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Phase II trial

A multicenter phase II study of preoperative chemoradiotherapy with S-1 plus oxaliplatin for locally advanced rectal cancer (SHOGUN trial)

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ABSTRACT

Purpose: This study was designed to evaluate the safety and efficacy of adding oxaliplatin to preoperative chemoradiotherapy (CRT) with S-1 in patients with locally advanced rectal carcinoma (LARC).

Patients and methods: This was a multicenter phase II study in patients with histologically proven clinical stage T3 or T4 (any N, M0) LARC. Patients preoperatively received oral S-1 (80 mg/m^2/day on days 1–5, 8–12, 22–27, and 29–33) and infusional oxaliplatin (60 mg/m^2 days on 1, 8, 22, and 29) plus radiotherapy (50.4 Gy), with a chemotherapy gap in the third week of radiotherapy. Pathological complete response (pCR) was the primary endpoint. Secondary endpoints included toxicity, compliance, R0 resection rate, and downstaging rate.

Results: A total of 45 patients were enrolled at six centers in Japan. All 45 patients received CRT, and 44 underwent operation. A pCR was achieved in 12 (27.3%) of the 44 patients who underwent surgery. Near-total tumor regression was confirmed in 47.7%. There were no grade 4 adverse events, and 11.1% of the patients had grade 3 adverse events. R0 resection was achieved in 95.5% of the patients.

Conclusion: Preoperative CRT with S-1 plus oxaliplatin had a high pCR rate and a favorable toxicity profile.

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Previous clinical trials have shown that preoperative chemoradiotherapy (CRT) enhances local control in patients with locally advanced rectal carcinoma (LARC) [1,2]. Fluorouracil, currently the most widely used radiosensitizer, plus radiotherapy has become the standard regimen for CRT. In addition, oral fluoropyrimidines such as capecitabine and S-1 have been combined with radiotherapy in patients with rectal cancer owing to the convenience of oral preparations over infusional fluorouracil. S-1 is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2, 4-dihydropyridine (CDHP) and potassium oxonate in a molar ratio of 1:0.4:1. This oral dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine preparation is widely used to treat various types of solid tumors in East Asia and Europe [3]. CDHP was shown to enhance the antitumor activity of irradiation in vivo in a human cancer xenograft model [4]. Sadahiro et al. reported that a S-1-based CRT regimen had a pathological complete response (pCR) rate of 22%, a downstaging rate of 78%, and a favorable toxicity profile in a phase I/II study of preoperative concurrent CRT with S-1 in patients with LARC [5]. These findings have provided a rationale for the evaluation of S-1-based CRT regimens.

Oxaliplatin, a platinum derivative, is a relatively new cytotoxic agent, and combination chemotherapy with a fluoropyrimidine and oxaliplatin has become a standard regimen for metastatic colorectal cancer [6,7]. S-1 plus oxaliplatin has been shown to be a feasible regimen with promising antitumor activity in patients with metastatic colorectal cancer [8]. The SOFT trial demonstrated that S-1 plus oxaliplatin and bevacizumab is non-inferior to FOLFOX plus bevacizumab and effective as first-line chemotherapy

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for metastatic colorectal cancer [9]. Therefore, CRT with S-1 plus oxaliplatin is expected to be more effective than a fluoropyrimidine plus radiotherapy, currently the standard regimen for CRT.

Several phase III trials have evaluated oxaliplatin in combination with fluoropyrimidine-based CRT as neoadjuvant therapy for LARC (Table 3). In the STAR-01 [10], ACCORD 12/0405 PRODIGE 2 [11], NSABP R-04 [12], and PETACC-6 studies [13], fluoropyrimidine plus oxaliplatin was not significantly superior to fluoropyrimidine alone. In these negative studies, the rates of grade 3–4 toxicity were significantly higher in the fluoropyrimidine plus oxaliplatin group than in the fluoropyrimidine alone group, and compliance with all components of preoperative CRT was remarkably lower in the former. The lack of a beneficial effect of adding oxaliplatin to fluoropyrimidine-based CRT was mainly attributed to increased acute toxic effects and complications, resulting in poor compliance with all components of preoperative CRT, including radiotherapy. However, the CAO/ARO/AIO-04 phase III trial [14,15] showed that the addition of oxaliplatin to fluorouracil contributed to improved pCR and disease-free survival (DFS) at 3 years as compared with fluorouracil alone, with no significant difference in grade 3–4 toxicities or postoperative complications. The better response in the fluoropyrimidine plus oxaliplatin group was ascribed to the excellent compliance rates. Rödel et al. claimed that the incorporation of a "chemotherapy gap" in the third week of radiotherapy apparently promoted compliance with all components of preoperative CRT. The CRT regimen used in the SHOGUN trial similarly included a "chemotherapy gap" in the third week of radiotherapy. The benefit of including a chemotherapy gap should be further studied.

In our preliminary study, patients with rectal cancer received escalating doses of oxaliplatin combined with fixed doses of S-1 and pelvic radiotherapy [16]. The recommended dose of oxaliplatin was established to be 60 mg/m^2 (evaluated as dose level 3) [16]. In the present multicenter phase II clinical trial, we tested the hypothesis that preoperative CRT with S-1 plus oxaliplatin with a chemotherapy gap is effective and safe for the management of LARC.

Patients and methods

Patient eligibility

The JACCRO CC-04: SHOGUN trial was a multicenter phase II study, approved by the central ethics committee of the Japan Clinical Cancer Research Organization (JACCRO) and the institutional review boards of all participating centers. Each patient provided written informed consent before participating in the study. This study is registered with ClinicalTrials.gov, number NCT01227239.

Patients 20–80 years of age who had a histologically confirmed diagnosis of non-metastatic, primary adenocarcinoma (well/mod) of the middle or lower rectum (cT3–T4, any N, M0) were eligible for enrollment. Additional eligibility criteria included a T stage of T3 or T4 on computed tomography (CT) plus magnetic resonance imaging (MRI); a resectable tumor as prospectively defined by the surgeon in charge; good general condition enabling major surgery (Eastern Cooperative Oncology Group performance status 0 or 1); and normal liver, renal, and bone marrow functions. Exclusion criteria were as follows: prior chemotherapy for rectal cancer or any prior pelvic irradiation; a history of malignant disease; severe heart disease, uncontrolled infection or metabolic disorders; or severe neurologic impairment or inflammatory bowel disease.

Study design and treatment

Concurrent chemotherapy consisted of an infusion of oxaliplatin (60 mg/m^2) on days 1, 8, 22, and 29 plus oral S-1 (80 mg/m^2/day) on days 1–5, 8–12, 22–27, and 29–33. Preoperative 3-dimensional conformal radiotherapy was started at the same time as chemotherapy. A total dose of 50.4 Gy was delivered with photons ($\geqslant$10 MV) in 28 fractions over the course of 5.6 weeks (1.8 Gy/day), using a 3- or 4-field technique. A chemotherapy gap was thus incorporated in the third week of radiotherapy (Fig. 1). The clinical target volume of radiotherapy included the following volumes: (1) the primary gross tumor volume plus 5 mm in all directions except for the craniocaudal margin, which had to be least 2 cm; (2) lymph nodes 1 cm or more in diameter; (3) the mesorectum; (4) regional lymph nodes (the internal iliac, obturator, and presacral lymph nodes up to L5/S1); and (5) invaded surrounding organs (in T4 disease). The radiotherapy protocol of JACCRO CC-04 did not allow any volume reduction in the planned target volume. All radiotherapy protocols, verification films, and radiotherapy charts were reviewed by the Radiotherapy Quality Assurance Committee of the JACCRO CC-04 trial. Before we initiated the JACCRO CC-04 trial, participating radiation oncologists had a start-up meeting to reach a consensus concerning the clinical target volume. The radiation therapy investigator reviewed anonymous data on radiotherapy planning via the Internet before each course of radiotherapy.

Surgery, including mesorectal excision or tumor-specific mesorectal excision techniques, was performed between 6 and 10 weeks after the completion of CRT. Oral S-1 based-adjuvant chemotherapy was recommended for postoperative treatment.

Study assessments

The tumor response was confirmed by a central pathological review with all specimens from the six participating centers evaluated at one institution, and a pCR was defined as the absence of viable tumor cells in the primary tumor of the resected specimen, pathologically evaluated according to the tumor regression grade (TRG). The TRG was assessed according to General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus of the Japanese Society for Cancer of the Colon and Rectum [17]. Downstaging was defined as any reduction in the pathological T or N stage after operation as compared with the clinical T or N stage before starting treatment. Patients were observed for complications up to 28 days after operation. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Fleming's one-stage design was used to estimate the required sample size for this phase II study. We estimated that 45 patients were required to test the hypothesis that the pCR rate was greater than 30% with 80% power and to reject the hypothesis that the pCR rate was less than or equal to 15% at a significance level of 5% (one sided).

Results

Patient demographics and clinical characteristics

From August 2011 through October 2012, a total of 45 patients were enrolled in this phase II study at six centers in Japan. The clinical tumor stage was cT3 in 42 patients and cT4 in 3; 35 patients had clinical evidence of lymph-node metastasis (cN+). The patient and tumor characteristics at baseline are summarized in Table 1.

Efficacy

The Radiotherapy Quality Assurance Committee of JACCRO CC-04 confirmed that all patients completed radiotherapy without any