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Clinical Trial Results

Administration Method of Adjuvant Tegafur-Uracil and Leucovorin Calcium in Patients with Resected Colorectal Cancer: A Phase III Study

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Key Words. Colorectal cancer • Phase III • Tegafur-uracil • Leucovorin calcium

Trial Information

- **ClinicalTrials.gov Identifier**: UMIN000005594
- **Sponsor**: Clinical Study Group of the Osaka University Colorectal Group (CSGOCG)
- **Principal Investigator**: Taishi Hata
- **IRB Approved**: Yes

Lessons Learned

- The 3-year disease-free survival rate of the twice-daily regimen was not inferior to that of the conventional three-times-daily regimen, and the twice-daily regimen did not lead to an increase in adverse events.
- The effectiveness of the twice-daily regimen highlights an increased number of treatment options for patients. This will facilitate personalized medicine, particularly for elderly or frail patients who may experience more severe side effects from the combination therapy.

Abstract

Background. Tegafur-uracil (UFT)/leucovorin calcium (LV) is an adjuvant chemotherapy treatment for colorectal cancer. We conducted a multicenter randomized trial to assess the noninferiority of a twice-daily compared with a three-times-daily UFT/LV regimen for stage II/III colorectal cancer in an adjuvant setting.

Methods. Patients were randomly assigned to group A (three doses of UFT [300 mg/m^2 per day]/LV [75 mg per day]) or B (two doses of UFT [300 mg/m^2 per day]/LV [50 mg per day]). The primary endpoint was 3-year disease-free survival.

Results. In total, 386 patients were enrolled between July 28, 2011, and September 27, 2013. The 3-year disease-free survival rates of group A (n = 194) and B (n = 192) were 79.4% and 81.4% (95% confidence interval, 72.6–84.4–74.5–85.9), respectively. The most common grade 3/4 adverse events in group A and B were diarrhea (3.9% vs. 7.3%), neutropenia (2.9% vs. 1.6%), increase in aspartate aminotransferase (4.0% vs. 3.9%), increase in alanine aminotransferase (6.2% vs. 6.8%), nausea (1.7% vs. 3.4%), and fatigue (1.1% vs. 2.3%).

Conclusion. Group B outcomes were not inferior to group A outcomes, and adverse events did not increase. ***The Oncologist*** 2021;26:e735–e741

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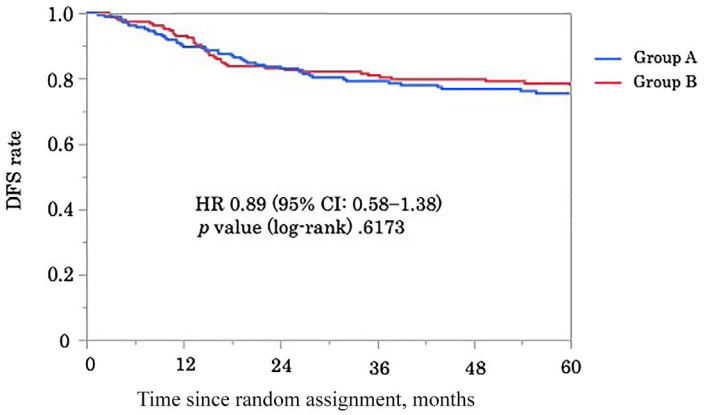
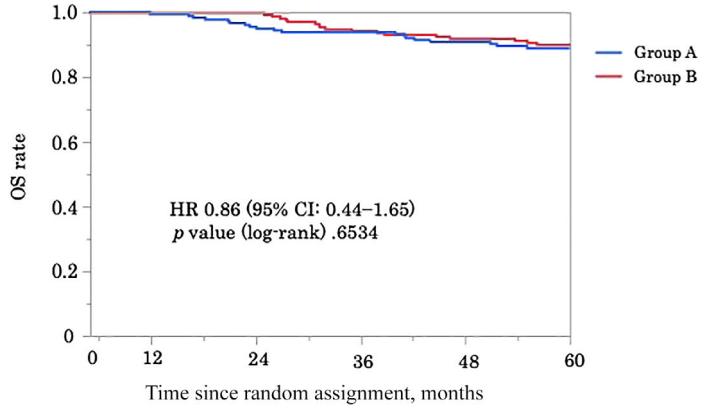


Number at risk						
Group A	185	165	149	139	124	95
Group B	188	171	149	141	131	103

Figure 1. Kaplan-Meier estimates of probability of disease-free survival as measured since the date of random assignment. Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio.



Number at risk						
Group A	185	183	170	164	148	115
Group B	188	184	180	167	154	123

Figure 2. Kaplan-Meier estimates of the probability of overall survival as measured since the date of random assignment. Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Discussion

Studies assessing the effectiveness of adjuvant chemotherapy after colon cancer surgery from the 1980s to the 1990s have demonstrated with stage III colon cancer [1]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-06 trial5 was initiated in 1997. A phase III study of patients with stage II or III colon cancer was conducted with the objective of verifying the noninferiority of UFT/LV therapy to fluorouracil/LV therapy (the Roswell Park Memorial Institute [RPMI] method) and proved [2]. Conventional three-times-daily oral administration of UFT/LV therapy is indicated (approximately every 8 hours), avoiding 1 hour before and after meals. This method of administration is cumbersome, so this study was conducted with the aim of investigating the noninferiority of a twice-daily regimen of UFT/LV therapy relative to that of a three-times-daily regimen. Figures 1 and 2 show Kaplan-Meier plots for disease-free and overall survival.

Trial Information	
Disease	Colorectal cancer
Stage of Disease/Treatment	Adjuvant
Prior Therapy	None
Type of Study	Phase III, randomized
Primary Endpoint	Progression-free survival
Secondary Endpoints	Toxicity, overall survival

Additional Details of Endpoints or Study Design

The eligibility criteria for participation in this study included (a) histologically proven stage II or III primary colorectal adenocarcinoma (eliminating appendiceal cancer), (b) having undergone curability A resection, (c) being aged between 20 and 80 years at the time of enrollment, (d) having an Eastern Cooperative Oncology Group performance status of 0 or 1, (e) having undergone no prior therapy except the operation, (f) being capable of oral intake, (g) satisfying the following clinical test values within 2 weeks before enrollment (neutrophil count, $\geq$1,500/mm^3; platelet count, $\geq$100,000/mm^3; hemoglobin level, $\geq$9.0 g/dL; total bilirubin level, <2.0 mg/dL, aspartate aminotransferase/alanine aminotransferase level, <100 IU/L; and serum creatinine level: <1.5 mg/dL), and (h) being able to commence treatment within 8 weeks after surgery.

Exclusion criteria: The exclusion criteria included (a) active multiple primaries with a disease-free interval of <5 years; (b) serious postoperative complications (e.g., postoperative infection, ruptured suture, and gastrointestinal hemorrhage); (c) serious complications (e.g., interstitial pneumonia or lung fibrosis, heart failure, renal failure, hepatic failure, and poorly controlled diabetes); (d) severe diarrhea (watery feces); (e) severe infectious disease(s); (f) a medical history of serious anaphylaxis or allergy to any drug; (g) undergoing treatment with 5-fluorocytosine; (h) women who were pregnant, intending to become pregnant, or were lactating at any time during the study and men whose partners were intending to become pregnant during the course of the study; (i) patients with a psychiatric disease or psychiatric symptoms who were considered unable to participate in the clinical study; and (j) other cases that were considered ineligible for enrollment by the doctor.

Study design: This was a noninferiority design. For the NSABP C-06, NSABP C-03, and Intergroup-0035 trials [3–5], the 3-year disease-free survival (DFS) rates of stage II and III patients were 74.5%, 64.0%, and 68.0%, respectively. We therefore predicted that the 3-year DFS rate of the control group (group A) would be 75%. Based on the above, treatment results may have fluctuated to 66% for stage II and III 3-year DFS rates. The noninferiority tolerance limit value in this test was therefore set to 9% (75% − 66% = 9%). Compared with three administrations, the ease of two administrations facilitated treatment. Indeed, for cases in which administration three-times-daily was challenging (patients who had to perform duties or went out, etc.), medication compliance was improved by twice-daily administrations. In the phase III Adjuvant Chemotherapy for Gastric Cancer trial [8] that examined the utility of S-1 for the surgery only group, the outcomes of postoperative adjuvant chemotherapy were affected by drug compliance in stage II and III gastric cancer patients receiving postoperative adjuvant chemotherapy. In that study, the convenience of administration in group B (test group) was improved relative to that in group A. Therefore, the 3-year DFS rate of group B (test group) was set at 78.5%, which was expected to improve by approximately 3.5% compared with that for group A. The sample size required was 179 patients per group, based on a 75% 3-year DFS rate in group A, 78.5% 3-year DFS rate in group B, 9% noninferiority tolerance limit, one-sided α = 0.025, power of 80%, registration period of 3 years, and follow-up period of 5 years. In consideration of a 5% dropout rate, each group required 190 patients, for 380 total patients.

Randomization and masking: Each registered patient was randomly assigned to the control (group A) or test (group B) treatment groups. The minimization method was used as the randomization method, with stage (II vs. III) and tumor location (colon vs. rectum) as adjustment factors.

Statistical analysis: The efficacy analysis for DFS and overall survival (OS) was based on the intent-to-treat (ITT) population, including randomized patients who were included in the study and received chemotherapy. The safety analysis was based on patients who were included in the ITT population and whose safety information was reported after the first dose of the study treatment. The primary outcome measure was DFS, defined as the time from study enrollment until any disease recurrence or death as a result of any cause. The secondary outcome measure was OS, defined as the time from study enrollment until death as a result of any cause. DFS and OS were analyzed using a stratified log-rank test with allocation adjustment factors in the ITT analysis set. We also estimated the survival curves and 3- and 5-year survival rates using the Kaplan-Meier method. Post hoc subgroup analyses were performed to better understand the treatment effects for the subsequent 3 years after study enrollment. The interaction between treatment and each subgroup was tested using a two-sided likelihood ratio test. Independent prognostic and predictive factors were evaluated using the stratified Cox proportional hazards regression model of multivariate analysis. In all cases, the significance level was set at a two-sided $p < .05$. Analysis was performed using JMP Pro 13.1.0 software and SAS 9.4M5 (SAS Institute Inc., Cary, NC).

Investigator's Analysis	Active and should be pursued further

Drug Information: Group A

Tegafur-Uracil/Leucovorin Calcium	
Generic/Working Name	Tegafur-uracil/leucovorin calcium
Company Name	Taiho Pharmaceutical Co., Ltd. Tokyo. Japan
Drug Type	Small molecule
Dose	300 mg/m^2
Route	oral (po)
Schedule of Administration	Divided into three doses administered approximately 8 hours apart, avoiding 1 hour before and after meals. The schedule of 28-day oral administration followed by a 7-day rest period was repeated. Five 35-day cycles were repeated.
Leucovorin Calcium	
Generic/Working Name	Leucovorin calcium

Company Name	Pfizer Inc., New York, NY
Dose	75 mg per
Route	oral (po)
Schedule of Administration	Divided into three doses concomitant with UFT.

Drug Information: Group B	
Tegafur-Uracil/Leucovorin Calcium	
Generic/Working Name	Tegafur-uracil/leucovorin calcium
Company Name	Taiho Pharmaceutical Co., Ltd. Tokyo. Japan
Dose	300 mg/m^2
Route	oral (po)
Schedule of Administration	Divided into two doses, avoiding 1 hour before and after meals. The schedule of 28-day oral administration followed by a 7-day rest period was repeated. Five 35-day cycles were repeated.
Leucovorin calcium	
Generic/Working Name	Leucovorin calcium
Company Name	Pfizer Inc., New York, NY
Dose	50 mg per
Route	oral (po)
Schedule of Administration	Divided into two doses concurrently with UFT.

Patient Characteristics: Group A	
Number of Patients, Male	98
Number of Patients, Female	87
Stage	Stage II or III
Age	Median (range): 68 (28–80) years
Performance Status: ECOG	0 — 171 1 — 14 2 — 0 3 — 0 Unknown — 0
Other	
Cancer Types or Histologic Subtypes	Well differentiated adenocarcinoma, 52 Moderately differentiated adenocarcinoma, 123 Poorly differentiated adenocarcinoma or Signet-ring cell carcinoma, 5 Mucinous adenocarcinoma, 5

Patient Characteristics: Group B	
Number of Patients, Male	106
Number of Patients, Female	82
Stage	Stage II or III
Age	Median (range): 67 (40–83) years
Performance Status: ECOG	0 — 174 1 — 14 2 — 0 3 — 0 Unknown — 0

Cancer Types or Histologic Subtypes	Well differentiated adenocarcinoma, 59 Moderately differentiated adenocarcinoma, 114 Poorly differentiated adenocarcinoma or Signet-ring cell carcinoma, 7 Mucinous adenocarcinoma, 8

Primary Assessment Method: Group A

Title	3-year disease-free survival
Number of Patients Screened	194
Number of Patients Enrolled	185
Number of Patients Evaluable for Toxicity	185
Number of Patients Evaluated for Efficacy	185
Evaluation Method	Recurrence

Outcome Notes

Relative dose intensity: The relative dose intensities were significantly different between groups A and B (67.3% vs. 74.8%, respectively; $p = .03$).

Disease-free survival: In this study, the primary endpoint was 3-year DFS. The 3-year DFS rates of group A and B were 79.4% (95% confidence interval [CI], 72.6–84.4) and 81.4% (95% CI, 74.5–85.9), respectively. This result met the condition of a 9% noninferiority tolerance limit. A stratified log-rank test resulted in a $p = .6948$, indicating that group B (twice-daily regimen) outcomes were not inferior to those of group A (conventional three-times-daily regimen).The 5-year DFS rates of group A and B were 76.2% (95% CI, 68.5–81.2) and 78.7% (95% CI, 71.1–83.3), respectively (Fig. 1). This analysis included both stage II and III patients. We subsequently analyzed the stages separately. For stage II patients, the 3-year DFS rates of group A and B were 85.4% (95% CI, 74.2–92.2) and 84.6% (95% CI, 72.8–91.2), respectively, with no significant difference between the groups. For stage III patients, the 3-year DFS rates of group A and B were 76.4% (95% CI, 67.4–82.7) and 79.7% (95% CI, 71.0–85.5), respectively, with no significant difference between the groups.

Overall survival: The 5-year OS rates of groups A and B were 89.7% (95% CI, 83.3–92.8) and 91.0% (95% CI, 84.8–93.8), respectively, with no significant difference between the groups ($p = .6534$; (Fig. 2)

Safety: The frequency of adverse events was not significantly different between the groups. Anorexia was slightly more common in group B than in group A.

Primary Assessment Method: Group B

Title	3-year disease-free survival
Number of Patients Screened	192
Number of Patients Enrolled	188
Number of Patients Evaluable for Toxicity	188
Number of patients Evaluated for Efficacy	188
Evaluation Method	Recurrence

Outcome Notes

Relative dose intensity: The relative dose intensities were significantly different between groups A and B (67.3% vs. 74.8%, respectively; $p = .03$).

Disease-free survival: In this study, the primary endpoint was 3-year DFS. The 3-year DFS rates of A and B were 79.4% (95% CI, 72.6–84.4) and 81.4% (95% CI, 74.5–85.9), respectively. This result met the condition of a 9% noninferiority tolerance limit. A stratified log-rank test resulted in a $p = .6948$, indicating that group B (twice-daily regimen) outcomes were not inferior to those of group A (conventional three-times-daily regimen). The 5-year DFS rates of group A and B were 76.2% (95% CI, 68.5–81.2) and 78.7% (95% CI, 71.1–83.3), respectively (Fig. 1). This analysis included both stage II and III patients. We subsequently analyzed the stages separately. For stage II patients, the 3-year DFS rates of group A and B were 85.4% (95% CI, 74.2–92.2) and 84.6% (95% CI, 72.8–91.2), respectively, with no significant difference between the groups. For stage III patients, the 3-year DFS rates of group A and B were 76.4% (95% CI, 67.4–82.7) and 79.7% (95% CI, 71.0–85.5), respectively, with no significant difference between the groups.

Overall survival: The 5-year OS rates of group A and B were 89.7% (95% CI, 83.3–92.8) and 91.0% (95% CI, 84.8–93.8), respectively, with no significant difference between the groups ($p = .6534$; Fig. 2)

Safety: The frequency of adverse events was not significantly different between the groups. Anorexia was slightly more common in group B than in group A.

Adverse Events

	Group A, three-times-daily regimen (n = 177)				Group B, twice-daily regimen (n = 178)			
Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
WBC	9 (5.1)	8 (4.5)	1 (0.6)	0 (0)	11 (6.2)	5 (2.8)	1 (0.6)	0 (0)
Neu	8 (4.5)	8 (4.5)	5 (2.8)	0 (0)	6 (3.4)	14 (7.9)	1 (0.6)	0 (0)
Plt	9 (5.1)	2 (1.1)	0 (0)	0 (0)	12 (6.7)	0 (0)	1 (0.6)	0 (0)
Aspartate aminotransferase	31 (17.5)	2 (1.1)	6 (3.4)	1 (0.6)	40 (22.5)	9 (5.1)	5 (2.8)	2 (1.1)
Alanine aminotransferase	33 (18.6)	3 (1.7)	8 (4.5)	3 (1.7)	34 (19.1)	10 (5.6)	8 (4.5)	4 (2.2)
T-bil	47 (26.6)	19 (10.7)	2 (1.1)	0 (0)	31 (17.4)	30 (16.9)	2 (1.1)	1 (0.6)
Cr	14 (7.9)	0 (0)	1 (0.6)	0 (0)	13 (7.3)	5 (2.8)	0 (0)	0 (0)
Fatigue	45 (25.4)	18 (10.2)	2 (1.1)	0 (0)	38 (21.3)	22 (12.4)	4 (2.2)	0 (0)
Peripheral neuropathy	6 (3.4)	3 (1.7)	0 (0)	0 (0)	6 (3.4)	5 (2.8)	0 (0)	0 (0)
Palmar-plantar	12 (6.8)	4 (2.3)	1 (0.6)	0 (0)	12 (6.7)	5 (2.8)	3 (1.7)	0 (0)
Anorexia	29 (16.4)	22 (12.4)	4 (2.3)	0 (0)	28 (15.7)	21 (11.8)	9 (5.1)	0 (0)
Diarrhea	29 (16.4)	23 (13.0)	7 (4.0)	0 (0)	34 (19.1)	26 (14.6)	12 (6.7)	1 (0.6)
Nausea	24 (13.6)	21 (11.9)	3 (1.7)	0 (0)	29 (16.3)	17 (9.6)	6 (3.4)	0 (0)
Vomiting	12 (6.8)	5 (2.8)	2 (1.1)	0 (0)	11 (6.2)	4 (2.2)	3 (1.7)	0 (0)
Febrile neutropenia	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: Cr, Creatinine; Neu, neutrophil; Plt, platelet; T-bil, Total bilirubin; WBC, white blood cell.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Globally, the standard adjuvant chemotherapy for colorectal cancer is FOLFOX or CAPEOX, which contains two cytotoxic agents [6–10]. These combination regimens have been reported to be effective, even in elderly patients [14, 15]. However, for elderly or frail patients, the administration of a single agent is occasionally warranted to avoid toxicity and is considered as an option [13–16]. With the growing elderly population worldwide, the demand for single-agent regimens may increase concomitantly.

Capecitabine has been reported as a useful drug in an adjuvant setting as a single agent. However, it is associated with a high incidence of hand-foot syndrome [17], which may not be acceptable to certain patients. Conversely, tegafur-uracil (UFT)/leucovorin calcium (LV) rarely results in hand-foot syndrome. UFT is a first generation dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine drug. It is an oral agent that combines uracil, a competitive inhibitor of DPD, with the 5-fluorouracil prodrug tegafur in a 4:1 molar ratio. LV can be used in combination with UFT to further enhance the effect of UFT. This regimen was approved and has been used in Japan since 1983.

However, it requires a three-times-daily administration, avoiding 1 hour before and after meals. Therefore, the administration of this regimen is more complex than that of capecitabine, which is taken twice daily after meals.

Initially, we conjectured that the UFT dose per administration would be higher in the twice-daily regimen than in the three-times-daily regimen, thereby increasing the risk of hematotoxicity. However, no significant differences between the groups were observed, at least partly because the relative dose intensity of group B was lower than that of group A.

In this study, compliance for the twice-daily regimen was poorer than that of the three-times-daily regimen, although no significant difference in 3-year DFS was observed. This result contradicted our hypotheses. One explanation could be a high blood UFT concentration due to a large UFT dose per administration in the twice-daily regimen.

Several study limitations should be noted. First, the study was not conducted in multiple countries. Therefore, the findings may not be applicable to patients globally. Second, we did not directly compare the twice-daily UFT/LV regimen and capecitabine, which is the standard single agent in European countries. Third, it remains unclear why the outcome of the twice-daily regimen was superior despite decreased relative dose intensity compared with that of the three-times-daily regimen, as we did not measure the maximum drug concentration of UFT. Finally, we were unable to identify why compliance for the twice-daily regimen was poorer than that for the three-times-daily regimen.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board

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