

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)

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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

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 criteria
- (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 $\geq 1500/\text{mm}^3$
 - (b) Platelet count $\geq 100\,000/\text{mm}^3$
 - (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 $\geq 38^{\circ}\text{C}$
- (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 oxaliplatin 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 12 courses for pathological Stage II or III patients only.

Perioperative chemotherapy arm

In the perioperative chemotherapy arm, mFOLFOX6 will be administered every 2 weeks for six courses preoperatively unless disease progression is observed on CT or MRI performed in Week 2 of Course 3. TME with LND will be performed as described above between Days 14 and 42 after the preoperative chemotherapy. Postoperative 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, Sano 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 Oita 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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References

- Matsuda A, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the monitoring of cancer incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2013;44:388–96.
- MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993;341:457–60.
- Moriya Y, Sugihara K, Akasu T, et al. Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. *Eur J Cancer* 1995;31A:1229–32.
- Kusters M, Beets GL, van de Velde CJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. *Ann Surg* 2009;249:229–35.
- Fujita S, Akasu T, Mizusawa J, et al. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. *Lancet Oncol* 2012;13:616–21.
- Akiyoshi T, Watanabe T, Miyata S, et al. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease? *Ann Surg* 2012;255:1129–34.
- Gijn WV, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *Lancet Oncol* 2011;15:575–82.
- Kim TH, Jeong SY, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 2008;15:729–37.
- Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012;3:CD004078 doi:10.1002/14651858.CD004078.pub2.
- Hamaguchi T, Shirao K, Moriya Y, et al. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). *Cancer Chemother Pharmacol* 2011;67:587–96.
- André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109–16.
- Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. *Int J Clin Oncol* 2015;20:207–39.
- Cercek A, Weiser MR, Goodman KA, et al. Complete pathologic response in the primary of rectal or colon cancer treated with FOLFOX without radiation. *J Clin Oncol* 2010;28:15s (suppl; abstr 3649).
- Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. *J Clin Oncol* 2014;32:513–8.
- Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol* 2011;29:11–6.
- Japanese Society of Cancer of the Colon and Rectum *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus*. 8th edn. Tokyo: Kanehara, 2013 (in Japanese).
- Sobin L, Wittekind C *TNM Classification of Malignant Tumours*. 7th edn. New York: Wiley-Liss, 2009.
- Akasu T, Iinuma G, Takawa M, et al. Accuracy of high-resolution magnetic resonance imaging in preoperative staging of rectal cancer. *Ann Surg Oncol* 2009;16:2787–94.
- Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometric* 1982;38:163–70.
- Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659–63.