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ORIGINAL ARTICLE

Randomized phase II trial of the prophylactic use of celecoxib for the prevention of oxaliplatin-related peripheral vascular pain in Capeox (YCOG1205)

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Abstract

Purpose Capeox is widely used as an adjuvant chemotherapy regimen of colorectal cancer that does not require central vein catheter insertion. However, oxaliplatin-related vascular pain with peripheral administration is a major adverse event. We assessed the preventive effect of Celecoxib on oxaliplatin-related vascular pain.

Methods A multicenter study of the Yokohama Clinical Oncology Group (YCOG) in Japan. This study was an open label, randomized non-comparative phase II study between Capeox without Celecoxib (C+ Group) and with it (C− group). The primary endpoint was the appearance frequency of grade ≥ 2 vascular pain according to the Verbal Rating Scale (VRS).

Results Between October 2012 and February 2014, 81 patients were recruited to this study and randomly divided into 2 groups: 38 patients in the C− group and 39 patients in the C+ group. Four cases were excluded at the analysis stage because they had not received the allocated intervention. The rate of grade ≥ 2 vascular pain was 55.3% in the C− group and 53.8% in the C+ group ($p = 1.000$).

Conclusions Celecoxib was unable to prevent oxaliplatin-related vascular pain in this study. However, it may be able to decrease the vascular pain that patients already have.

Keywords Oxaliplatin · Vascular pain · Celecoxib · Colon cancer · Capeox

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Introduction

Adjuvant chemotherapy including oxaliplatin is recommended in patients with stage II or III colorectal cancer [1–5]. Combined 5FU and oxaliplatin chemotherapy (FOLFOX) and capecitabine and oxaliplatin chemotherapy (Capeox) are widely used for this purpose. Because FOLFOX therapy requires the insertion of a central vascular catheter, the continuous administration of 5FU for 48 h, and a visit to the hospital every 2 weeks, Capeox is beginning to be used widely in Japan and some European countries.

Oxaliplatin is associated with characteristic adverse events of neuropathy and vascular pain. While vascular pain is not an issue with FOLFOX, as it is administered via the central vascular catheter, it is problem for some patients receiving Capeox. It was reported that 59% of patients for 2.9 days with Capeox without a central vascular catheter experienced transient vascular pain [6]. Some patients require a central vascular catheter insertion during treatment

due to vascular pain. Oxaliplatin-related vascular pain due to peripheral administration is thus a factor impeding the spread of Capeox therapy, and reducing vascular pain is a very important issue.

Celecoxib is a type of nonsteroidal anti-inflammatory drug (NSAID) and a cyclo-oxygenase (COX)-2 specific inhibitor with only a weak effect on COX-1. We selected this NSAID in an attempt to decrease vascular pain because this celecoxib has a lower rate of gastrointestinal and renal adverse events [7] than other NSAIDs. In addition, we suspected that it might be able to prevent pre-malignant adenomas [8–10] with potential chemopreventive effects against colon cancer by targeting COX-2 [11], vascular endothelial growth factor, NF-κB, caspase-3 [12], and the Wnt/-catenin signaling pathway [13, 14].

We performed a randomized controlled trial (RCT) to evaluate the clinical beneficial effects of celecoxib on oxaliplatin-related vascular pain.

Materials and methods

This study was multicenter, open label, randomized non-comparative phase II study. This study was approved by the relevant Institutional Review Board (IRB) at Yokohama Clinical Oncology Group (YCOG) hospitals. All patients with colon and rectosigmoid cancer received adjuvant chemotherapy of Capeox at YCOG hospitals in Japan between October 2012 and February 2014 (UMIN: 000008814). Eligible patient were 20–80 years old with pathological stage II and III colon cancer within 10 weeks after curative colorectal surgery who had an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and were using low-dose aspirin. Patients were excluded if they had a severe cardiovascular risk, severe dysesthesia, analgesic drug use, or a history of hypersensitivity, including aspirin-induced asthma and gastrointestinal ulcer. The institutional review boards of all participating hospitals approved the study.

Consenting patients were randomly assigned to the C+ group (Capeox therapy with 400 mg/day of celecoxib) or the C− group (Capeox therapy only) with stratification by PS, internal use of low-dose aspirin, and institution (Fig. 1). Oxaliplatin was administered according to the general regimen (Capeox: 130 mg/m^2 oxaliplatin on day 1 plus 2000 mg/m^2 capecitabine twice a day from the evening on day 1 to the morning on day 15, every 3 weeks) (Fig. 2). The patients in the C+ group took celecoxib as a premedication 2 h before starting oxaliplatin twice a day (400 mg/day) on days 1–21. If the patients in the C− group had vascular pain of grade ≥ 2 during this treatment, they were allowed to start the administration of celecoxib in the same way as C+ Group patients.

We used the Verbal Rating Scale (VRS) and Visual Analogue Scale (VAS) for the assessment of vascular pain by a medical therapist blinded to the patients' celecoxib administration. The VRS and VAS are commonly used pain scales. VRS is a four-point (Grade 0 = none, Grade 1 = mild pain, Grade 2 = moderate pain, Grade 3 = severe pain) categorical verbal rating scale. The VAS is a straight horizontal line 100 mm in length; the ends are defined as the extreme limits of the parameter to be measured orientated from the left (worst) to the right [best; i.e. from no pain (0) to the worst pain imaginable (100 mm)]. The patients marked the intensity of pain they were currently experiencing on the line, and the degree of pain was expressed by the length [15].

The primary endpoint was the frequency of grade ≥ 2 vascular pain assessed using the VRS. Patients who developed

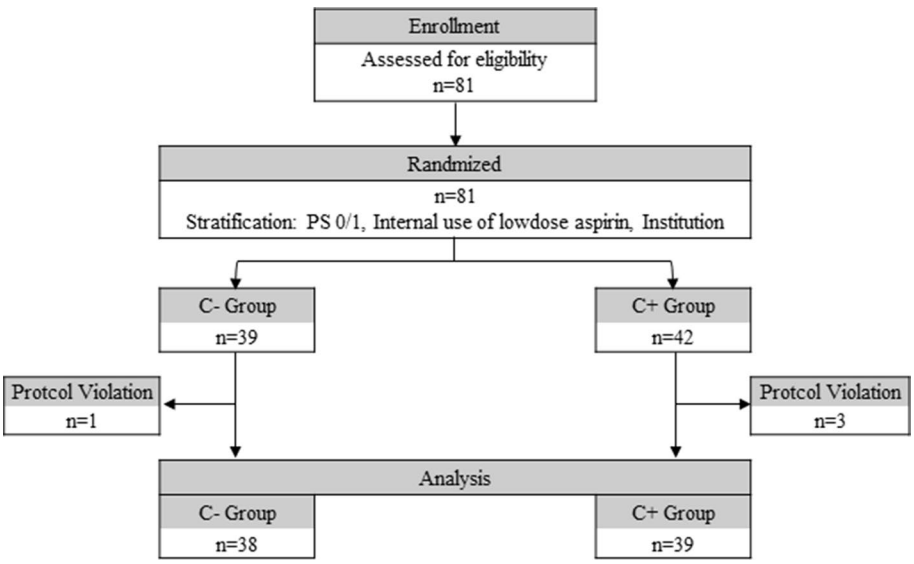

Fig. 1 Consort diagram

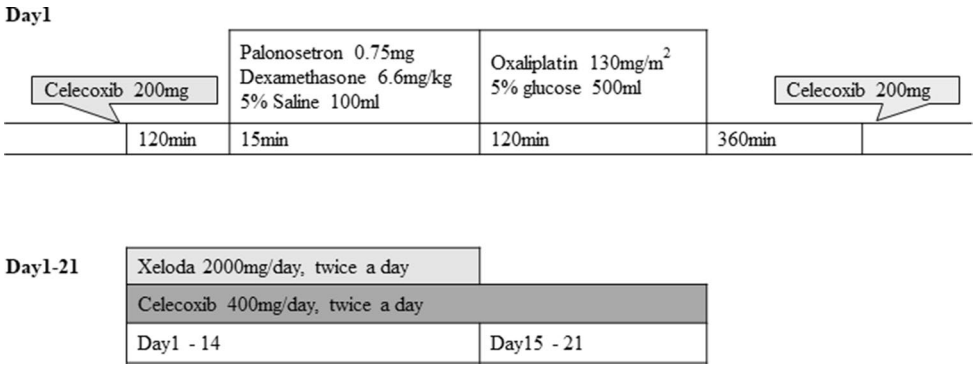

Fig. 2 Regimen of this study

grade ≥ 2 vascular pain in the C− Group received celecoxib, and we also examined the effect of the drug.

Statistical analyses

It was reported that 59% of patients with Capeox without a central vascular catheter experienced transient vascular pain [6]. The expectation for celecoxib to reduce severe vascular pain was 20% based on a study in which parecoxib (another NSAID) was effective in reducing the frequency and severity of propofol-related vascular pain. To detect this reduction at a 5% level of significance with 90% power, and taking into account a placebo effect of about 20% [16], 35 patients were deemed to be required for each group. Therefore, we included 40 patients in each group.

The *t* test and Mann–Whitney's *U* test were used in pairwise comparisons. The frequency of pain and its severity were compared using Fisher's exact test. A *p* value of 0.05 was considered significant.

Results

Between October 2012 and February 2014, 81 patients were recruited at 9 institutions and randomized into 2 groups: 42 patients in the C+ group and 39 patients in the C− group. Three patients in the C+ group and one in the C− group did not receive the allocated intervention. Therefore, 77 patients were evaluable for the analysis (C+ group: 39 patients, C− group: 38 patients). The characteristics of the 77 patients are shown in Table 1. The mean age was 64.1 years in the C− group and 65.1 years in the C+ group, and there were 24 and 26 men in each group, respectively. Stage II and III colon cancer were noted 16 (19.5%) and 61 (80.5%) patients in the C+ and C− groups, respectively. The difference in the patient characteristics between the two groups was not significant.

VRS grade ≥ 2 vascular pain was noted in 21 (55.3%) and 21 (53.8%) patients in the C− and C+ group, respectively, ($p = 1.000$) and the VAS was 5.51 and 5.22, respectively (Table 2). Adverse events are shown in Table 3. There was one case of grade 3 duodenal ulcer in the C+ group. Although the patient needed surgical treatment, he quickly recovered. Two patients had creatinine elevated in the C+ group. No patients had symptoms associated with cardiovascular events, and there were no severe adverse events requiring intensive care or related to death.

Table 1 Patients characteristics

	C− Group $n = 38$	C+ Group $n = 39$
Age, mean (SD), year	64.1 (11.9)	65.1 (10.1)
Gender, *n*, %		
Male	24 (63.2)	26 (66.7)
Female	14 (36.8)	13 (33.3)
ECOG Performance score, *n*, %		
0	38 (100.0)	39 (100.0)
1	0 (0.0)	0 (0.0)
Stage, *n*, %		
II	6 (15.8)	10 (25.6)
III	32 (84.2)	29 (74.4)
Comorbidity, *n*, %		
Hyper tension	2 (5.2)	0 (0.0)
Diabetes mellitus	2 (5.2)	0 (0.0)

ECOG Eastern Cooperative Oncology Group

Table 2 Outcome of vascular pain

	C− Group $n = 38$	C+ Group $n = 39$	Odds ratio (95% CI)	*p* value
VRS ≥ Grade 2, *n*, %				
No	16 (42.1)	17 (43.6)		
Yes	21 (55.3)	21 (53.8)		
Unknown	1 (2.6)	1 (2.6)	1.49 (−20.97 to 23.96)	1.000
VAS, mean, cm	5.51	5.22		0.652

Table 3 Adverse events

	C− Group ($n=38$)				C+ Group (n=39)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
General disorders	6 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)	7 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)
WBC decreased	7 (18.4)	10 (26.3)	0 (0.0)	0 (0.0)	5 (12.2)	10 (24.4)	0 (0.0)	0 (0.0)
Neutropnea	0 (0.0)	5 (13.2)	8 (21.1)	0 (0.0)	1 (2.4)	9 (22.0)	5 (12.2)	0 (0.0)
Plt decreased	13 (34.2)	8 (21.1)	1 (2.6)	0 (0.0)	14 (34.2)	1 (2.4)	1 (2.4)	0 (0.0)
Anemia	14 (36.8)	2 (5.3)	0 (0.0)	0 (0.0)	13 (31.7)	3 (7.3)	0 (0.0)	0 (0.0)
T-Bil elevation	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
AST elevation	12 (31.6)	0 (0.0)	1 (2.6)	0 (0.0)	9 (22.0)	3 (7.3)	0 (0.0)	0 (0.0)
ALT elevation	6 (15.8)	2 (5.3)	0 (0.0)	0 (0.0)	6 (14.6)	3 (7.3)	0 (0.0)	0 (0.0)
ALP elevation	9 (23.7)	1 (2.6)	0 (0.0)	0 (0.0)	7 (17.01)	0 (0.0)	0 (0.0)	0 (0.0)
Cr increased	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
Fever up	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Fatigue	9 (23.7)	3 (7.9)	1 (2.6)	0 (0.0)	9 (22.0)	5 (12.2)	3 (7.3)	0 (0.0)
HFS	8 (21.1)	4 (10.5)	6 (15.8)	0 (0.0)	6 (14.6)	6 (14.6)	11 (26.8)	0 (0.0)
Anorexia	8 (21.1)	4 (10.5)	3 (7.9)	0 (0.0)	10 (24.4)	5 (12.2)	4 (9.8)	0 (0.0)
Diarrhea	3 (7.9)	2 (5.3)	2 (5.3)	0 (0.0)	7 (17.01)	1 (2.4)	6 (14.6)	0 (0.0)
Nausea	10 (26.3)	7 (18.4)	2 (5.3)	0 (0.0)	13 (31.7)	2 (4.9)	2 (4.9)	0 (0.0)
Vomiting	0 (0.0)	1 (2.6)	2 (5.3)	0 (0.0)	1 (2.5)	1 (2.4)	1 (2.4)	0 (0.0)
Mucositis oral	0 (0.0)	1 (2.6)	1 (2.6)	0 (0.0)	5 (12.2)	2 (4.9)	2 (4.9)	0 (0.0)
Peripheral sensory neuropathy	16 (42.1)	10 (26.3)	5 (13.2)	0 (0.0)	19 (46.3)	11 (26.8)	4 (9.8)	0 (0.0)
Allergic reaction	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)	1 (2.4)	0 (0.0)
Duodenum ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

WBC white blood cell, *Plt* platelet, *T-bil* total bilirubin, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *Cr* creatinine, *HFS* hand foot syndrome

Fourteen of the 21 patients in the C− group who developed grade ≥2 vascular pain received celecoxib. The other seven declined the administration. Seven of the 14 patients showed a reduction in vascular pain below grade 2.

Discussions

To our knowledge, this report was the first focusing on vascular pain caused by oxaliplatin in a Phase II trial.

Capeox and FOLFOX have been widely administrated not only as adjuvant chemotherapy but also for unresectable or recurrent colorectal cancer. However, most patients receiving oxaliplatin chemotherapy develop peripheral neuropathy [17]. Patients with not only peripheral neuropathy but also oxaliplatin-related vascular pain due to peripheral administration have a seriously impaired quality of life (QOL). Unfortunately, no drugs have yet been proven effective in alleviating peripheral neuropathy and vascular pain.

Some methods for preventing vascular pain have been explored. These include warming the arm [18], warming the solution [19, 20], extending the administration duration (Japanese article only), diluting the solution [21], and adding dexamethasone to the infusion solution for neutralization [22, 23]. Vascular pain has been attributed to osmotic pressure and a low solution pH [22, 24]. However, given that the previous reports have all involved only a few cases and were not randomized, their findings have been unsuitable for use as evidence.

Although the present study failed to provide evidence supporting the efficacy of celecoxib for relieving oxaliplatin-related vascular pain, it was the first to explore the issue of oxaliplatin-related vascular pain. Parecoxib, which is an NSAID similar to celecoxib, was effective in reducing the frequency and severity of propofol-related vascular pain [25]. Our study unfortunately showed that celecoxib was not effective as a prophylactic agent against vascular pain caused by oxaliplatin. However, celecoxib was effective in patients who were already in pain. According to Nagao, fast-acting oxycodone hydrochloride hydrate also decreased vascular pain significantly in patients who were already suffering from pain [26]. Whether or not fast-acting oxycodone hydrochloride hydrate was suitable as a premedication for vascular pain due to oxaliplatin is unclear.

No adverse events were noted with celecoxib aside from one case of grade 3 duodenal ulcer (Table 3). We instructed the patient to properly ingest a proton pump inhibitor after the occurrence. No patients developed renal dysfunction, asthmatic attack, or cardiovascular events. Cardiovascular adverse are major adverse events associated with celecoxib [27, 28]. The APC study, which compared the efficacy and safety of Celecoxib (200 or 400 mg twice daily) and a placebo for reducing the occurrence of colorectal adenomatous polyps, was stopped because the patients receiving 400 mg of celecoxib twice daily showed a significantly increased risk of serious cardiovascular events and had a hazard ratio for death from cardiovascular events of 3.4 (95% confidence interval 1.4–7.8) compared to the placebo group [27]. This trial concluded that celecoxib use was associated with a dose-related increase in the composite endpoint of death from cardiovascular events and suggested that cardiovascular harm may result from the use of higher-than-approved doses of the drug. We fortunately noted no severe cardiovascular events in the present study, possibly because we selected the relatively low dose of 200 mg twice daily.

Several limitations associated with the present study warrant mention. First, this study was not a closed-label study, which may have resulted in some bias. Second, it is difficult to distinguish between vascular pain and acute peripheral neuropathy. We targeted vascular pain, but it may have been difficult for patients to distinguish these entities.

In conclusion, Celecoxib was unable to prevent oxaliplatin-related vascular pain in this study. However, it may be able to decrease the vascular pain that patents already have.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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