Background

Oxaliplatin, a third-generation platinum anticancer drug, has been shown to be effective for the treatment of metastatic colorectal cancer (CRC) [1, 5, 9, 21]. Currently, the FOLFOX chemotherapy regimen, consisting of oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (LV), has become the standard regimen as first-line treatment for metastatic colorectal cancer [5, 9, 21]. The European adjuvant trial for colon cancer (MOSAIC) demonstrated significant improvement in 3-year disease-free survival when oxaliplatin was added to infusional 5-FU and LV [1].

One of the well-known dose-limiting factors of oxaliplatin is a delayed-onset, cumulative, dose-related peripheral neuropathy, characterized by persistent paresthesias affecting the hands and feet, and which does not remit between cycles of treatment [5, 18]. Persistent peripheral neuropathy with pain or function impairment interfering with activities of daily living (grade 3) occurs in 10–20% of patients receiving total oxaliplatin doses >750–850 mg/m^2 [5, 9, 21]. Of great concern is the development of persistent peripheral neuropathy that requires complete discontinuation of oxaliplatin, regardless of its efficacy, to avoid a debilitating neuropathy, which may take 6–10 months to resolve [5, 7]. Although this neuropathy is largely reversible, safety data from the MOSAIC trial determined that at 4 years, a small minority of patients (<5%) have grade 3 persistent peripheral neuropathy after 6 months of adjuvant FOLFOX4 treatment [2]. Various schedules have been pursued to reduce neuropathy. A randomized trial of FOLFOX4 versus scheduled intermittent oxaliplatin (OPTIMOX 1) was associated with a slight reduction in grade 3 neuropathy (17.9% versus 13.3%, $P = 0.12$) without lack of efficacy in response or progression-free survival [22]. Despite equivalent efficacy, the OPTIMOX 1 "stop and go" strategy has not been widely adopted for all patients. This is probably as a result of variability in management of patients by different physicians, heterogeneity of the disease, and inability to reinstitute oxaliplatin at the time of progression, often because of persistent neuropathy [7].

For patients with unresectable metastatic disease, the duration of treatment is indefinite, extending until disease progression or until the treatment is no longer tolerated. Hence, it is imperative to manage appropriately the persistent peripheral neuropathy, which causes deteriorating in the quality of life during treatment. No single strategy, including calcium (Ca)–magnesium (Mg) supplementation [8, 11, 12] and various antineuropathic and antiepileptic medications [4, 10], has proven effective for preventing or reducing the cumulative neuropathy associated with oxaliplatin.

One possible approach to prevent grade 3 sensory neurotoxicity during treatment is to wait for the complete recovery of paresthesia or dysesthesia from persistent neurotoxicity until 29 days, followed by the subsequent course without dose modification. If paresthesia or dysesthesia continues over 29 days, the dose of oxaliplatin is reduced in the subsequent course, to maintain the antitumor effect of FOLFOX. We conducted the present phase II study to investigate this novel "wait and go" strategy.

Methods

The eligibility criteria for inclusion onto the study were as follows: adenocarcinoma of the colon or rectum; unresectable metastases; at least one measurable lesion of 1 cm or a residual nonmeasurable lesion; adequate bone marrow (hemoglobin >9.0 g/dl, leukocyte count lower limits of normal −12,000/mm^3, neutrophils <1,500/mm^3, platelet count 100,000/mm^3), liver (AST and ALT 2.5 upper limits of normal [UNL], total bilirubin 1.5 UNL, alkaline phosphatases 2.5 UNL), and renal function (creatinine less than UNL); Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; and age 20–80 years. Previous adjuvant fluoropyrimidine chemotherapy, if given, must have been completed at least 2 weeks before inclusion. Patients with uncontrolled infection, massive ascites or pleural effusion, brain metastases, second malignancies, bowel obstruction, current watery diarrhea, a history of oxaliplatin-based adjuvant chemotherapy, or disease confined to previous radiation fields were excluded. Written informed consent was required and the Ethical Committee approved the study.

Chemotherapy

Eligible patients were treated with the FOLFOX4 regimen [1, 9, 21]. Each cycle comprised oxaliplatin 85 mg/m^2 and l-LV 100 mg/m^2 intravenously (IV) administered simultaneously for 2 h followed by 5-FU 400 mg/m^2 IV bolus followed by 5-FU 600 mg/m^2 infusion for 22 h on day 1, and the same therapy, without the oxaliplatin, administered on day 2 (total 46 h after the initial 2 h IV) of a 14-day treatment cycle. Pretreatment with a 5-hydroxytryptamine-3 antagonist and dexamethasone was strongly recommended, although the administration of intravenous calcium and magnesium was not permitted in order to prevent oxaliplatin-induced neuropathy. Treatment was continued until disease progression (PD), unacceptable toxicity, or patient choice.

Toxicity was assessed before starting each 2-week cycle using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0. A specific scale was used for sensory neurotoxicity: grade 1 is brief paresthesia with complete regression before the next cycle, grade 2 is persistent paresthesia or dysesthesia without functional impairment over the next cycle, and grade 3 is painful paresthesia or persistent functional impairment (Table 1).

Table 1 Specific scale for sensory neurotoxicity

Grade	Sensory neurotoxicity
1	Brief paresthesia with complete regression before the next cycle (<15 days)
2	Persistent paresthesia or dysesthesia without functional impairment over the next cycle (≧15 days)
3	Painful paresthesia or persistent functional impairment

Chemotherapy was delayed until recovery if neutrophils <1,500/mm^3, platelets <75,000/mm^3, or for significant persistent non-hematological toxicity. If grade 4 neutropenia, grade 3/4 thrombocytopenia, or grade 3/4 gastrointestinal toxicities occurred, the FU dose was reduced to 300 mg/m^2 for the bolus component and 500 mg/m^2 for the infusion component and the oxaliplatin dose was reduced to 65 mg/m^2. In the case of grade 2 paresthesia at a new cycle of treatment, the next cycle of FOLFOX4 was delayed until the recovery of paresthesia from persistent neurotoxicity for up to 2 additional weeks (<29 days). If it persisted for 29 days, the oxaliplatin was reduced to 65 mg/m^2. If grade 3 paresthesia was present during treatment, oxaliplatin was omitted from the regimen.

Treatment was discontinued if subsequent reduction was indicated.

Evaluation

Pretreatment evaluation included complete patient histories, physical examinations, complete blood cell counts, biochemistry involving liver and renal functions, urinalysis, tumor markers including CEA and CA19-9, chest roentgenogram, electrocardiogram, and computed tomographic scans of the abdomen and chest. According to NCI-CTC version 3.0, toxicity and laboratory variables in complete blood cell counts, biochemistry, and urinalysis were assessed weekly during the first course, on days 1 and 15 from the second through to the sixth course and at least once during subsequent courses. CT scans were repeated to evaluate lesions every two courses and tumor markers were measured at the same time. Responses were evaluated according to the RECIST criteria [20]. To confirm partial response (PR) (30% or greater decrease in the sum of the longest dimensions of target lesions, referenced against the baseline sum of the longest dimensions of target lesions together with stabilization or decrease in size of nontarget lesions) or complete response (CR) (disappearance of all target and nontarget lesions together with normalization of tumor marker levels), tumor measurements were repeated no less than 4 weeks after objective response was firstly obtained. Responses were assessed by external review.

Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Progression-free survival (PFS) was the time from treatment initiation to first documentation of disease progression detected by the external review or death from any cause (censored at second-line chemotherapy). Time-to-treatment failure (TTF) was the time from treatment initiation to discontinuation of treatment, first documentation of disease progression by the external review, or death from any cause.

Statistical evaluations

The phase II study was designed to test the null hypothesis that the true response probability is less than the clinically significant level of 25%. The response rate of first-line FOLFOX was reported to be from 45 to 50%. The alternative hypothesis of the response rate in this study was >45%, because the "wait and go" strategy to prevent grade 3 paresthesia might diminish the response. The probability of accepting treatment with a response probability (25%) was $P = 0.05$. The probability of rejecting treatment with a response rate of 45% was $P = 0.2$; therefore, the required number of patients was estimated to be 49. Allowing for a patient ineligibility rate of about 20%, we planned to enroll 60 patients. The 95% confidence interval (CI) was calculated for the RR, PFS, and TTF. OS, PFS, and TTF were calculated by the Kaplan–Meier method.

Results

Patients' characteristics

We enrolled 58 patients between March 2006 and April 2008, all of whom met all eligibility requirements and received at least one course of treatment. Patient characteristics are summarized in Table 2, and all patients were evaluated for toxicity and response. The median age of patients was 67.5 years (range, 37–80 years); 48 patients had an ECOG PS of 0 and 10 patients had an ECOG PS of 1. There were 13 patients with advanced disease with primary tumors and 45 patients in recurrent status. Primary sites were the colon in 35 patients and the rectum in 23 patients. Metastatic sites were in the liver in 39 patients, lungs in 17, lymph nodes in 21, and peritoneum in 11.

Safety

All 58 patients enrolled in the phase II study were assessable for safety and received 481 treatment courses (median, 8 courses; range, 1–16 courses). The median relative dose intensity was 76.9% for oxaliplatin, 76.7% for bolus FU, and 77.8% for infusion FU. The causes of treatment discontinua-

Table 2 Patients' profile ($n = 58$)

Characteristic	No. of patients %
Median age, years (range)	67.5 (37–80)
Sex	
Male	36
Female	22
ECOG PS	
0	48
1	10
2	0
Disease status	
Advanced	3
Recurrent	45
Primary tumor	
Colon	35
Rectum	23
Differentiation	
Well	11
Moderate	42
Poor	5
Metastatic sites	
Liver	39
Lymph node	21
Lung	17
Peritoneum	11
Others	4
No. of metastatic sites	
0	0
1	25
>1	33

Table 3 Observed adverse events according to number of patients

Event	Number of patients ($n = 58$)				
	NCI-CTC grade, version 3				
	1	2	3	4	3/4, %
Leucopenia	10	28	6	0	10.3
Neutropenia	0	9	9	10	32.8
Anemia	12	14	1	0	1.7
Thrombocytopenia	28	6	2	0	3.4
Anorexia	12	9	0	0	0
Nausea	15	6	0	0	0
Vomiting	6	2	0	0	0
Fatigue	12	6	0	0	0
Diarrhea	4	2	1	0	1.7
Constipation	1	0	0	0	0
Stomatitis	4	0	0	0	0
Abnormal AST	27	5	1	0	1.7
Abnormal ALT	17	4	0	0	0
Hyperbilirubinemia	7	1	0	0	0
Neuropathy[a]	24	13	4	–	6.9

[a] A specific scale was used for neuropathy (Table 1)

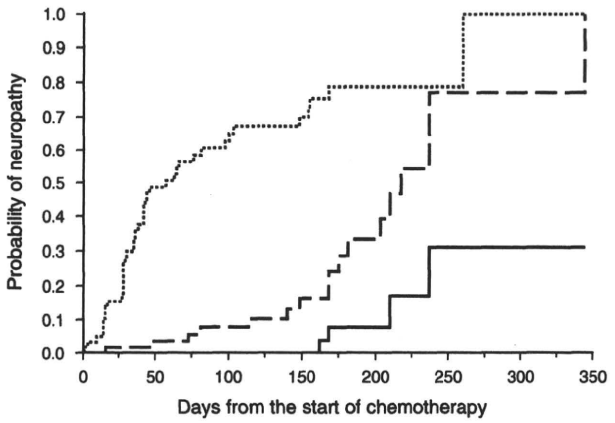

Fig. 1 Cumulative incidence of neuropathy. *Solid line*, grade 3 neuropathy ($n = 4$); *broken line*, grade 2 neuropathy ($n = 13$); *dotted line*, grade 1 neuropathy ($n = 24$)

tion were disease progression in 20 patients (34.5%), delayed recovery from toxicity such as neutropenia, thrombocytopenia, and liver dysfunction in 6 patients, withdrawal of consent, mainly due to economic issues, in eight cases, surgery for metastases in five patients, allergic reaction in five patients, subsequent reduction in four patients, and grade 3 paresthesia in four patients (6.9%). There were no serious unexpected adverse events and no treatment-related deaths.

The overall incidences (%) of hematological and non-hematological toxicities in the phase II study are listed in Table 3. Grade 3/4 neutropenia was the most common adverse event and occurred in 32.8% of all 58 patients. No patient had febrile neutropenia. With the exception of paresthesia, major non-hematological toxicities were liver dysfunction, anorexia, stomatitis, and diarrhea. Grade 3 non-hematological toxicities were diarrhea (1.7%) and nausea (1.7%). We observed grade 1 paresthesia in 24 patients (41.4%), grade 2 in 13 patients (22.4%), and grade 3 in four patients (6.9%). Cumulative incidence of paresthesia is shown in Fig. 1. The median times to onset of paresthesias were 54.5 days for grade 1 and 213.5 days for grade 2, respectively. Grade 3 paresthesia was observed from 162 to 237 days from the start of chemotherapy. The median cumulative doses of oxaliplatin associated with paresthesia were 255 mg/m^2 for grade 1,764 mg/m^2 for grade 2, and 973 mg/m^2 for grade 3.

The dose reductions were required in 16 of all 58 patients (27.6%). Among these 16 patients, the reasons for dose reduction were grade 4 neutropenia in eight patients, grade 3/4 gastrointestinal toxicities in one patient, grade 3/4 thrombocytopenia in three patients, and grade 2 paresthesia in only one patient. The treatment delay within 2 weeks was observed in 50 of all 58 patients (86.2%) among 171 of

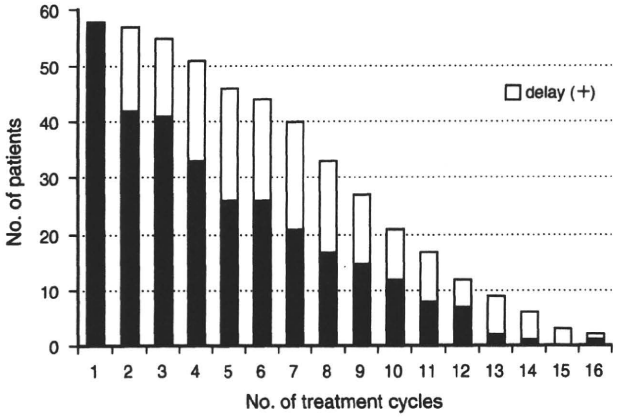

Fig. 2 The frequency of treatment delays in terms of treatment cycle. *Black bar*, numbers of patients who started the treatment within 29 days from the initial day of the previous chemotherapy cycle; *White bar*, numbers of patients who started the treatment over 29 days from the initial day of the previous chemotherapy cycle

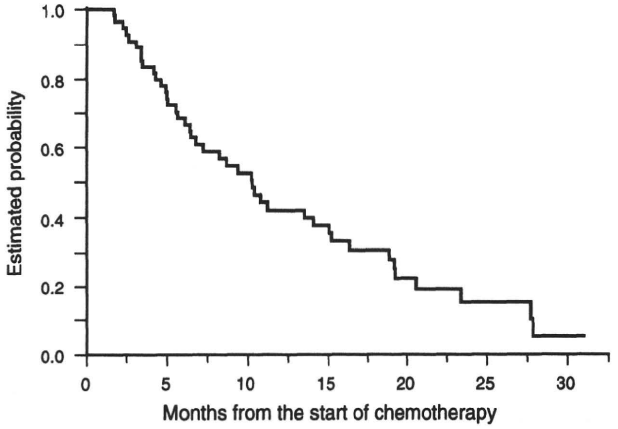

Fig. 3 Kaplan–Meier estimates of progression-free survival ($n = 58$)

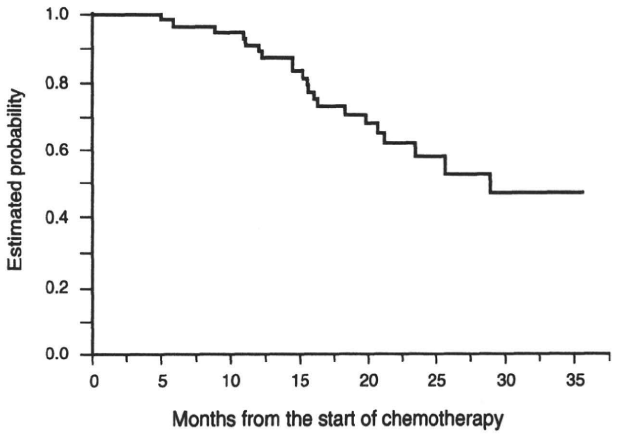

Fig. 4 Kaplan–Meyer estimates of overall survival ($n = 58$)

all 481 treatment courses (35.6%). The frequency of treatment delay over 2 weeks was from 40.9 to 100% after the fourth treatment course (Fig. 2).

Efficacy

The response was assessed as CR, PR, stable disease (SD) (less than a 30% reduction and less than a 20% increase in the sum of the longest dimensions of target lesions, referenced against the baseline sum of the longest dimensions of target lesions together with stabilization or decrease in size of nontarget lesions), and progressive disease (PD) in 2, 20, 25, and 8, respectively, of the 55 patients in the efficacy analysis set (three were not assessable). The RR was 40.0% (95% CI 28.1–53.2%) and the disease control rate (CR + PR + SD) was 85.5% (95% CI 73.8–92.4%).

The median follow-up period was 15.5 months as of the data cut-off date, October 15, 2009. The median PFS was 10.2 months (95% CI 6.4–14.0 months) (Fig. 3), median overall survival time (MST) was 27.6 months (95% CI 20.6–35.6 months) (Fig. 4), and median TTF was 5.0 months (95% CI 3.6–5.1 months). The patients who received the second-line chemotherapy or the surgery for metastases without PD were censored at the date of image examination immediately before the second-line chemotherapy or the surgery for metastases in PFS analysis. The 1- and 2-year survival rate of MST was 89.0% (95% CI 80.7–97.3%) and 57.8% (95% CI 42.3–73.4%), respectively. Of the 58 patients, 46 (79.3%) discontinued treatment and received second-line chemotherapy.

Discussion

We set out to determine whether the "wait and go" strategy for FOLFOX4 in the treatment of metastatic colorectal cancer would be effective. This is the first study of FOLFOX4 with the novel "wait and go" strategy, which minimizes painful paresthesia or persistent functional impairment during treatment by a 2-week wait for the recovery of paresthesia or dysesthesia from persistent neurotoxicity at the new cycle of treatment. Using this strategy, a very promising efficacy, low incidence of painful paresthesia or persistent functional impairment of 6.9% was obtained in our phase II study: an RR of 40.0%, a median PFS of 10.2 months, and an MST of 27.6 months with a 1-year survival rate of 89.0%. Our efficacy results are comparable to those of other recently reported FOLFOX4 regimens for metastatic colorectal cancer, although the RR of 40.0% is slightly lower than previously reported rates of 45% [9] to 49.5% [5]. One possible explanation might be that the frequency of treatment delay of up to 2 weeks in almost 40% of cases in the fourth and fifth treatment course might diminish the confirmation rate of response (Fig. 2). However, it is true that the RR of 40.0% with 95% CI from 28.1 to 53.2% met the primary endpoint of this study.

In this study, the allowance for a patient ineligibility rate was set at 20%, which is twice the ordinary rate of 10%, because the aim of this study was to evaluate the new "wait and go" strategy concept. Fortunately, all 58 accrued patients were treated with this strategy. During this study, the new molecular targeting drug, bevacizumab, was approved at April 2007 by the Japanese regulatory authorities, and the combination of bevacizumab and chemotherapy including the FOLFOX4 regimen became one of the standard therapies for metastatic colorectal cancer in Japan. The introduction of bevacizumab to clinical practice slowed patient accrual in this trail. At 2 years from the start of this study, the number of enrolled patients reached 58 patients, which was more than the required 49 patients initially estimated as necessary for statistical evaluation of this trial. We halted accrual of patients in April 2008 in accordance with the recommendation of the safety monitoring committee.

The grading system, originally developed by Levi and co-workers [16], takes into account both intensity and duration of symptom-related oxaliplatin-induced neurological toxicity. At present, the most commonly used neurological toxicity scale is the NCI-CTC, which considers only the intensity of neuropathy. Our grading system used in this study was consistent with that by Levi et al. [16, 17], in terms of the consideration of both intensity and duration of symptom-related oxaliplatin-induced neurological toxicity. The duration reported by Levi et al. was within 1 week or 2 weeks [16, 17]. Because the new cycle of FOLFOX4 is begun every 2 weeks, we decided on 2 weeks as an appropriate period to evaluate grade 1 or 2 paresthesia. However, the criteria for grade 3 neurological toxicity (painful paresthesia or persistent functional impairment) used in our study are similar to that of the NCI-CTC. Thus, our criteria are appropriate to indirectly compare the frequency of grade 3 neurological toxicity between other clinical trials and this trial.

The frequency of grade 3 neurological toxicity was 6.9% in this trial. In a European trial in advanced colorectal cancer, 18% of patients assigned to the FOLFOX4 regimen had grade 3 neurosensory toxicity during treatment [5]. The same rate was observed among patients assigned to the FOLFOX4 regimen in a North Central Cancer Treatment Group study in metastatic colorectal cancer [9]. In the Multicenter International Study of Oxaliplatin/5-Fluorouracil, Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), 12.4% of patients treated with FOLFOX4 developed grade 3 paresthesia during therapy [1]. The rates of grade 3 neurotoxicity in those studies are higher than the 6.9% observed in this study. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 study, the incidence of grade 3 neurotoxicity was reported to be 8.4% among patients treated with the FLOX regimen (500 mg/m^2 FU intravenous (IV) bolus weekly for 6 weeks plus 500 mg/m^2 LV IV weekly for 6 weeks with 85 mg/m^2 oxaliplatin IV administered on weeks 1, 3, and 5 of each 8-week cycle for three cycles [13, 14]). This lower incidence of grade 3 neurological toxicity was speculated to be partly due to the scheduled rest in the FLOX regimen. The 2-week wait in the FOLFOX4 regimen depending on the persistency of neurological toxicity might prevent grade 3 neurological toxicity, even in metastatic disease.

The dose reduction and discontinuation of oxaliplatin due to neurological toxicity has varied in different trials. Rothenberg et al. reported the 85 mg/m^2 oxaliplatin in FOLFOX4 was reduced to 65 mg/m^2 in cases of persistent paresthesia or dysesthesia with preserved function, but not activities of daily living (grade 2), or temporary (7–14 days) paresthesia or dysesthesia with pain or function impairment that interferes with activities of daily living (grade 3) [18]. Oxaliplatin was omitted from the regimen until recovery in the case of grade 2 persistent paresthesia or dysesthesia, or grade 3 temporary (1–14 days) paresthesia or dysesthesia. The incidence of grade 3 cumulative neuropathy is reported to be 3%. This lower incidence might be explained by the 6 cycles as the median number of treatment cycles, due to the second-line setting for progressive colorectal cancer after the irinotecan-containing regimen. In the study on first-line FOLFOX reported by de Gramount et al. [5], oxaliplatin was reduced in cases of persistent ($\geq$14 days) paresthesia or temporary (7–14 days) painful paresthesia or temporary functional impairment. In cases of persistent ($\geq$14 days) painful paresthesia or persistent functional impairment, oxaliplatin was omitted from the regimen until recovery. Paresthesia with pain and cumulative paresthesia interfering with function occurred in 10.5 and 16.3% of patients, respectively. The dose intensity was 76% for FU and 73% for oxaliplatin during all cycles, which is similar to the 76.7% for bolus FU and 77.8% for infusion FU and 76.9% for oxaliplatin in our study. Considering the similar dose intensity of oxaliplatin, the "wait and go" strategy might effectively prevent painful paresthesia or persistent functional impairment compared with previously reported conventional methods to reduce the dose and to discontinue oxaliplatin.

Our data have some limitations. First, our results were obtained in a single-armed phase II study including small number of patients. Additionally, FOLFOX4 was used without molecular targeting drugs such as bevacizumab [19] or anti-human epidermal growth factor receptor monoclonal antibodies [3, 6]. The independent studies are warranted to extrapolate this "wait and go" strategy to molecular targeting drug-containing regimens. Second, the primary endpoint in this trial was the RR, not the reduction in neurotoxicity. Prospective phase III trials, including larger numbers of patients, are needed to corroborate our

results. However, we believe that our results suggest that this "wait and go" strategy could be a treatment of choice for patients who are reluctant to encounter persistent neurological toxicity, especially in the palliative setting, with or without molecular targeting drugs. Third, we evaluated the neurological toxicity based on clinicians' reports. In 2006, the FDA recommended that patient-reported outcomes should be considered the gold standard in addition to physician observation. Written in layman language, patient-reported outcomes have been advocated by the NCI since 2006 alongside NCI-CTC. Patients' assessment tools should be used for greater accuracy of interpretation of patient-reported outcomes [15, 23].

In conclusion, the "wait and go" strategy may be effective to prevent painful paresthesia or persistent functional impairment during treatment while maintaining the efficacy of the FOLFOX4 regimen for metastatic colorectal cancer. Further evaluation is needed to examine whether this strategy can be compared with the "stop and go" strategy [22].

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Conflict of interest No authors have any conflict of interest.

Appendix

The following investigators participated in the study: Mitsugu Kochi, Ken Hagiwara (Nihon University School of Medicine, Tokyo, Japan); Yuki Tanabe (Asahikawa Medical University, Hokkaido, Japan); Eiji Meguro, Akinori Takagane, Makoto Kobayashi (Hakodate Goryokaku Hospital, Hokkaido, Japan); Hiroyuki Shibata, Kou Miura (Tohoku University, Miyagi, Japan); Masayuki Sato (Miyagi Cancer Center, Miyagi, Japan);, Yutaka Hoshino, Fumihiko Osuka (Fukushima Medical University, Fukushima, Japan); Michitaka Nagase (Jichi Medical University, Tochigi, Japan); Miki Adachi (IUHW Mita Hospital, Tokyo, Japan); Kenji Katsumata (Tokyo Medical University, Tokyo, Japan); Masanori Yoshino (Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan); Reiji Aotake, Koji Doi (Fukui Red Cross Hospital, Fukui, Japan); and Takuji Fukui (Midori Municipal Hospital, Aichi, Japan).

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