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CLINICAL INVESTIGATION **Rectum**

PHASE I STUDY OF PREOPERATIVE CHEMORADIATION WITH S-1 AND OXALIPLATIN IN PATIENTS WITH LOCALLY ADVANCED RESECTABLE RECTAL CANCER

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Purpose: To perform a Phase I study of preoperative chemoradiation (CRT) with S-1, a novel oral fluoropyrimidine, plus oxaliplatin in patients with locally advanced rectal cancer, to determine the maximum tolerated dose and the recommended dose.

Methods and Materials: Radiotherapy was delivered to a total of 45 Gy in 25 fractions and followed by a coned-down boost of 5.4 Gy in 3 fractions. Concurrent chemotherapy consisted of a fixed dose of oxaliplatin (50 mg/m^2/week) on Days 1, 8, 22, and 29 and escalated doses of S-1 on Days 1–14 and 22–35. The initial dose of S-1 was 50 mg/m^2/day, gradually increasing to 60, 70, and 80 mg/m^2/day. Surgery was performed within 6 ± 2 weeks.

Results: Twelve patients were enrolled and tolerated up to Dose Level 4 (3 patients at each dose level) without dose-limiting toxicity. An additional 3 patients were enrolled at Dose Level 4, with 1 experiencing a dose-limiting toxicity of Grade 3 diarrhea. Although maximum tolerated dose was not attained, Dose Level 4 (S-1 80 mg/m^2/day) was chosen as the recommended dose for further Phase II studies. No Grade 4 toxicity was observed, and Grade 3 toxicities of leukopenia and diarrhea occurred in the same patient (1 of 15, 6.7%). Pathologic complete responses were observed in 2 of 15 patients (13.3%).

Conclusions: The recommended dose of S-1 was determined to be 80 mg/m^2/day when combined with oxaliplatin in preoperative CRT, and a Phase II trial is now ongoing. © 2011 Elsevier Inc.

Rectal cancer, Preoperative chemoradiotherapy, S-1, Oxaliplatin, Phase I study.

INTRODUCTION

Preoperative chemoradiation (CRT) is now one of the standard treatment options for patients with locally advanced resectable rectal cancer (LARC). Although total mesorectal excision, a progressive surgical technique, has improved overall outcomes in such patients, the addition of perioperative CRT may offer further improvements, with local control rates better than seen with preoperative rather than postoperative CRT (1–3).

The most frequently studied and representative chemotherapeutic agent used during preoperative CRT is 5-fluorouracil (5-FU). Doses and schedules of concurrent 5-FU during radiotherapy (RT) are not standardized and differ across reported trials. The administration of 5-FU sometimes requires hospitalization or central venous access because continuous infusion offers better efficacy and lower toxicity than do bolus injections (1, 4). Oral fluoropyrimidines, such as uracil and tegafur (UFT) or capecitabine, have therefore been substituted for 5-FU in several trials of preoperative CRT and have shown equivalent efficacy and less toxicity than intravenous 5-FU (5–9).

S-1 is a novel oral fluoropyrimidine, consisting of three compounds—tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo)—in a molar ratio of 1:0.4:1. Tegafur is converted to 5-FU and acts as an effector; CDHP increases antitumor activity by inhibiting the degradation of 5-FU; and Oxo, an inhibitor of orotate phosphoribosyltransferase, reduces gastrointestinal (GI) toxicity such as diarrhea by

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inhibiting the phosphorylation of 5-FU in the GI tract. S-1 has shown antitumor activity in patients with various GI cancers, including colorectal cancer, when given as either monotherapy or in combination chemotherapy (10–13). S-1 also acts as a radiosensitizer in human colon cancer xenografts (14), and the results of several trials of concurrent CRT with S-1 for treatment of various tumor types have been recently reported (15–19).

Whereas preoperative CRT with fluoropyrimidines has shown efficacy in terms of local control, such treatments have failed to enhance either disease-free or overall survival (2, 3). These findings suggest that fluoropyrimidines alone are insufficient for preventing later distant metastases and do not yield effective systemic tumor control. To improve such control, several trials of preoperative CRT with fluoropyrimidines and other cytotoxic agents have been performed (4, 20–26).

Oxaliplatin, a platinum derivative, is a newer cytotoxic agent, and combination chemotherapy with fluoropyrimidines plus oxaliplatin has become a standard chemotherapeutic regimen for patients with metastatic colorectal cancer (27). The combination of oxaliplatin plus S-1, as a fluoropyrimidine, has also shown feasibility and promising antitumor activity in patients with metastatic colorectal cancer (11, 13).

On the basis of these results, we choose a newer preoperative CRT regimen, consisting of oxaliplatin plus S-1. In this Phase I study, we determined the maximum tolerated dose (MTD) and the recommended dose (RD) of S-1 when combined with oxaliplatin as preoperative CRT, and we assessed the feasibility of this combination.

METHODS AND MATERIALS

Patient population

Patients with locally advanced, nonmetastatic, histologically confirmed adenocarcinoma of the rectum were enrolled. To be eligible, patients were required to have (*1*) histologically confirmed adenocarcinoma of the rectum; (*2*) a distal tumor margin located 0–12 cm from the anal verge, confirmed by rigid sigmoidoscopic examination; (*3*) a clinically confirmed T3 lesion or involvement of regional nodes (N+), as determined by magnetic resonance imaging (MRI) with or without endorectal ultrasound; (*4*) locally advanced and nonmetastatic disease that would be curable by surgical resection; (*5*) age >18 years; (*6*) Eastern Cooperative Oncology Group performance status ≤2; (*7*) no prior chemotherapy, immunotherapy, or RT; and (*8*) adequate hematologic, hepatic, and renal function. Patients with distant metastases; any unresected synchronous colon cancer; current or impending obstructive symptoms; prior history of another malignancy within 5 years of study entry, except for basal cell carcinoma of the skin or carcinoma *in situ* of the uterine cervix; any condition accompanied by lack of integrity of the upper GI tract, such as significant gastric or small bowel resection or malabsorption syndrome; or any condition indicating unsuitability for CRT, were excluded. All patients provided written informed consent before study entry, and the study protocol was approved by the institutional review board of our institution.

Treatment

The treatment scheme is shown in Fig. 1. Radiotherapy was delivered to the pelvis through three (posterior–anterior and two lateral) fields or four (anterior–posterior, posterior–anterior, and two lateral) fields, using an energy of 6 MV or 15 MV delivered by a linear accelerator (Clinac 1800 instrument; Varian Medical Systems, Palo Alto, CA), with each patient in the prone position. The total dose was 50.4 Gy, with a daily dose of 1.8 Gy administered on 5 days of each week for a total of 45 Gy to the whole pelvis, followed by a 5.4-Gy boost to the primary tumor. The superior border of the pelvic field was the bottom of L5, and the inferior border was 3 cm distal to the tumor. The anterior border was located 3 cm anterior to the tumor, and the posterior margin was 1 cm behind the posterior margin of the sacrum. The target volume included the primary tumor, perirectal fat tissue, and the internal iliac and presacral lymph nodes.

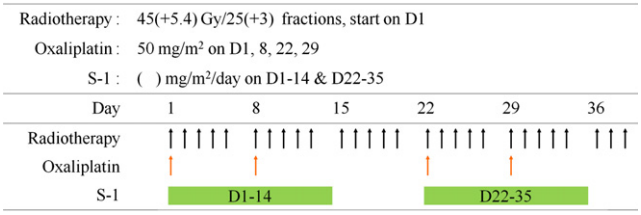

Fig. 1. Treatment scheme.

Concurrent chemotherapy consisted of a fixed dose of oxaliplatin (50 mg/m^2/week) on Days 1, 8, 22, and 29, and escalating doses of S-1 on Days 1–14 and 22–35. Patients had drug holidays during the third week (Days 15–21) and the last 3 days of RT. A 5-hydroxytryptamine type-3 receptor antagonist was given as emesis prophylaxis before drug administration. Compliance to S-1 was monitored by counting of remaining pills during each outpatient visit. Surgery was performed within 6 ± 2 weeks after the completion of CRT. The first choice for surgery was total mesorectal excision, with the final decisions on surgical procedure (abdominoperineal or anterior resection) made by the surgeons, following the recommendation of the multidisciplinary team.

Dose-limiting toxicity

Treatment-related adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, version 3.0. Dose-limiting toxicity (DLT) was defined as (*1*) Grade 4 neutropenia; (*2*) Grade ≥3 febrile neutropenia or thrombocytopenia; (*3*) any other Grade ≥3 nonhematologic toxicity, including nausea, vomiting, and diarrhea, which did not improve within 2 days after appropriate management was commenced; (*4*) a treatment interruption lasting more than 2 weeks; or (*5*) an inability, for any reason, to administer more than 50% of the scheduled doses of S-1 or oxaliplatin.

Dose-escalation scheme

In the present study, the doses and schedules for oxaliplatin and RT were fixed, with only S-1 being prescribed using a dose-escalation schedule. The initial dose of S-1 was 50 mg/m^2/day (Level 1), with doses escalated to 60 mg/m^2/day (Level 2), 70 mg/m^2/day (Level 3), and 80 mg/m^2/day (Level 4). At each dose level, a new adjusted dose table for S-1 according to body surface area was defined (Table 1). The MTD was defined as the dose level of S-1 that produced DLT in 2 or more of 6 patients. Three patients were entered into each dose level; if DLT occurred in 1 or 2 of the first 3 patients, 3 additional patients were treated with the same dose of S-1. If no DLT was observed in the initial 3 patients or in only 1 of 6 patients, the dose was increased to the next level. On the basis of several Phase II trials of S-1, together with other cytotoxic agents,