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Concomitant Use of DPP-4 Inhibitors May Prevent the Development of Oxaliplatin-Induced Peripheral Neuropathy: A Retrospective Cohort Study

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ABSTRACT

Oxaliplatin-induced peripheral neuropathy (OIPN) causes numbness and pain in the limbs, often leading to interruption of chemotherapy and representing a significant clinical problem. Previous basic studies have suggested that the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin may prevent OIPN. To evaluate whether concomitant use of DPP-4 inhibitors could prevent the development of OIPN in clinical practice, we retrospectively analyzed data from 1180 patients who initiated oxaliplatin treatment at Kyushu University Hospital between January 1, 2009 and December 31, 2019. The primary endpoint was the occurrence of OIPN of any grade. Kaplan–Meier analysis with cumulative doses demonstrated a significantly lower incidence of OIPN in the DPP-4 inhibitor group ($p = 0.0422$). After propensity score matching to adjust for patient backgrounds, the protective association remained significant ($p = 0.0389$). Furthermore, Cox proportional hazards analysis incorporating gender, age, regimen, and concomitant DPP-4 inhibitor use as covariates confirmed that DPP-4 inhibitor use was an independent protective factor for OIPN (HR = 0.690; 95% CI, 0.490–0.972; $p = 0.034$). These findings suggest that concomitant use of DPP-4 inhibitors may moderate the development of OIPN in patients receiving oxaliplatin.

1 | Introduction

Various cancer chemotherapy regimens include oxaliplatin, and oxaliplatin-containing regimens are particularly important in the chemotherapy of colorectal cancer [1–3]. However, oxaliplatin is known to cause oxaliplatin-induced peripheral neuropathy (OIPN), whose main symptoms are numbness and neuralgia in the limbs, in a dose-dependent manner [4, 5] and these symptoms are known to last for several months to years [6]. The mechanism of OIPN is known to be oxaliplatin-induced damage to neuronal cell bodies in the dorsal root ganglia of the spinal cord, resulting in downstream axonal degeneration and loss of myelin sheath [7, 8]. These neuropathies result in the development of OIPN, which is clinically problematic because it reduces the patient's quality of life and interrupts chemotherapy. However, there is no drug recommended for the prevention of OIPN in the various guidelines [9, 10].

Dipeptidyl peptidase 4 (DPP-4) inhibitors are oral hypoglycemic agents that inhibit DPP-4 and are used to treat type 2 diabetes. DPP-4 is an enzyme that degrades the incretins, glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), and DPP-4 inhibitors lower blood glucose levels by blocking them [11–13]. DPP-4 inhibitors have also been reported to have protective effects against central and peripheral nerve diseases due to their antioxidant, anti-inflammatory, and neuroprotective effects [14–18]. In the past, alogliptin, a DPP-4 inhibitor, has been shown to have a preventive effect

Study Highlights

- What is the current knowledge on the topic?
  - Oxaliplatin-induced peripheral neuropathy (OIPN), characterized by numbness and neuropathic pain in the extremities, develops in a dose-dependent manner and may persist for months to years. OIPN impairs quality of life and often results in the discontinuation of chemotherapy, yet no pharmacological agents are currently recommended for prevention in clinical guidelines. The dipeptidyl peptidase-4 (DPP-4) inhibitor, an antidiabetic agent that inhibits responsible for degrading the incretins, has demonstrated antioxidant, anti-inflammatory, and neuroprotective effects. Preclinical studies using cultured cells and rat models have shown that alogliptin, a DPP-4 inhibitor, can prevent OIPN.
- What question did this study address?
  - Although DPP-4 inhibitor has shown efficacy in preclinical models, its clinical effectiveness remains unclear. This retrospective cohort study evaluated whether concomitant use of DPP-4 inhibitor could suppress OIPN in patients receiving oxaliplatin-containing regimens. Kaplan–Meier curves and log-rank tests compared OIPN incidence between patients with and without DPP-4 inhibitor, and Cox proportional hazards models identified factors influencing OIPN onset.
- What does this study add to our knowledge?
  - Concomitant use of DPP-4 inhibitor was associated with a significantly lower incidence of OIPN, suggesting its potential efficacy in prevention.
- How might this change clinical pharmacology or translational science?
  - This is the first retrospective cohort study to report that DPP-4 inhibitor may prevent OIPN. As an already approved medication with an established safety profile, DPP-4 inhibitor could be smoothly translated into oncology practice. If confirmed by prospective studies, its use may provide a novel preventive strategy, ultimately improving both patient quality of life and treatment outcomes.

against OIPN in basic studies using cultured cells and a rat model [19].

The purpose of this study is to test whether concomitant DPP-4 inhibitors reduce the incidence of OIPN by means of a retrospective cohort study.

2 | Methods

2.1 | Ethical Declarations

This research complies with the Declaration of Helsinki, the Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects, and the Act on the Protection of Personal Information. Approval was obtained from the Ethical Review Committee for Observational Research of the Regional Department of Kyushu University School of Medicine (Approval No. 24059–00).

Because this study involved patients who had previously visited Kyushu University Hospital, it was difficult to obtain informed consent again. For this reason, information about the study was made publicly available on the website to inform study subjects and guarantee them the opportunity to refuse to participate in the study.

2.2 | Study Design and Population

This retrospective cohort study compared the subsequent development of OIPN in oxaliplatin-treated patients with and without DPP-4 inhibitors. Patient data were obtained from the medical records of patients aged 18 years and older who started treatment with oxaliplatin-containing regimens at Kyushu University Hospital between January 1, 2009, and December 31, 2019.

2.3 | Exposure

Patients were classified according to whether they were taking DPP-4 inhibitors, vildagliptin, sitagliptin, alogliptin, linagliptin, saxagliptin, or teneligliptin as their usual oral medication. No patient data were available for patients' taking anagliptin. Exposure was determined by whether DPP-4 inhibitors were being used as usual oral medications at the time oxaliplatin therapy was initiated. The duration of DPP-4 inhibitor administration was not adequately described and was difficult to extract; therefore, it was not used in the analysis.

2.4 | Propensity Score Matching

Fourteen covariates were used for propensity score matching: sex, age, BMI, BSA, CCr, ALT, AST, cancer type, regimen, uses of statin, proton pump inhibitor, calcium channel blocker, analgesic adjunct, opioid. A logistic regression analysis using these variables was used to calculate a propensity score for each patient, and matching was performed on a one-to-one basis. Caliper was set to 0.2*SD (standard deviation) for nearest neighbor matching. The matching was performed using JMP Pro 17 for windows (JMP Statistical Discovery LLC 920 SAS Campus Drive Cary, NC, US).

2.5 | Definition of Results

A Kaplan–Meier curve was constructed with cumulative incidence of OIPN on the vertical axis and cumulative dose on the horizontal axis. The reason is that chronic neuropathy caused by oxaliplatin has been reported to tend to occur in proportion to its cumulative dosage [4, 5]. The primary endpoint was the occurrence of OIPN (any grade). The occurrence and severity of OIPN were documented according to the Common Terminology Criteria for Adverse Events (CTCAE), version

TABLE 1 | Patient background (before propensity score matching).

Characteristic	no DPP-4 inhibitors ($N=1089$)	DPP-4 inhibitors ($N=91$)	p
Sex (Male/Female)	632/457	62/29	0.060[a]
Age: median (Min–Max)	**63 (19–86)**	**67 (45-83)**	**<0.001**[b]
BMI (kg/m^2): median (Min–Max)	**21.5 (12.0–42.0)**	**23.1 (15.3–35.2)**	**<0.001**[b]
BSA (m^2): median (Min–Max)	**1.60 (1.12–2.20)**	**1.65 (1.23–2.02)**	**0.026**[b]
CCr (mL/min): median (Min–Max)	**83.8 (15.0–261.6)**	**72.7 (6.6–197.3)**	**0.009**[b]
ALT (IU/L): median (Min–Max)	16 (2–608)	18 (4–76)	0.063[b]
AST (IU/L): median (Min–Max)	21 (7–1138)	23 (9–101)	0.060[b]
Cancer type			
Colorectal: No. (%)	**821 (75.4)**	**56 (61.5)**	**<0.001**
Gastric: No. (%)	**153 (14.0)**	**14 (15.4)**	
Pancreatic: No. (%)	**74 (6.8)**	**18 (19.8)**	
Small bowel: No. (%)	**13 (1.2)**	**1 (1.1)**	
Others: No. (%)	**28 (2.6)**	**2 (2.2)**	
Regimen (base)			
FOLFOX, FOLFOXIRI or FOLFIRINOX: No. (%)	490 (45.0)	45 (49.5)	0.178[a]
CAPOX: No. (%)	451 (41.4)	32 (35.2)	
SOX: No. (%)	146 (13.4)	14 (15.4)	
Other: No. (%)	2 (0.2)	0 (0)	
Use of statins: No. (%)	**134 (12.3)**	**28 (30.8)**	**<0.001**[a]
Use of proton pomp inhibitors: No. (%)	**233 (21.4)**	**38 (41.8)**	**<0.001**[a]
Use of calcium channel blockers: No. (%)	**196 (18.0)**	**37 (40.7)**	**<0.001**[a]
Use of analgesic adjuncts: No. (%)	35 (3.2)	2 (2.2)	0.593[a]
Use of opioids: No. (%)	67 (6.2)	7 (7.7)	0.561[a]

Note: The bold text indicates statistical significance at $p<0.05$.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CAPOX, capecitabin + oxaliplatin; SOX, tegafur + gimeracil + oteracil potassium + oxaliplatin; CCr, creatinine clearance; FOLFOX, 5-FU + levofolinate + oxaliplatin; FOLFOXIRI (for colorectal) and FOLFIRINOX (for pancreatic), 5-FU + levofolinate + oxaliplatin + irinotecan.

[a]χ^2 test.

[b]Mann–Whitney's *U*-test.

4.0 or 5.0, depending on the time of assessment. When explicit CTCAE grading was not available in the medical records, severity was retrospectively determined based on information extracted from clinicians 'notes, including patients' reported symptoms and descriptions of daily functioning. The ability to prevent the development of OIPN has an important impact on the patient's ability to continue cancer treatment in the future and on the patient's quality of life [20, 21]. The expression of OIPN did not distinguish between acute and chronic neuropathy.

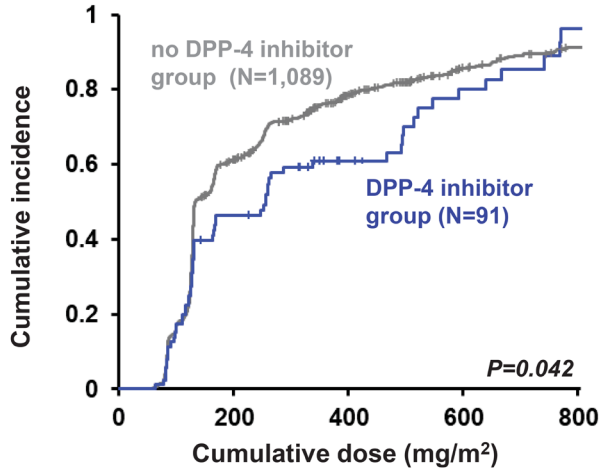
2.6 | Censored Cases

Patients who discontinued oxaliplatin due to other side effects, such as myelosuppression, or were lost to follow-up because they were transferred to a different hospital during the study period were considered censored cases.

2.7 | Statistical Analysis

Patient backgrounds were compared in the DPP-4 inhibitor and no DPP-4 inhibitor groups. Comparison parameters were sex, age, BMI, BSA, CCr, ALT, AST, cancer type, regimen, cumulative oxaliplatin dose, use of statin, proton pump inhibitor, calcium channel blocker, analgesic adjunct, and opioid. Among the parameters, sex, cancer type, regimen, use of statin, proton pump inhibitor, calcium channel blocker, analgesic adjuvant, and opioid were nominal data, and χ^2 tests were used. Age, BMI, BSA, CCr, ALT, AST, and cumulative oxaliplatin doses were continuous data. Given the nonparametric nature of these data, they were analyzed using the Mann–Whitney's *U* test. The above data were collected up to date at the start of oxaliplatin treatment and were not missing.

First, Kaplan–Meier curves were generated for cumulative dose and OIPN expression, and log-rank tests were performed. Next,



No. at risk					
no DPP-4i	1,089	373	158	71	34
DPP-4i	91	40	19	8	1

FIGURE 1 | Calculative incidences of oxaliplatin-induced peripheral neuropathy (before propensity score matching). Kaplan–Meier curve was constructed with oxaliplatin-induced peripheral neuropathy (any grade) on the y-axis and the cumulative dose of oxaliplatin on the x-axis. Differences in cumulative incidence between two groups were analyzed using the log-rank test.

Cox proportional hazards analyses were performed incorporating factors reported to influence OIPN (sex, regimen, and age) as covariates [22–27]. Regimens were categorized as CAPOX therapy (capecitabine plus oxaliplatin) and other regimens. The reason for classifying the regimens as CAPOX and others is that CAPOX therapy has already been reported to affect neuropathy [27] and the dosage is high (130 mg/m^2). Other oxaliplatin-containing regimens, such as FOLFOXIRI therapy, have a dose of 85 mg/m^2. Therefore, the relationship between cumulative dose and time of onset can be visualized by distinguishing the analysis from CAPOX therapy. All analyses were performed using JMP Pro 17 for windows with a statistical significance level of $p = 0.05$.

3 | Results

3.1 | Patient Background (Before Propensity Score Matching)

The study included 1180 patients who started a regimen containing oxaliplatin. Of the 1180 patients, 91 (7.7%) were in the DPP-4 inhibitor group and 1089 (92.3%) were in the DPP-4 inhibitor non-treated group. The demographic characteristics of each group are shown in Table 1. Age was significantly higher in the DPP-4 inhibitor group than in the non-treated group (63 [19–86] vs. 67 [45–83]: $p < 0.001$). Body mass index (BMI) was also significantly higher in the DPP-4 inhibitor group than in the non-treated group (21.5 [12.0–42.0] vs. 23.1 [15.3–35.2]: $p < 0.001$). Body surface area (BSA) was also significantly higher in the DPP-4 inhibitor group than in the non-treated group (1.60 [1.12–2.20] vs. 1.65 [1.23–2.02]: $p = 0.026$). Creatinine clearance (CCr) was significantly lower in the DPP-4 inhibitor group than in the non-treated group (83.8 [15.0–261.6] vs. 72.7 [6.6–197.3]: $p = 0.009$). There was also a significant difference in cancer type ($p < 0.001$). Statin uses were also significantly higher in the DPP-4 inhibitor group than in the no-treatment group (134 (12.3%) vs. 28 (30.8%): $p < 0.001$). Proton pump inhibitor uses were also significantly higher in the DPP-4 inhibitor group than in the non-treated group (233 (21.4%) vs. 38 (41.8%): $p < 0.001$). Calcium channel blocker uses were also significantly higher in the DPP-4 inhibitor group than in the non-treated group (196 (18.0%) vs. 37 (40.7%): $p < 0.001$). There was also a differential trend in gender (male/female) (632/457 vs. 62/29; $p = 0.060$), ALT levels (16 [2–608] vs. 18 [4–76]; $p = 0.063$), and AST levels (21 [7–1138]; $p = 0.060$).

3.2 | Analysis of OIPN Expression (Before Propensity Score Matching)

In the log-rank test, the incidence of OIPN was significantly lower in the DPP-4 inhibitor group than in the non-treated group ($p = 0.042$, Figure 1).

3.3 | Patient Background (After Propensity Score Matching)

Propensity score matching was performed on 91 DPP-4 inhibitor-treated patients, matching 90 DPP-4 inhibitor-treated patients to 90 DPP-4 inhibitor-naive patients. The demographic characteristics of each group are shown in Table 2. There were no differences in patient background, such as cancer type or percentage of proton pump inhibitor use, seen prior to matching.

3.4 | Analysis of OIPN Expression (After Propensity Score Matching)

The incidence of OIPN was significantly lower in the DPP-4 inhibitor group than in the non-treated group ($p = 0.039$, log-rank test, Figure 2).

Cox proportional hazards analysis incorporating gender, age, and regimen as covariates showed that DPP-4 inhibitor use was a factor significantly reducing the occurrence of OIPN (Hazard Ratio (HR) = 0.690; 95% confidence interval (CI), 0.490–0.972; $p = 0.034$) (Figure 3).

4 | Discussion

The purpose of this study was to test whether concomitant use of DPP-4 inhibitors reduces the incidence of OIPN in patients who started treatment with oxaliplatin at Kyushu University Hospital from 2009 to 2019 by means of a retrospective cohort study. In a retrospective cohort study of 1180 patients extracted from medical records, log-rank tests showed a significantly lower incidence of OIPN with concomitant DPP-4 inhibitors. The results suggest that DPP-4 inhibitors may be effective against OIPN, but it has been reported that age, sex, and other factors may affect the occurrence of OIPN [22–28]. The study found differences between DPP-4 inhibitor-treated and non-treated

TABLE 2 | Patient background (after propensity score matching).

Characteristic	no DPP-4 inhibitors ($N=90$)	DPP-4 inhibitors ($N=90$)	p
Sex (Male/Female)	63/27	61/29	0.747[a]
Age: median (Min–Max)	68 (43–82)	67 (45–83)	0.750[b]
BMI (kg/m^2): median (Min–Max)	23.4 (16.2–37.3)	23.1 (15.3–35.2)	0.591[b]
BSA (m^2): median (Min–Max)	1.67 (1.28–1.98)	1.64 (1.23–2.02)	0.678[b]
CCr (mL/min): median (Min–Max)	79.2 (26.0–160.8)	72.3 (6.6–197.3)	0.202[b]
ALT (IU/L): median (Min–Max)	17 (7–140)	18 (4–76)	0.114[b]
AST (IU/L): median (Min–Max)	21 (7–330)	23 (9–101)	0.199[b]
Cancer type			
Colorectal: No. (%)	62 (68.9)	56 (62.2)	0.845[a]
Gastric: No. (%)	11 (12.2)	14 (15.6)	
Pancreatic: No. (%)	13 (14.4)	17 (18.9)	
Small bowel: No. (%)	1 (1.1)	1 (1.1)	
Others: No. (%)	3 (3.3)	2 (2.2)	
Regimen (base)			
FOLFOX, FOLFOXIRI or FOLFIRINOX: No. (%)	46 (51.1)	44 (48.9)	0.811[a]
CAPOX: No. (%)	33 (36.7)	32 (35.6)	
SOX: No. (%)	11 (12.2)	14 (15.6)	
Other: No. (%)	0 (0)	0 (0)	
Use of statins: No. (%)	30 (33.3)	27 (30.0)	0.631[a]
Use of proton pomp inhibitors: No. (%)	35 (38.9)	37 (41.1)	0.761[a]
Use of calcium channel blockers: No. (%)	38 (42.2)	36 (40.0)	0.762[a]
Use of analgesic adjuncts: No. (%)	3 (3.3)	2 (2.2)	0.650[a]
Use of opioids: No. (%)	8 (8.9)	7 (7.8)	0.787[a]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CAPOX, capecitabine + oxaliplatin; CCr, creatinine clearance; FOLFIRINOX (for pancreatic), 5-FU + levofolinate + oxaliplatin + irinotecan; FOLFOX, 5-FU + levofolinate + oxaliplatin; FOLFOXIRI (for colorectal) and SOX, tegafur + gimeracil + oteracil potassium + oxaliplatin.
[a]χ^2 test.
[b]Mann–Whitney's *U*-test.

patients in age, BMI, BSA, CCr, cancer type, use of statins, proton pump inhibitors, and calcium channel blockers. It has been reported that women are more likely than men to express OIPN [23, 24]. As for age, there are reports that the incidence of OIPN is significantly higher in older age groups [25, 26]. BMI and BSA have been reported to increase the expression of OIPN for larger values of these [29–31]. There are also reports of liver function markers being associated with the expression of OIPN [32]. Statins and proton pump inhibitors have been reported to decrease the incidence of OIPN [33, 34]. Calcium channel blockers are also known to reduce the incidence of acute OIPN [35]. Therefore, propensity score matching was performed to correct for differences in patient background. Using logistic regression analysis with 14 items collected as patient background (sex, age, BMI, BSA, CCr, ALT, AST, cancer type, regimen, use of statins, proton pump inhibitors, calcium channel blockers, analgesic adjuvants, and opioids) as covariates, the probability of DPP-4 inhibitor use was calculated as a propensity score. Calipers were set at 0.2* standard deviation (SD), which is within standard practice for propensity scores, and 1:1 nearest neighbor matching was performed. The results showed no differences between the two groups based on sex, age, cancer type, or statin use. The same analysis was then performed for the expression of OIPN, which was significantly lower. This finding strongly suggests that DPP-4 inhibitors may be effective in preventing OIPN.

In this study, sex, age, and regimen were included as covariates in the multivariate Cox proportional hazards analysis. It has been reported that the incidence of OIPN is higher in women than in men [23, 24] and that age also has an effect [22, 25, 26, 28]. Since CAPOX therapy has already been reported to affect neuropathy [27], we included it as a covariate separately for CAPOX or other regimens. In our multivariate analysis, the incidence of OIPN was significantly higher in women than in men, consistent with previous reports [23, 24]. As for age, some reports suggest that the expression of OIPN is significantly lower in older patients

[22, 28], while others suggest that age is not related to the expression of OIPN [36, 37]. Our finding that age was not significantly associated with OIPN expression is consistent with these latter reports. Additionally, a meta-analysis on risk factors for OIPN reported that regimen was not a factor [38], which was consistent with our results.

Although the mechanisms underlying OIPN have not been fully elucidated, oxaliplatin forms DNA crosslinks, and neuronal injury is thought to originate in the cell body. Oxidative stress and inflammation occurring in the soma are believed to subsequently lead to axonal degeneration. In addition, oxidative stress has been implicated in the development of OIPN [8, 39, 40], and reactive oxygen species generated in dorsal root ganglion cells following oxaliplatin administration have been reported to cause neuronal cell body damage and axonal degeneration [7, 8]. Our laboratory previously demonstrated that alogliptin, a DPP-4 inhibitor, exerted preventive effects against OIPN in both in vivo and in vitro models [19]. Although the mechanism by which DPP-4 inhibitors prevent OIPN remains unclear, studies of alogliptin have shown suppression of morphological changes in neuronal axons. DPP-4 inhibitors have been reported to possess antioxidant, anti-inflammatory, and neuroprotective properties [14–18]. Reductions in inflammation and oxidative stress in the sciatic nerve and dorsal root ganglia may therefore contribute, at least in part, to the OIPN-suppressive effects of DPP-4 inhibitors. Furthermore, GLP-1 and pituitary adenylate cyclase-activating polypeptide (PACAP) are known substrates of DPP-4. GLP-1 increases the expression of antioxidant factors (e.g., SOD2, GPx) via cAMP elevation and CREB phosphorylation [41], suggesting a potential role in suppressing oxaliplatin-induced cellular injury. In rats, the GLP-1 analog exenatide has been shown to promote recovery from OIPN [42]. PACAP has also been reported to markedly extend neurite-like processes in dorsal root ganglion neurons [43]. These DPP-4 substrates may therefore contribute to the prevention of OIPN. Conversely, DPP-4 inhibitors did not suppress paclitaxel-induced peripheral neuropathy, which originates from axonal injury. This finding suggests that DPP-4 inhibitors may not directly protect axons but instead suppress neuronal cell body injury, thereby preventing OIPN. However, many aspects of the in vivo actions of DPP-4 inhibitors remain unclear, and further basic research is required to elucidate their mechanisms.

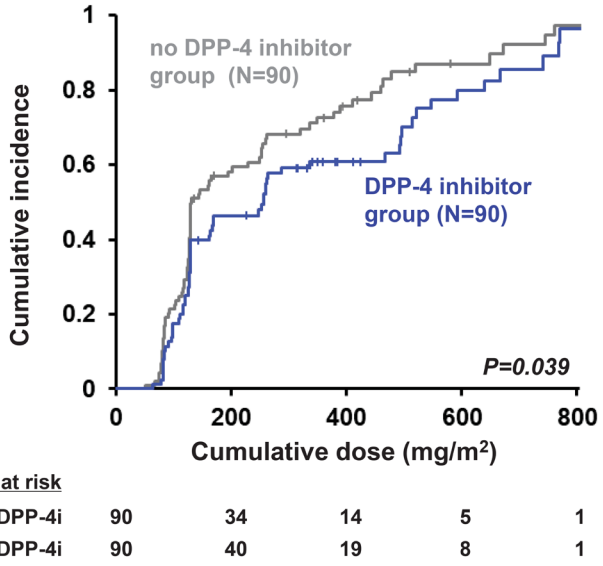


FIGURE 2 | Calculative incidences of oxaliplatin-induced peripheral neuropathy (after propensity score matching). Kaplan–Meier curve was constructed with oxaliplatin-induced peripheral neuropathy (any grade) on the y-axis and the cumulative dose of oxaliplatin on the x-axis. Differences in cumulative incidence between two groups were analyzed using the log-rank test.

Although DPP-4 inhibitors may suppress the development of OIPN, their clinical application, particularly in non-diabetic patients, requires careful consideration. DPP-4 inhibitors have recently attracted attention for their pleiotropic effects in cancer. Some studies have suggested potential antitumor effects depending on cancer type, indicating possible therapeutic benefits for cancer patients [44, 45]. Conversely, earlier reports suggested an increased risk of certain cancers [46, 47], although more recent studies have shown no association between DPP-4 inhibitors and cancer incidence [48], indicating that further investigation is needed. Beyond oncology, although rare, DPP-4 inhibitors have been associated with gastrointestinal symptoms, pancreatitis, and retinopathy [49]. Among antidiabetic agents, hypoglycemia is the most important adverse effect requiring caution; however, DPP-4 inhibitors are known to have a low risk of hypoglycemia and are considered highly safe. In Japan, they are among the most frequently prescribed first-line antidiabetic medications [50], and combination therapy with other antidiabetic agents is common. In addition, because some DPP-4 inhibitors can be used regardless of renal function, they are suitable for a wide

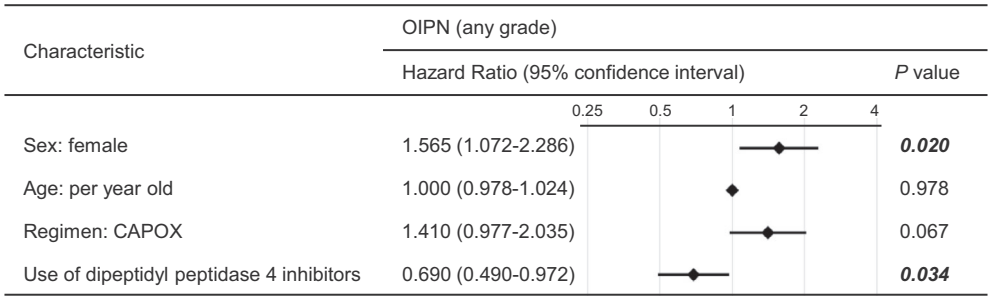


FIGURE 3 | Multivariate analysis of variables associated with oxaliplatin-induced peripheral neuropathy. Cox proportional hazards analysis with factors reported to influence oxaliplatin-induced peripheral neuropathy (sex, regimen, age, DPP-4 inhibitor use) as covariates was performed on the data after propensity score matching.

range of patients, including those with diabetic nephropathy [51]. Given these characteristics, the use of DPP-4 inhibitors as a preventive agent for OIPN in diabetic patients scheduled to receive oxaliplatin-based chemotherapy may be acceptable from both safety and ethical perspectives.

In contrast, evidence regarding the efficacy and safety of DPP-4 inhibitors in non-diabetic patients is insufficient, and the possibility of unexpected short- or long-term adverse events cannot be excluded. It is therefore essential to carefully evaluate whether it is ethically appropriate to expose non-diabetic patients to the potential risks of DPP-4 inhibitor–related adverse events solely for the purpose of preventing peripheral neuropathy. Large-scale studies are needed to identify patient subgroups for whom DPP-4 inhibitor use may be appropriate.

This study was a single-center retrospective investigation, and the limited sample size made it difficult to perform analyses with sufficient statistical power in subgroups with specific background factors. In particular, incorporating diabetes, a known risk factor for OIPN [52], as a covariate in the propensity score matching model was not feasible. Nevertheless, the finding that OIPN incidence was lower in the DPP-4 inhibitor group, in which all patients had diabetes, provides even stronger support for the potential effectiveness of DPP-4 inhibitors. To conduct more rigorous analyses, multicenter studies involving larger patient populations are required. In addition, the assessment of OIPN incidence and severity was based on medical record documentation and therefore relied in part on subjective evaluations. Notably, acute OIPN is characterized by cold-induced dysesthesia that typically resolves within a short period and is clinically distinct from chronic OIPN, although its incidence is high. In this study, some cases did not clearly differentiate acute from chronic OIPN in the medical records, suggesting that the effects of DPP-4 inhibitors on acute OIPN could have materially influenced the observed results. Because retrospective cohort studies often lack sufficient information for evaluating neurological disorders, prospective studies will be necessary in the future. Although previous basic research has reported preventive effects of DPP-4 inhibitors on OIPN, the present study was unable to investigate the mechanisms underlying these effects. Clarifying these mechanisms will be essential for strengthening the validity of this study and advancing their potential clinical application.

In conclusion, this study suggests that concomitant use of DPP-4 inhibitors may prevent the development of OIPN; however, careful evaluation based on further investigations is required to determine their efficacy and clinical applicability.

Author Contributions

Yusuke Koura, Keisuke Mine, Shunsuke Fujita, Takehiro Kawashiri, Yusuke Mori, Mami Ueda, Risa Kaneko, Takeshi Hirota, Mayako Uchida, and Daisuke Kobayashi wrote the manuscript. Yusuke Koura, Keisuke Mine, Shunsuke Fujita, Takehiro Kawashiri, Yusuke Mori, Mami Ueda, Risa Kaneko, Takeshi Hirota, Mayako Uchida, and Daisuke Kobayashi designed the research. Yusuke Koura, Keisuke Mine, Shunsuke Fujita, and Takehiro Kawashiri performed the research. Yusuke Koura, Keisuke Mine, Shunsuke Fujita, and Takehiro Kawashiri analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain information that might compromise the privacy of research participants.

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