original article

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Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer

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Background: A combination of irinotecan with continuous intravenous infusions of 5-fluorouracil (5-FU) and leucovorin (LV) is often used to treat advanced colorectal cancer. However, recent concerns about safety and convenience have prompted the development of new oral fluoropyrimidine derivatives and improved regimens. This phase II study evaluated the efficacy and safety of the oral fluoropyrimidine S-1 plus irinotecan in patients with previously untreated advanced or recurrent colorectal cancer.

Patients and methods: Forty eligible patients with histologically confirmed colorectal adenocarcinoma received this treatment. S-1 was administered orally on days 1 to 14 of a 21-day cycle. Patients were assigned on the basis of body surface area (BSA) to receive one of the following oral doses twice daily: 40 mg (BSA < 1.25 m^2), 50 mg (BSA ≥ 1.25 to < 1.50 m^2), or 60 mg (BSA ≥ 1.50 m^2). Irinotecan (150 mg/m^2) was administered by intravenous infusion on day 1.

Results: A total of 327 courses of treatment were administered to 40 patients. Five patients had complete responses, and 20 had partial responses. The overall response rate was 62.5% (95% confidential interval, 47.5%–77.5%). Median progression-free survival was 8.0 months (95% confidential interval, 5.2–11.4 months). The rates of grade 3 or 4 toxicity were as follows: neutropenia, 15%; anemia, 7.5%; anorexia, 12.5%; and diarrhea, 7.5%.

Conclusions: Combined treatment with S-1 and irinotecan is an effective, well tolerated, and convenient regimen in patients with advanced colorectal cancer. Our findings suggest that combined treatment with S-1 and irinotecan is a promising regimen, offering benefits in terms of safety and survival as compared with conventional regimens in patients with advanced colorectal cancer.

Key words: S-1, irinotecan, colorectal cancer, phase II study

original article

introduction

Irinotecan, a potent inhibitor of topoisomerase I, extends survival significantly as compared with best supportive care or 5-fluorouracil (5-FU) infusion as second-line therapy for advanced colorectal cancer. Two randomized phase III trials have shown that a combination of irinotecan plus intravenous bolus or continuous intravenous infusion of 5-FU and leucovorin (LV) as first-line treatment provides a survival benefit, with a median overall survival time (MST) of 14.8 to 17.4 months in patients with advanced colorectal cancer [1]. However, recent reports have expressed concern about high rates of toxicity and early treatment-related mortality among patients receiving combined treatment with irinotecan plus bolus 5-FU and LV [2-3]. Meta-analysis has shown that infusional 5-FU regimens may be a safer option and are superior to bolus 5-FU regimens in terms of tumor response [4]. Consequently, irinotecan plus infusional 5-FU and LV has been considered superior to irinotecan plus bolus 5-FU and LV. However, administration of infusional 5-FU is becoming more complex because of the need for vascular access devices and portable delivery systems. The use of an indwelling central venous catheter and a portable pump may also lead to problems such as infection, thrombosis, and higher health-care costs. Such problems have increased the need for new oral fluoropyrimidine agents and safer and more effective combination regimens for advanced colorectal cancer.

S-1 is an oral fluoropyrimidine preparation developed by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) that combines tegafur with two 5-FU modulators, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [5]. Tegafur, a prodrug of 5-FU, is converted to 5-FU mainly in liver and tumor cells. CDHP, a reversible inhibitor of dihydropyrimidine dehydrogenase, suppresses the degradation of 5-FU, thereby maintaining high concentrations of 5-FU in plasma and tumor cells [5–6]. CDHP also decreases cardiotoxic and neurotoxic effects by reducing the production of F-β-alanine (FBAL), the main catabolite of 5-FU [7–8]. After oral administration, Oxo is selectively distributed to the small and large bowel. High concentrations of Oxo in these organs inhibit the phosphorylation of 5-FU to fluoropyrimidine monophosphate, catabolized by orotate phosphoribosyltransferase within

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gastrointestinal mucosal cells, thereby reducing the incidence of diarrhea [9].

Several clinical trials of S-1 monotherapy have been conducted. Dose-limiting toxicity was myelosuppression in Japanese studies and diarrhea in European and North American studies [10–13]. In phase II trials of S-1 as a single agent, response rates ranging 19% to 39% were obtained in patients with advanced colorectal cancer [14–16]. These studies demonstrated that S-1 had a high response rate and good compliance in patients with advanced colorectal cancer treated on an outpatient basis. Several regimens combining S-1 and irinotecan were subsequently developed. Yamada et al. conducted a phase I and pharmacokinetic study to assess the maximum tolerated dose and recommended dose of S-1 combined with irinotecan [17]. That study recommended that 150 mg/m^2 of irinotecan is given on day 1 with 40 mg/m^2 of S-1 twice daily on days 1 to 14 of a 21-day cycle. We conducted this phase II study to validate the safety profile and effectiveness of S-1 combined with irinotecan in patients with advanced colorectal cancer.

patients and methods

eligibility

To be eligible for this study, patients had to have histologically or cytologically confirmed advanced or recurrent colorectal adenocarcinoma with metastatic measurable lesions. Other eligibility criteria included an age of ≥20 to <75 years, an Eastern Cooperative Group (ECOG) performance status (PS) of ≤2, a leukocyte count of ≥3000 to ≤12 000/μl, a hemoglobin of ≥8 g/dl, a platelet count of ≥100 000/μl, a serum bilirubin level of ≤1.1 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤100 U/l, a serum creatinine level of ≤1.1 mg/dl (for men) or ≤0.7 mg/dl (for women), the ability to ingest food, and no high medical risks. Patients who had received prior chemotherapy or radiotherapy were excluded; however, those who had received adjuvant chemotherapy completed at least 6 months before study entry were eligible. All patients gave written informed consent before enrolment.

treatment schedule

S-1 was available as capsules containing 20 or 25 mg of tegafur. Patients were assigned on the basis of body surface area (BSA) to receive one of the following oral doses twice daily, within an hour after breakfast and supper: 40 mg (BSA <1.25 m^2), 50 mg (BSA ≥1.25 to <1.50 m^2), or 60 mg (BSA ≥1.50 m^2). S-1 was given for 14 consecutive days followed by a 7-day rest period. Irinotecan was administered as a 90-minute intravenous infusion in a dose of 150 mg/m^2 on day 1, after the initial oral dose of S-1. Courses of treatment were repeated every 21 days until confirmation of either disease progression or unacceptable toxicity.

If laboratory abnormalities not meeting the eligibility criteria developed after the start of treatment, subsequent courses of treatment were withheld until the resolution of such abnormalities to the levels defined in the eligibility criteria. If ≥grade 2 non-hematological toxicity other than constipation, alopecia, pigmentation, or taste disturbance occurred, subsequent courses of treatment were also withheld until symptoms resolved. If the eligibility criteria were not met by day 35 of a cycle, the patient was excluded from further study. If the serum bilirubin level exceeded 1.5 mg/dl, the serum creatinine level exceeded the eligibility criteria, or other ≥grade 3 toxicity developed, the treatment course was interrupted until symptoms, laboratory abnormalities, or both had resolved. If treatment was resumed, S-1 was given until day 14 of the cycle, not for the full 14 days. If the previous treatment course was delayed or interrupted because of toxicity, the dose of irinotecan was reduced by 25 mg/m^2 for subsequent courses. If 125 mg/m^2 of irinotecan was not tolerated, the dose was reduced to 100 mg/m^2. If 100 mg/m^2 of irinotecan was poorly tolerated, the patient was excluded from further study. The dose of S-1 was unchanged if the dose of irinotecan was reduced. Only if skin reactions occurred, the dose of S-1 was reduced in subsequent courses as follows: 60 mg, 50 mg, and 40 mg of S-1 twice daily were reduced to 50 mg, 40 mg, and 25 mg twice daily, respectively. Once lowered, the doses of S-1 and irinotecan were not increased.

Supportive treatments were given as required. The use of colony-stimulating factors was allowed if medically justified. A 5-hydroxytryptamine-3-receptor antagonist and dexamethasone were given to all patients in a 30-min intravenous infusion before administration of irinotecan. All patients received oral dexamethasone on days 2 and 3 of each cycle.

evaluation

Patients who received at least one treatment course were included in safety and efficacy analyses. Before study entry, patients underwent physical examination, chest X-ray, and computed tomographic scans of the abdomen and chest. Patients were re-examined at 6-week intervals to evaluate target lesions. Responses were evaluated according to the RECIST criteria [18]. Complete and partial responses required subsequent confirmation of response after an interval of at least 4 weeks. Pretreatment evaluations comprised an electrocardiogram, urinalysis, and laboratory tests, including a complete blood cell count and serum chemistry profiles. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. Toxicity and laboratory variables were assessed weekly during the first treatment course and on days 1 and 15 from the second through sixth treatment courses. Safety profiles and dose intensity were determined for up to six courses of treatment per patient.

statistical methods

Response rates with 5-FU plus LV, or with irinotecan as a single agent were approximately 20% in previous clinical trials in patients with advanced colorectal cancer. With a combination of irinotecan, 5-FU, and LV as first-line treatment for advanced colorectal cancer, the response rate was about 40%. We calculated the required sample size for this study on the basis of a target activity level of 40% and a minimum activity level of 20%, with α and β error of 0.1. The required number of patients was estimated to be 36. A stopping rule was included in this study. This trial would have been stopped if there were less than four patients with response among the first 19 patients. Survival was calculated by the Kaplan-Meier method from the date of starting treatment.

results

patients' characteristics

Between April 2004 and February 2005, we enrolled 41 patients with advanced colorectal carcinoma. One patient was excluded from the study because of another active malignancy. The other 40 patients met all eligibility requirements. Their characteristics are shown in Table 1. All eligible patients received at least one course of treatment. Three patients had received prior adjuvant chemotherapy (bolus 5-FU and ℓ-LV in 2, and an oral fluoropyrimidine derivative in (1). Nine patients had primary sites with metastatic lesions at study entry. The median follow-up time was 12 months. The 40 patients had received

Table 1. Patients' characteristics

No. of patients	40
Age, years	
Median	60
Range	23–70
Sex	
Male	27
Female	13
PS (ECOG)	
0	35
1	5
Primary lesions	
Colon	25
Rectum	15
No. of organs involved	
1	13
2	16
≥3	11
Sites of metastasis	
Liver	33
Lung	17
Lymph nodes	13
Primary site	9
Abdominal mass	4
Others	3
Prior therapy	
Surgery for primary lesions	31
Surgery for metastatic lesions	3
Adjuvant chemotherapy	3
Others	1
Mean body surface area (BSA, m^2)	
Mean	1.60
Range	1.39–1.84
No. of patients according to the initial dose of S-1, assigned on the basis of BSA	
40 mg twice daily (<1.25 m^2)	2
50 mg twice daily (≥1.25 to <1.50 m^2)	7
60 mg twice daily (≥1.50 m^2)	31

a total of 327 treatment courses (median, nine courses; range, one to 16+ courses).

response

All 40 patients had at least one measurable lesion. Responses to treatment are shown in Table 2. Five patients had a complete response (CR). Two of these patients had lung metastasis, one had lung and liver metastases, and two had liver and abdominal lymph node metastases. Response was not evaluated in two patients. One patient refused to continue treatment, and another discontinued treatment because of toxicity before the initial evaluation of response. At a median follow-up time of 12 months, the median progression-free survival (PFS) time was 8.0 months (range, 1.4 to 13.8+ months; 95% confidence interval, 5.2 to 11.4 months) (Figure 1). Because there were only seven deaths, the median overall-survival time could not be calculated. Among 25 patients who had complete or partial responses, the median time to response was 1.5 months (range, 1.2 to 4.2 months). The median duration of response was 8.0 months (range, 2.8 to 11.9+ months).

Table 2. Response rates

Response	No. of patients
Complete response	5
Partial response	20
Stable disease	11
Progressive disease	2
Not evaluated	2
Overall response rate: 62.5% (25/40)	
95% confidential interval [%] 47.5–77.5	

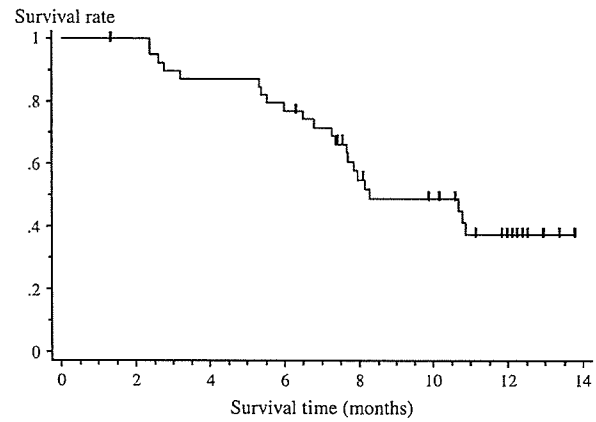

Figure 1. Progression-free survival of 40 patients with previously untreated colorectal cancer who received a combination of S-1 and irinotecan. Median progression-free survival was 8.0 months (95% confidential interval, 5.2 to 11.4 months).

toxicity

A total of 200 treatment courses were administered to the 40 eligible patients to define safety profiles for up to six treatment courses per patient. Toxicity is summarized according to the worst grade per patient in Table 3. There were no treatment-related deaths. The most common type of hematological toxicity was anemia; however, the incidence of grade 3 or 4 anemia was very low. The most common type of non-hematological toxicity was fatigue, which was usually mild. Toxicity is summarized according to the worst grade for the 200 courses of treatment in Table 4. Cumulatively, myelosuppression and gastrointestinal toxicity were most common reactions, but were generally mild. The incidence of grade 3 or 4 toxicity was less than 5% for all events.

Treatment was discontinued because of toxicity in seven of the 40 patients. The reasons for discontinuing treatment were as follows: grade 3 anorexia or nausea, 3 patients; grade 3 diarrhea, one; grade 3 elevation of AST, one; grade 2 cardiac ischemia, one; and refusal to continue treatment because of prolonged mild fatigue and nausea, one. The patient with the grade 3 elevation of AST was confirmed to have severe multiple liver metastasis at study entry. There was no evidence of disease

Table 3. Toxicity in all 40 patients during one to six treatment courses

Toxicity (n = 40)	Grade (NCI-CTC, ver. 3.0)				All grades (%)	Grade ≥3 (%)
	1	2	3	4		
Anemia	28	5	3	0	90	7.5
Leukopenia	13	10	0	0	57.5	0
Neutropenia	5	20	5	1	77.5	15.0
Thrombocytopenia	2	1	1	0	10	2.5
Diarrhea	13	10	3	0	65	7.5
Fatigue	29	5	0	0	85	0
Anorexia	20	7	5	0	80	12.5
Nausea	22	3	1	0	65	2.5
Vomiting	12	0	1	0	32.5	2.5
Stomatitis	21	4	0	0	62.5	0
Febrile neutropenia	4	2	1	0	17.5	2.5
Rash	8	2	0	0	25	0
Ocular diseases	5	1	0	–	15	0
Hand-foot syndrome	6	0	0	–	15	0
Hyperbilirubinemia	16	3	1	0	50	2.5
Elevation of AST/ALT	20	4	2	0	65	5.0

progression, but the patient could not continue treatment because of prolonged liver dysfunction with mild fatigue and anorexia. The patient who had mild cardiac ischemia recovered soon after the withdrawal of treatment. The investigator decided against resuming treatment. All patients received the initial doses of S-1 and irinotecan on day 1 of the first treatment course on an inpatient basis. All subsequent treatment courses were administered on an outpatient basis.

dose intensity

The mean dose intensity of irinotecan was 130 mg/m^2/3 weeks. The mean relative dose intensity of irinotecan was 87%. The dose of irinotecan was reduced according to the study protocol in five of the 40 patients (12.5%). The reasons for reducing the dose of irinotecan were as follows: diarrhea, three patients; anorexia, one; and hyperbilirubinemia, one. The mean relative dose intensity of S-1 was 82%. S-1 had good compliance: 96% of the scheduled dose was administered during one to six treatment courses. The dose of S-1 was reduced according to the study protocol in three of the 40 patients (7.5%). The reasons for dose reduction were as follows: stomatitis, 1 patient; ocular diseases, 1; and anorexia, 1. During one to six treatment courses (a total of 200 courses), treatment was delayed for at least 1 week because of toxicity in 12 of the 40 patients (25%). The incidences of toxic reactions responsible for treatment delays were as follows: neutropenia or leukopenia, 3%; diarrhea, 2%; hyperbilirubinemia, 2%; and other reactions, 4.5%.

discussion

This study assessed the efficacy and safety of combined treatment with S-1 and irinotecan in patients with previously untreated colorectal cancer. Our results showed that S-1 plus irinotecan was very effective, with a response rate of 62.5% and median PFS of 8.0 months. In previous phase III studies of irinotecan with infusional 5-FU and LV, response rates ranged from 31% to 62% [1, 19–22]. Median time to progression (TTP) or PFS was 6.7 to 8.7 months. Although there are limitations in comparing the results of different studies, the response rate and PFS in our study were similar to those reported in previous studies of irinotecan with infusional 5-FU and LV.

Toxicity was generally mild and manageable on an outpatient basis. The most common hematological toxicity was anemia, because the baseline hemoglobin level was grade 1 or less than the lower limit of normal in nearly all patients. Meanwhile, neutropenia was considered the most frequent type of treatment-related hematological toxicity. The most common type of non-hematological toxicity was fatigue, which was not severe but prolonged. The incidences of grade 3 or 4 diarrhea and anorexia were low. However, patients with anorexia had other related toxic reactions, such as diarrhea, dehydration, fatigue, and neutropenia. In patients who had moderate anorexia or diarrhea, treatment with S-1 was temporarily discontinued, or the start of the next treatment course was delayed at least 1 week. Consequently, either neutropenia or leukopenia was the most common reason for delaying subsequent courses of treatment. Neutropenia, diarrhea, nausea, and vomiting frequently occurred in previous studies of combined treatment with irinotecan plus infusional 5-FU and LV [1, 19–22]. Our results suggested that both the incidences and intensities of these toxic reactions with S-1 plus irinotecan were similar to those with a combination of irinotecan plus infusional 5-FU and LV.

Prolonged mild ocular toxicity, including epiphora and blurred vision, was relatively frequent, especially in patients who received long-term treatment. Such toxicity occasionally led to delay of treatment and was most likely caused by 5-FU. The safety database of the manufacturer of S-1 indicates that the incidence of ocular toxicity is less than 5%. Systemic therapy with 5-FU has been reported to cause epiphora due to stenosis and fibrosis of tear ducts [23]. Another study has suggested that epiphora is often reversible on stopping treatment [24]. Subsequent courses of treatment should therefore be delayed and appropriate local therapy administered in patients with ocular toxicity. Unfortunately, one patient in our study underwent surgery of the tear ducts. Patients who have persistent ocular toxicity should therefore be referred to an ophthalmologist.

The mean relative dose intensity of both S-1 and irinotecan in our study exceeded 80%. We calculated the dose intensity of S-1 in a similar manner to S-1 as a single agent. The dose intensity of irinotecan in our study was less than that of irinotecan combined with infusional 5-FU plus LV. In another phase I study of S-1 plus irinotecan, S-1 was administered twice daily for 3 weeks in combination with irinotecan on days 1 and 15 of a 5-week cycle [25]. The recommended dose was 80 mg/m^2 of irinotecan. The dose intensity of irinotecan in a 5-week schedule was very similar to that with our regimen. These findings suggest that the use of higher doses of irinotecan would probably require a lower dose of S-1 to maintain toxicity, especially neutropenia, diarrhea, or prolonged fatigue, within acceptable levels. Overall, compliance with a combination of S-1 and irinotecan was good; in addition, our regimen was more convenient and easier to administer than a combination of

Table 4. Toxicity in all 200 treatment courses during one to six courses

Toxicity (n = 200)	Grade (NCI-CTC, ver. 3.0)				All grades (%)	Grade ≥3 (%)
	1	2	3	4		
Anemia	147	13	5	0	82.5	2.5
Leukopenia	59	13	0	0	36	0
Neutropenia	49	57	8	1	57.5	4.5
Thrombocytopenia	8	2	1	1	6	1.0
Diarrhea	39	13	4	0	28	2.0
Fatigue	88	7	0	0	47.5	0
Anorexia	57	9	5	0	35.5	2.5
Nausea	46	4	1	0	25.5	0.5
Vomiting	12	1	1	0	7	0.5
Stomatitis	42	4	0	0	23	0
Febrile neutropenia	7	2	1	0	5	0.5
Rash	9	2	0	0	5.5	0
Ocular conditions	19	1	0	–	10	0
Hand-foot syndrome	14	0	0	–	7	0
Hyperbilirubinemia	27	3	1	0	15.5	0.5
Elevation of AST/ALT	65	5	2	0	36	1.0

irinotecan plus infusional 5-FU and LV. Our results indicate that most patients can receive S-1 plus irinotecan on an outpatient basis.

Capecitabine is also an oral fluoropyrimidine derivative. Studies of a combination of capecitabine plus irinotecan reported response rates ranging from 47% to 61% and a median PFS or TTP of 6.1 to 8.3 months in patients with colorectal cancer [26–27]. The incidence of grade 3 or 4 diarrhea with capecitabine plus irinotecan was greater than 20% in both studies, clearly higher than that with S-1 plus irinotecan. In addition, the incidence of grade 3 or 4 hand-foot syndrome with capecitabine plus irinotecan was higher than that with S-1 plus irinotecan. Moreover, both irinotecan and capecitabine are metabolized by carboxylesterases in the liver to an active metabolite, SN-38, and to an intermediate metabolite, 5′-deoxy-5-fluoropyrimidine, respectively. The complex metabolism of both capecitabine and irinotecan can thus theoretically lead to pharmacokinetic drug–drug interactions [28]. In contrast, previous phase I trials of our regimen for S-1 and irinotecan showed no change in the plasma concentrations of 5-FU, FBAL, or SN-38 as compared with the concentrations after administration of S-1 or irinotecan alone [17]. A combination of S-1 and irinotecan, may therefore be safer and more convenient than a combination of capecitabine and irinotecan. A combination of oral uracil/tegafur (UFT) and irinotecan has also been found to be well tolerated and active, with a median TTP of 6 months [29]. However, the incidence of grade 3 or 4 neutropenia, which required a reduction in the dose, was 35% at the recommended dose level. Our results suggest that S-1 plus irinotecan may be better tolerated than UFT plus irinotecan. Available evidence thus indicates that a combination of S-1 and irinotecan is better tolerated than combinations of other oral fluoropyrimidines plus irinotecan.

In conclusion, our results suggest that combined treatment with S-1 and irinotecan is a promising regimen, offering benefits in terms of safety and survival as compared with conventional regimens in patients with advanced colorectal cancer. Future studies must objectively confirm that S-1 plus irinotecan can replace a combination of infusional 5-FU and LV plus irinotecan, without negatively affecting efficacy or safety. We firmly believe that further trials comparing S-1 plus irinotecan with a combination of irinotecan plus infusional 5-FU and LV are warranted.

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Phase I/II Study of Oxaliplatin with Weekly Bolus Fluorouracil and High-Dose Leucovorin (ROX) As First-Line Therapy for Patients with Colorectal Cancer

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Background: Infusional fluorouracil (5-FU) and leucovorin (LV) with oxaliplatin is one of the current standard regimens for the treatment of patients with metastatic colorectal cancer. Weekly bolus 5-FU with high-dose LV (Roswell Park Memorial Institute Regimen: RPMI) is the most commonly used regimen in Japan. The objectives of this study were to determine the recommended dose (RD) of RPMI combined with oxaliplatin and to evaluate the toxicity and efficacy at the RD.
Methods: The subjects were 18 patients with metastatic colorectal cancer. Oxaliplatin (85 mg/m^2) was given intravenously over 2 h on days 1 and 15 with *l*-LV (250 mg/m^2) given intravenously over 2 h and 5-FU as an intravenous bolus on days 1, 8, and 15. This treatment was repeated every 4 weeks. The dose of 5-FU was escalated from 400 mg/m^2 (level 1) to 500 mg/m^2 (level 2).
Results: A total of 14 patients received level 1, and 4 received level 2. Three of the patients had dose-limiting toxicity (DLT) in cycle 1 of level 2 (grade 3 thrombocytopenia, grade 4 neutropenia and grade 2 neutropenia in one patient each), requiring that treatment was delayed for longer than 7 days. None of the 14 patients given level 1 had DLT or grade 3 or 4 gastrointestinal toxicity. Sensory neuropathy occurred in all patients. Objective response rates were 61% in the 18 patients studied and 64% at level 1. The median time to progression was 171 days, and the median overall survival time was 603 days in the 18 patients studied.
Conclusions: Oxaliplatin (85 mg/m^2) with weekly bolus 5-FU (400 mg/m^2) and high-dose *l*-LV (250 mg/m^2) is recommended for further phase III studies in patients with metastatic colorectal cancer.

Key words: colorectal cancer – bolus 5-fluorouracil – leucovorin – oxaliplatin – RPMI

INTRODUCTION

Infusional fluorouracil (5-FU) and leucovorin (LV) with oxaliplatin is one of the current standard regimens for first- and second-line chemotherapy in patients with metastatic colorectal cancer (1–3). The combination of oxaliplatin with infusional 5-FU and LV (FOLFOX4) has been shown to be superior to infusional 5-FU plus LV (LV5FU2) and single-agent oxaliplatin in terms of response rate, median time to progression (TTP), and alleviation of tumor-related symptoms in patients with metastatic colorectal cancer who have disease progression after irinotecan with bolus 5-FU plus leucovorin (IFL, Saltz regimen) (2). Objective response rates were 9.9% for FOLFOX4, 1.3% for oxaliplatin alone and 0% for LV5FU2 ($P < 0.0001$). Median TTP was 4.6 months for FOLFOX4, 1.6 months for oxaliplatin and 2.7 months for LV5FU2 ($P < 0.0001$).

FOLFOX4 has also been evaluated as first-line therapy, and a randomized study (N9741) has shown a significantly better response rate, median TTP and median overall survival time (MST) as compared with conventional regimens (3). The response rate in patients given FOLFOX4 (45%) was higher than that in patients given IFL (31%, $P = 0.002$). Moreover, TTP was significantly longer with FOLFOX4 (8.7 months)

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than with IFL (6.9 months; $P = 0.0014$). The MST in patients treated with FOLFOX4 was 19.5 months as compared with only 15.0 months in those treated with IFL ($P = 0.0001$).

Infusional 5-FU regimens were shown by de Gramont (4) to provide a higher response rate with marginal survival benefit as compared with bolus 5-FU regimens. However, infusional 5-FU with LV has the drawbacks of increased inconvenience, cost and morbidity, related to the use of a portable infusion pump and a central venous catheter. Weekly bolus 5-FU with high-dose LV (RPMI regimen) is the most commonly used schedule in Japan and the United States, and bolus 5-FU plus low-dose LV with irinotecan (modified Saltz regimen) has been shown to have high antitumor activity with a favorable toxicity profile in Japanese patients (5–8). Single-agent oxaliplatin (130 mg/m^2) in a tri-weekly regimen has also been found to be effective and tolerable in Japanese as well as Western patients (9). Phase II studies of oxaliplatin as second-line therapy in patients with fluoropyrimidine-pretreated metastatic colorectal cancer reported objective response rates of 9–11% and an MST of 8.2–11.3 months (10–11). However, whether bolus 5-FU plus LV can be combined safely with oxaliplatin in Japanese patients remains unclear.

The primary objectives of this phase I/II study were to estimate the maximal tolerated dose (MTD) and determine the recommended dose of bolus 5-FU plus *l*-LV in combination with oxaliplatin. In the phase II part, we also evaluated the toxicity and antitumor activity of this regimen at the recommended dose.

PATIENTS AND METHODS

PATIENT ELIGIBILITY

Patients with histologically confirmed colorectal cancer who had measurable metastatic disease were eligible for the study. Prior chemotherapy and radiotherapy for metastatic disease were not permitted. Patients who had received adjuvant oral fluorouracil-based therapy were eligible if they had remained free of disease for at least 6 months after the completion of such therapy. Other eligibility criteria included an age of 20–75 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate baseline bone marrow function (white blood cell [WBC] count more than the lower limit of normal at each hospital and <12 000/μl, neutrophil count >2000/μl and platelet count >100 000/μl), hepatic function (serum bilirubin level 1.5 times the upper limit of normal or less, and serum aspartate aminotransferase and alanine aminotransferase 2.5 times the upper limit of normal or less) and renal function (serum creatinine level 1.5 times the upper limit of normal or less); and a life expectancy of at least 12 weeks. All patients gave written informed consent.

Patients were excluded if they had symptomatic brain metastasis; pre-existing watery diarrhea; concomitant nonmalignant disease, such as cardiac, pulmonary, renal or hepatic disease; or uncontrolled infection. This study was approved by the institutional review board of each center. Before enrollment, all patients underwent a physical examination (including documentation of measurable disease), a complete blood cell count with differential count, serum chemical analysis, chest radiography, electrocardiography, and computed tomographic (CT) scanning or magnetic resonance imaging (MRI).

TOXICITY AND RESPONSE CRITERIA

Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI-CTC) (12). Neurotoxicity was reported according to the following grading scale: grade 1, dysesthesia or paresthesia that completely regressed within 6 days; grade 2, dysesthesia or paresthesia persisting for 7 days or longer; and grade 3, dysesthesia or paresthesia causing functional impairment. During the study, all patients were evaluated weekly for signs and symptoms of toxicity. Complete blood cell counts including differential count; liver function tests; measurement of urea nitrogen, creatinine and electrolyte levels; and urinalysis were performed weekly in cycle 1 and every 2 weeks in subsequent cycles.

The response of measurable and assessable disease sites was evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) (13). Tumor dimensions were assessed by CT scanning or MRI every month to confirm response and every 2 months subsequently. Partial response (PR) was defined as more than a 30% decrease in the sum of the products of the greatest perpendicular diameters of measurable lesions, without the development of any new lesions. Stable disease was defined as a steady state of response less than a PR or as progression of <20% over the course of at least 6 weeks. Progressive disease (PD) was defined as an unequivocal increase of at least 20% in the sum of the products of the greatest perpendicular diameters of individual lesions. The appearance of new clinically significant lesions also constituted a PD.

TREATMENT PLAN

Oxaliplatin was supplied as a freeze-dried powder in 100 mg vials by Yakult Honsha Co., Ltd. (Tokyo, Japan) and was reconstituted in a solution of 5% glucose in water. The reconstituted solution was then diluted with 250 ml of 5% glucose infusion solution. Oxaliplatin was administered as a 2 h infusion every 2 weeks. The duration of infusion could be extended to 6 h in patients who had pharyngolaryngeal dysesthesia during infusion. *l*-Leucovorin (Wyeth Ltd., Tokyo, Japan) was administered at a dose of 250 mg/m^2 in 500 ml of 5% glucose solution, given as a 2 h intravenous infusion on days 1, 8 and 15 of a 28 day cycle. 5-FU (Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) was given by bolus intravenous injection 1 h after starting the *l*-LV infusion. All patients received premedication with a 5-hydroxytryptamine-3-receptor antagonist with or without dexamethasone, given as a 30 min drip infusion before chemotherapy. Treatment cycles were repeated every 4 weeks. Treatment was routinely given on an outpatient basis, except for cycle 1 of the dose-escalation portion of the protocol (see below). Subsequent treatment was withheld until the

WBC, neutrophil,and platelet counts were >3000, 1500 and 75 000 μl, respectively, and diarrhea, stomatitis and hand-foot syndrome had resolved to grade 0 or 1. Treatment was repeated until the onset of disease progression or severe toxicity.

Dose-Escalation Schedule

The dose of oxaliplatin was fixed at 85 mg/m^2 and that of *l*-LV was fixed at 250 mg/m^2. 5-FU was studied in dose levels of 400 and 500 mg/m^2. A minimum of three patients were studied per dose level. Dose-limiting toxicity (DLT) was defined as any of the following findings during cycle 1: (i) a neutrophil count of <500/μl, (ii) grade 3 febrile neutropenia, (iii) a platelet count of <50 000/μl, (iv) grade 3 or 4 non-hematologic toxicity, excluding nausea, anorexia, and electrolyte imbalance according to the NCI-CTC, or (v) a longer than 1 week delay in treatment as a result of drug-related toxicity in the dose-escalation portion of the protocol. If DLT occurred in 1 of the first 3 patients assigned to a given dose level, 3 other patients were additionally assigned to receive that dose level. The MTD was defined as the dose that induced DLT during cycle 1 in at least 50% of the subjects. In the second portion of the study, the recommended dose was given to 11 other patients to confirm tolerability.

The dose was modified for each patient according to a nomogram, based on hematologic or non-hematologic toxicity. If DLT occurred, the subsequent dose of oxaliplatin was reduced to 75% of the initial dose and that of 5-FU was decreased by one dose level. If the WBC count on days 8, 15 and 22 was <3000/μl, the neutrophil count <1500/μl, or the platelet count <75 000/μl, further treatment was delayed for up to 1 week until recovery. Recombinant granulocyte colony-stimulating factor was subcutaneously injected if patients had grade 4 neutropenia or grade 3 febrile neutropenia, but prophylactic use was not allowed.

RESULTS

Patient Characteristics

From March 2002 to March 2003, a total of 18 patients were enrolled. All patients received at least one cycle of the study treatment. The first 7 patients participated in the dose-escalation portion of the protocol. After identification of the MTD, 11 other patients received the recommended dose below the MTD to further evaluate the tolerability and toxicity of the study regimen. The patient characteristics are summarized in Table 1. Two patients had received adjuvant oral fluorouracil-based therapy.

Toxicity

No DLT occurred during cycle 1 in the first 3 patients given a dose of 400 mg/m^2 of 5-FU. Two of the 3 patients initially treated with 500 mg/m^2 of 5-FU had dose-limiting myelosuppression. One patient had grade 3 thrombocytopenia, and the other had prolonged grade 2 neutropenia, requiring that

Table 1. Patient characteristics

Characteristic	Level 1 (n = 14)		Level 2 (n = 4)	
	No. of patients	(%)	No. of patients	(%)
Age (years)				
Median	60.0		67.5	
Range	37–68		55–73	
Sex				
Male	8	57	3	75
Female	6	43	1	25
ECOG performance status				
0	12	86	3	75
1	2	14	1	25
Primary tumor				
Colon	9	64	4	100
Rectum	5	36	0	0
Metastatic site*				
Liver only	8	57	2	50
Lung only	2	14	0	0
Others	4	29	2	50
No. of metastatic sites				
1	13	93	3	75
≥2	1	7	1	25

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Target lesion according to RECIST criteria.

Table 2. Toxicity, worst grade per patient

Level	1 (n = 14)					2 (n = 4)				
Dose of 5-FU	400 mg/m^2					500 mg/m^2				
	Grade					Grade				
	1	2	3	4	1–4 (%)	1	2	3	4	
Anorexia	8	6	0	0	100	1	1	1	0	
Nausea	8	3	0	0	79	2	1	0	0	
Vomiting	4	5	0	0	64	3	0	0	0	
Diarrhea	4	3	0	0	50	1	2	0	0	
Stomatitis	3	2	0	0	36	0	0	0	0	
Fatigue	7	1	0	0	57	2	0	0	0	
Injection site reaction	8	3	0	0	79	3	0	0	0	
Allergic reaction	1	1	0	0	14	0	0	0	0	
Sensory neuropathy	0	14	0	–	100	0	4	0	–	
Alopecia	1	0	–	–	7	2	0	–	–	
Neutropenia	5	4	2	0	79	0	2	1	1	
Leukopenia	2	4	0	0	43	0	4	0	0	
Thrombocytopenia	6	4	0	0	71	1	1	2	0	
AST elevation	5	3	0	0	57	2	0	0	0	
ALT elevation	3	6	0	0	64	2	0	0	0	

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Objective response

	No. of patients	PR	SD	PD	Response rate (%) (95% CI)
Level 1 5-FU 400 mg/m^2	14	9	5	0	64 (35–87)
Level 2 5-FU 500 mg/m^2	4	2	2	0	50 (7–93)
All patients	18	11	7	0	61 (36–83)

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval

treatment was delayed for longer than 1 week. The fourth patient given 5-FU 500 mg/m^2 had grade 4 neutropenia. DLT thus comprised neutropenia and thrombocytopenia. The recommended dose was determined to be 400 mg/m^2 of 5-FU in combination with 250 mg/m^2 of *l*-LV and 85 mg/m^2 of oxaliplatin (Table 2).

Eleven patients were subsequently enrolled in the second portion of this study.

Combined with the 3 initially treated patients, a total of 14 patients received the recommended dose. The median number of administered cycles was 5.5 (range, 2–11), and the total number of cycles in the 14 patients was 74. At the recommended dose, 2 patients (14%) had grade 3 neutropenia; there was no grade 4 toxicity. The relative dose intensity was 82.5% for oxaliplatin and 84.9% for 5-FU during the first 6 cycles. The causes of treatment discontinuation at the recommended dose were PD in 8 patients, almost a complete response in 1, delayed recovery from thrombocytopenia in 2 and sensory neuropathy in 3.

Sensory neuropathy occurred in all patients. There was no neurotoxicity with functional impairment in this study. The most common types of non-hematologic toxicity were anorexia, nausea, vomiting and diarrhea. No patient had grade 3 or 4 gastrointestinal toxicity at the recommended dose. Most cases of nausea and vomiting responded to dexamethasone and granisetron or other antiemetic drugs, and good oral intake was maintained. Another mild adverse event related to treatment was injection site reactions (79%). Two patients had mild allergic reactions such as skin rash or fever, typical platinum-related reactions.

Response to Therapy

The objective tumor response was determined by an external review board. Of the 14 patients given the recommended dose (level 1) 9 had a PR, yielding a response rate of 64% (95% CI: 35–87%). One of 9 responders underwent hepatectomy following this chemotherapy. Two of the 4 patients given level 2 had a PR. In the 18 patients studied, the response rate was 61% (95% CI: 36–83%), the median time to progression was 171 days (95% CI: 142–227 days) and the median overall survival time (cut-off date: March 27, 2005) was 603 days (95% CI: 442–979 days) (Fig. 1). The 1-year and 2-year survival rates were 94 and 31%, respectively.

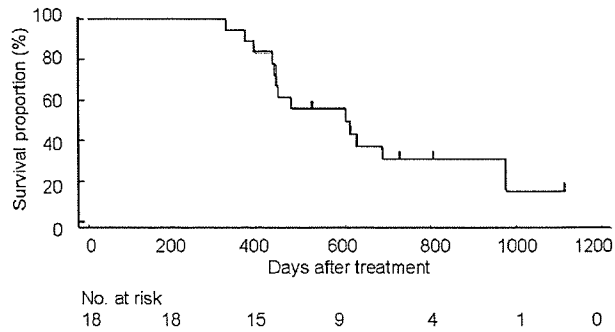

Figure 1. Overall survival in all patients.

DISCUSSION

Our results suggest that bolus 5-FU plus *l*-LV with oxaliplatin may be a safe and effective first-line treatment for metastatic colorectal cancer. The recommended dose was determined to be 400 mg/m^2 of 5-FU plus 250 mg/m^2 of *l*-LV on days 1, 8 and 15 with 85 mg/m^2 of oxaliplatin on days 1 and 15 of a 28 day cycle. DLT comprised neutropenia and thrombocytopenia at level 2. At the recommended dose (level 1), the toxicity profile was acceptable, with grade 3 neutropenia occurring in 14% of the patients; there was no other grade 3 or 4 hematologic or non-hematologic toxicity, including neurotoxicity (table3).

Two consecutive compassionate-use studies of oxaliplatin were conducted in North America until December 2000 in more than 5000 patients with metastatic colorectal cancer who had had treatment failure with at least 1 prior chemotherapy regimen (14). Patients were assigned to treatment with either single-agent oxaliplatin or oxaliplatin plus 5-FU with or without LV in various regimens. The most frequently used regimen was RPMI with oxaliplatin, received by 43–45% of the patients in both studies. Continuous infusion of low-dose 5-FU (Lokich regimen) was given to 14–20% of the patients, a modified Mayo regimen to 9–15% and LV5FU2 to only 8–10%. US and Canadian oncologists have preferred bolus regimens in combination with oxaliplatin, despite the availability of infusion schedules. The incidence of grade 3 and 4 hematologic toxicity was 17% with RPMI plus oxaliplatin and 52% with FOLFOX4 and that of grade 3 and 4 gastrointestinal toxicity was 28% with RPMI and 18% with FOLFOX4. Neurological toxicity occurred at a rate of 2% with RPMI and 8% with FOLFOX4.

Hochster et al. (15) reported the results of phase II studies of weekly bolus 5-FU (500 mg/m^2, days 1, 8 and 15, every 4 weeks) plus low-dose LV (20 mg/m^2, days 1, 8 and 15, every 4 weeks) with oxaliplatin (85 mg/m^2, days 1 and 15, every 4 weeks) (bFOL), given as first-line therapy to patients with metastatic colorectal cancer. The response rate was 63%, with a median TTP of 9.0 months and an MST of 15.9 months. Common toxicity included grade 3 and 4 neutropenia in 10% of patients, grade 3 and 4 diarrhea in 29%, and grade 3 cumulative neuropathy in 12%. Welles et al. (16) reported the results of a randomized phase II study assessing the safety and tolerability of 3 oxaliplatin-based regimens as first-line

treatment for advanced colorectal cancer ('TREE 1' study). One arm was bFOL; the other 2 arms were modified FOLFOX6 (oxaliplatin 85 mg/m^2, LV 350 mg, 5-FU bolus 400 mg/m^2 and infusional 2400 mg/m^2 over the course of 46 h, every 2 weeks) and CapeOx (oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1000 mg/m^2 twice daily for 14 days, every 3 weeks). The primary endpoint was the overall incidence of grade 3 and 4 toxicity during the first 12 weeks of each study therapy, and secondary endpoints were overall response rate and TTP. The overall incidence of grade 3 and 4 toxicity was significantly higher with modified FOLFOX6 (mFOLFOX6) (77%) than with bFOL (44%, $P < 0.001$). Moreover, mFOLFOX6 (37%) had a significantly higher incidence of grade 3 and 4 neutropenia than bFOL (14%, $P < 0.01$) and CapeOx (8%) ($P < 0.001$). Grade 3 and 4 diarrhea occurred in similar proportions of patients given bFOL (22%), mFOLFOX6 (22%) or CapeOx (25%). The overall response rate did not significantly differ among the 3 arms and was 52% (21/40) with mFOLFOX6, 38% (14/37) with bFOL and 50% (17/34) with CapeOx. Median times to discontinuation of study therapy were 5.7 months with mFOLFOX6, 4.8 months with bFOL and 4.2 months with CapeOx. These results suggested that bFOL is as active and safe as the other two regimens.

Other schedules of bolus 5-FU and low-dose LV (Mayo Clinic regimen) with oxaliplatin have also been investigated. Zori Comba et al. (17) reported the results of a phase II study of the Mayo Clinic regimen (5-FU 425 mg/m^2, days 1–5, every 4 weeks) plus low-dose LV (20 mg/m^2, days 1 to 5, every 4 weeks) with oxaliplatin (85 mg/m^2, days 1 and 15, every 4 weeks) in previously untreated patients with metastatic colorectal cancer. The response rate was 45%, with a median TTP of 3.9 months. Grade 3 and 4 neutropenia occurred in 23% of the patients, diarrhea in 34%, vomiting in 14% and stomatitis in 14%. This regimen was unacceptable because of the high incidence of severe toxicity. Ravaioli et al. (18) used the Machover scheme (5-FU 350 mg/m^2, days 1–5, every 3 weeks) and low-dose LV (20 mg/m^2, days 1–5, every 3 weeks) with oxaliplatin (130 mg/m^2, day 1, every 3 weeks) as first-line treatment for metastatic colorectal cancer. The response rate was 40%, with a median TTP of 5.9 months and an MST of 14 months. Grade 3 or severer neutropenia or diarrhea occurred in 20 and 29% of the patients, respectively. Sørbye et al. (19) performed a phase II study of Nordic bolus 5-FU (500 mg/m^2, days 1 and 2, every 2 weeks) and low-dose LV (60 mg/m^2, days 1 and 2, every 2 weeks) with oxaliplatin (85 mg/m^2, day 1, every 2 weeks) (Nordic FLOX), given as first-line therapy to patients with metastatic colorectal cancer. The response rate was 62% with a median TTP of 7.0 months and an MST of 16.1 months. Common toxicity included grade 3 and 4 neutropenia in 58% of patients, grade 3 and 4 diarrhea in 7%, and grade 3 cumulative neuropathy in 13%. Febrile neutropenia developed in 8%. That study concluded that Nordic FLOX is an effective and feasible regimen, despite the high incidence of neutropenia.

In our study, the most frequent types of non-hematologic toxicity were mild anorexia, nausea, vomiting, fatigue and diarrhea. Grade 3 neutropenia occurred in only 14% of our patients at the recommended dose. Our regimen was active and safe and may thus be a new alternative treatment for metastatic colorectal cancer. Further clinical phase II/III studies should compare RPMI plus oxaliplatin with FOLFOX to more objectively confirm our findings before our regimen is widely used clinically.

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Adjuvant Chemotherapy with Uracil–Tegafur for Pathological Stage III Rectal Cancer after Mesorectal Excision with Selective Lateral Pelvic Lymphadenectomy: A Multicenter Randomized Controlled Trial*

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Background: Although adjuvant radiotherapy was proved to be effective for local control of rectal cancer even after standardized mesorectal excision, the role of adjuvant chemotherapy after such standardized surgery remains to be clarified. We aimed to assess the efficacy of a combination of uracil and tegafur for pathological stage III rectal cancer treated by standardized mesorectal excision with selective lateral pelvic lymphadenectomy.
Methods: We randomly assigned patients with completely resected stage III rectal cancer, who underwent standardized mesorectal excision with selective lateral pelvic lymphadenectomy, to receive either oral uracil–tegafur (400 mg/m^2 tegafur per day) for one year or no treatment. Standardization and quality control of the surgery and pathological techniques were ensured by use of the guidelines of the Japanese Society for Cancer of the Colon and Rectum. The primary endpoint was relapse-free survival. The secondary endpoint was overall survival.
Results: We enrolled and randomized 276 patients. Excluding two ineligible patients, 274 were included in the analysis. Planned interim analysis 2 years after accrual termination revealed significant prolongation of relapse-free survival ($P = 0.001$) and overall survival ($P = 0.005$) in the uracil–tegafur group. The 3-year relapse-free survival and overall survival rates were 78 and 91% in the chemotherapy group and 60 and 81% in the surgery-alone group, respectively. Local recurrence rates were low in both groups. Grade 3 events occurred in 17% of the chemotherapy patients, but no grade 4 or more events occurred.
Conclusion: Adjuvant chemotherapy with uracil–tegafur improves survival of patients with stage III rectal cancer after standardized mesorectal excision with selective lateral pelvic lymphadenectomy.

Key words: adjuvant chemotherapy – uracil–tegafur – rectal cancer – surgery

INTRODUCTION

The quality of surgical procedures has prognostic significance for local control and survival in rectal cancer (1,2). However, the lack of standardization for surgery and limitations of surgical information in previous adjuvant trials is well documented (3). The Dutch Colorectal Cancer Group was the first to adopt standardized mesorectal excision (4,5) in a rectal cancer adjuvant study (6). Mesorectal excision involves complete resection of the mesorectum by precise, sharp dissection under direct visualization (4,5) and is recommended in the Guidelines 2000 for Colon and Rectal Cancer Surgery (5).

The Dutch group clearly showed that preoperative radiotherapy is effective for local control even when standardized mesorectal excision is performed (6). Previous studies evaluating adjuvant radiotherapy, but not using standardized surgery, also showed its advantages in local control and

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survival (7,8). Therefore adjuvant radiotherapy has been recommended as the standard treatment. However, this approach was challenged by the results of a randomized trial which revealed no additional survival benefit from radiotherapy when chemotherapy was administered (9). Furthermore, radiotherapy entails risks of morbidity and mortality (6,7,10–12).

We started the National Surgical Adjuvant Study of Colorectal Cancer 01 randomized trial at the same time as the Dutch trial started (6). The aim of our trial was to evaluate the efficacy of postoperative adjuvant chemotherapy with a combination of uracil and tegafur (a prodrug of fluorouracil) taken orally after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in stage III rectal cancer. Selective lateral pelvic lymphadenectomy is defined as selective application of extended lateral pelvic lymph node dissection, to resect the iliac and obturator lymph nodes when lateral pelvic lymph node involvement is clinically suspected (5,13–15).

We adopted mesorectal excision with selective lateral pelvic lymphadenectomy alone as the control treatment because it was the standard for stage III rectal cancer in Japan (13–15). We did not choose adjuvant radiotherapy because, in addition to the reasons mentioned above, local recurrence rate after mesorectal excision with selective lateral pelvic lymphadenectomy in Japan had been 7–15% in high-volume centers (14,15). Instead, we used oral uracil–tegafur, which was reported to be effective as adjuvant therapy for lung cancer in recent studies (16), because previous studies suggested efficacy of uracil–tegafur for prolonging disease-free survival in rectal cancer (17,18). Bolus fluorouracil and folinic acid, the present world standard for stage III colon cancer, was not used, because folinic acid was not approved in Japan until 1999. We present the results of the planned interim analysis at a median follow-up of 3 years.

METHODS

Patients and Study Design

Enrollment began in October 1996. Eligible patients had undergone a microscopically verified complete resection of pathological stage III adenocarcinoma of the rectum according to the 1992 Tumour Node Metastasis (TNM) Classification of Malignant Tumours (International Union Against Cancer) (19), by standardized mesorectal excision with selective lateral pelvic lymphadenectomy. Other inclusion criteria were the center of the tumor being located between the levels of the first sacral bone and the anal canal; an age of 20–75 years; the absence of preoperative anticancer treatment, previous cancer and synchronous multiple cancers; an Eastern Cooperative Oncology Group performance status of 0, 1 or 2; a leukocyte count of at least 4000/mm^3; a platelet count of at least 100 000/mm^3; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; a serum total bilirubin level of at most 1.2 mg/dl; a blood urea nitrogen level of at most 25 mg/dl; a serum creatinine level of at most 1.5 mg/dl; normal electrocardiogram; and an absence of severe postoperative complications uncontrolled by the time of registration.

An open-label study design was used. After written informed consent had been obtained, we randomly assigned the patients to postoperative adjuvant treatment with uracil–tegafur or to surgery alone. Randomization was performed by telephone or fax at the central trial office within 42 days after operation. Patients were allocated by the minimization method with Zelen's adjustment for inter-institutional imbalance. The factors used for balancing were the site of the primary tumor (above versus below the rectovesical fossa or rectouterine fossa), primary tumor stage (pT1 or pT2 versus pT3 or pT4) and N stage (pN1 or pN2 versus pN3). The primary endpoint was relapse-free survival and the secondary endpoint was overall survival. The trial was approved by the institutional review board of each participating center.

TREATMENT

Quality Control for Surgery and Pathology

All of the 28 participating centers are the high-volume centers which treated more than 100 colorectal cancer patients per year and institutional members of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (13). The JSCCR has held a general assembly and sessions intended to improve treatment of colorectal cancer twice every year, and has standardized treatment. The JSCCR has provided guidelines for standardized surgical treatment and pathological evaluation (13). All procedures and pathological evaluations were in accordance with the fifth edition of the guidelines published in 1994 (13).

Mesorectal excision was the baseline procedure for all patients. The definitions of the mesorectum and mesorectal excision were the same as those from the Guidelines 2000 (5,13–15). In addition, extended lateral pelvic lymph node dissection (5,13–15) was performed in cases with clinically suspected lateral lymph node disease, as recommended by the JSCCR guidelines (13–15).

The quality of surgery was monitored by the surgeon's report on the location and clinical stage; extent of the resection of the bowel; mesorectum; and lymph nodes, and the pathologist's documentation of the pathological stage; number of resected and positive lymph nodes in each lymph node group; extent of bowel resection; and anal, oral and radial margin status (13).

Adjuvant Chemotherapy

In the treatment group, uracil–tegafur (UFT®, Taiho Pharmaceutical Co., Tokyo, Japan; 400 mg/m^2 tegafur per day) in the form of 100 mg units (100 mg of tegafur plus

224 mg of uracil) was given orally twice daily for 5 consecutive days every weekday for 1 year, starting 6 weeks postoperatively. The dose was rounded up or down to the nearest 100 mg. All patients but one received 3 units of uracil–tegafur (300 mg of tegafur and 672 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the units as prescribed.

Adverse events were graded according to the toxicity grading criteria of the Japan Clinical Oncology Group, which consist of the Common Toxicity Criteria of the National Cancer Institute with minor modifications (20). Grades range from 0 (none) to 5 (fatal) (20). If a moderate (grade 2) adverse event occurred, the dose of uracil–tegafur was reduced to 250 mg/m^2 per day of tegafur. Treatment was stopped if, despite dose reduction, there was anything of the following: a grade 2 or higher adverse event, a leukocyte count of <3000/mm^3, an aspartate aminotransferase or alanine aminotransferase level of more than 2.6 times the upper limit of the normal range, a total bilirubin level of more than two times the upper limit of the normal range, moderate or severe anorexia, one or more vomitings per day or four or more bowel movements per day.

Follow-up

All the patients were evaluated every 4 months for the first 2 years after surgery and every 6 months for the next 3 years. The evaluation included a physical examination, a complete blood count, blood chemical tests, serum tumor markers, chest roentgenography, and abdominal ultrasonography or computed tomography. A pelvic computed tomography was performed every 6 months. In addition, patients receiving uracil–tegafur had a physical examination, a complete blood count and blood chemical tests every month during the first year.

Statistical Analysis

The sample size was calculated by the method of Schoenfeld and Richter. The study was designed to detect a hazard ratio for relapse or death of 0.67 in the uracil–tegafur group compared with the control group with 80% power at a two-sided α-level of 0.05. Assuming a 5-year relapse-free survival rate of 50% in the surgery-alone group, a 2-year accrual period and a 5-year follow-up, the targeted sample size was 400. In April 2000, the accrual period was extended to 5 years based on the actual accrual rate.

Interim analysis was planned 2 years after accrual termination. Early termination would be considered at the time of the interim analysis if the one-sided P-value of the log-rank test for the primary endpoint was below 0.005, according to the Lan-DeMets spending function method.

Relapse-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, or death from any cause, and overall survival was defined as the time from surgery until death from any cause. All comparisons between the treatment groups were made on the intention-to-treat principle. Survival curves were estimated by the Kaplan–Meier method, and differences in survival were evaluated with the log-rank test.

RESULTS

Accrual and Interim Analysis

From October 1996 to April 2001, 276 patients were enrolled and randomly assigned to one of the two treatment groups (Fig. 1). The study group decided to stop recruitment in April 2001, because a rapid, further enrollment could not be expected and evaluation of the treatment would be possible through a meta-analysis including the data obtained from this study and existing data (17,18,21). Planned interim analysis was conducted by the data and safety monitoring committee on 13 December 2003. Sufficient results favoring the treatment arm caused the committee to recommend a prompt disclosure of the results. This report is based on the results presented to the data and safety monitoring committee.

Patient Population

Of the 276 enrolled patients 2 (one in each group) proved to be ineligible so that data from 274 patients (139 in the uracil–tegafur group and 135 in the surgery-alone group) were included in the analysis (Fig. 1). The characteristics of the patients are shown in Table 1 and were well balanced in the two groups.

Quality of Surgery

The quality of the surgical procedures (Table 2) was similar in both groups. All patients underwent at least mesorectal excision. Extended lateral pelvic lymph node dissection was added in 38% of the patients, most of whom had a tumor

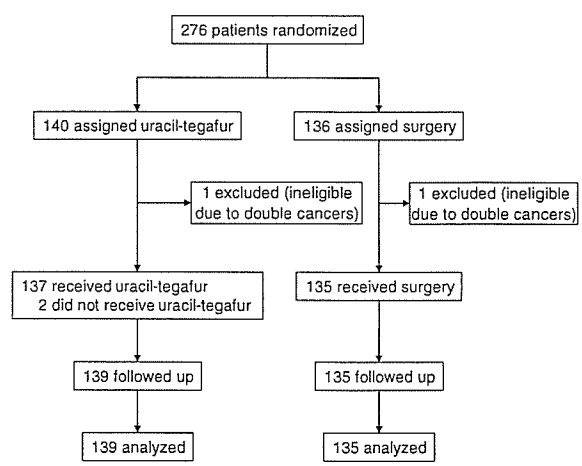

Figure 1. Study profile.

Table 1. Characteristics of the patients

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Age (years, mean [range])	58 (32–75)	57 (30–75)
Sex		
Female	56	53
Male	83	82
Location of the center of the tumor		
Below the promontrium	43	39
Below the lower edge of the second sacral bone	39	43
Below the rectouterine fossa or rectovesical fossa	57	53
Pathological tumor stage*		
T1	8	11
T2	21	16
T3	94	90
T4	16	18
Pathological nodal stage*		
N1	88	89
N2	22	22
N3	29	24
Positive lateral pelvic lymph node	11	7
Type of resection		
Anterior resection	113	109
Hartmann operation	1	0
Abdominoperineal resection	24	25
Other	1	1

*The 1997 TNM Classification of malignant tumors (International Union Against Cancer).

Table 2. Quality of surgery

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Lymph node dissection		
Mesorectal excision	89	81
Mesorectal excision plus extended lateral pelvic lymphadenectomy	50	54
Distal margin of the mesorectum		
2–4 cm	7	2
≥4 cm or total mesorectal excision	132	133
Distal margin of the bowel (cm)		
Median (range)	3 (0.3–10.5)	3.5 (0.5–8)
Number of resected lymph nodes		
Median (range)	21 (1–80)	20 (2–108)

locating below the rectovesical fossa or rectouterine fossa. Distal margins of the mesorectum and rectum were sufficient in both groups. Anal, oral and radial margins were microscopically negative in all the patients. More than 12 lymph nodes were resected in 80% of the patients. The rate of positive lateral pelvic lymph node metastasis was 17% (18/104) in the patients who underwent extended lateral pelvic lymph node dissection.

Table 3. Adverse events

Adverse event	Uracil–tegafur Grade of Toxicity*			Surgery alone Grade of Toxicity*		
	2	3	4	2	3	4
	% of patients					
Leukopenia	5	0	0	1	0	0
Thrombocytopenia	1	0	0	0	0	0
Anemia	4	0	0	2	0	0
Increase in bilirubin	51	9	0	17	2	0
Increase in aspartate aminotransferase	4	2	0	2	0	0
Increase in alanine aminotransferase	10	3	0	6	1	0
Anorexia	7	1	0	1	1	0
Nausea or vomiting	3	1	0	1	1	0
Diarrhea	5	1	0	1	1	1
Skin eruption	6	1	0	0	0	0
Alopecia	0	0	0	0	0	0

*Adverse events were graded according to the toxicity criteria of the Japan Clinical Oncology Group, which consists of the Common Toxicity Criteria of the National Cancer Institute with minor modifications. Grades range from 0 (none) to 5 (fatal).

Adverse Events and Compliance

Of the 139 patients assigned to the uracil–tegafur group, 137 actually took uracil–tegafur and two withdrew from the trial before drug administration (Fig. 1). Moderate (grade 2) and severe (grade 3) events were observed in 65 and 17% of the patients in the uracil–tegafur group and in 39 and 4% of the patients in the surgery-alone group, respectively. Observed adverse events are listed in Table 3. A life-threatening (grade 4) event occurred only in one patient in the surgery-alone group. There was no fatal event.

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence and those who died. The rate of compliance, with or without dose reduction, was 93% at 3 months, 88% at 6 months, 83% at 9 months and 80% at 12 months. The reasons for discontinuation of uracil–tegafur were a cancer recurrence (18 patients), an adverse event (8 patients), patient withdrawal due to adverse events (10 patients) and patient withdrawal due to other causes (4 patients).

Relapse-free Survival

The median follow-up among surviving patients was 3.0 years. At the last follow-up, 32 patients in the uracil–tegafur group

and 53 in the surgery-alone group had recurrence or had died (Table 4). The 3-year estimate of relapse-free survival for the uracil–tegafur group was 78% (95% CI 71–86%). That for the surgery-alone group was 60% (95% CI 51–69%) (Fig. 2). Patients receiving uracil–tegafur had significantly better relapse-free survival than those undergoing surgery alone ($P = 0.0014$). The hazard ratio for any recurrence in the uracil–tegafur group as compared with the surgery-alone group was 0. 52 (95% CI 0. 33–0. 81).

Overall Survival

At the last follow-up, 12 patients in the uracil–tegafur group and 27 in the surgery-alone group had died. The 3-year estimate of overall survival for the uracil–tegafur group was 91% (95% CI 86–97%). That for the surgery-alone group was 81% (95% CI 73–88%) (Fig. 2). Thus patients with uracil–tegafur

Table 4. Pattern of the first recurrence

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Local alone	6 (4%)	9 (7%)
Anastomotic recurrence	3	4
Pelvic recurrence	3	5
Distant alone	23 (17%)	39 (29%)
Liver metastasis	11	21
Lung metastasis	7	15
Liver and lung metastases	1	0
Others	4	3
Local plus distant recurrences	2	4
Death from other diseases	1	1
Overall events	32 (23%)	53 (39%)

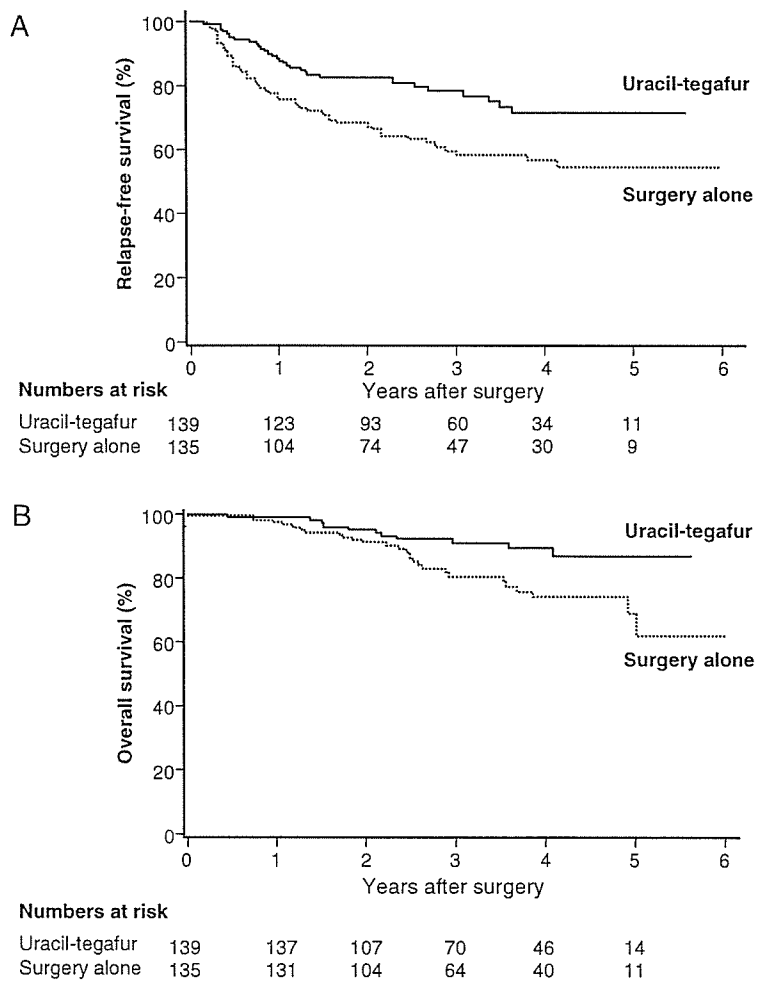

Figure 2. (A) Kaplan–Meier estimates of relapse-free survival. (B) Kaplan–Meier Estimates of overall Survival. At 3 years, the rate of relapse-free survival was 78% in the uracil–tegafur group and 60% in the surgery-alone group ($P = 0.0014$). The rate of overall survival was 91% in the uracil–tegafur group and 81% in the surgery-alone group ($P = 0.0048$).

had significantly better overall survival than those with surgery alone ($P = 0.0048$). The hazard ratio for death in the uracil–tegafur group compared with the control group was 0.42 (95% CI 0. 21–0.83).

Pattern of Recurrence

Details of the pattern of first recurrence are shown in Table 4. At the last follow-up, the rates of overall local recurrence were 5.8% (8/139) for the uracil–tegafur group and 9.6% (13/135) for the surgery-alone group. Adjuvant uracil–tegafur reduced the rates of distant metastases. The rates of overall distant metastases were 18% (25/139) for the uracil–tegafur group and 32% (43/135) for the surgery-alone group. Liver and/or lung metastases composed the majority of distant metastases in both treatment groups.

DISCUSSION

This trial demonstrated the efficacy of postoperative adjuvant chemotherapy with uracil–tegafur after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in pathological stage III rectal cancer. At the planned interim analysis, we found that the 3-year estimate of both relapse-free survival (78%) and overall survival (91%) of the uracil–tegafur group were significantly better than the surgery-alone group (60 and 81%, respectively). The data and safety monitoring committee concluded that the results confirmed the findings of previous studies (17,18) and a recent meta-analysis (21) which showed the effectiveness of uracil–tegafur for rectal cancer.

Rates of local recurrence have been reported to be 20–36% in series of non-standardized, conventional surgery for stage III rectal cancer, with a follow-up of 5 years (3,7,8). For experienced surgeons in mesorectal excision, however, they are 7.5–12% (22,23). At a median follow-up of 3 years, the local recurrence rate was 9.6% in the surgery-alone group of our trial. Although comparisons of such figures should be interpreted cautiously, this shows that a standardized mesorectal excision with selective lateral pelvic lymphadenectomy may achieve good results even in a multicenter setting. Moreover, it may possibly be better than the 2-year local recurrence rate of 8.2% in the mesorectal-excision-alone group of the Dutch trial (6), considering that 56% of patients of the Dutch trial had stage 0–II tumors (6).

Lateral pelvic lymph node metastases from rectal cancer occur outside the mesorectum and appear to account for a major cause of local recurrence. The incidence of lateral pelvic lymph node metastases was reported to be 9–14% (14,15). If the patients have such metastases and undergo only mesorectal excision, the patients have apparent residual tumor in case of recognizable metastases or develop local recurrence after seemingly curative surgery in unrecognizable metastasis cases. Extended lateral pelvic lymph node dissection is a surgical procedure to resect such macroscopic or microscopic metastases (5,14,15). Therefore, this procedure potentially has a similar local-control effect to adjuvant radiotherapy. Whether lateral dissection can be an alternative to radiotherapy should be tested in a randomized controlled trial assessing local control, survival, mortality and morbidity. To conduct such trials, accuracy for detection of lateral pelvic metastases may be a problem. Indeed, in our trial, only 17% of the patients who underwent lateral dissection actually had lateral metastases. To avoid such over-treatment, an accurate diagnostic modality detecting metastasis is necessary.

Between 1990 and 1994, the JSCCR registered 25 224 patients with colorectal cancer. (24) Among them, 2789 patients had curative resection of stage III rectal cancer and their 3-year overall survival rate was 75% (24). In the surgery-alone group of our trial, the 3-year overall survival was 81%. Introduction of revised guidelines, standardized surgical procedures assured by precise documentation and participation of colorectal specialists from high-volume centers may have contributed to this improvement. Quality of surgery is already known as an independent prognostic factor for survival in rectal cancer (1,2), and case volume per surgeon also influences the outcome (3,25).

However, the quality of surgery has no influence on the initial occurrence of distant metastases (1). Even when better-quality surgery reduces local recurrence, occult distant metastases necessitate further treatment to improve survival. We found that, in addition to the efficacy of mesorectal excision with selective lateral pelvic lymphadenectomy, uracil–tegafur further decreased the rate of local recurrence from 9.6 to 5.8%. The rate of distant metastasis was almost halved from 32 to 18%, including a substantial reduction in the rates of liver and lung metastases. Uracil–tegafur appears to improve survival mainly through reduction of distant metastases when applied along with such operations.

The recent meta-analysis assessing randomized controlled trials using oral fluorouracil-based adjuvant chemotherapy for stage I–III colorectal cancer revealed that 1-year chemotherapy reduced the risk of death by 11% ($P = 0.04$) and the risk of recurrence or death by 15% ($P < 0.001$) as compared with surgery alone (21). However, of the three previous randomized trials that compared uracil–tegafur adjuvant therapy with surgery alone in rectal cancer, two revealed significantly improved relapse-free survivals, but none demonstrated an advantage in overall survival (17,18). In these trials, eligible stages were I–III, the dosage of tegafur was 400 mg per day, the compliance was 48–70% and local recurrence rates in surgery-alone group were 19–34% (17,18,21). The significantly better relapse-free and overall survivals in our uracil–tegafur group may be attributable to a selection of stage III patients, a higher dosage of 600 mg per day, better compliance and better quality of surgery. In the meta-analysis, hazard reduction was more marked in early-stage disease (21). In contrast, our results show that a higher dosage may also be effective for advanced-stage disease.

We found that 1-year treatment with uracil–tegafur was safe and well tolerated. Grade 3 events occurred in 16.5% of the patients and consisted mainly of increases in bilirubin

and aminotransferases. No grade 4 or grade 5 events were observed. Previous colon cancer adjuvant trials showed that the overall incidences of grade 3 or more events in patients treated with different regimens were 38% or more for fluorouracil plus folinic acid (26,27), 38% for uracil–tegafur plus folinic acid (27), 30% for capecitabine (26) and more than 41% for oxaliplatin with fluorouracil plus folinic acid (28). The most frequent events included neutropenia, diarrhea, vomiting and hand-foot syndrome. Therefore, the safety profile of uracil–tegafur compares favorably with those of the previous regimens. Consequently, 80% of our patients completed 1 year of treatment, including dose modification. A study using a therapy preference questionnaire demonstrated that, after having experienced both oral and intravenous fluorouracil regimens, most patients preferred an oral regimen (29). The most important reasons for their preference included the convenience of taking the medication at home, less stomatitis and diarrhea, and preference of pills over injections (29). In addition, we should mention that uracil–tegafur is less expensive than the other regimens in this country, where medical costs are becoming an increasingly important issue.

Thus the most significant findings of our trial can be summarized as follows. Peroral monotherapy using uracil–tegafur achieved survival prolongation of stage III rectal cancer patients, without an addition of any other active agents, including folinic acid. This makes it possible to provide less toxic, yet effective, and convenient adjuvant chemotherapy for such patients.

However, several issues may limit the wider applicability of our findings. The numbers of patients recruited were smaller than those of recent rectal cancer adjuvant trials (6,7), although our trial was aimed solely at stage III tumor. The median follow-up time of our study was only 3 years, though disease-free survival with 3-year follow-up is suggested to be an appropriate primary endpoint to replace overall survival with 5-year follow-up (30). We used mesorectal excision with selective lateral pelvic lymphadenectomy that is a standard treatment only in Japan, and did not use mesorectal excision with radiotherapy, a world-standard combination. We could not use fluorouracil plus folinic acid, a standard adjuvant chemotherapy for stage III colon cancer, and neither the recently reported effective regimens including capecitabine and oxaliplatin (26–28). While the standard adjuvant chemotherapy course for colorectal cancer is 6 months (26–28), we opted for chemotherapy of 1 year. Therefore, the appropriateness of our approach should be tested further through comparison with recent standard adjuvant radiotherapy and chemotherapy.

In conclusion, radiotherapy has been considered to be standard adjuvant therapy worldwide for stage III rectal cancer. The present study indicates that uracil–tegafur treatment improves relapse-free survival and overall survival after mesorectal excision with selective lateral pelvic lymphadenectomy. This approach may become one of the treatment options for stage III rectal cancer and may deserve comparison with other treatment approaches.

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