Prospective Feasibility Study to Evaluate Neoadjuvant-synchronous S-1 + RT for Locally Advanced Rectal Cancer: A Multicenter Phase II Trial (UMIN ID: 03396)

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In Western countries, the standard treatment for locally advanced rectal cancer is preoperative chemoradiotherapy followed by total mesorectal excision. However, in Japan, the treatment results without preoperative chemoradiotherapy are by no means inferior; therefore, extrapolation of the results of preoperative treatment in Western countries to Japan is controversial. We consider that survival may be improved by preoperative chemoradiotherapy with new anticancer agents as they are expected not only to decrease the local recurrence rate but also to prevent distant metastases. We are conducting a multicentre Phase II study to evaluate the safety and efficacy of neoadjuvant chemoradiotherapy using S-1 in patients with locally advanced rectal cancer. The primary endpoint is the rate of complete treatment of neoadjuvant chemoradiotherapy. Secondary endpoints are the response rate of neoadjuvant chemoradiotherapy, short-term clinical outcomes, rate of curative resection and pathological evaluation. The short-term clinical outcomes are adverse events of neoadjuvant chemoradiotherapy and surgery-related complications. Thirty-five patients are required for this study.

Key words: rectal cancer – neoadjuvant chemoradiotherapy – S-1

INTRODUCTION

The standard treatment for locally advanced rectal cancer is well known to differ between Japan and Western countries. In Western countries, multimodal therapies such as preoperative short-term intensive radiotherapy or conventional long-term radiotherapy in combination with 5-fluorouracil (5-FU)-based chemotherapy have gained widespread acceptance for the treatment of locally advanced rectal adenocarcinoma (1). These treatments provide improved local control when compared with surgery alone, although only one study has shown a survival benefit (2). The local control benefit of preoperative radiotherapy remains relevant even in the era of total mesorectal excision (TME) (3). The addition of chemotherapy to preoperative conventional long-term radiotherapy (RT) has been demonstrated to be feasible, with enhanced tumoricidal effects (4). In Japan, TME or tumor-specific mesorectal excision followed by adjuvant chemotherapy without preoperative treatment is a standard strategy, and lateral lymph node (LN) dissection is added in patients with lower rectal cancer (5). The results of the surgical treatment without RT in Japan are by no means inferior to those in Western countries that do use RT with surgery. Therefore, extrapolation of the results of preoperative treatment in Western countries to Japan is controversial.

Recently, new anticancer agents have markedly improved the response rate and prognosis of unresectable and recurrent colorectal cancer. Locally advanced rectal cancer may be controlled by the addition of new anticancer agents. In Western countries, new treatment strategies have been tested, including the addition of new cytotoxic drugs and/or
molecular-targeted drugs to fluoropyrimidine-based chemoradiotherapy concurrently or before chemoradiotherapy (6,7). On the other hand, there is a concept that oral chemotherapy has major advantages over intravenously administered treatment in terms of pharmacoeconomic considerations and patient preferences, because oral treatment can be administered on an outpatient basis, thereby reducing the length of patients’ hospital stays (8). Over time, the role of oral chemotherapy in the treatment of malignant disease is expected to become increasingly significant. S-1 (TS-1, Taiho Pharmaceutical) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil) and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 (9,10). The rate of response to treatment with S-1 alone exceeded around 40% in two Phase II trials involving patients with advanced or recurrent colorectal cancer (11,12). Furthermore, S-1 has been demonstrated to enhance the radiation response of human colon cancer xenografts resistant to 5-FU (13). In 2011, Sadahiro et al. (14) reported that the efficacy of chemoradiotherapy with S-1 seems to be equivalent to the efficacy reported for chemoradiotherapy with capecitabine. However, the dose of S-1 (100 mg/m²) in our study is different from that of S-1 (80 mg/m²) in the above-mentioned study. We planned the present study in order to obtain the more excellent efficacy.

We consider that survival may be improved by preoperative treatment with new anticancer agents, S-1 as they are expected to decrease local recurrence due to their effect of bulk reduction, to obtain a high rate of complete treatment of neoadjuvant chemoradiotherapy and to prevent distant metastases.

We conducted our own Phase II study to confirm the safety and efficacy of the chemoradiotherapy using S-1 before surgery. Our administration schedule of S-1 is 100 mg/m²/day for 5 days, and followed by no administration for 2 days. The total dose of S-1 per week is 500 mg/m²/week. Because the total dose of S-1 per week in our study (500 mg/m²) is less than the standard amount per week (560 mg/m²), Phase I trial has not been conducted.

The institutional review board of each participating center approved the study protocol. This study was registered at the UMIN Clinical Trial Registry as UMIN000003396 (http://www.umin.ac.jp/ctr/index.htm).

**PROTOCOL DIGEST OF THE OITA TRIAL**

**PURPOSE**

To evaluate the feasibility and efficacy of neoadjuvant CRT for locally advanced rectal cancer.

**STUDY SETTING**

A multi-institutional (17 specialized centers), interventional Phase II trial. This study is registered with UMIN-CTR, number C003396.

**RESOURCES**

This study was supported by a part of Grants-in-Aid for Clinical Cancer Research from the Japanese Ministry of Health, Labour and Welfare (22-Clinical Cancer-027).

**ENDPOINTS**

The primary endpoint is the rate of complete treatment of neoadjuvant chemoradiotherapy. Secondary endpoints are the response rates of neoadjuvant chemoradiotherapy, short-term clinical outcomes, rate of curative resection and pathological evaluation. The short-term clinical outcomes are adverse events of neoadjuvant chemoradiotherapy, surgery-related complications. The response rate is evaluated using RECIST, and the adverse events including preoperative chemoradiotherapy and surgical complication are evaluated using CTCAE v4.0.

**ELIGIBILITY CRITERIA**

Tumors are staged according to the TNM classification system.

**INCLUSION CRITERIA**

For inclusion in the study, patients must fulfill the following requirements before neoadjuvant chemoradiotherapy: (i) histologically proven rectal carcinoma; (ii) tumor located in the rectum (Ra,Rb,P); (iii) cancer classified as T3–4, N0–3 and M0, according to the TNM classification system; (iv) no bowel obstruction; (v) age >20 and <80 years; (vi) sufficient organ function; (vii) no history of gastrointestinal surgery; (viii) no history of chemotherapy or radiotherapy and (ix) provide written informed consent.

**EXCLUSION CRITERIA**

The exclusion criteria are as follows: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (ii) critical drug sensitivity to S-1; (iii) severe pulmonary emphysema, interstitial pneumonitis or ischemic heart disease; (iv) pregnant or lactating women; (v) severe mental disease; and (vi) continuous systemic steroid therapy.

**TREATMENT METHOD**

For the locally advanced rectal carcinoma, two cycles of neoadjuvant chemotherapy with S-1 (100 mg/m² on Days 1–5, 8–12, 22–26 and 29–33) is administered, and
irradiation (total 45 Gy/25 fr, 1.8 Gy/day, on Days 1–5, 8–12, 15–19, 22–26 and 29–33) is performed.

ADDITIONAL TREATMENT

Resection of the rectum with D3 lymphadenectomy is performed according to the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, 6th edn, 1998 (in Japanese)). Operation is performed during the 4th and 8th week after the end of the neoadjuvant chemoradiation therapy. Proposed operations are anterior resection with or without covering ileostomy and anterior peritoneal resection. When the preoperative and intraoperative findings demonstrate that the lateral LNs metastasis is not suspected, lateral LNs dissection is not performed. The adjuvant chemotherapy is not specified.

FOLLOW-UP

Patients are observed by their surgeon every 3–4 months after operation. Blood tests, abdominal computed tomography and plain chest X-ray are carried out at each visit.

STUDY DESIGN AND STATISTICAL METHOD

This trial is designed to achieve the feasibility and efficacy of neoadjuvant CRT with S-1 for locally advanced rectal cancer in terms of completion rate, efficacy and adverse events of neoadjuvant chemoradiation and curative resection rate. If the feasibility and efficacy of neoadjuvant CRT with S-1 is shown, neoadjuvant CRT with S-1 will be the preferred treatment. The planned sample size is 35 patients, which was calculated by Southwest Oncology Group’s two-stage attained design (16) based on a target rate of treatment completion of 90% and a minimum completion rate of 70%, with an a error of 0.05 and b error of 0.15.

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Conflicting of interest statement

None declared.

References