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Phase II trial

Phase II study of preoperative chemoradiotherapy (CRT) with irinotecan plus S-1 in locally advanced rectal cancer

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ABSTRACT

Background and purpose: The aim of this study is to evaluate the efficacy and safety of preoperative radiation therapy combined with S-1 and irinotecan (SI) in LARC.

Materials and methods: Patients were considered LARC if they had a T3/T4 lesion or node positive. Weekly doses of 40 mg/m^2 irinotecan were intravenously administered once per week during weeks 1–5 of radiotherapy. S-1 (70 mg/m^2) was given from Monday to Friday in all weeks of radiotherapy. 3-D conformal radiotherapy was given at daily fractions of 1.8 Gy for 5 days for a total dose of 50.4 (45 + 5.4) Gy. Surgery was performed 4–6 weeks following the completion of chemoradiation.

Results: Between June 2006 and November 2007, 43 pts were enrolled. The stage was: cT3 24 patients, cT4 6 patients; 28 patients were cN+. Forty-one patients completed the chemoradiation and 42 patients underwent operation: a low anterior resection was performed in 36 patients, a total colectomy in 1 patient, and an abdominal perineal resection in 5 patients. T downstaging was observed in 50%; 23 N+ patients became N− (55%). The complete pathological response was observed in 9 patients (21%). The 3-year locoregional failure rate, distant failure rate, disease-free survival, and overall survival were 9.5%, 18.6%, 72.1%, and 94.3%, respectively. Only three patients experienced G3 diarrhea; one had G3 sepsis and two had septic shock. Hematological toxicity (G3–G4) was observed in five patients.

Conclusions: This study demonstrated the efficacy of preoperative CRT with S-1 and irinotecan with 21% of complete response. However, prompt recognition and management of infection is needed to use it in patients with locally advanced rectal cancer.

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On the basis of the results of three randomized trials, Preoperative 5-FU-based chemoradiotherapy (CRT) is regarded as a standard of care for locally advanced rectal tumors (LARC). In these trials, preoperative radiotherapy (RT) plus 5-fluorouracil provides improved tumor downstaging and local control; however, this has not translated into an improvement in distant metastasis as well as survival outcomes [1–3].

Because newer chemotherapeutic treatments (capecitabine, S-1, oxaliplatin, irinotecan) have improved the outcomes in patients with metastatic CRC, the rationale for the incorporation of new agents in the treatment of rectal cancer is to enhance downsizing and downstaging, including pCR, as well as to improve control at distant sites. In addition, pathologic complete response (pCR) and tumor regression grades have been used as early surrogate markers that correlate with long-term outcome and as endpoints in neoadjuvant trials that evaluate novel combinations [4–8]. However, the integration of these agents, in an effort to increase efficacy, may result in increased acute toxicities, as well as possible late toxicities. Thus, novel approaches to integrate more effective therapy into the combined-modality programs are still needed to enhance the disease control rate and to increase the proportion of patients achieving a pCR.

Irinotecan, a potent inhibitor of topoisomerase I, has now become standard therapy in the first and second-line treatment of metastatic colorectal cancer in combination with bolus or infusional 5-FU [9]. By interfering with DNA replication, irinotecan also showed radiosensitizing properties in preclinical studies, which revealed maximum synergistic effects when irinotecan was administered 1 h before irradiation [10].

S-1 is a fourth-generation oral fluoropyrimidine, similar to UFT and capecitabine, which was developed to replicate the results of protracted continuous infusion of 5-FU. This drug combines tegafur

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as an effector and two 5-FU modulators, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (oxo), which sustains higher plasma concentration of 5-FU and reduces gastrointestinal toxicity [11].

Since both S-1 and irinotecan have radiosensitising effects and have different mechanisms of action with individual activity in colorectal cancer, research efforts focused on using both drugs and radiotherapy as preoperative treatment of rectal cancer patients.

We have previously established a dosing regimen for weekly 40 mg/m^2 for 5 weeks in combination with S-1, 70 mg/m^2 (SI) on Monday to Friday. The preliminary efficacy in 16 patients included in the phase I trial was promising with 4 patients exhibiting pCR [12]. The objective of the present phase II trial is to assess the efficacy and safety of preoperative chemoradiotherapy with the SI regimen in LARC.

Patients and methods

Eligibility criteria

For this study, we enrolled patients up to 70 years of age with histologically proven adenocarcinoma of the rectum (12 cm from anal verge). Further eligibility criteria consisted of a locally advanced disease (T3–T4 N + M0 except T4 due to bony infiltration) according to computed tomography scans and rectal magnetic resonance imaging (MRI) scans, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 allowing major surgery, normal liver function, renal and bone marrow function (bilirubin $\leqslant$1.5 mg/dl and transaminases $\leqslant$3 times the upper limit of normal, serum creatinine $\leqslant$2 mg/dl, an absolute granulocyte count $\geqslant$1500 cells/mm^3, platelets $\geqslant$100,000 cells/mm^3, hemoglobin $\geqslant$9 g/dl), and written consent. The trial was approved by the ethics committee of Severance Hospital, Korea.

Staging

Pretreatment evaluation included a detailed history, a physical examination, and a routine complete blood work-up. All patients underwent a baseline colonoscopy, optional endoscopic ultrasound (EUS), a computed tomography (CT) of the abdominopelvis, and a MRI of the rectum. The criteria for positive lymph node metastasis include a short-axis diameter of $\geqslant$4 mm, a speculated or an indistinct border, or the presence of heterogeneity within the lymph node [13].

Treatment

Weekly doses of 40 mg/m^2 Irinotecan were intravenously administered 1 h before radiation on days 1, 8, 15, 22, and 29. 70 mg/m^2 of S-1 was given from Monday to Friday in all weeks of radiotherapy. All patients underwent 3-dimentional conformal radiotherapy. Radiotherapy was delivered using 6–10 MV photon beams. In most cases, the 3-port technique was used with 6 MV to the posterior portal and 10 MV to the lateral portals. When the target volume involved anterior pelvic structures, such as uterus and bladder, the 4-field box technique was applied. The clinical target volume encompassed gross tumor, mesorectum, and the regional lymphatics. The radiation field to the whole pelvis was defined as follows: the superior border at the L5/S1 junction, the inferior border at the inferior margin of the obturator foramen or 3 cm below the lowest tumor border, the lateral border at 1.5 cm lateral to the bony pelvis, the anterior border at 3 cm anterior to the tumor mass, and the posterior border at 0.5 cm posterior to the sacral posterior surface. The boost field encompassed the gross tumor with 2–3 cm margins in all directions. The dose of whole pelvis radiotherapy was 45 Gy in 25 fractions, and 5.4 Gy in 3 fractions boost to the gross tumor was applied.

Dose modifications were made for toxicity, using the National Cancer Institute Common Toxicity Criteria (NCI-CTC v2.0). For grade 3/4 hematological toxicity, radiotherapy was interrupted until grade 0/1 then continued, and chemotherapy interrupted until grade 0/1 then continued at an 80% dose. For grade 2/3 non-hematological toxicity, the daily review of radiotherapy took place and chemotherapy interrupted until grade 0/1 then continued at an 80% dose for grade 3. For grade 4 non-hematological toxicity, radiotherapy was interrupted and continued when toxicity resolved to grade 0/1 within 2 weeks, and chemotherapy discontinued permanently.

Evaluation

Resected specimens were routinely evaluated histologically for the resection margins and for determining the response to preoperative chemoradiotherapy. The CRM was histologically assessed by transverse slicing after fixation of the opened tumor area, which was considered positive when the tumor was at the CRM or the minimal distance between the tumor and CRM was $\leqslant$1 mm. Pathologic responses of the primary tumors were defined according to the Mandard regression grading system [14]. Grade I was recorded when no tumor cells remained in any sections (pathologic CR).

After surgery, the patients were followed to evaluate failure patterns and survival outcomes. Failure was defined by local recurrence, and regional and distant metastasis. Thirty days after the last planned treatment, an end-of-treatment evaluation was performed, which included physical examination, abdominopelvic CT scan, chest X-ray, hematologic, biochemical, CEA, and toxicity assessment. Subsequently, for the next 2 years, physical examination, hematologic, biochemical, CEA, and toxicity assessment were performed every 3 months and then every 6 months until 5 years. An abdominopelvic CT scan was performed every 6 months and chest CT scan every 12 months for 5 years. A colonoscopy was performed at approximately 1 year following the resection and repeated every 3 years.

Statistical methods

The primary endpoint was the pCR rate. The secondary endpoints included safety, compliance of treatment, local recurrence rate, distant failure rate, disease-free survival (DFS), and overall survival (OS). According to the two-stage phase II study of the Simon Minimax design, the treatment program was designed to reject a pCR rate less than 5% (P0) and to provide a statistical power of 90% in assessing the activity of the regimen in terms of a pCR of 20% (P1) for an α error less than 0.05. If 1 or fewer responses were observed during stage 1, then the trial ended early. If 4 or fewer responses were observed by the end of stage II, then no further investigation of the treatment was warranted. For a maximum of 38 patients, 29 were accrued during stage I and 9 patients during stage II. Because pCRs in six patients (19%) was observed, additional patients in stage II were enrolled. With a dropout rate of 10% and one additional case on behalf of a patient showing metastasis before surgery, a total of 43 patients were enrolled. Overall survival was calculated from the beginning of the treatment to death from any cause or the last follow-up, and disease-free survival was determined from the beginning of the treatment to the development and recurrence of rectal cancer, second primary cancer, or death. Recurrences were radiological confirmed or by biopsy. Overall survival and DFS were estimated using Kaplan–Meier plots.

Results

Forty-three eligible patients were enrolled between June 2006 and November 2007. The baseline characteristics of the patients