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Multicenter Phase II Study of FOLFOX6 for Previously Untreated Unresectable Metastatic Colorectal Cancer

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Abstract

Background: This phase II study investigated the safety and efficacy of an oxaliplatin, fluorouracil, and l-leucovorin regimen (FOLFOX6) in Japanese patients with previously untreated, unresectable metastatic colorectal cancer because oxaliplatin of FOLFOX6 was given at a previously untested dose of 100 mg/m^2.

Methods: Patients with metastatic colorectal cancer received FOLFOX6, consisting of oxaliplatin at a dose of 100 mg/m^2 in combination with l-leucovorin 200 mg/m^2 over 2 hours, and fluorouracil 400 mg/m^2 intravenous bolus followed by fluorouracil 2400 mg/m^2 over a 46-hour infusion, with cycles every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was to evaluate the objective response rate.

Results: Among 49 patients enrolled, two patients were considered unsuitable against the inclusion criteria due to non-measurable lesion and prior treatment, and one patient was unable to start treatment due to clinical disease progression. Accordingly, safety and efficacy were assessed in 46 and 47 patients, respectively. There was one complete response and 22 partial responses, resulting in an overall response rate of 49% (95% CI 34–64%). The median progression-free survival time was 8.8 months, and the median survival time was 24.5 months. Grade 3 or higher neutropenia and thrombocytopenia occurred in 50% and 2% of patients, respectively, and febrile neutropenia occurred in one patient. Grade 3 sensory neuropathy occurred in 13% of patients.

Conclusion: FOLFOX6 with oxaliplatin at 100 mg/m^2 was well-tolerated and effective in Japanese patients with unresectable metastatic colorectal cancer.

Keywords: Colorectal cancer; FOLFOX6; Phase II

Introduction

Oxaliplatin is a key drug for the treatment of metastatic colorectal cancer and 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) is recognized as one of the standard regimen for first-line chemotherapy [1,2]. Although both FOLFOX4 and FOLFOX6 have been used globally, FOLFOX4 involves two 22-hour FU infusions of fluorouracil (FU) every 2 weeks. The FOLFOX6 regimen has replaced FOLFOX4 in several countries, affording modestly greater convenience with one 2-day infusion [3]. Though its introduction to Japan was delayed compared to other countries, oxaliplatin in combination with infusional 5-FU and l-leucovorin (l-LV) was approved in Japan in March 2005, with the oxaliplatin dose limited to 85 mg/m^2 every 2 weeks. In Western countries, multiple regimens with a variety of oxaliplatin doses given every 2 or 3 weeks (FOLFOX4, FOLFOX6 and FOLFOX7), have been developed. Although FOLFOX4, modified FOLFOX6 with oxaliplatin at a dose of 85 mg/m^2, and oxaliplatin monotherapy at a dose of 130 mg/m^2 have shown good efficacy in Japanese patients, it remains unclear whether the efficacy and safety of FOLFOX6 with oxaliplatin at a dose of 100 mg/m^2 would be similar to those in Western patients [4-7]. Therefore, we conducted a phase II study of FOLFOX6 in Japanese patients with unresectable metastatic colorectal cancer to assess the efficacy and safety of FOLFOX6 with a dose of oxaliplatin of 100 mg/m^2.

At the same time, this study was planned as a preliminary step of further phase III study of surgery alone versus adjuvant FOLFOX6 after curative resection for colorectal liver metastasis. Although there

was even no data of safety of FOLFOX6 with oxaliplatin at 100 mg/m^2 for Japanese metastatic colorectal cancer patients, the current study also implied this.

Patients and Methods

Patient selection

The following eligibility criteria was used to screen patients for inclusion: histologically proven colorectal adenocarcinoma; unresectable advanced or recurrent disease; age range of 20-75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 [8]; no history of chemotherapy (however, adjuvant chemotherapy, completed more than 6 months before entry, was allowed); preserved organ function, including leukocyte of 4.0-12.0×10^9/L, platelets ≥100×10^9/L, aspartate aminotransferase and alanine aminotransferase concentrations ≤100 U/L, total bilirubin ≤1.5 mg/dL, and creatinine ≤1.1 mg/dL. Exclusion criteria included patients with active infection, uncontrolled heart disease, uncontrolled diabetes, pulmonary fibrosis or active pneumonitis, preexisting peripheral neuropathy, symptomatic brain metastasis, watery diarrhea, systemic use of corticosteroids, administration of blood products or granulocyte-colony stimulating factor within the prior 7 days, active concomitant malignancy, and pregnancy or lactation.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients.

Treatment plan

FOLFOX6 consisted of oxaliplatin 100 mg/m^2 intravenous (IV) with l-leucovorin (l-LV) 200 mg/m^2 IV administered simultaneously over 2 hours, and 5-FU 400 mg/m^2 IV bolus, followed by 5-FU 2400 mg/m^2 over a 46-hour infusion, repeated every 2 weeks until disease progression or unacceptable toxicity. Antiemetic prophylaxis with a 5-hydroxytryptamine-3 antagonist and dexamethasone was administered prior to chemotherapy. The duration of infusion could be extended to 6 hours in patients who had pharyngolaryngeal dysesthesia during oxaliplatin infusion. The use of implantable ports and disposable or electronic pumps allowed chemotherapy to be administered on an outpatient basis.

Dose modification and treatment delay

Dose modification criteria are summarized in Table 1. If grade 3 sensory neuropathy did not recover by the start of subsequent cycle, treatment could be continued with 5-FU and l-LV. We discontinued treatment if disease progression was diagnosed clinically or radiologically, if a serious adverse event arose, if a treatment cycle was delayed due to an adverse event continuing for longer than 3 weeks, if an adverse event meant a subsequent dose reduction was needed after a prior reduction, if the patient refused treatment, or if discontinuation of therapy was judged necessary by the treating physician for other reasons.

If leukocyte count decreased to <3,000/L, platelet count decreased to <100,000/L, temperature reached ≥ 38.0°C, or grade 2 or higher nonhematologic toxicity (excluding anorexia) developed, treatment was delayed for up to 3 weeks.

Toxicity	Grade	5-FU bolus (mg/m^2)	5-FU infusion (mg/m^2)	Oxaliplatin (mg/m^2)
Neutropenia	4	300	2000	75
Febrile neutropenia	3-4	300	2000	75
Thrombocytopenia	3-4	300	2000	75
Nausea or vomiting*	3-4	300	2000	75
Diarrhea*	3-4	300	2000	75
Stomatitis	3	300	2000	None
	4	200	1500	75
Skin events	3-4	200	1500	None
Neuropathy	2-3	None	None	75
*Despite optimal prophylactic or supportive care, if toxicity occurs, dose modification will be done				

Table 1: Dose modification

Dose-limiting toxicity and maximum tolerated dose

At first, six patients were to be started at the dose of oxaliplatin 100 mg/m^2 (dose level 1). If three patients experienced Dose-Limiting Toxicity (DLT), this dose level was determined to be the Maximum Tolerated Dose (MTD), and oxaliplatin at 85 mg/m^2 (dose level 0) would be explored. If two or less patients had DLT, the 100 mg/m^2 dose would be considered for further evaluation in additional patients. In the case that dose level 1 was not acceptable due to DLT, the regimen would be deemed not feasible.

Dose-limiting toxicities were defined any of the following findings during cycle 3 on day 8: grade 4 neutropenia lasting for 5 days or longer; grade 4 neutropenia with fever ≥38.0°C; grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding; grade 3 or 4 nonhematological toxicities other than nausea, vomiting, anorexia, fatigue, constipation, or electrolyte abnormality; and next cycle was delayed for 8 days or longer.

Study assessments

We did physical examination and laboratory tests at least once weekly until cycle 3 and every 2 weeks in subsequent cycles, and assessed all adverse events, except neurotoxicity, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. Neurotoxicity was recorded according to the grading scale of Neurotoxicity Criteria of Debiopharm as follows: grade 1, dysesthesia or paresthesia completely regressing within 6 days; grade 2, dysesthesia or paresthesia persisting for 7 days or longer; and grade 3, dysesthesia or paresthesia causing functional impairment.

Antitumor activity was evaluated per RECIST guidelines, and CT scans were taken every 8 weeks independent of the treatment schedule [8]. We calculated response rates with interval confirmation at least 4 weeks apart. Radiographic reviews for eligibility of enrolled patients and clinical response were performed by each institutional physician and the investigators. We also evaluated oxaliplatin's known

neurotoxicity, checking for functional impairment and residual neuropathy after discontinuation of protocol treatment. If neurotoxicity disappeared completely, the date was recorded.

Statistical considerations

This was a phase II, multicenter, single-arm, clinical study conducted at 17 institutions in Japan. The primary endpoint was objective response rate. Secondary endpoints were safety, overall survival, and Progression-Free Survival (PFS). We measured overall survival from the date of registration to the date of death and censored at the date of last contact for survivors. We calculated PFS to the date disease progression was detected, or death, and censored at the date on which progression-free status was verified.

The required sample size was calculated to be at least 44 patients based on the null hypothesis assumption of a 25% response rate versus the alternative hypothesis of a 42% response rate, with 90% power and a one-sided significance level of α=0.2. Response rate targets were derived from previously reported phase II studies (response rates of 27% in FOLFOX6 and 42% in FOLFOX7) at the time this study was conducted [3,9]. PFS and overall survival were estimated using the Kaplan-Meier method. Safety was analyzed in all patients who received at least one dose of study treatment. The anticipated patient accrual time was 6 months and the follow-up period was 2 years after the last patient was enrolled. The cut-off date for the final analysis was April 30, 2008.

Results

Patient characteristics

A total of 49 patients from 10 institutions were enrolled into the study between April 2005 and September 2005. Two patients were ineligible because of prior chemotherapy and non-measureable lesion, respectively. These patients were excluded from all analyses according to the Full Analysis Set principle, therefore, a total of 47 patients analyzed for treatment response. One patient could not receive treatment due to rapid disease progression after registration. Data from the remaining 46 patients were analyzed to assess safety. Patient characteristics are summarized in Table 2.

Category	No. patient (%)
Sex	
Male	28 (60%)
Female	19 (40%)
Age (years)	
Median (range)	61 (35–73)
ECOG performance status	
0	39 (83%)
1	6 (13%)
2	2 (4%)
Primary tumor resection	
Present	36 (77%)
Absent	11 (23%)
Primary tumor site	
Colon	27 (57%)
Rectum	20 (43%)
Tumor differentiation*	
Well	21 (45%)
Moderately	23 (49%)
Poorly	1 (2%)
Prior adjuvant chemotherapy	
Present**	6 (13%)
Absent	41 (87%)
Prior radiotherapy	
Absent	47 (100%)
Metastatic site	
Liver	31 (66%)
Lung	21 (45%)
Distant lymph node	17 (36%)
Peritoneum	4 (9%)

ECOG: Eastern Cooperative Oncology Group

*Two patients did not have detailed histology type (adenocarcinoma, only); **All 6 patients had received fluoropyrimidine plus leucovorin regimens

Table 2: Patient characteristics (n = 47)

DLT

In the first step, one of six patients at dose level 1 (oxaliplatin 100 mg/m^2) had DLT of grade 3 nausea and anorexia. Therefore, dose level 1 was determined as the recommended dose for the additional patients.

Treatment exposure

A total of 452 cycles were administered for 46 patients. The median number of dose administrations was 10 (range, 1-16). The median relative dose intensity was 76.8% for oxaliplatin, 78.8% for bolus 5-FU and 79.9% for infusional 5-FU during the study period until time to treatment failure. Median cumulative oxaliplatin dose was 880 mg/m^2 (range, 100–1280 mg/m^2). The causes of treatment discontinuation were progressive disease in 21 patients, delayed recovery from thrombocytopenia in 2, diarrhea in 1, sensory neuropathy in 8, hypersensitivity reactions in 3, physician-directed discontinuation in 6 (prolonged partial response in 5 and surgery in 1), and patient refusal in 5 (adverse events of fatigue and neuropathy in 2, complete response in 1, admission to the psychiatric ward in 1, and cost in 1). The most common causes of treatment delay were leukopenia and/or neutropenia in 27 patients and thrombocytopenia in 19 patients.

Adverse events

Table 3 summarizes the major adverse events of chemotherapy. Grade 3 or greater neutropenia was observed in 50% of patients, however, febrile neutropenia occurred in only one patient. Although some grade of thrombocytopenia was observed in 85%, only one patient (2%) had grade 3 or greater thrombocytopenia. The most common nonhematologic toxicities were anorexia, nausea, elevation of transaminase, and sensory neuropathy. Hypersensitivity reactions occurred in 6 patients (grade 2 in 4 patients and grade 3 in 2 patients), but all subsided after the intravenous administration of antihistamine or hydrocortisone. Of these 6 patients, 3 patients had concomitant disease progression, but the remaining 3 patients discontinued treatment due to the hypersensitivity reaction. Sensory neuropathy occurred in most patients (94%); grade 1 (21%), grade 2 (58%) and grade 3 (13%). Of 8 patients who discontinued treatment due to sensory neuropathy, 4 patients received oxaliplatin-containing regimen after recovery from sensory neuropathy. When protocol treatment was discontinued due to pre-specified reasons (disease progression, severe adverse event, toxicity-related treatment delay over 3 weeks, patient refusal of treatment, or physician-directed discontinuation), 35 patients (76%) had some grade of sensory neuropathy. Of these 35 patients, six patients had sensory neuropathy with functional impairment.

	Gr1	Gr2	Gr3	Gr4	All	Gr3/4
	no. of patients				%	%
Hematological toxicity						
Leukocytes	8	30	3	0	89	7
Neutrophils	3	15	17	6	89	50
Hemoglobin	30	4	2	1	80	7
Platelets	31	7	1	0	85	2
Non-hematological toxicity						
Anorexia	28	2	2	0	70	4
Nausea	26	1	2	0	63	4
Vomiting	9	2	1	0	26	2
Mucositis	18	1	2	0	46	4
Diarrhea	13	4	0	0	37	0
Hand-foot syndrome	6	0	0	0	13	0
Hyperpigmentation	15	0	-	-	33	-
Taste alteration	12	1	-	-	28	-
Febrile neutropenia	-	-	1	0	2	2
Bilirubin	8	0	0	0	17	0
AST	35	6	2	0	94	4
ALT	19	11	2	0	70	4
Creatinine	7	3	0	0	22	0
Sensory neuropathy*	10	27	6	-	94	13

AST: aspartate transaminase; ALT: *alanine* aminotransferase *Sensory neuropathy was evaluated using Neurotoxicity Criteria of Debiopharm

Table 3: Adverse events (n = 46)

Objective response rate and survival

One patient had complete response and 22 patients had partial responses. The objective tumor response was thus 49% (95% Confidence Interval (CI), 34-64%). Twenty-one patients had stable disease, two had progressive disease, and one was unable to be evaluated due to lost to follow-up by patient refusal due to sensory neuropathy. Of 23 responders, one underwent hepatectomy following the chemotherapy protocol. Survival data were finally updated on April 30, 2008. Figure 1 showed PFS and overall survival curves of the 47 eligible patients. Median PFS was 8.8 months (95% CI, 5.3-12.3 months) while median overall survival was 24.5 months (95% CI, 20.7 - 28.3 months).

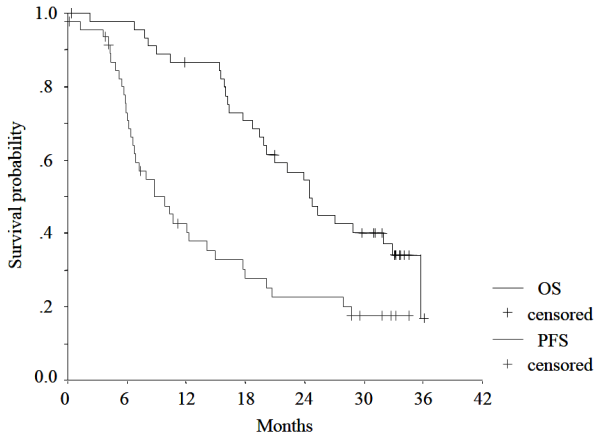

Figure 1: Kaplan-Meier curve for overall survival (black line) and progression-free survival (gray line)

Post study treatment

At the end of the follow-up period, 38 (83%) of the 46 patients who discontinued protocol treatment received poststudy chemotherapy. Details of poststudy chemotherapy were as follows: irinotecan-containing regimens in 19 (irinotecan alone in 4, FOLFIRI in 11, irinotecan plus mitomycin C in 1, S-1 plus irinotecan in 3); modified FOLFOX6 with oxaliplatin at 85 mg/m^2 in 8; sLV5FU2 in 6; hepatic arterial 5-FU infusion in 3; and UFT/LV in 2 patients. Clinical response data to those therapies were not available. Of the 6 patients who did not receive poststudy chemotherapy, 1 patient achieved complete response without evidence of subsequent recurrence, 2 patients had follow-up only because of good partial response although protocol treatment (included infusional 5-FU and l-LV without oxaliplatin) was recommended, 2 patients were lost to follow-up, and 1 patient received best supportive care.

Discussion

A variety of chemotherapy regimens have been evaluated since the introduction of oxaliplatin, which caused renewed interest in clinical

research of the treatment for advanced colorectal cancer. FOLFOX was one of the standard treatment, along with FOLFIRI (bolus/infusional 5-FU and l-LV plus irinotecan) and CapeOx (capecitabine plus oxaliplatin) [10,11]. In Japan, FOLFOX4 or modified FOLFOX6 have been commonly used given that the dosage of oxaliplatin is limited to 85 mg/m^2 every 2 weeks. Although the efficacy and safety of monotherapy with oxaliplatin 130 mg/m^2 every 3 weeks in Japanese patients are similar to those reported in Western studies, those of FOLFOX6 with oxaliplatin at a dose of 100 mg/m^2 remained to be elucidated.

The present phase II study demonstrated that FOLFOX6 with oxaliplatin at 100 mg/m^2 had promising antitumor activity in Japanese patients with metastatic colorectal cancer, with a response rate of 49% and an acceptable toxicity profile. The efficacy of FOLFOX6 in the present study was similar to that in previous studies. The response rate of FOLFOX regimens in the past are 50.7% and 58.5% for FOLFOX4 with oxaliplatin at 85 mg/m^2 [1,12], 41% for modified FOLFOX6 at 85 mg/m^2 [13], 44.9% for FOLFOX6 at 100 mg/m^2 [14], and 59.2% for FOLFOX7 at 130 mg/m^2 [12]. Although one limitation of our study is the possibility of selection bias, median PFS was 8.8 months and overall Median Survival Time (MST) was 24.5 months. Since the introduction of irinotecan and oxaliplatin, the PFS and MST of metastatic colorectal cancer patients have been reported to be about 8.0–9.0 and 16.2–20.6 months, respectively, in previous studies of first-line chemotherapy with FOLFOX [1,2,10,13,15]. Recently, MST has reached over 24 months with the advent of molecular target drugs [13]. Although there are limitations in comparing the results of different studies, available evidence suggests that FOLFOX6 with oxaliplatin at a dose of 100 mg/m^2 is also an effective treatment option for Japanese patients with metastatic colorectal cancer in addition to FOLFOX4 and modified FOLFOX6.

FOLFOX6 in our study was generally well-tolerated, providing a safety profile consistent with previous FOLFOX regimens. The most critical adverse event was sensory neuropathy, which was a major reason for treatment discontinuation aside from disease progression. Neuropathy deteriorated to functional impairment (i.e. grade 3 sensory neuropathy) in 6 patients (13%). Of these, 5 patients regressed to grade 2 or better, but the remaining patient had prolonged grade 3 sensory neuropathy for more than 2 years at the end of the study period. Hematological adverse events were also reported: grade 3 or 4 neutropenia occurred in 50% of patients, and febrile neutropenia occurred in only one patient. The frequency of these adverse events was similar to those of non-Japanese studies (C95-1, N9741, OPTIMOX1, FOCUS study); grade 3 sensory neuropathy was reported in 3-18.2% and grade 3 or 4 neutropenia in 25-50% [12,16-18].

Severe adverse event was also minimized by dose modifications, allowing patients to continue with treatment in our study. As such, there was a high proportion (67%) of treatment delay due to hematological toxicity including leukopenia, neutropenia, and thrombocytopenia. At present, careful monitoring for sensory neuropathy and appropriate dose reductions or cessation should remain a standard practice despite differences in the dose of oxaliplatin in the various FOLFOX regimens.

In conclusion, the results of the present study confirmed the activity of FOLFOX6 with oxaliplatin at 100 mg/m^2 against Japanese metastatic colorectal cancer. FOLFOX6 also had acceptable safety profile. However, sensory neuropathy attributable to oxaliplatin at 100 mg/m^2 may be serious, leading to treatment delay or discontinuation. On the basis of the results of this phase II study, a phase III study (JCOG0603) of modified FOLFOX6 with a reduced dose of oxaliplatin at 85 mg/m^2 after curative resection for colorectal liver metastasis is ongoing [19].

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