Clinical Trial Note

A Phase II/III randomized controlled trial comparing perioperative versus postoperative chemotherapy with mFOLFOX6 for lower rectal cancer with suspected lateral pelvic node metastasis: Japan Clinical Oncology Group Study JCOG1310 (PRECIOUS study)

Masayuki Ohue1,*, Satoru Iwasa2, Yukihide Kanemitsu3, Tetsuya Hamaguchi2, Manabu Shiozawa4, Masaaki Ito5, Masayoshi Yasui1, Hiroshi Katayama6, Junki Mizusawa6, and Yasuhiro Shimada7, on behalf of the Colorectal Cancer Study Group/Japan Clinical Oncology Group

1Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, 2Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, 3Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, 4Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, 5Department of Colorectal Surgery, National Cancer Center Hospital East, Chiba, 6JCOG Data Center/Operations Office, National Cancer Center, Tokyo, and 7Clinical Oncology Division, Kochi Health Sciences Center, Kochi, Japan

*For reprints and all correspondence: Masayuki Ohue, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan. E-mail: ohue-ma@mc.pref.osaka.jp

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Abstract

A randomized phase II/III trial was started in May 2015 comparing perioperative versus postoperative chemotherapy with modified infusional fluorouracil and folinic acid with oxaliplatin for lower rectal cancer patients with suspected lateral pelvic node metastasis. The standard arm is total mesorectal excision or tumor-specific mesorectal excision with lateral pelvic node dissection (LND) followed by postoperative chemotherapy (modified infusional fluorouracil and folinic acid with oxaliplatin; 12 cycles). The experimental (perioperative chemotherapy) arm is six courses of modified infusional fluorouracil and folinic acid with oxaliplatin before and six courses after total mesorectal excision with lateral pelvic node dissection. The aim of this trial is to confirm the superiority of perioperative chemotherapy. A total of 330 patients will be enrolled over 7 years. The primary endpoint in Phase II part is proportion of R0 resection and that in Phase III part is overall survival. Secondary endpoints are progression-free survival, local progression-free survival, etc. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000017603 [http://www.umin.ac.jp/ctr/index-j.htm].

Key words: randomized controlled trial, lower rectal cancer, lateral pelvic node metastasis, lateral pelvic node dissection, mFOLFOX6

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Backgrounds and rationale

Colorectal cancer is one of the main leading causes of death from cancer worldwide (1). The prevention, early diagnosis and development of improved treatments for colorectal cancer are very urgent tasks. In the treatment of locally advanced lower rectal cancer, preoperative chemoradiation (CRT) followed by total mesorectal excision or tumor-specific mesorectal excision (TME) is the standard surgical procedure in Europe and North America (2). In Japan, however, TME with lateral pelvic node dissection (LND) is the standard procedure (3), with a similar incidence of local recurrence to the treatment with CRT and TME (4). The Japan Clinical Oncology Group (JCOG) has conducted a randomized controlled trial (JCOG0212) to confirm the non-inferiority of the TME over the TME with LND for clinical stage II or stage III patients without suspected lateral pelvic node metastasis (LNM) (5). However, patients with lower rectal cancer with LNM are considered to be a high-risk group and have a worse prognosis than those without LNM, with a 5-year overall survival of ~40% (6). TME with LND should be strongly considered for R0 resection when the tumor invades beyond the extent of TME (beyond TME).

With regard to adjuvant treatment, several recent papers have reported that additional CRT with TME does not improve survival and is not efficient for the treatment of LNM (7, 8). However, postoperative adjuvant chemotherapy with 5-fluorouracil has been shown to improve the survival of patients with resectable rectal cancer (9, 10). In addition, a more intensive adjuvant treatment with oxaliplatin, fluorouracil and leucovorin (FOLFOX) improved the overall survival of patients with stage II or III colon cancer (11). Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 recommended 5-FU + leucovorin, UFT + leucovorin, Cape, FOLFOX and CapeOX as adjuvant chemotherapy for stage III colorectal cancer (12). Among them, we reached a conclusion that adjuvant FOLFOX6 would be the most appropriate as a standard treatment for lower rectal cancer with suspected LNM. FOLFOX may be effective in a neoadjuvant setting for lower rectal cancer (13, 14). In this study, modified infusional fluorouracil and folinic acid with oxaliplatin (mFOLFOX6) was adopted as an adjuvant FOLFOX regimen because it has been used in several Phase III studies (15).

We hypothesized that the preoperative introduction of chemotherapy might improve compliance with the protocol, helping to prevent the dissemination of micrometastases and improve survival compared with postoperative chemotherapy. Although we suggested 6 courses of preoperative mFOLFOX6 followed by 12 courses of postoperative mFOLFOX6 as a candidate for the experimental arm, administering a total of 18 courses of mFOLFOX6 prompted concerns about the neurotoxicity. For this reason, a total of 12 courses of mFOLFOX6, comprising 6 courses of preoperative and 6 courses of postoperative therapy, were deemed appropriate for adjuvant chemotherapy. We therefore designed the new trial JCOG1310 comparing perioperative versus postoperative chemotherapy with mFOLFOX6 for lower rectal cancer with suspected LNM.

Protocol digest of JCOG1310

Purpose

The purpose of this trial was to confirm the superiority of perioperative mFOLFOX6 to postoperative mFOLFOX6 in the treatment of lower rectal cancer with suspected LNM.

Study setting

This trial is a multi-institutional, prospective, open-label, randomized Phase II/III trial.

Endpoints

In Phase II part, the primary endpoint is the proportion of R0 resection, and the secondary endpoints are the proportion of operative complications and proportion of patients who complete 12 cycles of chemotherapy. In Phase III part, the primary endpoint is the overall survival which is the time from randomization to death from any cause, and the secondary endpoints are as follows: progression-free survival, local progression-free survival, proportion of patients with R0 resection, overall response rate of preoperative chemotherapy in the perioperative chemotherapy arm, pathological complete response rate in the perioperative chemotherapy arm, proportion of patients who complete 12 cycles of chemotherapy, incidence of adverse events, incidence of serious adverse events, proportion of operative complications, proportion of surgery without resection of adjuvant organs, proportion of anus-preservation and proportion of anus-preservation without stoma. Adverse events and postoperative complications were assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Eligibility criteria

Rectal carcinoma is classified according to the 8th edition of Japanese Classification of Colon and Rectal Carcinoma (16) and the 7th edition of TNM classification (17).

Inclusion criteria

Prior to enrollment in this trial, the patients must meet all of the following criteria:

(i) Pathologically proven adenocarcinoma or adenosquamous carcinoma
(ii) Primary tumor located in the upper rectum, lower rectum or anal canal
(iii) Lower border of the tumor located between the peritoneal reflection and the anal verge
(iv) cT2, cT3 and cT4 tumor on computed tomography (CT) or magnetic resonance imaging (MRI), except for a T4b tumor invading the trigone of the bladder, urethra or sacrum
(v) Lateral pelvic nodes with a short axis diameter of ≥10 mm on CT or MRI of 5-mm-thick slices (cN3) (5, 18)
(vi) No distant metastasis on CT or MRI (cM0)
(vii) Aged 20–74 years old
(viii) PS 0 or 1 on ECOG
(ix) No prior chemotherapy or treatment such as rectal resection, pelvic lymph node dissection or pelvic irradiation for any malignancies
(x) No other colorectal carcinoma, except cTis or cT1a
(xi) Adequate organ function as evidenced by the following laboratory findings within 14 days prior to enrollment
   (a) Neutrophil count ≥ 1500/mm³
   (b) Platelet count ≥ 100 000/mm³
   (c) Total bilirubin ≤ 2.0 mg/dl
   (d) Aspartate aminotransferase ≤ 100 IU/l
   (e) Alanine aminotransferase ≤ 100 IU/l
   (f) Creatinine ≤ 1.5 mg/dl
(xii) Open surgery is planned
(xiii) Written informed consent given.

Exclusion criteria
Prior to enrollment in this trial, the patients must not meet any of the following criteria:

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma
(ii) Infectious disease requiring systemic therapy
(iii) Positive for HBs antigen
(iv) Body temperature ≥38°C
(v) Pregnant, possibly pregnant or breast-feeding
(vi) Severe mental disease
(vii) Currently treated with systemic steroids or immunosuppressive agents
(viii) Interstitial pneumonia, pulmonary fibrosis or severe emphysema on chest CT
(ix) Uncontrollable diabetes mellitus or routine administration of insulin
(x) Unstable angina pectoris or previous myocardial infarction within the past 6 months.

Randomization
Following confirmation of the eligibility of patients using the web-based system to the JCOG Data Center, the patients will be randomized to either the postoperative chemotherapy arm or the perioperative chemotherapy arm of the study. The minimization method will be used for the randomization of patients, thereby balancing the arms of the study according to gender, tumor depth (T2-3 versus T4) and the institution.

Treatment methods
Surgery
TME with LND will be performed via open surgery for all of the patients in accordance with reported methods (2,3,5). LND includes at least both sides of the common iliac nodes, proximal internal iliac nodes, distal internal iliac nodes and obturator nodes. Dissection of other lateral pelvic nodes and inguinal lymph nodes, and combined resection, such as total pelvic exenteration, of the surrounding organs or tissues are permitted to obtain R0 resection (16). For surgical quality control and assurance, intraoperative photographs will be taken.

Postoperative chemotherapy arm
One course of mFOLFOX6 consists of an intravenous injection of oxalaplatin 85 mg/m² with leucovorin 200 mg/m² over 2 hours followed by a fluorouracil 400 mg/m² bolus and 2400 mg/m² continuous infusion over 46 hours. After the R0 resection, postoperative chemotherapy with mFOLFOX6 will be initiated between days 29 and 56 after surgery and repeated every 2 weeks for 6 courses for pathological Stage 0–III patients.

Follow-up
Patients will be followed-up every 3 months for the first 3 years, and subsequently every 3 months for the next 3 years. Follow-up evaluations will include a clinical examination, a blood cell count, serum chemical tests, carcinoembryonic antigen and cancer antigen (CA19-9) as tumor marker tests and thoracic/abdominal/pelvic CT at 6-month intervals.

Study design and statistical methods
This trial is designed to confirm the superiority of the perioperative chemotherapy to the postoperative chemotherapy in terms of overall survival. In Phase II part, the primary endpoint is the proportion of R0 resection. When this proportion in the perioperative arm drops >10% below that in the postoperative arm, this study will be terminated. If the expected value of the primary endpoint is 95% in both groups, 30 patients will be required in each group in order to maintain a false-negative rate of 5%.

In Phase III part, we hypothesize that the 5-year overall survival of the perioperative arm will be greater than that of the postoperative arm (50%) by 10%. If the overall survival is significantly longer with perioperative chemotherapy than postoperative, the perioperative regimen will be concluded as the new standard treatment. According to the method of Schoenfeld and Richter (19), the required sample size will be 326 patients (163 patients per arm), with a one-sided alpha level of 5% and a power of 70% and 203 events are expected to occur during 7 years of accrual and 5 years of follow-up. Given that some patients will likely be lost to follow-up, the total target sample size is set at 330 patients.

Interim analysis and monitoring
We plan to conduct three interim analyses. The first interim analysis, which is a primary analysis of Phase II part, will be carried out after 60 patients have been enrolled, to determine whether this trial can proceed to Phase III status. The second interim analysis will be conducted after half of the planned number of patients has been enrolled. The third interim analysis will be conducted after the planned number of patients has been enrolled and their protocol treatment has finished. The multiplicity will be adjusted using the Lan-DeMets method with the O’Brien and Fleming-type alpha spending function (20).

The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and determine if the trial should be terminated early. The trial will be terminated (i) when the proportion of R0 resection in the perioperative arm is >10% lower than that in the postoperative arm in the first interim analysis, (ii) when the overall survival in the perioperative arm is inferior to that in the postoperative arm at the second or third interim analyses, (iii) when the overall survival of the perioperative arm is significantly superior to that in the postoperative arm, even with adjustment for multiplicity at the second or third interim analyses or (iv) when treatment-related deaths occur in seven patients of either arm. The JCOG Data Center and study coordinator will conduct central monitoring and issue a monitoring report every 6 months to evaluate the study progress and improve the data integrity and patient safety. For quality assurance, site visit audits will be performed by the JCOG Audit Committee (not on a study-specific basis but for the study group).
Clinical trials registry
This trial was registered at the UMIN Clinical Trials Registry as UMIN000017603 (http://www.umin.ac.jp/ctr/index-j.htm).

Participating institutions (listed from north to south)
Sapporo-Kosei General Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center Jichi Medical University, Saitama Medical University International Medical Center, National Cancer Center Hospital East, Chiba Cancer Center, Juntendo University Urayasu Hospital, National Cancer Center Hospital, Kyorin University School of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Toho University School of Medicine Ohashi Hospital, Kanagawa Cancer Center, Yokohama City University Medical Center, Saiseikai Yokohamashi Nanbu Hospital, Hiratsuka City Hospital, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Ishikawa Prefectural Central Hospital, Nagano Municipal Hospital, Gifu University School of Medicine, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Fujita Health University, National Hospital Organization Kyoto Medical Center, Osaka University Faculty of Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka General Medical Center, Osaka Medical College, Sakai city hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Hyogo College of Medicine, Sanos Hospital, Shimane University Faculty of Medicine, Okayama Saiseikai General Hospital, Hiroshima City Hospital, Hiroshima Prefectural Hospital, Hiroshima City Asa Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Science Center, Kurume University School of Medicine, Kumamoto University School of Medicine and Otta University Hospital. In each institution, approval by the institutional review board is obtained before starting patient accrual.

Conflict of interest statement
None declared.

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