

Examination of the Effect of Proton Pump Inhibitors on the Anticancer Activity of Oxaliplatin

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Abstract. *Background/Aim:* Oxaliplatin (L-OHP) is absorbed by cancer cells via organic cation transporter1-3 (OCT1-3). However, proton pump inhibitors (PPIs) suppress the function of OCT1-3. This study investigated whether PPIs attenuate the antitumor effect of L-OHP. *Patients and Methods:* Colorectal cancer patients who received FOLFOX (L-OHP + 5-fluorouracil: 5-FU) + bevacizumab therapy at Nagasaki University Hospital from October 1, 2010 to September 30, 2019 were retrospectively investigated. Patients were categorized into two groups with or without PPIs use. Progression-free survival (PFS) between the two groups was compared using the log-rank test. L-OHP was added to the intestinal epithelial Caco-2 cell line with or without the PPI rabeprazole, and then cell viability was analyzed using the WST-8 cell proliferation assay. *Results:* The median PFS was 11.4 months in the group with PPIs and 9.7 months in the group without PPIs ($p=0.736$). No significant effect of 1-10 μM rabeprazole was observed on the antitumor effect of L-OHP. Plasma concentrations of rabeprazole at clinical doses are 1.0-1.3 μM . *Conclusion:* Even if L-OHP interacts with PPIs, clinical doses of PPIs were considered to have minimal effect on the antitumor effect of L-OHP.

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Oxaliplatin (L-OHP), a platinum complex anti-cancer agent, covalently binds to DNA strands in cancer cells and inhibits DNA replication and transcription. L-OHP-based chemotherapy plays a central role in chemotherapy for colorectal (1, 2), small intestine (3), gastric (4), and pancreatic cancers (5). However, endogenous or acquired tumor resistance causes L-OHP treatment failure. Previous studies have shown that the organic cation transporters 1-3 (OCT1-3), which belong to SLC22 family, promote intracellular uptake of L-OHP and are also important determinants of L-OHP-induced cytotoxicity (6). In addition, other studies have suggested that OCT expression in cancer tissues is associated with the anticancer effect of L-OHP. Among colorectal cancer patients who received L-OHP-based chemotherapy, those with high OCT2 expression had significantly longer progression-free survival (PFS) than those with low OCT2 expression (7, 8).

Proton pump inhibitors (PPIs) are drugs that act on the proton pump of gastric parietal cells and suppress the secretion of gastric acid, and are widely used for the treatment of gastroesophageal hyperacidity (9). Approximately 20% of cancer patients are administered PPIs to improve their gastrointestinal symptoms (10). Previous studies have shown that PPIs inhibit cisplatin transport to tumor tissue *via* OCT2 dysfunctions (11, 12). We hypothesized that the combined use of L-OHP and PPIs could reduce the accumulation of L-OHP in tumor tissues, and consequently reduce the anticancer effect of L-OHP.

In the present study, the anticancer effects of L-OHP in combination with PPIs were retrospectively investigated in colorectal cancer patients who received modified FOLFOX and bevacizumab (a combination of L-OHP, 5-Fluorouracil: 5-FU, and bevacizumab). Additionally, we investigated the effect of PPI combination on the antitumor effect of L-OHP in Caco-2 cells, which are cultured intestinal epithelial cells derived from the human colon and express OCT1-3 (13).

Patients and Methods

Patients. This retrospective study was performed in accordance with the Declaration of Helsinki (Ninth revision: Fortaleza, Brazil, 2013) and approved by the Nagasaki University Ethics Committee (No. 21031517). The effects of FOLFOX and bevacizumab were retrospectively investigated in stage IV colorectal cancer patients who were administered FOLFOX and bevacizumab as first-line treatment at Nagasaki University Hospital (Nagasaki, Japan) from October 2010 to September 2019. The exclusion criteria included patients whose PFS could not be evaluated due to transfer to another hospital. The treatment schedule of FOLFOX plus bevacizumab was as shown below; Bevacizumab 5 mg/kg was administered for 90 min for the first time and 30 min for the second and subsequent doses, followed by L-OHP 85 mg/m² for 2 h at the same time as levofolinate calcium 200 mg/m². After the administration of levofolinate calcium and L-OHP was completed, 5-FU bolus (rapid intravenous infusion) 400 mg/m² and 5-FU infusion (46-h continuous infusion) 2,400 mg/m² were sequentially administered. The dosage of anticancer agents was allowed to be reduced at the discretion of the physicians.

Data collection and assessment. We obtained data on age, sex, weight, performance states (PS), blood biomedical parameters included serum creatinine (SCr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum albumin (ALB). Patients were categorized into two groups: those with and those without PPIs use. The end point of this study was PFS (the period up to the first confirmed date of disease progression or death). The cutoff date was December 31, 2020. Survival plots were estimated by the Kaplan-Meier method and PFS between the two groups was compared using the log-rank test.

Chemicals. Oxaliplatin I.V. infusion solution was purchased from Nippon Kayaku Co., Ltd (Tokyo, Japan). Fetal bovine serum (FBS) was purchased from Nichirei Biosciences Inc. (Tokyo, Japan). Dulbecco's modified Eagle's medium (DMEM) with high glucose was obtained from GIBCO BRL (Grand Island, NY, USA), antibiotics (10,000 Unit/ml penicillin and 10,000 µg/ml streptomycin), and other culture reagents were purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan). Cimetidine was obtained from Sigma-Aldrich (Darmstadt, Germany), Rabeprazole from Cayman CHEMICAL (Ann Arbor, MI, USA). All other chemicals were of the highest purity available.

Cell culture. Caco-2 cells derived from human colon cancer were obtained from RIKEN BRC CELL BANK (Kobe, Japan). Cells were maintained in DMEM containing 10% FBS, 1% non-essential amino acids, 1 mM Na-pyruvate, 100 unit/ml penicillin and 100 µg/ml streptomycin under a humidified 5% CO₂ atmosphere maintained at 37°C.

Cytotoxicity assay. The Cell Counting Kit-8 (CCK-8) was purchased from Dojindo Laboratories (Kumamoto, Japan). CCK-8 is a kit for measuring the number of living cells and uses WST-8 [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt] as a color development reagent. NADH acidified by dehydrogenase in living cells reduces WST-8 via 1-Methoxy PMS. The reduced WST-8 produces water-soluble formazan with maximum absorption near 450 nm. In brief, Caco-2 cells were

Table I. Patient characteristics.

	n=33
Sex (male)	21 (63.6%)
Age (years)	67 (60-71)
Weight (kg)	57.8 (46.6-64.1)
Performance status	
0-1	29 (87.9%)
Laboratory data	
Serum creatinine (mg/dl)	0.75 (0.63-0.94)
AST (IU/l)	22 (18-38)
ALT (IU/l)	18 (13-24)
Serum albumin (g/dl)	3.9 (3.5-4.0)

Categorical data are shown by frequencies and percentages, and continuous variables by medians plus interquartile ranges. AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

incubated with 3,000 cells/well on 96-well plates. After 24 h, L-OHP 1 µM was added to the medium and exposed for another 24 h. Ten µl of CCK-8 solution was added to each well for 4 h, and the absorbance at 450 nm was measured using a plate reader (Infinite M Plex, Tecan, Männedorf, Switzerland). In some experiments, cells were pre-incubated with cimetidine (pre-incubation; 1 h, 2 mM), which is a positive control of OCT1-3 inhibition, or rabeprazole (pre-incubation; 1 h, 1 µM, 10 µM, and 100 µM), which is an inhibitor of OCT1-3.

Statistical analysis. Differences between the two groups were assessed using Fisher's exact test for categorical data and Wilcoxon's rank sum test for continuous data. Baseline characteristics are summarized with frequencies and percentages for categorical data and medians plus interquartile range for continuous data. The effect of the combination of L-OHP with PPIs on PFS in colorectal cancer patients was analyzed by log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using the COX proportional hazards model.

All *in vitro* assay data are represented by the mean±standard error of three independent observations. Cell viability against controls was compared by Dunnett's multiple comparison test. All tests were two-sided. The level of significance was set at *p*-value<0.05. Analyses were performed using JMP Pro version 16 (SAS Institute Inc, Cary, NC, USA).

Results

Retrospective study. Patient characteristics are shown in Table I and Table II. Twenty-one patients (63.6%) were men. The median age and weight were 67 years and 57.8 kg, respectively. Twenty-nine patients (87.9%) were PS 0-1. The median SCr, AST, ALT, and ALB were 0.75 mg/dl, 22 IU/l, 18 IU/l, 3.9 g/dl, respectively. Seven patients (21.2%) received PPIs: 5 received rabeprazole 10 mg, 1 lansoprazole 15 mg, and 1 lansoprazole 30 mg. There was no significant difference in patient characteristics between the group with PPIs and the group without. The median PFS in all patients was 10.7 months. In addition, the median PFS in the group with PPIs was 11.4 months and that in the group without PPIs was 9.7 months (HR=1.15, 95%CI=0.49-2.72, *p*=0.736) (Figure 1).

Table II. Patient characteristics in the proton pump inhibitor (PPIs) group and the group without PPIs.

	With PPIs (n=7)	Without PPIs (n=26)	p-Value
Patient characteristics			
Sex (male)	4 (57.1%)	17 (65.4%)	0.686 ^a
Age (years)	71 (63-72)	66 (59-70)	0.453 ^b
Weight (kg)	64.1 (39.7-72.5)	56.9 (46.9-63.5)	0.523 ^b
Performance status			
0-1	5 (71.4%)	24 (92.3%)	0.190 ^a
Laboratory data			
Serum creatinine (mg/dl)	0.61 (0.59-1.07)	0.76 (0.66-0.90)	0.552 ^b
AST (IU/l)	24 (20-41)	22 (18-38)	0.741 ^b
ALT (IU/l)	18 (15-29)	18 (12-23)	0.724 ^b
Serum albumin (g/dl)	3.9 (3.6-4.1)	3.9 (3.5-4.0)	0.451 ^b
Usage of medicine			
Dosage of anti-cancer agents			
Oxaliplatin	80.8 (79.8-84.2)	82.7 (80.5-84.0)	0.901 ^b
5-Fluorouracil (bolus)	382 (357-388)	384 (359-394)	0.708 ^b
5-Fluorouracil (infusion)	2,374 (2,288-2,395)	2,379 (2,355-2,394)	0.468 ^b
Breakdown of PPI			
Rabeprazole (10 mg/day)	5 (71.4%)	–	
Lansoprazole (15 mg/day)	1 (14.3%)	–	
Lansoprazole (30 mg/day)	1 (14.3%)	–	

Categorical data are shown by frequencies and percentages, and continuous variables by medians plus interquartile ranges. ^aFisher's exact test; ^bthe Wilcoxon rank-sum test. AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

In vitro experiments. The viability of Caco-2 cells was significantly reduced to 86% with the addition of 1 μ M L-OHP ($p < 0.05$). One and 10 μ M rabeprazole did not affect the cytotoxicity of L-OHP. However, cimetidine (OCT1-3 inhibitor) and 100 μ M rabeprazole decreased the cytotoxicity of L-OHP (Figure 2).

Discussion

To investigate the effect of PPIs on the cytotoxicity of L-OHP, we performed a retrospective study on data from clinical patients and an *in vitro* analysis using cell culture. Our retrospective study showed that PPIs did not affect the therapeutic effect of L-OHP. The results of the experiments with Caco-2 cells showed that 100 μ M rabeprazole reduced L-OHP-induced cytotoxicity, but 1 and 10 μ M did not.

For the treatment of patients with colorectal cancer, L-OHP is used in combination with fluorouracil-based anticancer drugs such as 5-fluorouracil, tegafur, or capecitabine (1, 2, 14, 15). In addition, patients with stage IV or recurrent colorectal cancer are commonly administered molecular-targeted drugs along with the fluorouracil-based anti-cancer agents. Thus, we focused on patients with stage IV colorectal cancer who received combination therapy with modified FOLFOX6 plus bevacizumab, which is one of the molecular-targeted drugs (16). In our retrospective study, the median PFS of patients who received modified FOLFOX6 plus bevacizumab was 10.7

months, which is slightly shorter than that of a previous clinical trial (11.5 months). One reason may be that the patient backgrounds differ between our study and those of the previous clinical trial. Eligibility criteria, such as PS 0-1 and no serious damage to major organs, were set in the clinical trial (17). Wong *et al.* investigated the effects of PPIs on the effectiveness of CapeOX or FOLFOX used as adjuvant chemotherapy for patients with stage II-III colorectal cancer. The results showed that PPIs adversely affected recurrence-free survival in patients with colorectal cancer treated with CapeOx, but not significantly in patients treated with FOLFOX, potentially implicating a pharmacokinetic interaction between PPIs and capecitabine (18). In our study, PPIs did not show a significant effect on the PFS of colorectal cancer patients who received FOLFOX plus bevacizumab, and the results were similar to those reported previously (18). In another study, the use of PPIs was shown to reduce tumor reactivity and survival in patients treated with pembrolizumab (19). The efficacy of immune checkpoint inhibitors such as pembrolizumab has been reported to be associated with gut microbiota. PPIs are thought to influence the efficacy of cancer immunotherapy by resulting in lower abundance of gut commensals. L-OHP is not an immune checkpoint inhibitor, thus the impact of PPIs use is different.

L-OHP is transported intracellularly *via* OCT1-3. Previous studies have shown that cimetidine, the OCT1-3 inhibitor, inhibits the intracellular uptake and accumulation of L-OHP, resulting in the suppression of L-OHP-induced cytotoxicity

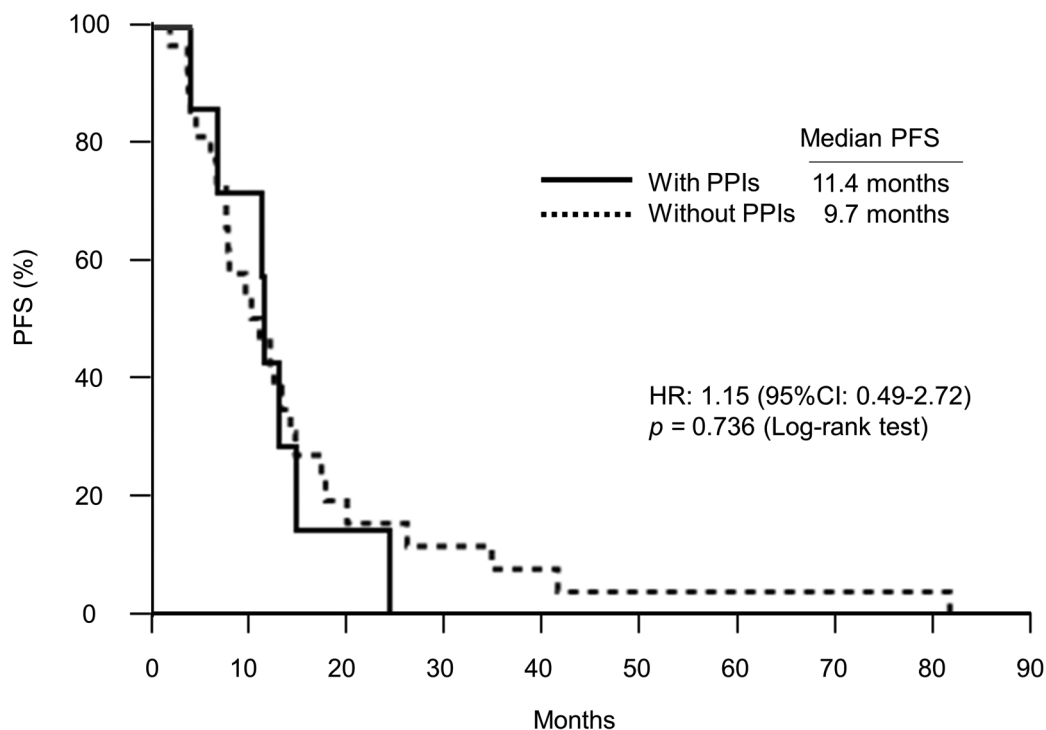


Figure 1. Comparison of progression-free survival (PFS) between the with proton pump inhibitors (PPIs) group and the without PPIs group. PFS in patients was analyzed by log-rank test. No significant difference was found between the two groups. Data cutoff date: December 31, 2020. HR: Hazard ratio; 95%CI: 95% confidence interval.

(6). In the *in vitro* experiments with Caco-2 cells performed in this study, cimetidine suppressed L-OHP-induced cytotoxicity (Figure 2), which are consistent with previous studies.

PPIs that suppress gastric acid secretion induced dysfunction of OCT2 *in vitro* (20, 21). The IC_{50} values of rabeprazole (22), omeprazole (23), lansoprazole (24), pantoprazole (25), and tenatoprazole (26) for OCT2 are $5.7 \pm 0.5 \mu\text{M}$, $6.7 \pm 2.1 \mu\text{M}$, $9.5 \pm 3.8 \mu\text{M}$, $2.8 \pm 0.9 \mu\text{M}$, and $20.3 \pm 7.2 \mu\text{M}$, respectively. In addition, the IC_{50} value of rabeprazole (22) for OCT1 and OCT3 is the lowest compared to omeprazole (23), lansoprazole (24), pantoprazole (25), and tenatoprazole (26). In this study we selected rabeprazole, which has the lowest IC_{50} value among the PPIs commercially available in Japan, and investigated the effect of rabeprazole on the cytotoxicity caused by L-OHP. In our experiment, high-dose rabeprazole ($100 \mu\text{M}$) significantly reduced L-OHP-induced toxicity, but 1 or $10 \mu\text{M}$ rabeprazole did not. The maximum plasma concentration of rabeprazole after a single dose is $1.0\text{--}1.3 \mu\text{M}$, and the calculated portal blood concentration is $4.7 \mu\text{M}$ (20). Combined with the results of our retrospective study, clinical doses of PPIs were considered to have minimal effect on the antitumor effect of L-OHP. Itagaki *et al.* showed that high concentrations of

rabeprazole inhibited the intracellular uptake of rhodamine 123, while low concentrations did not (27). Since Rhodamine 123 is a high affinity substrate for OCT1 and 2 (28), this study also supports our results.

This study has some limitations. First, our retrospective study was conducted in clinical patients who used L-OHP in combination with 5-FU and bevacizumab. Pantoprazole, one of the PPIs, was shown to enhance the cytotoxicity of 5-FU (29). Therefore, PFS in patients receiving PPIs may be affected by interactions with 5-FU in addition to L-OHP. Second, this was a retrospective study conducted in a single hospital and included a small number of cases. As a means of overcoming these research limitations, we conducted research using cell lines. Since the results of the *in vitro* experiments and those of the retrospective study were in agreement, it is reasonable to conclude that the clinical dose of PPIs has minimal effect on the therapeutic effect of L-OHP. Third, the mechanism by which low concentrations of rabeprazole did not suppress the cytotoxicity of L-OHP is unknown. Other studies have shown that human copper transporter (CTR) 1 also mediates L-OHP uptake (30, 31). The ATPase copper transporting alpha (ATP7A) is also known to be involved in L-OHP efflux (31). We will investigate the effect of high concentrations of PPIs on these

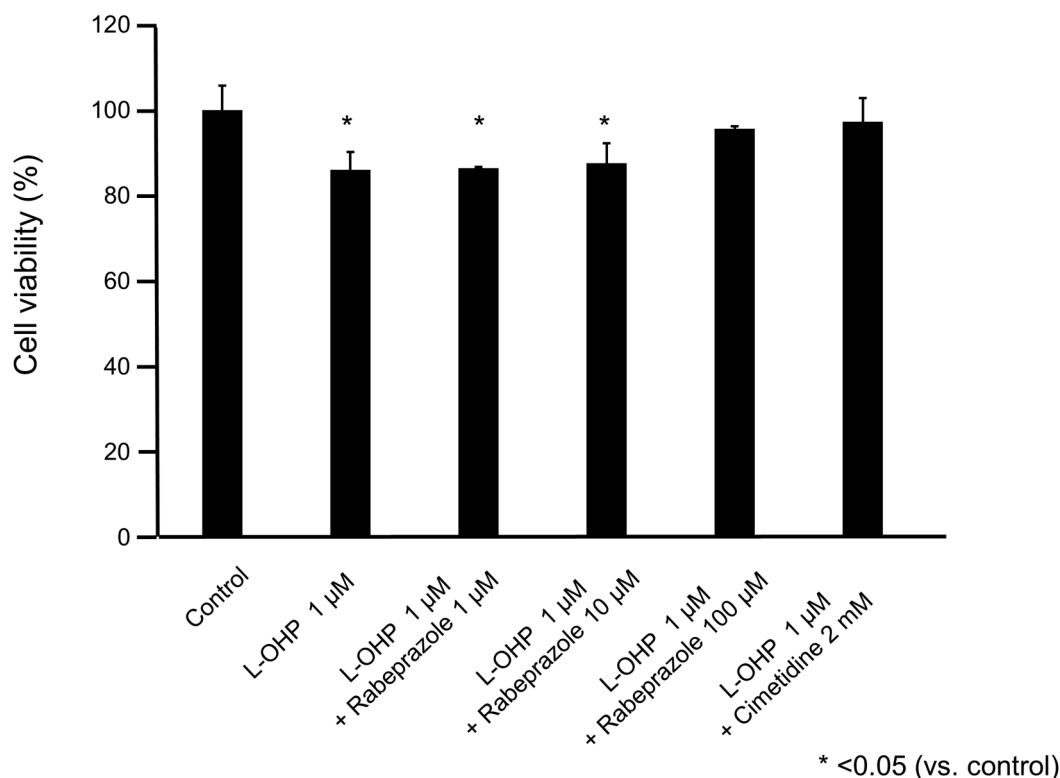


Figure 2. Cell viability of Caco-2 cells under each drug stimulation was measured using the WST-8 assay. In some experiments, cells were pre-incubated with cimetidine (pre-incubation; 1-h, 2 mM) or rabeprazole (pre-incubation; 1-h, 1 µM, 10 µM and 100 µM). Cell viability against controls was compared by Dunnett's multiple comparison test. The viability of Caco-2 cells was significantly reduced with the addition of 1 µM oxaliplatin (L-OHP). Cimetidine (organic cation transporter 1-3 inhibitor), or 100 µM rabeprazole, suppressed the cytotoxicity of L-OHP. * $p < 0.05$ vs. control.

transporters and further validate the intracellular uptake of L-OHP when PPIs are co-administered.

In conclusion, even if L-OHP interacts with PPIs, clinical doses of PPIs were considered to have minimal effect on the antitumor effect of L-OHP. These results provide valuable information regarding the administration of PPIs in patients receiving L-OHP.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

JH, HN, TH and YK were involved in study design and data interpretation. JH, KS, HH and YK were involved in the sample collection and data analysis. JH and KS prepared the manuscript. All Authors reviewed and approved the final manuscript.

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