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Research Article

Preventive Effect and Safety of Pregabalin for FOLFOX-Related Peripheral Neurotoxicity in Patients with Advanced and Recurrent Colorectal Cancer: The Perpetual Study Estimated by United Sections in Gifu for Colorectal Cancer (Perseus CRC-01 Study)

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4. Keywords

Colorectal cancer; Neuropathic pain; Pregabalin; Adverse effects

1. Abstract

In patients with colorectal cancer, peripheral nerve symptoms as an adverse effect of oxaliplatin (L-OHP) can result in dose restrictions of L-OHP. Presently, there is no effective cure for the peripheral neuropathy caused by L-OHP. The objective of this study was to investigate the effect of PGN in unresectable and metastatic colorectal cancer patients with peripheral neuropathy. Target patients were those receiving L-OHP preparations FOLFOX6 or FOLFOX7 administered to treat unresectable and metastatic colorectal cancer and who suffered from Grade 1 or higher peripheral neuropathy according to CTCAE ver.4.0 (JCOG).The primary endpoint was a change in the evaluation of the onset of peripheral neuropathy to Grade 2 with the administration of pregabalin (PGN) after an accumulated dose of > 500 mg/m2 L-OHP was reached. Nine patients were enrolled in the ProspectiveI study period from December 2014 to March 2017.PGN was taken orally by 7 of the 9 patients; the other 2 patients refused to takeit. One patient stopped the oral intake of PGN because of conversion surgery after reaching the accumulated dose point, and the other patient refused oral PGN by stroll of adverse effects. The efficacy of the administration of PGNas supportive therapy against peripheral neuropathy was confirmed in 6 of the 9(66.7%) patients after they reached an accumulated dose of > 500 mg/m2L-OHP.,InConclusion,Step 1 of this prospective study showed acceptable efficacy and safety of PGN. Therefore, we will begin to plan Step 2.

2. Trial Registration: UMIN000012936: Registered 9 December 2014: Prospectively Registered.

3. Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events
JCOG : Japan Clinical Oncology Group
DXT: Duloxetine
GABA: Gamma-Aminobutyric Acid
GJG: Goshajinkigan
L-OHP: Oxaliplatin
PGN: Pregabalin, VEGF: Vascular Endothelial Growth Factor
EGFR: Epidermal Growth Factor Receptor
ECOG: Eastern Cooperative Oncology Group

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4. Introduction

FOLFOXtherapy, which uses oxaliplatin (L-OHP) with fluorouracil plus leucovorin, is one of the standard chemotherapies for unresectable and metastatic colorectal cancer. It was approved in Japan for progressive unresectable and metastatic colorectal cancer in April 2005 and became widely used in first-line combination chemotherapy. Recently, anti- vascular endothelial growth factor (VEGF) monoclonal antibodies and anti- epidermal growth factor receptor (EGFR) monoclonal antibodies such as molecular targeted drugs have appeared, and the efficacy of their combination with FOLFOX or FOLFIRI therapy has been confirmed [1-3]. In addition, this combination therapy has achieved a median survival time of more than 30months [4]. Although chemotherapy for colorectal cancer has progressed greatly; L-OHP, as one example, can cause peripheral neuropathy as one serious adverse reaction, and prophylaxis against such reactions is critical to ensuring that colorectal cancer patients can continue their chemotherapy. PGN is used to manage the neuropathic pain of diabetic peripheral neuropathy and post herpetic neuralgia. We believe that PGN as prophylactic therapy against adverse drug reactions can be prospectively investigated in the future. Therefore, the objective of this study was to investigate the effect of PGN in unresectable and metastatic colorectal cancer patients with peripheral neuropathy.

5. Material and Method

The objective of the present study was to investigate the efficacy and safety of PG Nagainst peripheral neuropathy that develops as an adverse drug reaction to the administration of L-OHP in colorectal cancer patients. This was a single-center prospective study that used a central registration method [5].

The target patients were those who receive dL-OHP preparations FOLFOX6 or FOLFOX7to treat unresectable and metastatic colorectal cancer and who experienced Grade 1 or higher peripheral neuropathy according to CTCAE (Common Terminology Criteria for Adverse Events) ver.4.0 (JCOG [Japan Clinical Oncology Group]) [6].

We enrolled 9 patients in Step 1 of this study performed by the Department of Surgical Oncology, Gifu University School of Medicine and which ran from December 2014 to March 2017 (**Figure1**).

The patients needed to meet each of the following inclusion criteria to be considered eligible for enrollment: 1) Colorectal cancer confirmed by histology; 2) ability to undergo chemotherapy (patients with possible confirmed recurrence and those with recurrence> 6 months after adjuvant chemotherapy in which L-OHP was not used; 3) presence of an evaluable lesion according to RECIST (ver. 1.1) and ECOG Performance Status of 0 to 1; 4) age 20–75 years old at the time informed consent was obtained; 5) duration of survival was thought to be > 12 weeks from the start

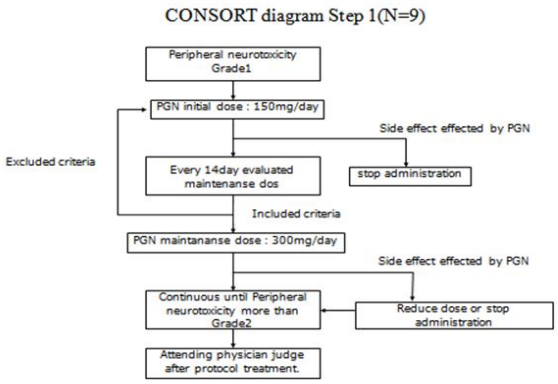

Figure1: CONSORT Diagram: PerSeUS CRC-01 study Step 1.

of FOLFOX treatment; and 6) oral administration was possible.

The primary endpoint was a change in the evaluation of the onset of peripheral neuropathy to Grade 2with the administration of PGN after an accumulated dosage of > 500 mg/m^{2}L-OHPhad been reached. Several setting designs were performed in this study using Simon's 2-stage design [7]. If this study satisfied the prescribed endpoint, it would be possible to enroll the remaining patients and accumulate additional cases. The standard of evaluation was defined by the physician and the pharmacist in charge,

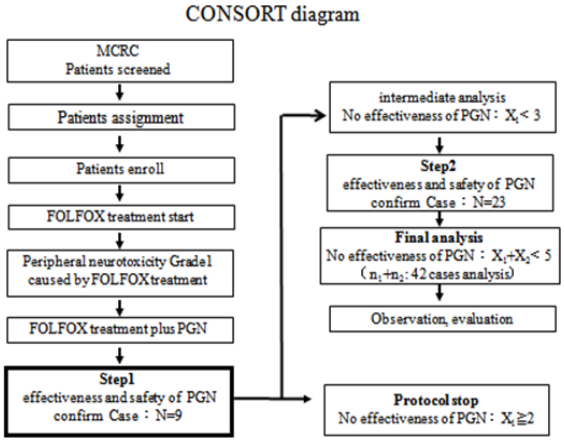

Figure 2: CONSORT Diagram: PerSeUS CRC-01 protocol.

and the evaluation was performed by these same two people (**Figure 2**).

6. Statistical Analysis

All data are presented as the mean ± standard deviation. The data were analyzed with the Student *t*-test, Wilcoxon signed-rank test, Kaplan-Meier method, log-rank test, and Pearson's product-moment correlation coefficient to determine statistical significances. A two-sided p-value of <0.05 was considered to indicate statis-

tical significance. All statistical analyses were performed using SPSS 11.5J software (SPSS Japan, Inc., Tokyo, Japan).

7. Results

Between December 2014and March 2017, 9patients were enrolled at the Department of Surgical Oncology of Gifu University School of Medicine. Intermediate analysis of this study was performed following the enrollment of the first 9 patients. If this study satisfied the prescribed endpoint, it would be possible to enroll the remaining patients and accumulate additional cases.

These9 patients comprising 7 men and 2 women with a median age of 64.3 (range, 50–73) years were divided into two treatment groups: the Anti-EGFR antibody treatment group (n=3) and the Anti-VEGF antibody treatment group (n=6).Primary sites of colorectal cancer were the cecum (n=1), ascending colon (n=1), descending colon (n=1), sigmoid colon (n=1), Rs (Rectum) (n=2), Ra(Rectum) (n=1), and Rb (Rectum) (n=2).

Intermediated analysis of the Step1 results showed no exacerbation of adverse events of greater thanGrade2.The results of the administration of PGN after the accumulated dose of L-OHP was

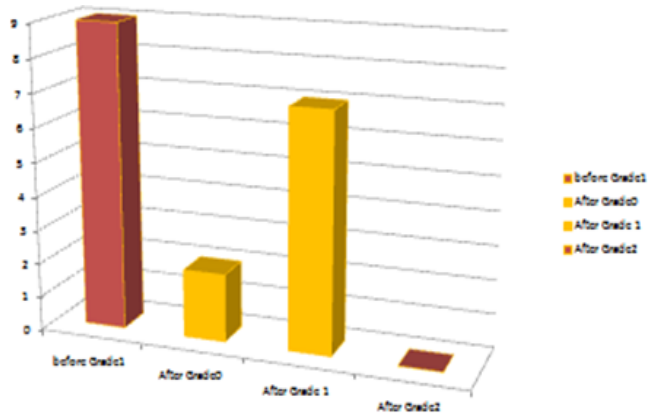

Figure 3: Effect of pregabalin on symptom improvement among patients with peripheral neurotoxicity.

reached showed that 6 patients remained at Grade 1, 1 patient improved to Grade 0, and no patient experienced exacerbation to Grade 3 (**Figure 3**).

PGN was administered orally in 7 of the 9 patients, and the other 2 patients refused oral intake by hesitate adverse event of PGN. One patient stopped oral intake of PGN due to conversion surgery(after reaching an accumulated dose of> 500 mg/m^2L-OHP). The other patient refused oral intake of PGN by stroll ofadverse effects. The efficacy of PGN supportive therapy for peripheral neuropathy was shown in 6 of the 9(66.7%)patients after reaching an accumulated dose of > 500 mg/m^2L-OHPwas reached (**Table 1**). Adverse effects of chemotherapy included diarrhea in 8 (88.8%) patients, vomitingin 5 (55.6%), thrombocytopenia in 5 (55.6%),stomatitis in 4 (44.4%),acne-like rash of Grade 1/2in 3

Table 1: Patient demographics of Per Se US CRC-01 study subjects.

Sex	Age	Chemotherapy	Outcome	Site	Metastasis	Grade	PGN intake
M	50	mFOLFOX6+Cmab	PR	S	synchronous	1	300
M	64	mFOLFOX6+pmab	PR	Rb	synchronous	1	300
F	73	mFOLFOX6+Cmab	SD	D	synchronous	0	300
M	72	mFOLFOX6+Cmab	PR	Rs	synchronous	1	150
M	68	mFOLFOX6+Cmab	PR	Rs	synchronous	1	300
M	68	mFOLFOX6+Bmab	SD	C	synchronous	1	150
F	72	mFOLFOX6+Bmab	PR	A	synchronous	1	Adverse event
M	50	mFOLFOX6+Bmab	PR	Rs	synchronous	1	None
M	60	mFOLFOX6+Cmab	PD	Rb	synchronous	1	None

Table 2: Incidence of adverse events.

	N=9	
	Grade1/2	Grade3/4
Vomiting	5 (55.6%)	0 (0%)
Nausea	1 (11.1%)	0 (0%)
Stomatitis	4 (44.4%)	1 (11.1%)
Diarrhea	8 (88.8%)	1 (11.1%)
Neutropenia	1 (11.1%)	6 (66.7%)
Thrombocytopenia	5 (55.6%)	0 (0%)
Fatigue	0 (0%)	0 (0%)
Hypertension	1 (11.1%)	1 (11.1%)
Proteinuria	0 (0%)	0 (0%)
Bleeding	0 (22.2%)	0 (0%)
Acne-like rash	3 (33.3%)	0 (0%)
Hypomagnesemia	1 (11.1%)	0 (0%)
Dry skin	0 (0%)	0 (0%)
Dizzy	1 (11.1%)	1 (11.1%)
Somnolence	1 (11.1%)	0 (0%)
Edema	0 (0%)	0 (0%)

(33.3%), and neutropenia of Grade 3/4 in 6 (66.7%),but these effects were mild and did not prevent administration in any of the patients (**Table 2**).

8. Discussion

Peripheral nerve symptoms such as dysesthesia of the upper and lower limbs can result in dose restrictions of L-OHP. The main characteristic adverse reactions of L-OHP are chills as an acute symptom and dose-dependent peripheral neuropathy as a symptom related to dose accumulation [8].

The acute symptom is thought to result from oxalate, which is a metabolic product of L-OHP, and chelate formed by the Ca^{2+}effect on the Na^{+} channel of the nerve cell membrane [9]. The acute symptom develops in 85-95% cases, but it is transient and improves after several hours or a few days [10]. However, the accumulation-related symptom is thought to result from L-OHP

accumulating in the ganglion root. When the index of L-OHP reaches an accumulated dose of 780-850 mg/m^2 of L-OHP, peripheral nerve symptoms develop with the functional disorder observed in about 15%of patients [11]. Therefore, lowering the dose or stopping the administration of L-OHP either improves or causes the peripheral nerve symptoms to disappear. In addition, recovery from the peripheral nerve symptoms takes about 13 weeks [12].

Many studies have evaluated means to reduce the peripheral nerve symptoms of L-OHP. One representative study, the OPTIMOX1 study, evaluated the Stop & Go method of L-OHP introduction. At the time serious peripheral nerve symptoms develop, the Stop & Go method discontinues only L-OHP of the FOLFOX treatment, and if peripheral nerve symptoms improve, this method re-introduces the L-OHP. The OPTIMOX1 study reduced peripheral nerve symptoms of more than Grade3, but re-introduction of L-OHP performed according to schedule was only achieved in 40% of patients. The most problematic point was that an inadequate amount of L-OHP was administered [13].

In addition, Ca/Mg, *goshajinkigan* (GJG), and duloxetine (DXT) were reported effective in the support of Grade 3peripheral nerve symptoms in Phase III studies evaluating the administration of Ca/Mg against the adverse event of peripheral nerve symptoms. The CONcePT study evaluated the effect of Ca/Mg given before and after L-OHP introduction on the adverse event of peripheral nerve symptoms. Intermediate analysis showed reduction of the tumor response rate by introduction of Ca/Mg, and the study was cancelled [14].

The N04C7 study evaluated the adverse event of peripheral nerve symptoms when Ca/Mg was given before the introduction of L-OHP. However, following the results of the intermediate analysis of the CONcePT study, enrollment was stopped. The onset of peripheral nerve symptoms of more than Grade 2 in the CTCAE occurred in 41% of the Ca/Mg group and 22% of the placebo group [15]. Also, the specific scale of L-OHP was significantly different between the Ca/Mg group and placebo group, more than Grade2 decreased with 51%, 28% (p=0.018) by 41%, 22% (p=0.038) [16].

The N08CB study evaluated L-OHP accumulation-related peripheral nerve symptoms by comparing three groups, one given Ca/Mg before and after L-OHP introduction, one given Ca/Mg before and a placebo given after L-OHP introduction, and one given a placebo before and after L-OHP introduction. However, the differences between the three groups were not significant [17].

The GONE study, a randomized Phase II trial, indicated the possibility that GJG reduced the peripheral nerve symptoms of L-OHP. This study evaluated whether GJG reduced the incidence of peripheral nerve symptoms of > Grade2 after 8 courses of FOLFOX treatment in the GJG group and placebo group. The GJG group showed a tendency towards a low 38.6% incidence of > Grade 2 peripheral nerve symptoms versus that of 51.1% in the placebo group [18,19]. However, an intermediate analysis of the GENIUS study, a randomized Phase III trial, found no suppressant effect of GJGon peripheral nerve symptoms [20].

The CALGB170601 study, a Phase III trial of DXT, evaluated the pain suppressant effect of DXT in taxane and L-OHP groups against peripheral nerve symptoms and suggested that DXT was effective for peripheral nerve symptoms. There were significant differences between the DXT group and the placebo group. Various methods have been considered to reduce the peripheral nerve symptoms of L-OHP in these trials, but the clear actions to be taken have not yet been established. Currently, although various methods to reduce the peripheral nerve symptoms of L-OHP have been evaluated, no obvious evidence has been established as to which method is best [20].

PGN (Lyrica®; Pfizer),considered a miscellaneous analgesic and anticonvulsant, was approved by the U.S. Food and Drug Administration approval on December 30, 2004.It is used to manage the neuropathic pain of diabetic peripheral neuropathy and post herpetic neuralgia. It is also approved as adjunctive therapy to treat partial-onset seizures in adult patients. Pharmacologically, PGN is structurally derived from the inhibitory neurotransmitter gamma-amino butyric acid (GABA) although it does not bind directly to GABA receptors. Rather, PGN binds to the α_2-Δ site of voltage-gated Ca channels in tissue of the central nervous system. Such modulation of the calcium channel may reduce the release of many neurotransmitters, but the alteration of Ca channel function by PGN is not the same as that caused by Ca-channel blockers. Dizziness, somnolence, dry mouth, edema, blurred vision, and weight gain are the adverse reactions seen most often withPGN.It is important to control these adverse reactions resulting from the oral intake of PGN [21].

Recently, the effectiveness of PGN against peripheral nerve symptoms induced by L-OHP was reported. Reported their retrospective study of23 patients with peripheral nerve symptoms of Grade2 or 3 with L-OHP use and evaluated the effectiveness of PGN [21]. Improvement of the peripheral nerve symptoms was found in 44% based on the dosage of PGN. In addition, improvement or maintenance of peripheral nerve symptom grade was found in 70%. As the main adverse events due to PGN, sleepiness, headaches, and dizziness occurred in22%,26%,and 57% of patients [22]. We also evaluated 32 patients receiving PGN for peripheral nerve symptoms due to L-OHP and paclitaxel (unpublished data).The peripheral nerve symptoms before and after treatment with PGN were significantly reduced as shown by the drop in the Numeric Rating Scale score from 5.54 to 3.61

($p<0.01$).Similarly, peripheral nerve symptoms of > Grade2 significantly decreased from 59% before to 22% after PGN treatment ($p<0.01$).We also evaluated the effectiveness according to the dose of PGN, which was initially administered at150mg/day, and treatment was maintained at 200mg/day.

FOLFOX is recommended as standard treatment because of its improvement in survival rate and high effectiveness against tumors. However, peripheral nerve symptoms caused by L-OHP can force the discontinuation and cancellation of therapy. The establishment of therapy to reduce the adverse event of peripheral nerve symptoms with L-OHP in the clinical setting is urgently required. Thus, we planned this prospective study of the effectiveness and safety of PGN with FOLFOX therapy. The efficacy of PGNsupportive therapy against peripheral neuropathy was shown in 6 of the 9(66.7%) enrolled patients. The effectiveness of PGN was confirmed in Step1 of this prospective study. Based on Step 1 of the results of this study, we hope to further develop Step2 . Therefore, the planning of Step2 of this study will commence, and we continue to enroll new patients. at present.

9. Conclusion

In this Study,thesmall number of patients and lack of placebo group are the major limitations But this prospective Step1 study investigated the efficacy and safety of PGN for peripheral neuropathy that develops as an adverse drug reaction to L-OHP administration in patients with unrespectable and metastatic colorectal cancer. Acceptable efficacy and safety of PGN was shown in the present study, and therefore we will begin the planning of Step 2.

10. Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author/first author on reasonable request.

11. Informed Consent

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

12. Research Involving Human Participants

This study was conducted in accordance with the principles of the 1975 Declaration of Helsinki after receiving approval from the Institutional Review Board of the Gifu University Graduate School of Medicine (specific approval number: 28-448). The target patients received a full explanation of the study objective and contents of the therapy, after which informed consent was obtained. Personal information should be protected and patients should be treated with the utmost care so as to minimize the affects of the study on their physical and mental well-being and personality. In terms of informed consent, to obtain the patient's full understanding, the investigator or sub-investigator should provide the patient with the informed consent form, in which essential items are described, and give both oral and written explanations in detail about the contents of the study.

13. Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author/first author on reasonable request.

14. Competing Interests

K. Yoshida received grants, personal fees, and nonfinancial support from Chugai Pharmaceutical Co., Ltd. during the conduction of this study; grants and personal fees from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., and Yakult Honsha Co., Ltd. and grants from Bristol-Myers Squibb and Kyowa Hakko Kirin Co., Ltd. outside the submitted work; honoraria from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Yakult Honsha Co., Ltd.; and had a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd. and LaRoche, Ltd. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. All remaining authors declare that they have no conflicts of interest.

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