patients with Stage II and III disease (83.3 vs. 42.2%; $P < 0.05$); mortality rates between the two groups were similar. However, morbidity, especially

pancreatic fistula, has occurred in 30% of patients in the extended resection group (7). A Phase II trial of TS-1 for neoadjuvant chemotherapy against resectable type 4 GC has been carried out (4). Unfortunately, the 2-year survival rate after neoadjuvant chemotherapy did not reach the expected level (4). Additionally, Fujitani et al. conducted a Phase II trial of TS-1 plus cisplatin as neoadjuvant chemotherapy against resectable type 4 and large type 3 GC. They reported that survival rates over 3 years were only 26.0% (8). Therefore, a new treatment modality for type 4 GC is required.

Saikawa et al. (9) investigated the efficacy of chemoradiotherapy (CRT) (TS-1 and low-dose divided cisplatin therapy with radiotherapy followed by chemotherapy alone) for unresectable gastric adenocarcinoma, and reported a high response rate (65.5%; 19/30), a high R0 resection rate (33.3%; 10/30) and a high pathological complete response rate (13.3%; 4/30). Additionally, a Phase I study of neoadjuvant CRT consisting of TS-1 and low-dose divided cisplatin for patients with resectable advanced GC has been carried out (10). In this Phase I study, a maximum tolerated and a recommended dose (RD) of cisplatin were reported. Seven out of the 10 patients enrolled in the study completed pre-operative treatment without dose-limiting toxicity (DLT), and underwent surgery without major surgical complications. The pathological complete response rate was 10% (1/10) (10). Thus, CRT with TS-1 + cisplatin should be a promising treatment for advanced GC.

Consequently, we have developed a new regimen that involves the addition of consecutive radiotherapy to the established systemic chemotherapy regimen of TS-1 and bolus cisplatin, for the treatment of type 4 GC and large type 3 GC similar to type 4 GC, which showed the same prognosis (11). We have also initiated a Phase I/II study because we have no experience of CRT concurrent with TS-1 plus bolus cisplatin. After the completion of the present study, we have planned a Phase III study comparing TS-1, cisplatin and radiation, the findings of which will be compared with the JCOG0501 trial.

The Protocol Review Committee of the OGSF approved our study protocol in September 2012 and the study was initiated in October 2012. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000008964 (<http://www.umin.ac.jp/ctr/index.htm>).

PROTOCOL DIGESTS OF THE STUDY (OGSG1205)

PURPOSE

PHASE I

The objective of the Phase I study is to evaluate the maximum tolerated dose (MTD) and DLTs, to determine the RD of TS-1 plus cisplatin in combination with radiation therapy in patients with type 4 and large type 3 GC.

PHASE II

The objective of the Phase II study is to evaluate the efficacy and safety of CRT combined with TS-1 plus cisplatin in patients with type 4 or large type 3 GC.

STUDY SETTING

The setting is a multi-institutional open-label Phase I/II trial.

ENDPOINTS

PHASE I

The primary endpoint of the Phase I study is the number of patients with DLTs. The secondary endpoint is the pathological complete response rate.

PHASE II

The primary endpoint of the Phase II study is the pathological complete response rate in all eligible patients, including the patients who received treatment at the RD level in the Phase I study. The pathological complete response rate is defined as the presence of no viable cancer cells, both in the primary tumor site and in the lymph nodes. The secondary endpoints are the response rate, progression-free survival, overall survival, operation transitional rate, rate of R0 resection, rate of treatment completion, rate of down-staging and rates of postoperative complications and adverse events.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

For inclusion in the study, patients will be required to fulfill all of the following criteria:

- (i) The patient must have clinically resectable, histologically proven common gastric carcinoma.
- (ii) The macroscopic type of carcinoma must be type 4 or type 3 GC.
- (iii) In type 3 GC, the tumor must be ≥ 8 cm in diameter.
- (iv) There must be an absence of peritoneal metastasis or a negative finding from peritoneal washing cytology confirmed by staging laparoscopy.
- (v) The presence of lymph node metastasis must be limited in the category of regional gastric lymph nodes (1).
- (vi) Tumor invasion of the esophagus must be ≤ 1 cm, with no involvement of the duodenum.
- (vii) Patients must be in the age range 20–75 years.
- (viii) (viii) The Eastern Cooperative Oncology Group performance status must be 0 or 1.
- (ix) No previous therapy against GC should have been carried out.
- (x) Previous chemotherapy, CRT or radiotherapy against GC should not have been undertaken.

- (xi) No typical bleeding from GC and stenosis of gastrointestinal tract should have occurred.
- (xii) Adequate organ functions are required.
- (xiii) Sufficient oral intake is required.
- (xiv) Written informed consent is obtained from all patients.

EXCLUSION CRITERIA

Patients will be excluded from the study if they meet any of the following criteria:

- (i) The occurrence of simultaneous or metachronous (within 5 years) double cancers, with the exception of intramucosal tumor that is curable with local therapy.
- (ii) A history of severe drug hypersensitivity.
- (iii) The presence of active bacterial or fungal infection, and a body temperature >38°C.
- (iv) Pregnancy or lactation in women of childbearing potential.
- (v) The presence of unstable angina, heart failure or a history of myocardial infarction within 6 months.
- (vi) Patients requiring systemic steroid medication.
- (vii) Patients requiring the administration of phenytoin or warfarin potassium.
- (viii) The presence of severe diarrhea.
- (ix) The presence of antigen-positive serum hepatitis B surface and/or antibody positive serum hepatitis C virus.
- (x) The presence of uncontrollable hypertension, collagen disease or diabetes mellitus.
- (xi) The presence of interstitial pneumonitis, lung fibrosis or severe emphysema.

- (xii) Patients determined to be inappropriate for this study.

REGISTRATION

After confirmation of the fulfillment of the eligibility criteria, patient registration at the OGSG Data Center will be completed by telephone or fax.

TREATMENT METHODS

CHEMOTHERAPY

Combined CRT will consist of TS-1, cisplatin and radiotherapy. TS-1 will be orally administered twice per day. In the Phase I section of this study, TS-1 will be administered from Days 1 to 14 at levels 0 and 1. At level 2, TS-1 will be administered from Days 1 to 14 and Days 22 to 35 (12). The dose of TS-1 administered at level 0 will be 60 mg/m²/day. At levels 1 and 2, the dose of TS-1 will be 80 mg/m²/day (12).

Cisplatin will be administered at a dose of 60 mg/m² at level 0 and 1 on Day 1 only. At level 2, cisplatin will be administered at a dose of 60 mg/m² on Days 1 and 22 (Fig. 1).

The RD for TS-1 and cisplatin will be determined in the Phase I section of the study and the RD will be administered in the Phase II section. The dose schema is shown in Fig. 1.

RADIOTHERAPY

Radiotherapy will be delivered using megavoltage (6–15 MV) X-rays by means of a multiple-field technique. Patients

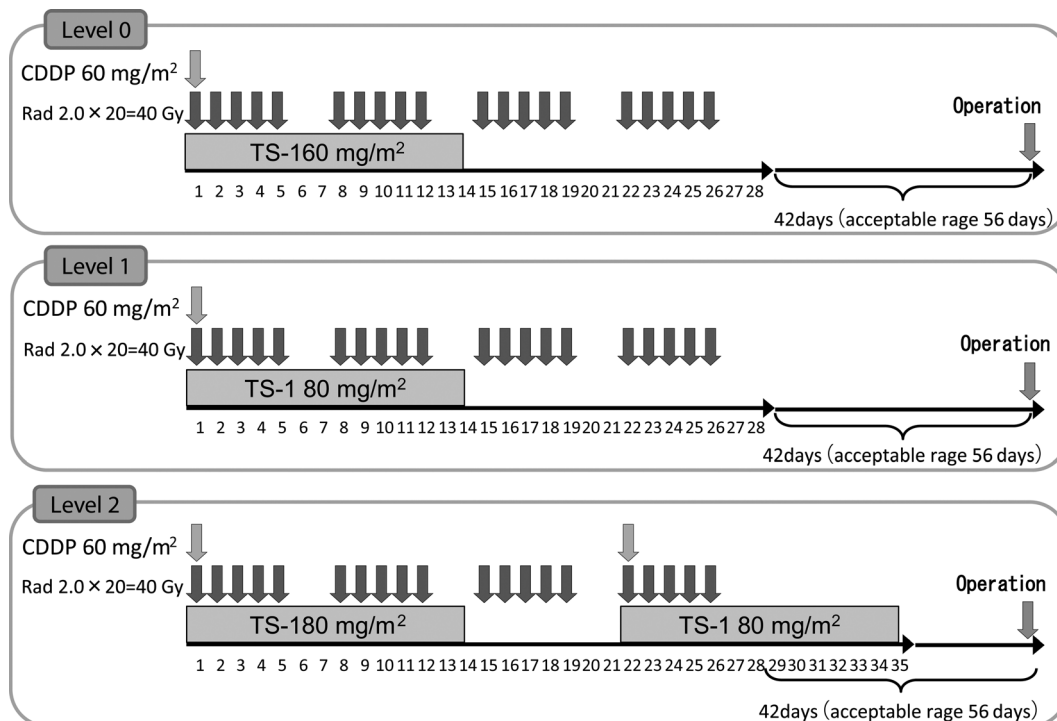


Figure 1. The schema of dose escalation of the Phase I study.

will receive 2 Gy/day of radiation 5 days per week from the initiation of chemotherapy, and the total radiation dose will be 40 Gy. Three-dimensional computed tomography (CT) simulation will be required. CT simulation and daily radiation therapy will be performed on an empty stomach at 3 h after dietary intake. The gross volume of the primary tumor (GTV primary) and the metastatic lymph nodes (GTV node) will be defined by CT and positron emission tomography, with reference to the upper gastrointestinal series. The clinical target volume (CTV) will include the GTV primary and the GTV node plus 1 cm margins that take into account sub-clinical extension. Elective nodal irradiation will not be performed. The planning target volume will be defined as the CTV plus 1–2 cm craniocaudally and 0.5–1 cm laterally, taking into account the setup variations and internal organ motion. The motion should be observed using a number of methods (four-dimensional CT, fluoroscopy or others). Dose administration will involve the following constraints: liver, $V_{30} < 30\%$ (<30% of the hepatic volume was exposed to more than 30 Gy); kidney, $V_{20} < 30\%$ (<30% of the bilateral kidney volume was exposed to more than 20 Gy), spinal cord, $V_{max} < 44$ Gy (the maximum dose was <44 Gy) and the small and large intestine, $V_{max} < 44$ Gy. To undertake quality assurance regarding radiotherapy at a total dose of 40 Gy, a conference involving radiation oncologists will be held.

DOSE ESCALATION METHOD

In the Phase I section of this study, there are three dose levels for TS-1 and cisplatin. Level 1 is the starting dose, and initially three patients are administered with this dose. In the case of exposure to DLT, an additional three patients will be required. When we have established DLT expression in 3/6 patients at level 1, the next step will be to start at level 0. In principle, the RD is one step down from the MTD. However in this study, if the MTD does not occur at level 2, we will recommend that level 2 be used as the RD.

DEFINITION OF DLT

DLT will be defined using the following criteria. The DLT observation period will extend from the date of initiation of

CRT to 42 days after the last radiotherapy session. The severity of toxicity will be assessed according to the Common Terminology Criteria for Adverse Events v 3.0 as follows:

- (i) Grade 4 neutrophils.
- (ii) Grade 4 platelets.
- (iii) Grade 3 febrile neutropenia lasting 4 days.
- (iv) Grade 3 non-hematologic toxicity except for appetite loss and general fatigue.
- (v) Inability to receive TS-1 for >10 days at levels 0 and 1 and >19 days at level 2

PHARMACOKINETIC ANALYSIS

The aim of the pharmacokinetic analysis is to analyze the influence of radiotherapy on TS-1 metabolism. Pharmacokinetic studies will be performed on six patients who have given their informed consent on Days 11–12. Plasma samples will be obtained before TS-1 administration and at 1, 2, 4, 6, 8 and 24 h after TS-1 administration. Radiotherapy will be delivered at 1.5–3 h after TS-1 administration. Samples will be collected in heparinized tubes and centrifuged, and the supernatant stored at -20°C until required. The schema of pharmacokinetic analysis is shown in Fig. 2.

SURGERY

All patients will be assessed at 4 weeks after the end of CRT by abdominal and pelvic CT to evaluate whether or not R0 resection (no residual tumor) can be carried out. At these examinations, in cases where (1) R0 resection can be carried out, (2) the white blood cell count is $\geq 2500/\text{mm}^2$ and (3) the platelet count is $\geq 100\,000/\text{mm}^2$, we will perform gastrectomy with en bloc D2 lymph node dissection at 7–9 weeks after the end of radiotherapy. In the total gastrectomy for an upper gastric tumor, the spleen will also be removed. In addition, involved adjacent organ(s), if any, will be removed to achieve an R0 resection. A laparoscopic gastrectomy will not be allowed. If resectable M1 disease (hepatic, peritoneal and/or lymphatic metastases) is found during surgery, it will be removed to achieve R0 resection. If R0 resection is impossible, the protocol treatment will be terminated.

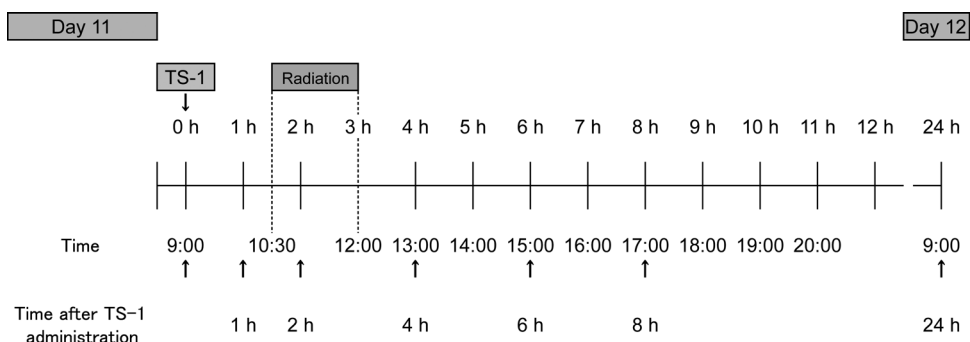


Figure 2. The schema of pharmacokinetic analysis.

POSTOPERATIVE CHEMOTHERAPY

After the R0 resection, adjuvant chemotherapy for TS-1 monotherapy will start within 6 weeks after gastrectomy and continue for 1 year.

FOLLOW-UP

After treatment, according to the protocol patients will be followed up every 6 months for 5 years.

STUDY DESIGN AND STATISTICAL ANALYSIS

This study is a Phase I/II trial that is being carried out to determine the RD of TS-1 plus cisplatin in combination with radiotherapy at a fixed dose in the Phase I section, and to evaluate the efficacy and safety in the Phase II section. The sample size in the Phase II section of this study will be 30 patients, including those treated at the RD level in the Phase I section. This sample size provides 90% power under the hypothesis that the expected pathological complete response rate will be 2%, and the threshold value will be 15% using one-sided testing at a 5% one-sided significance level.

MONITORING

In-house monitoring will be performed every 6 months by the OGSG Data Center to evaluate the progress of the study and to improve the quality of the study.

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Conflict of interest statement

None declared.

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