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Phase I trial

A multicenter phase I study of preoperative chemoradiotherapy with S-1 and irinotecan for locally advanced lower rectal cancer (SAMRAI-1)

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ABSTRACT

Background and purpose: Preoperative 5-fluorouracil-based chemoradiotherapy is a standard treatment for locally advanced lower rectal cancer (LALRC). We performed a phase I study to develop a new regimen combining irinotecan and S-1.

Materials and methods: Patients with LALRC (T3-4, N0-2) were studied. The radiation dose was 45 Gy in 25 fractions. S-1 (80 mg/m^2/day) was administered on days 1–5, 8–12, 22–26, and 29–33. Irinotecan was administered on days 1, 8, 22, and 29. The dose of irinotecan was initially 60 mg/m^2 (level 1). Surgery was performed 6–10 weeks after the chemoradiotherapy.

Results: Twenty patients were enrolled, of whom 18 patients were analyzed. Dose-limiting toxicity (DLT) did not occur in the first 3 patients treated with irinotecan at 80 mg/m^2 (level 2), but developed in 3 of the 6 patients who received irinotecan at 90 mg/m^2 (level 3). Then DLT occurred in 3 other patients at level 2. At level 2 or 3, DLT comprised neutropenia, thrombocytopenia, and diarrhea. Level 2 was designated as the maximum tolerated dose, and level 1 as a recommended dose (RD). The pathological complete response rate was 28%, and the down-staging rate was 56%.

Conclusions: Our results suggested that the RD of irinotecan when combined with preoperative S-1 and pelvic radiation was 60 mg/m^2.

Many studies have evaluated the effectiveness of preoperative chemo/radiotherapy in patients with locally advanced rectal cancer because it potentially offers advantages such as tumor shrinkage, lower toxicity than postoperative radiotherapy, and a higher sphincter preserving rate [1]. In a prospective randomized trial from the German Rectal Cancer Study Group, fluorouracil-based preoperative chemoradiotherapy showed improved local control rate and reduced treatment-related toxicities in compared with postoperative chemoradiotherapy for clinical stage II/III rectal cancer, although OS were similar results in both groups [2]. Thus, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology recommend 5-fluorouracil (5-FU)-based preoperative chemoradiotherapy as a standard treatment option for patients with rectal cancer who have T3, N0 disease, any T, N1-2 disease, or T4 disease [3].

Recently, several randomized controlled trials have been conducted to evaluate the effect of adding oxaliplatin to 5-FU-based regimens for preoperative chemoradiotherapy. However, oxaliplatin has been reported to increase toxicity. Some studies reported that oxaliplatin did not improve tumor response [4,5], whereas others reported that oxaliplatin improved tumor response [6] and disease-free survival [7]. The development of new regimens for preoperative chemoradiotherapy is thus needed to further enhance treatment response.

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S-1 is an oral fluoropyrimidine anticancer agent combining tegafur, a prodrug of 5-FU, with gimeracil and oteracil potassium in a molar ratio of 1:0.4:1. Gimeracil is dihydropyrimidine dehydrogenase (DPD) inhibitor that acts to maintain high levels of 5-FU in plasma and has been suggested to have radiosensitizing activity [8,9]. Oteracil potassium decreases gastrointestinal toxicity caused by 5-FU.

As for combined chemotherapy with S-1 plus irinotecan (IRIS), a randomized controlled trial (FIRIS study) showed that IRIS is non-inferior to a combination of fluorouracil, folinic acid, and irinotecan (FOLFIRI) in terms of progression-free survival time as second-line therapy for unresectable colorectal cancer [10]. IRIS is expected to become a useful regimen for the management of unresectable colorectal cancer because of several potential benefits, including a shorter infusion time and fewer hospital visits.

In a phase II trial performed by Sato et al., chemoradiotherapy with S-1 plus irinotecan had a histopathological complete response (pCR) rate of 34.7% in patients with locally advanced rectal cancer [11]. However, the clinical target volume for the primary tumor used typically included the perirectal lymph nodes. The target volumes used for radiotherapy in that study were much smaller than those generally used in North American and European practice, in which the internal iliac nodes and often the external iliac nodes were electively irradiated.

To further evaluate the safety and effectiveness of preoperative chemoradiotherapy with S-1 plus irinotecan, we extended the irradiated field to the standard range and performed a multicenter phase I study in patients with locally advanced lower rectal cancer (SAMRAI-1). Our primary purpose was to determine the RD of irinotecan. We also studied whether extension of the radiation field leads to increased toxicity (particularly gastrointestinal toxicity).

Methods and materials

Eligibility criteria

Eligible patients had to satisfy all of the following criteria: (1) a histologically confirmed diagnosis of rectal cancer (adenocarcinoma); (2) resectable clinical stage T3 or T4, N0-2 disease with the primary tumor located either above or below the peritoneal reflection, the inferior tumor margin located distally to the peritoneal reflection, and no enlarged nodules measuring $\geqslant$10 mm in diameter suggesting extramesorectal metastasis on computed tomography (slice width, $\leqslant$5 mm) (i.e., no distinct metastasis to lateral lymph nodes), as confirmed by imaging studies performed within 4 weeks before enrollment; (3) no hepatic, peritoneal, or distant metastasis; (4) an age of 20–80 years at enrollment; (5) no previous treatment; and (6) no severe compromise of main organ functions, with a white cell count of 4000/μL or more and less than 12,000/μL, a platelet count of 100×10^3/μL or more, a hemoglobin level of 9.0 g/dL or more, a total bilirubin level of 1.5 mg/dL or less, aspartate aminotransferase and alanine aminotransferase levels of less than twice the institutional upper limit of normal, a serum creatinine level of less than the institutional upper limit of normal, and an creatinine clearance rate of 50 mL/min or more. Patients also had to have ECOG performance status of 0 or 1 and to be able to orally receive drugs. Written informed consent was obtained from all patients before enrollment.

Exclusion criteria

Patients were excluded from the study if they had any of the following conditions: a history of serious drug hypersensitivity; active double cancer or multiple colorectal cancers; a genotype of UGT1A1*6/*6, UGT1A1*28/*28, or were heterozygous for both (UGT1A1*6/*28); active infection (fever of 38.0 °C or higher); serious complications (e.g., intestinal paralysis or intestinal obstruction); a history of interstitial pneumonia; diarrhea (watery stool); or positive test results for HBs antigen. In patients with a genotype of UGT1A1*6/*6 or UGT1A1*28/*28 or who were heterozygous for both UGT1A1*6/*28, treatment with irinotecan has been reported to possibly cause serious adverse events, especially neutropenia [12]. Therefore, patients with these genotypes were excluded from the present study.

Treatment

Radiotherapy

Radiotherapy was delivered with 10 MV X-rays in 1.8 Gy daily standard fractionation for a total dose of 45 Gy. Fig. 1 shows the target volume.

(1) Gross tumor volume

The gross tumor volume included the primary tumor, enlarged lymph nodes, and suspected sites of tumor invasion of adjacent organs. The primary lesion was evaluated on barium enema examination and MRI. To maintain consistency with the results of a study by Sato et al. [11], an enlarged lymph node with a diameter of 1 cm or more was defined as nodal metastasis in accordance with RECIST 1.0.

(2) Clinical target volume

The clinical target volume was derived by adding a 1 cm margin to the gross tumor volume and included the mesorectal lymph nodes (pararectal lymph nodes), internal iliac lymph nodes, and the obturator lymph nodes.

(3) Planning target volume

The planning target volume was derived by adding a margin of 1 cm to the clinical target volume. The superior margin of the typical irradiation field was defined as the level between the fifth lumbar and first sacral vertebrae. The inferior margin was 3 to 4 cm below the inferior edge of the primary lesion, as defined by a line to the inferior margin of the ischial tuberosity, in principle. Irradiation of the skin of the anal region was avoided as much as possible. The lateral margins were 1 cm lateral to the cavity of the lesser pelvis. The anterior margin was the posterior margin of the pubic symphysis, and the posterior margin was the center of the sacral bone on the lateral view. Completely different subgroups might be intermingled among patients who have enlarged lateral lymph nodes 1 cm or more in diameter. In the present study, we therefore studied patients with no lateral lymph node metastasis and did not perform prophylactic lymph-node dissection, which is commonly done in Japan. Because radiotherapy was given preoperatively, the same radiation dose was delivered to the planned target volume (PTV) in all patients.

The dose was prescribed to the beam isocenter or near to this point with tissue inhomogeneity correction for dose calculation. No tissue inhomogeneity correction was performed if there was too much air in the rectum.

To decrease the intestinal volume included in the treated field, the prone position was recommended for irradiation. To minimize exposure of the small intestine to radiation, the use of a belly board device was recommended, although fixation of body position was not required.

Chemotherapy

The dose of S-1 was determined according to body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; BSA $\geqslant$1.25 m^2 to