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ORIGINAL ARTICLE

The central vein access port and catheter in outpatient chemotherapy for colorectal cancer: a retrospective study of 101 patients

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Abstract
Purpose The central venous access port (CV-port) system was examined in a series of colorectal cancer (CRC) patients.
Methods One hundred and one CRC patients underwent chemotherapy with the 5-fluorouracil + oxaliplatin (FOLFOX) or 5-fluorouracil + irinotecan regimen. The complications of the CV-port system were retrospectively assessed.
Results The CV-port system was placed in a total of 101 patients. The patients received a total of 1035 courses of these regimens. Eight complications occurred in the 101 patients (7.9%). The complications included three instances of catheter rupture, two thrombotic events around the catheter, and three infections at the site of the port or catheter. The complications were identified after a median of nine courses (range 6–16) and 135 days after the placement of the CV-port system. Sixty-six of the 101 patients switched their regimen from FOLFOX to another regimen, and 4 of these 66 patients (6.1%) experienced complications associated with the CV-port system. There were 25 subjects who were admitted to the hospital emergency wing during the chemotherapeutic regimens, and 4 of these patients (16%) had complications associated with the CV-port system.
Conclusions The complications of the CV-port system occurred at a defined rate, therefore the early diagnosis and the appropriate treatment to address these complications is crucial.

Keywords Colorectal cancer · Outpatient chemotherapy · Central venous access port · Complication · Pinch-off

Introduction

Completely implantable port systems were first introduced in the early 1980s. A variety of anticancer agents have been administered while using the devices without difficulty, and the patient acceptance of this system is excellent [1]. Late complications may occur, including catheter rupture and embolization, venous thrombosis, pocket infection, and port-related bacteremia. However, these devices have a long working life and a low rate of patient complications, and are of great value to patients who require long-term or cyclic intravenous treatments [2]. These data support the increasing use in current oncologic medical practices. The gastrointestinal division originally used the central venous access port (CV-port) system, either for administering chemotherapy to patients with gastric cancer, to provide nourishment to patients with short bowel syndrome, or for the treatment of patients with other conditions. The CV-port system has been extensively used since its introduction in colorectal cancer (CRC) patients receiving the 5-fluorouracil + oxaliplatin (FOLFOX) or 5-fluorouracil + irinotecan (FOLFIRI) + bevacizumab [3] chemotherapy.

A summary of this study was presented at the 108th Annual Meeting of the Japan Surgical Society in 2008 and the 46th Annual Meeting of the Japan Society of Clinical Oncology in 2008.

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Patients and methods

Patients and chemotherapeutic regimens

One hundred and three CRC patients underwent FOLFOX or FOLFIRI chemotherapy between April 2005 and March 2008 at our institution. One hundred and one of the 103 patients (98%) underwent CV-port system placement. Two patients could not receive the CV-port, because one patient had a mechanical valve and the other experienced difficulty in the placement of the CV-port. The 101 remaining patients (range 27–82 years of age, with a median age of 62 years) underwent chemotherapy for unresectable metastatic CRC, and also underwent adjuvant chemotherapy following hepatectomy. The regimens consisted of the modified FOLFOX-6 (m-FOLFOX 6), FOLFOX-4, or FOLFIRI regimens. The regimens consisted of a continuous infusion of 5-fluorouracil (5-FU) using a portable disposable pump, which was manufactured by Baxter (Deerfield, IL, USA).

Ports and routes of access to the central vein and maintenance of ports

Central venous access ports were placed by surgeons in the CRC patients. An indwelling catheter was inserted from the right subclavian vein at the lateral side using diagnostic imaging guidance and fluoroscopy to confirm that the catheter was placed in the superior vena cava. The ports were placed at the jugular vein or the inguinal vein if the surgeon experienced difficulty placing it in the subclavian vein. All 101 patients had a single-lumen Groshong 8-F catheter and an MRI-Port (CR Bard, Summit, NJ, USA) implanted. The first one or two courses of the regimen were administered while the patients were hospitalized in order to monitor any adverse events. The CV-port was put in place, and the patients were educated about the chemotherapy. After one or two courses of chemotherapy in the hospital, the patients underwent chemotherapy every 2 weeks as outpatients. Their ports were punctured by a doctor with a Huber-pointed needle. The doctor confirmed whether there was redness, swelling, or pain around the port, and confirmed that the natural drip was smooth before the patient was connected to the pump. The state of the catheter was regularly checked with chest X-rays every 3 months. The needle was removed without a saline flush after chemotherapy by the patients themselves or their family doctor.

The frequency and types of complications involving CV-ports and catheters were retrospectively evaluated. We also examined the instances of emergency hospital outpatient admission during chemotherapy and the reasons for changing to other regimens. The purpose of the present study was to demonstrate the placement methods and maintenance of the CV-port system for preventing and identifying late complications.

Results

A total of 101 patients underwent the FOLFOX regimen, and a total of 750 courses were administered (median 8 courses per patient). Forty of the 101 patients also received the FOLFIRI regimen, and a total of 270 courses were administered (median 6 courses). An overall total of 1035 courses were administered (median 10). Eight patients had central vein access port and catheter complications (7.9%). The complications associated with the central vain access port and catheter occurred at a median of 9 courses (range 6–16) and at a median time of 135 days after putting the CV-port system in place (Table 1).

Table 1 Complications of the central venous access port and catheter

	Total patients	Patients with complications
Number of patients	101	8
Sex, male/female	66/35	6/2
Age, median (range)	62 (27–82)	69 (65–81)
Courses of chemotherapy, median (range)	10 (1–25)	9 (6–16)

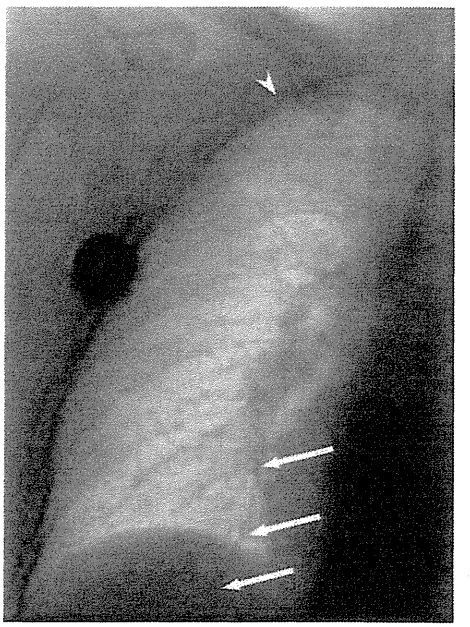

Fig. 1 Pinch-off syndrome and fracture of the catheter. The catheter was transected between the clavicle and the first rib (*arrowhead*), and the tip of the catheter was wedged into the pulmonary artery (*arrow*)

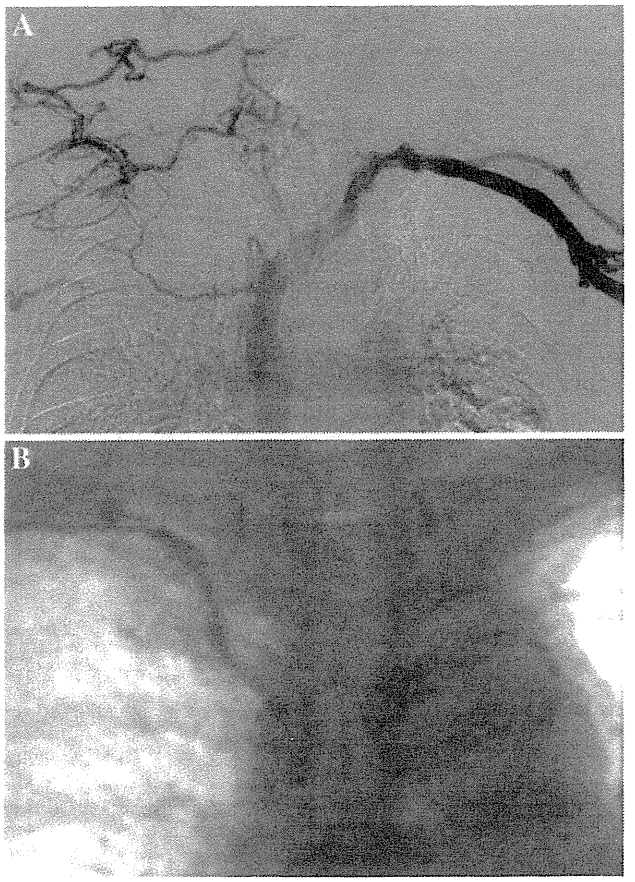

Fig. 2 A case of thrombosis around the site of the catheter (fibrin-sheath formation). **a** Contrast medium was injected from the bilateral median veins; however, the contrasting effect was not seen in the right subclavian vein, and it was concluded that a collateral pathway had developed. **b** There was no outflow of contrast media from the catheter tip, and a light contrasting effect was observed around the catheter

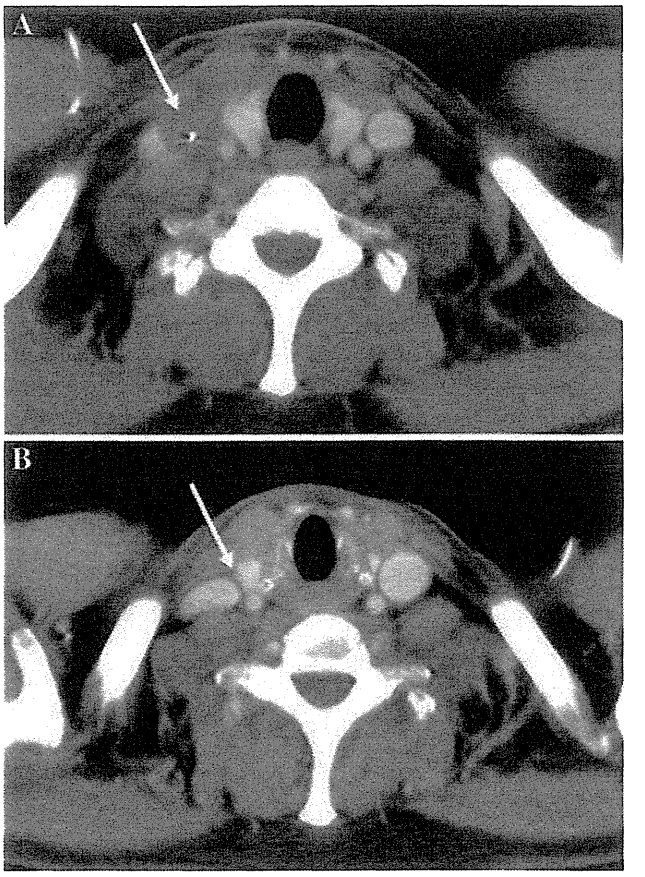

Fig. 3 Cases of thrombosis in the internal jugular vein. **a** The tip of the catheter was detected in an internal jugular vein and there was thrombosis around the catheter (*arrow*), as observed on contrast computed tomography. **b** Thrombosis in the internal jugular vein improved (*arrow*) after 5 months of warfarin treatment

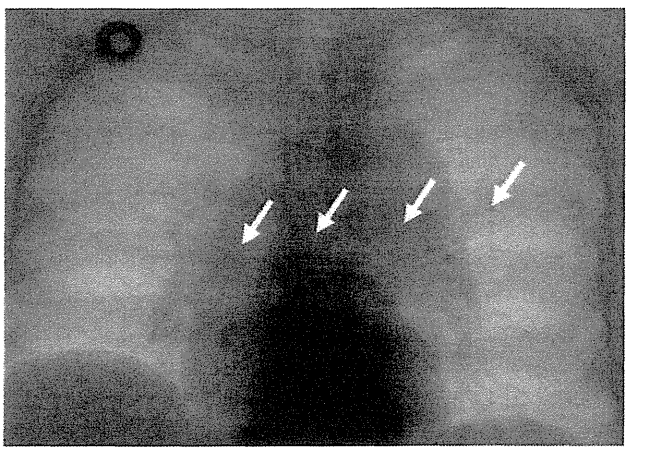

Fig. 4 Port connector rupture, connection portion coming off. The catheter was wedged into the pulmonary artery (*arrow*). The catheter was not fractured, and the rupture was judged to be caused by the catheter separating from the port connector

The incidents involved catheter pinch-off syndrome (POS) and fracture of the catheter ($n = 1$, Fig. 1), thrombosis around the catheter ($n = 2$, Figs. 2, 3), the connection portion of the port and catheter coming off ($n = 1$, Fig. 4), the flexure of the catheter ($n = 1$, Fig. 5), and the infection of the site of the port or catheter ($n = 3$) (Table 2).

Sixty-six of the 101 patients changed their regimen from FOLFOX to other regimens. Thirty-seven subjects were switched because of progressive disease (56.1%), 22 patients switched due to an adverse event (33.3%), and 4 patients were switched because of complications associated with the CV-port system (6.1%). The adverse events included peripheral neuropathy in 13 patients (19.7%), allergy in 5 patients (7.6%), and myelosuppression, interstitial pneumonia, and one patient's request (Table 3).

There were 25 patients admitted to the emergency department during the FOLFOX or FOLFIRI chemotherapeutic regimen, and 3 of 25 patients (12.5%) had adverse effects including pyrexia with neutropenia, severe anorexia, and acute exacerbation of interstitial pneumonia. However,

4 subjects (16.7%) required an emergency hospital admission due to complications associated with the CV-port system (Table 4).

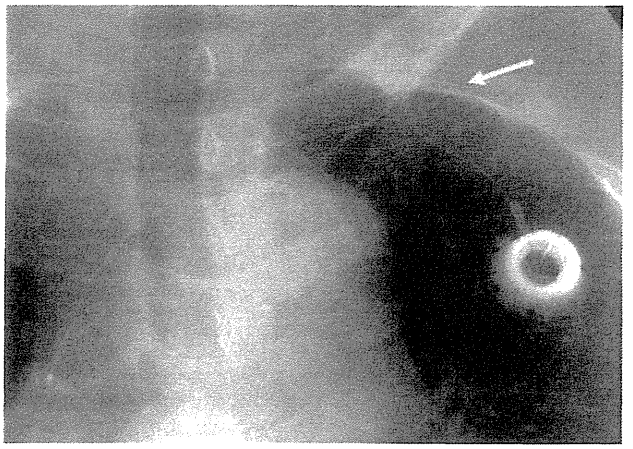

Fig. 5 Flexure and obstruction of the catheter. The catheter was bent in the subcutis (*arrow*), not in the subclavian vein, and was therefore manually repositioned

Discussion

FOLFOX or FOLFIRI regimen administration with a continuous infusion of 5-FU may be switched to a combination of an oral anticancer drug, such as S-1 or capecitabine, with irinotecan or oxaliplatin (IRIS, XELOX, etc.) [4–6]. However, the FOLFOX and FOLFIRI regimens are administered to CRC patients because there is a large amount of evidence indicating the efficacy, safety, and feasibility of these regimens.

Complications have been associated with the long-term placement of a CV-port and catheter [7–10]. The current series demonstrated complications in 8 of 101 patients (7.9%). The frequency of complications that occurred in association with the CV-port system during the chemotherapeutic treatment of outpatients in the present study was consistent with past reports. Several CRC patients required hospitalization for complications associated with the catheter. Furthermore, the complications of the CV-port and catheter caused some patients to change to another regimen (6.1%) or to require emergency treatment (16.7%). Outpatient chemotherapy was safely performed for the

Table 2 Summary of complications of central venous access-ports or catheters, excluding three patients with a catheter infection

Age (years)/sex	Chief complaint	Complication	Treatment
71/F (9)[a]	Pain around the port	Pinch off syndrome	Extraction of the catheter by interventional radiology
		Fracture of the catheter	Change to IRIS regimen
68/M (5)	Pain around the port	Thrombosis	Extraction of the catheter
		Fibrin sheath formation	Change to IRIS regimen
62/M (9)	Right neck pain	Thrombosis, dislocation	Extraction of the catheter
		Right internal jugular vein	Anticoagulant and change to the IRIS regimen
73/M (11)	Swelling around port	Port connector rupture	Extraction of the catheter by interventional radiology
		Connection portion coming off	Catheter replacement
81/M (13)	Poor infusion	Flexure of the catheter	Repositioning: stretch the catheter out
		Bent in subcutis	

IRIS regimen: combination therapy of S-1 and irinotecan

[a] Courses of chemotherapy in parentheses

Table 3 Reasons for changing from the FOLFOX regimen to another regimen

Reason (n = 66)	Number	Percentage	Age (years) Median	Sex M/F	Courses of chemotherapy
Progressive disease	37	56.1	61	24/13	8
Adverse events	22	33.3			
Peripheral neuropathy	13	19.7	63	10/3	10
Allergy	5	7.6	55	2/3	10
Myelosuppression	2	3.0	58	2/1	4
Interstitial pneumonia	1	1.5	75	1/0	8
Patient's request	1	1.5	44	0/1	2
Complication of CV-port system	4	6.1	69	3/1	12
Others	3	4.5	61	2/1	10

FOLFOX 5-fluorouracil + oxaliplatin, *CV-port* central venous access port

Table 4 Emergency hospital admissions during FOLFOX or FOLFIRI chemotherapy

Reason ($n = 25$)	Number	Percentage
Progressive disease	9	36
Adverse events	3	12
Peripheral neuropathy	0	0
Allergy	0	0
Myelosuppression	0	0
Interstitial pneumonia	1	4
Pyrexia with the neutropenia	1	4
Severe anorexia	1	4
Complication of CV-port system	4	16
Surgical site infection	2	8
Others	7	28

FOLFOX 5-fluorouracil + oxaliplatin, *FOLFIRI* 5-fluorouracil + irinotecan, *CV-port* central venous access port

majority of cases in our hospital. However, some issues remained, such as the occurrence of complications associated with the CV-port system, which led to changes to either another treatment regimen or to emergency hospital admission. These complications associated with the port and catheter included three instances of catheter rupture and embolization, venous thrombosis, and infection. We herein discuss the placement methods, the appropriate maintenance of CV-ports, and the measures taken to address these complications when they occur.

Catheter rupture and embolization

Pinch-off syndrome occurs when the CV access devices placed via the subclavian vein become obstructed due to thrombosis, impingement against a vein wall, or compression between the clavicle and the first rib. Luminal narrowing and complete catheter fracture occur in approximately 1% of catheter placements [11]. One case of catheter pinch-off was experienced at our institution during the study period. The patient did not report an active exercise history, but the subject had a small physique, weighed 45 kg, and was 145 cm in height. A catheter tip measuring 5 cm in length caused an embolus to a pulmonary artery. The catheter was withdrawn with a snare from the right inguinal vein by a radiologist. A puncture point is important to avoid pinch-off points. The catheter should be preferentially placed on the lateral side of the subclavian vein or in the internal jugular vein to avoid a pinch-off point [12]. Peripheral arm ports have been implanted in some CRC patients with no incidences of catheter POS [13]. The supraclavicular technique provides the best results with regard to the percutaneous introduction of large-bore central venous catheters [14]. At our institution, the most general approach from the right subclavian vein is the first choice of a puncture. There are no reports of cases that have an increased tendency to have pinch-offs, but we perform a puncture from another portion; namely, the right supraclavian vein or left subclavian vein, not the right subclavian vein, due to the fact that patients who actively exercise or have a small physique may experience POS.

Port connector rupture is usually caused by the method used to place the CV-port device. The method for connecting a port and catheter varies with the CV-port device, and the surgeon must confirm the type of CV-port device and the method used to ensure a proper connection.

Venous thrombosis

Catheter-related central venous thrombosis (CRCVT) occurs at a rate of 12–66% [15, 16]. In a prospective study, CRCVT was observed in 63 of 95 (66%) patients; however, it was symptomatic in only 4 of 63 (6%) of these patients [15]. There is no prognostic marker for venous thrombotic complications [16]. Three recent clinical trials investigated the effects of prophylactic anticoagulation with either low molecular weight heparin or low dose warfarin in cancer patients who had central venous devices [17–19]. However, these studies did not support the routine use of prophylactic anticoagulation in cancer patients with venous catheters to prevent catheter-induced thrombosis. Based on these results, routine anticoagulation is not recommended [20]. Anticoagulant administration just after the placement of the CV-port system is not used in our hospital. Two thrombosis cases were detected at our institution during the study period. These patients were diagnosed by injecting contrast media from the port and median vein on the port insertion side. The IRIS regimen (a combination therapy of the oral anticancer drug S-1 and irinotecan) was administered for the current patient series when the CV-port could not be replaced due to thrombosis. In the present study, thrombosis improved after the administration of anticoagulant therapy. Both patients had the CV-port system put in place again, and the FOLFOX regimen was restarted.

Infection

A diagnosis of a catheter-related infection might be difficult in the absence of local signs of inflammation [21]. Routine device removal is not recommended for most patients. Empirical antibiotics are administered when the patient presents with sepsis or septic shock. Port systems must be removed in case of a persistent relapse of infection after antibiotic treatment, at signs of port or catheter tunnel infection, for unstable patients, or after the development of systemic complications [22, 23]. However, CRC patients undergoing perioperative chemotherapy have had highly

invasive surgery, and the general opinion is that these guidelines do not apply to most of these patients. A high fever after CRC resection is usually attributable to an infection at the surgical site or an infection of the CV-port system. In our hospital we experienced a patient who demonstrated complications associated with a biliary fistula after hepatectomy, who continued to have a high fever after antibiotic treatment. The CV-port system was withdrawn, but no bacteria were detected on the catheter. However, we thought that the CV-port system should be withdrawn in such a case, contrary to popular opinion.

In conclusion, the management of the CV-port system is an important factor in the administration of chemotherapy to outpatients with CRC. We have described proper CV-port system placement and have summarized a recent report about the tendencies of port complications. We have also explained measures that were used to treat the complications in our experimental cases. The chemotherapeutic treatment of outpatients with the CV-port system is therefore best performed when the physicians are aware of these complications and how to best treat patients for CV-port complications without compromising their anticancer treatment.

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Gastric Cancer
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ORIGINAL ARTICLE

A randomized phase-II trial comparing sequential and concurrent paclitaxel with oral or parenteral fluorinated pyrimidines for advanced or metastatic gastric cancer

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Abstract

Background The purpose of this study was twofold: (1) to compare S-1 with infusional 5-fluorouracil (FU) to determine which would be a better partner of paclitaxel (PTX), and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

Methods The 161 eligible patients were randomized into four arms to receive the following regimens: A (sequential), intravenous 5-FU at 800 mg/m^2 for 5 days every 4 weeks followed by weekly PTX at 80 mg/m^2; B (sequential), S-1 at 80 mg/m^2 for 4 weeks and 2-week rest followed by PTX; C (concurrent), intravenous 5-FU at 600 mg/m^2 for 5 days and weekly PTX at 80 mg/m^2 every 4 weeks; and D (concurrent), S-1 for 14 days and PTX at 50 mg/m^2 on days 1 and 8 every 3 weeks. The primary endpoint was the overall survival (OS) rate at 10 months.

Results The ten-month OS rates in arms A, B, C, and D were 63, 65, 61, and 73%, respectively. The OS was best in the concurrent S-1/PTX arm, with a mean survival time of

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15.4 months, but no significant difference was observed between the four arms. Response rates were higher in the concurrent arms than in the sequential arms.

Conclusion Our study did not show sufficient prolongation of survival with the concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with less toxicity. In patients who are ineligible for cisplatin (CDDP), sequential treatment starting with S-1 and proceeding to PTX would be a good alternative strategy, considering quality of life (QOL) and the cost-benefits of an oral agent as first-line treatment.

Keywords Advanced gastric cancer · Paclitaxel · S-1 · Sequential chemotherapy · Concurrent combination chemotherapy · Randomized phase-II trial

Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide [1]. Most patients (except those from northeast Asian countries) present with advanced, inoperable, or metastatic disease, and the 5-year survival rate is approximately 10–15%. Palliative chemotherapy for advanced disease improves survival as compared with the best supportive care [2–4]. Despite the innumerable efforts of investigators in various countries to test various chemotherapeutic and immunotherapeutic agents and combination regimens, there has been little progress in the therapy for patients with advanced gastric cancer.

Probably because there is less evidence regarding the treatment of gastric cancer compared to that of other malignancies, the standard treatment for gastric cancer differs from country to country, although most of the "standard" regimens do not have sufficient evidence. Moreover, the insurance systems in most western countries approve only first-line treatment, and in these countries, doublet or triplet therapies could be the standard choice, while some countries, including Japan, approve second- and greater-line strategies, where we can choose not only concurrent but also sequential strategies. Reflecting these historical and social circumstances, "standard" treatment for gastric cancer shows wide variety, with some confusion. In Japan, the evidence-based standard regimen involved continuous infusion of 5-fluorouracil (5-FU) only (JCOG9205) before the results of the Japan Clinical Oncology Group (JCOG) 9912 and SPIRITS trials had been obtained [5–7]. After the results of SPIRITS trial were shown, S-1 plus cisplatin (CDDP) has been accepted as the standard first-line treatment for patients with good condition, but S-1 without CDDP was also widely used in general practice. This means we still need an alternative strategy, whose sequence starts from a fluoropyrimidine (infusional 5-FU or oral S-1) with or without other agents.

As for candidates as the fluoropyrimidine partner, some potent agents have been approved for gastric cancer in the past two decades. One of the promising agents was paclitaxel (PTX) [8], which had shown beneficial results in single use or concurrent use with a fluoropyrimidine [9–12]. However, these studies were conducted as single-arm phase I–II trials. Hence, the choice between sequential and concurrent strategies for fluoropyrimidine and PTX remains unclear.

We therefore planned a randomized phase-II trial to compare the following four treatment regimens: A, sequential 5-FU monotherapy followed by PTX monotherapy; B, sequential S-1 monotherapy followed by PTX monotherapy; C, concurrent 5-FU plus PTX [11]; and D, concurrent S-1 plus PTX [12]. The purpose of the study was twofold: (1) to compare S-1 with infusional 5-FU to determine which was the better partner of PTX, and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

Patients and methods

The detailed study design and protocol treatment of this study has already been described by Morita et al. [13]. Below we outline a summary of the methodological issues in this study with the protocol (informed consent form) that was amended after the SPIRITS trial.

Eligibility criteria

Patients more than 20 years of age with histologically confirmed non-resectable advanced or recurrent gastric cancer were eligible. Patients who had undergone prior anti-tumor therapy (except for surgery and postoperative adjuvant chemotherapy) were excluded. Patients had to have adequate renal, hepatic, hematologic, and cardiac function, with an Eastern Cooperative Oncology Group performance status (PS) of 0–1. Patients had to be able to take food via the oral route to be considered for enrolment in the study.

The protocol was approved by the Institutional Review Board (IRB) of each institution, and written informed consent was obtained before treatment. Participating investigators were instructed to send an eligibility criteria report to the data center operated by the non-profit organization Epidemiological and Clinical Research Information Network (ECRIN). Eligible patients were registered and then randomized to receive either of the four treatment regimens (A, B, C, and D), using a centralized dynamic

randomization method with the following balancing factors: measurable disease according to criteria set by Response Evaluation Criteria in Solid Tumours (yes/no); disease type [inoperable advanced/postoperative recurrent (with postoperative chemotherapy)/postoperative recurrent (with no postoperative chemotherapy)]; PS (0/1); peritoneal metastasis based on diagnosis with images (yes/no); age (<75 years/≥75 years), and institution. Information regarding the necessary follow-up examinations and chemotherapy schedule was then sent from the ECRIN data center. The accrual started in December 2005 and was continued for 3 years.

Projected treatments

Based on previous trials, we adapted four promising regimens for this selection design trial [13]. Patients in arm A received sequential therapy with intravenous (i.v.) 800 mg/m^2 5-FU daily for 5 days every 4 weeks until progression, followed by PTX 80 mg/m^2 on days 1, 8, and 15 every 4 weeks. Patients in arm B received sequential therapy with 80 mg/m^2 of oral S-1 daily for 4 weeks and 2-week rest after the administration (total of 6 weeks per single course) until progression. This was followed by PTX, utilizing the same administration dose and schedule as that in arm A's second-line PTX. Patients in arm C received a combination therapy with 600 mg/m^2 5-FU (i.v.) daily for 5 days from day 1 and infusion of 80 mg/m^2 PTX on days 8, 15, and 22 every 4 weeks. Patients in arm D received a combination therapy with 80 mg/m^2 oral S-1 for 14 days from day 1 and infusion of 50 mg/m^2 PTX on days 1 and 8 every 3 weeks. In the sequential treatment arms A and B, the administration of 5-FU or S-1 monotherapy was discontinued if the following were observed: (1) disease progression or occurrence of new disease; (2) grade-4 nonhematological toxicities evaluated according to the Common Terminology Criteria for Adverse Events version 3.0; (3) adverse events causing patients to refuse treatment or causing a clinician to discontinue treatment; (4) increase in the tumor markers carcinoembryonic antigen (CEA) and/or cancer antigen (CA) 19-9 in two or more consecutive measurements or symptomatic progression (e.g., cancer pain and dysphagia). An irinotecan-containing regimen was recommended for use in case further lines of treatment were to be given.

Follow-up

Disease progression and occurrence of new disease were examined using radiographs, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, and thoracic CT and measurements of the tumor markers CEA and CA19-9. These examinations were performed at baseline and at least every 4–5 weeks during treatment. Blood tests and symptom checks were performed before treatment and at least every 2 weeks during treatment. In cases where therapy was discontinued owing to toxicity, clinicians followed up patients until they recovered from the effects of toxicity.

Study design and statistical methods

The primary aim of this study was to compare treatment regimens A–D in terms of the primary endpoint of the 10-month overall survival (OS) rate. In addition, OS and treatment failure curves were constructed as time-to-event plots using the Kaplan–Meier method [14]. Time-to-event curves were compared using log-rank tests and the hazard ratio (HR) estimated by Cox regression models [15]. The prevalence of grade-3 or grade-4 adverse events was compared between the treatment arms. Calculation of the sample size required 40 patients in each arm to assure 80% probability in order to select the best treatment arm [16] as long as the true expected 10-month OS rate exceeded that of any other arm by at least 15%. The total number of patients to be accrued was set at 160.

Protocol amendment after SPIRITS trial

After the results of the SPIRITS trial were publicized, standard first-line therapy in Japan shifted from monotherapies with 5-FU or S-1 to an S-1/CDDP combination. The protocol committee of the present trial discussed this issue and decided not to change the protocol treatments, because none of the treatment arms has actually been shown to be inferior to the S-1/CDDP combination. Instead, all patients who became candidates for accrual in the trial after the results of the SPIRITS trial were publicized were to be informed of the novel standard treatment in Japan, using a newly compiled explanatory note, and they were to be offered the alternative of receiving the combination therapy instead of participating in the trial. Each participating institution agreed on the use of the newly compiled explanatory note without correction in the study protocol itself, and case recruitment was re-started after the IRB approval of the amendment was obtained.

Results

A total of 161 patients were enrolled in the trial from December 2005 to November 2008. The numbers of patients in arms A, B, C, and D were 40, 40, 41, and 40, respectively. Two patients in arm A and two in arm C declined therapies before the start of the assigned treatment. Therefore, 38, 40, 39, and 40 patients in arms A, B,

C, and D, respectively, were considered to be eligible for evaluation (Fig. 1). Initial patient characteristics in the four arms were well matched (Table 1). The median age was 67 years (range 40–90 years).

Survival

The ten-month OS rates predetermined as the primary endpoint were 63, 65, 61, and 73% in arms A, B, C, and D, respectively. Although concurrent therapy with S-1 plus PTX demonstrated the best survival benefit among the four arms, the difference in OS rates between the arms with highest (D) and lowest (C) rates was less than the predetermined criterion (i.e., 15%). Kaplan–Meier survival curves did not show a significant difference between the four arms (Fig. 2). The survival rates in the sequential (A, B) and concurrent (C, D) arms were almost identical ($p = 0.93$) (Fig. 3a). In addition, no difference in survival was observed between the 5-FU-containing regimens (arms A and C) and the S-1-containing regimens (arms B and D) ($p = 0.83$) (Fig. 3b).

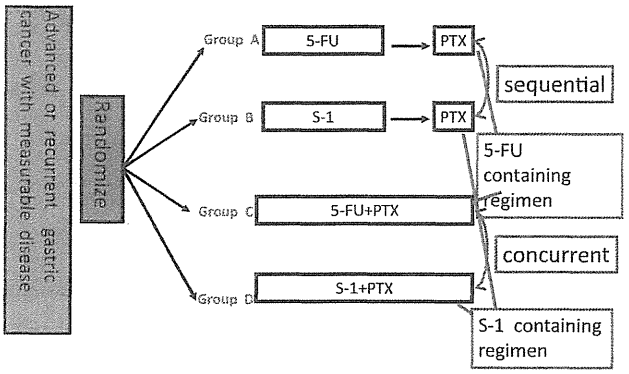

Fig. 1 CONSORT diagram that accounts for all patients. *5-FU* 5-fluorouracil, *PTX* paclitaxel

Time to treatment failure (TTF)

In arms A and B, TTF was calculated by the addition of the prior 5-FU or S-1 treatment period and the sequential PTX period. Median TTF values were 213, 222, 177, and 189 days in arms A, B, C, and D, respectively. No difference was observed between the four arms. However, Kaplan–Meier TTF curves for sequential and concurrent regimens showed better TTF in favor of sequential treatment compared with concurrent treatment (HR 0.71, 95%

Table 1 Patient characteristics

Treatment arm	Arm A 5-FU→PTX $n = 38$	Arm B S-1→PTX $n = 40$	Arm C 5-FU+PTX $n = 39$	Arm D S-1+PTX $n = 40$
Gender				
Male	25 (65.8%)	28 (70.0%)	28 (71.8%)	32 (80.0%)
Female	13 (34.2%)	12 (30.0%)	11 (28.2%)	8 (20.0%)
Age (years)				
Median	67.0	68.0	67.3	66.6
Range	48–79	51–81	40–82	47–90
74≤	31 (81.6%)	33 (82.5%)	31 (79.5%)	31 (77.5%)
≤75	7 (18.4%)	7 (17.5%)	8 (20.5%)	9 (22.5%)
Performance status				
0	29 (76.3%)	27 (67.5%)	25 (64.1%)	28 (70.0%)
1	9 (23.7%)	13 (32.5%)	14 (35.9%)	12 (30.0%)
Stage				
Non-resectable, no previous chemotherapy	31 (81.6%)	33 (82.5%)	32 (82.1%)	32 (80.0%)
Recurrent after curative surgery, adjuvant chemotherapy (+)	2 (5.3%)	1 (2.5%)	3 (7.7%)	3 (7.5%)
Recurrent after curative surgery, adjuvant chemotherapy (–)	5 (13.2%)	6 (15.0%)	4 (10.3%)	5 (12.5%)
Peritoneal metastasis				
Yes	9 (23.7%)	13 (32.5%)	5 (12.8%)	10 (25.0%)
No	29 (76.3%)	27 (67.5%)	34 (87.2%)	30 (75.0%)
Measurable disease				
Yes	19 (50.0%)	23 (57.5%)	17 (43.6%)	20 (50.0%)
No	19 (50.0%)	17 (42.5%)	22 (56.4%)	20 (50.0%)

5-FU 5-fluorouracil, *PTX* paclitaxel

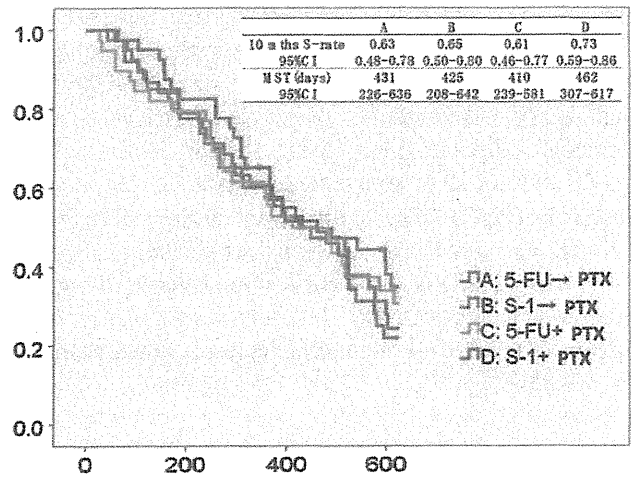

Fig. 2 Kaplan–Meier plot of overall survival in the four treatment arms. *S-rate* survival rate, *CI* confidence interval, *MST* median survival time

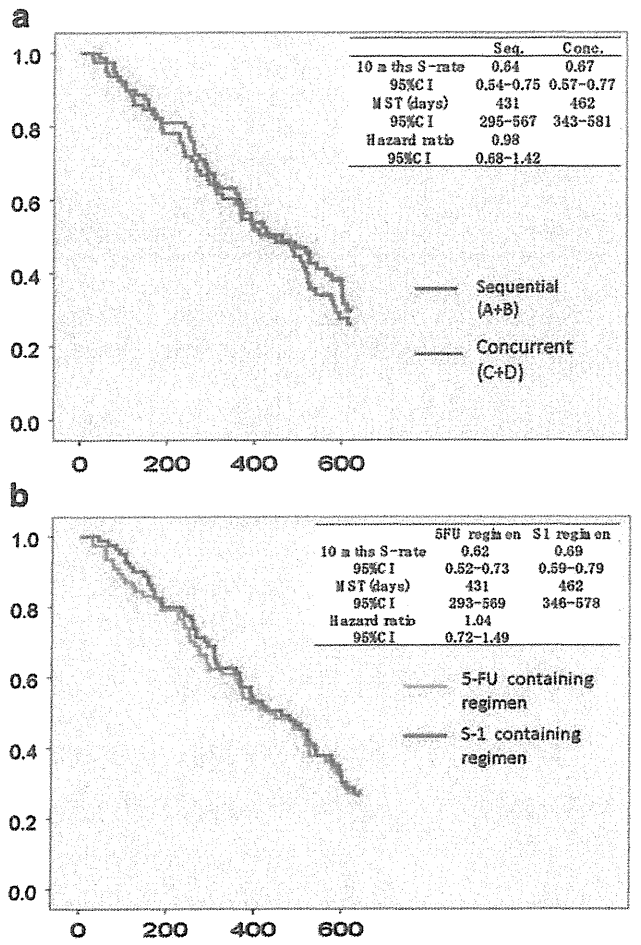

Fig. 3 Kaplan–Meier plot of overall survival by **a** sequential regimens (arms *A* and *B*) and concurrent regimens (arms *C* and *D*), **b** 5-FU-containing regimens (arms *A* and *C*) and S-1-containing regimens (arms *B* and *D*). *seq.* sequential, *conc.* concurrent

Table 2 Tumor response rates

Treatment arm/agent	*n* (With measurable lesion)	CR	PR	SD	PD	Response rate (%)
A						
5-FU	17	0	5	8	4	29.4
PTX	17	0	2	10	5	11.8
B						
S-1	20	1	4	10	5	25.0
PTX	14	1	1	10	2	14.3
C						
5-FU + PTX	13	0	9	2	2	69.2
D						
S-1 + PTX	19	1	7	11	0	42.1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

confidence interval [CI] 0.50–1.02, $p = 0.06$). A difference in TTF was not observed between the 5-FU-containing and S-1-containing regimens.

Response rates

The overall response rates in patients who had measurable disease are summarized in Table 2. Response rates were higher in the concurrent arms than in the sequential arms. The 5-FU and PTX combination regimen showed the best response rate among the four arms.

Toxicities

All patients could be assessed for hematological and non-hematological toxicities (Table 3). Ten of 78 patients (12.8%) who received sequential therapy and 26 of 79 patients (33.0%) who received concurrent therapy showed grade-3 or grade-4 neutropenia. With respect to hemoglobin decrease, 21 patients (26.2%) with the S-1-containing regimens showed grade-3 or grade-4 adverse events, whereas only 8 patients (10.4%) with the other regimens showed adverse events. No difference was observed in non-hematological toxicity.

Compliance

Compliance with S-1 treatment was inferior to that with 5-FU treatment. The median numbers of courses accomplished in the first- and second-line treatment of the

Table 3 Toxicities

	A: 5-FU→PTX (n = 38)	B: S-1→PTX (n = 40)	C: 5-FU+PTX (n = 39)	D: S-1+PTX (n = 40)
Hematological toxicities				
CTC Grade	>=3	>=3	>=3	>=3
Leucopenia (%)	7.9	7.5	10.3	7.5
Neutropenia (%)	13.2	12.5	25.6	22.5
Thrombocyte (%)	0.0	2.5	0.0	2.5
Hemoglobin (%)	10.5	32.5	10.3	20.0
Total Bil (%)	2.6	2.5	0.0	5.0
Hepatic Tox (%)	7.9	5.0	2.6	7.5
Non-hematological toxicities				
CTC Grade	>=3	>=3	>=3	>=3
Weight loss (%)	2.6	0.0	2.6	0.0
Fatigue (%)	0.0	0.0	0.0	0.0
Lassitude (%)	7.9	12.5	5.1	10.0
Anorexia (%)	10.5	12.5	7.7	10.0
Nausea (%)	2.6	5.0	5.1	2.5
Vomiting (%)	0.0	0.0	2.6	0.0
Stomatitis (%)	5.3	0.0	2.6	2.5
Diarrhea (%)	2.6	2.5	5.1	2.5
Neuropathy (%)	0.0	2.5	5.1	5.0

CTC Common Toxicity Criteria

sequential regimens were 4 (range 1–26) and 3 (range 1–8) in arm A and 6 (range 1–24) and 4 (range 1–30) in arm B, respectively. For the concurrent regimens, these numbers were 6 (range 1–24) and 7.5 (range 1–30) in arms C and D, respectively.

Discussion

The strategy for the chemotherapy of gastric cancer differs from country to country. In Japan, according to community standards, fluoropyrimidine monotherapy has been widely used as the first-line of a sequential strategy, whereas most western countries use doublet or triplet concurrent regimens without second-line treatment. In fact, little is known about whether concurrent regimens or a sequential strategy with satisfactory second- and greater-line treatments would be better. Although one trial has shown the superiority of doublet (S-1 with CDDP) treatment compared with S-1 alone even in Japan [7], other pivotal trials have failed to show the superiority of concurrent regimens [17, 18]. This suggests that sequential strategies may not be so bad if we can use adequate second- (and more)-line therapies in sequence. Thus, when we decided to evaluate PTX in a clinical trial, we created the study plan so as to evaluate whether PTX should be used in second-line (sequential) or in first-line (concurrent) treatment.

In accordance with the general rule in a randomized phase-II trial, in the present study we assumed that we should choose the best regimen in the aspect of 10-month overall survival (OS). However, as shown in the results, all four arms showed good survival times with very small differences. This finding suggests that the difference between concurrent and sequential strategies may be very small if we take enough care with the timing of regimen changes and are meticulous in surveying for clinical disease progression. Similar trends have been observed with some other malignancies; breast cancer is one of the examples. Several studies have been conducted to show the survival superiority of concurrent regimens, but superiority was seen only in TTF and the response rate (RR) [19, 20]. As a result, the sequential strategy is still used. Recently, the result of the GEST trial in pancreatic cancer showed a superior RR and a superior TTF in the combination arm. Despite this superiority, this concurrent strategy also failed to improve OS [21]. Our phase-II trial with its small sample size nevertheless suggests that the sequential strategy could be considered for the treatment of gastric cancer, along with other types of cancer, and that the sequential use of S-1 followed by paclitaxel (PTX) remains as an alternative for patients who are for some reason not indicated for the S-1/CDDP combination.

One more issue to be evaluated in our trial was the difference between infusional 5-FU and oral S-1. The results of a worldwide advanced gastric cancer trial (FLAGS trial) comparing S-1 plus CDDP (SF) versus 5-FU plus CDDP (CF) failed to show a superior effect of SF over CF [22]. The JCOG9912 trial has already shown no

inferiority of S-1 compared to infusional 5-FU in the first-line setting [6]. However, that trial did not limit the post-treatment, so the setting of PTX use in first- or second line mandatorily might show different results. The present study had started before the results of these two trials were disclosed. Consequently, it is important to check whether our results are in line with the data obtained in the JCOG9912 and the FLAGS trials. In our study, the OS, PFS, and RR for the 5-FU-containing and S-1-containing regimens were almost the same, without any significant differences, suggesting both oral and infusional fluorinated pyrimidine regimens have similar potency, a finding which would be confirmatory of the previous trials. In general, treatment with an oral agent would be more preferable both for the patients and for medical staff than a treatment requiring continuous intravenous infusion, with its risks of infection and thrombotic events.

In conclusion, our study did not show sufficient prolongation of survival with a concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with a lower incidence of neutropenia. In patients who are ineligible for CDDP, sequential treatment starting from S-1 and proceeding to PTX would be a good alternative strategy, considering the quality of life (QOL) and cost-benefits of an oral agent as first-line treatment.

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ORIGINAL ARTICLE

Phase II study of FOLFOX4 with "wait and go" strategy as first-line treatment for metastatic colorectal cancer

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Abstract
Purpose To evaluate the efficacy and safety of FOLFOX4 using "wait and go" strategy in treating metastatic colorectal cancer.
Methods The conventional FOLFOX4 was repeated every 2 weeks. We waited until the recovery of symptoms from persistent neurotoxicity within an added period of 2 weeks, before performing the next cycle ("wait and go" strategy).
Results We enrolled 58 patients, in whom a total of 481 cycles were administered (median 8 per patient; range 1–16). Toxicity was evaluated in 58 patients and response in 55. The major toxic effect was grade 3/4 neutropenia (33%). Painful paresthesia or persistent functional impairment was observed in 4 patients (7%). The response rate was 40% (95% confidence interval; 27.1–52.9%). The median progression-free survival time was 10.2 months, the 1-year survival rate was 89%, and the median overall survival time was 27.6 months.
Conclusions These findings indicate that this "wait and go" strategy reduces the frequency of persistent neuropathy while maintaining efficacy against metastatic colorectal cancer.

Keywords FOLFOX · Neuropathy · Metastatic colorectal cancer · Oxaliplatin · "Wait and go"

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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

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

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)

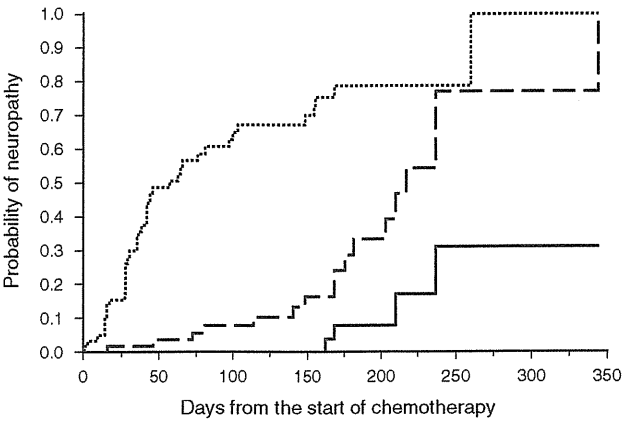

Fig. 1 Cumulative incidence of neuropathy. *Solid line*, grade 3 neuropathy ($n = 4$); *broken line*, grade 2 neuropathy ($n = 13$); *dotted line*, grade 1 neuropathy ($n = 24$)

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

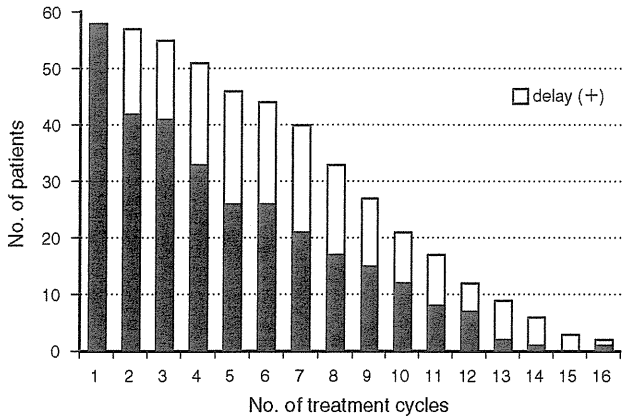

Fig. 2 The frequency of treatment delays in terms of treatment cycle. *Black bar*, numbers of patients who started the treatment within 29 days from the initial day of the previous chemotherapy cycle; *White bar*, numbers of patients who started the treatment over 29 days from the initial day of the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

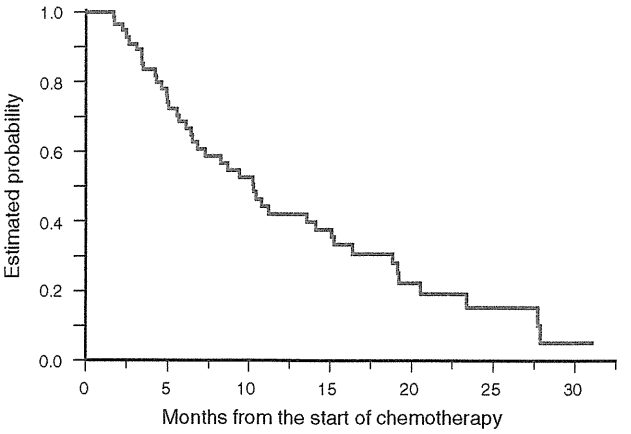

Fig. 3 Kaplan–Meier estimates of progression-free survival ($n = 58$)

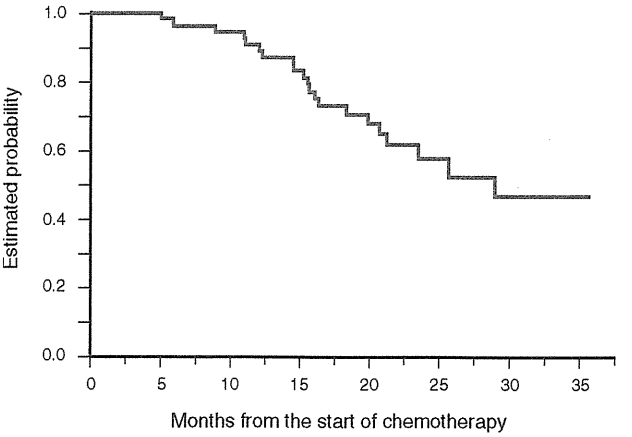

Fig. 4 Kaplan–Meyer estimates of overall survival ($n = 58$)

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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