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Effectiveness of Statins for Oxaliplatin-Induced Peripheral Neuropathy: A Multicenter Retrospective Observational Study

Kenshi Takechi¹  | Takehiro Kawashiri²  | Keisuke Mine² | Soichiro Ushio³  | Hirofumi Hamano⁴  | Noriko Hida⁵  | Kenji Momo⁶ | Masanobu Uchiyama⁷ | Mami Uchida⁸  | Mamoru Tanaka⁹ | Noriaki Hidaka⁹ | Hideki Yasui^{10,11} | Masahiro Ueda¹²  | Ryohei Fujii¹³  | Misaki Hashimoto¹³  | Yasutaka Sakamoto¹⁴  | Kana Uyama¹⁴ | Takahiro Niimura^{15,16}  | Yuki Hanai¹⁷  | Ayaka Tsuboya^{18,19}  | Keisuke Suzuki²⁰  | Naoya Kamiyama²¹  | Hiromi Hagiwara²²  | Naoto Okada²³ | Yoshito Zamami⁴ | Keisuke Ishizawa^{15,16,24}

¹Department of Drug Information Analysis, College of Pharmaceutical Sciences, Matsuyama University, Matsuyama, Japan | ²Department of Clinical Pharmacy and Pharmaceutical Care, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan | ³Department of Emergency and Disaster Medical Pharmacy, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan | ⁴Department of Pharmacy, Okayama University Hospital, Okayama, Japan | ⁵Department of Clinical Research and Development, Graduate School of Pharmacy, SHOWA Medical University, Shinagawa-ku, Japan | ⁶Department of Hospital Pharmaceutics, Graduate School of Pharmacy, SHOWA Medical University, Shinagawa-ku, Japan | ⁷Department of Oncology and Infectious Disease Pharmacy, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan | ⁸Department of Pharmacy, Fukuoka University Hospital, Fukuoka, Japan | ⁹Division of Pharmacy, Ehime University Hospital, Toon, Japan | ¹⁰Center for Clinical Research, Hamamatsu University Hospital, Hamamatsu, Japan | ¹¹Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan | ¹²Faculty of Pharmaceutical Sciences, Setsunan University, Osaka, Japan | ¹³Department of Pharmacy, Kansai Medical University Hospital, Osaka, Japan | ¹⁴Department of Pharmacy, Yokohama City University Hospital, Yokohama, Japan | ¹⁵Department of Clinical Pharmacology and Therapeutics, University of Tokushima Graduate School of Biomedical Sciences, Tokushima, Japan | ¹⁶Clinical Research Center for Developmental Therapeutics, Tokushima University Hospital, Tokushima, Japan | ¹⁷Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Japan | ¹⁸Department of Pharmacy, Kawasaki Municipal Tama Hospital, Kawasaki, Japan | ¹⁹Department of Hospital Pharmaceutics, School of Pharmacy, SHOWA Medical University, Shinagawa-ku, Japan | ²⁰Innovation Center for Translational Research, National Center for Geriatrics and Gerontology, Obu, Japan | ²¹Asahikawa Medical University Hospital, Asahikawa, Japan | ²²Nagoya City University Hospital, Nagoya, Japan | ²³Pharmacy Department, Yamaguchi University Hospital, Yamaguchi, Japan | ²⁴Department of Pharmacy, Tokushima University Hospital, Tokushima, Japan

Correspondence: Kenshi Takechi (k.takechi@g.matsuyama-u.ac.jp)

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ABSTRACT

Chemotherapy-induced peripheral neuropathy, including oxaliplatin-induced peripheral neuropathy (OIPN), can have a negative impact on patient quality of life for months or even years after discontinuation of chemotherapy. Statins are commonly used for lowering cholesterol; however, evidence indicates that statins have multiple pleiotropic effects. Although statins are anticipated to exert neuroprotective actions against OIPN, no large-scale investigations have been conducted in real-world clinical settings. Our investigation aimed to determine if statins protected against OIPN. This multicentre retrospective study enrolled Japanese patients with cancer, including those with colorectal cancer (CRC), who received oxaliplatin-containing chemotherapy between April 2009 and December 2019. Propensity score matching between groups was performed to assess the relationship between the occurrence of OIPN and statin use. Among the examined 2657 patients receiving oxaliplatin, 24.7% had Grade ≥ 2 OIPN. There was no significant

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difference in the incidence of OIPN between the statin and non-statin groups, even after propensity score matching. However, among the matched patients with CRC ($n=510$), statin use was associated with a significantly lower incidence of Grade ≥ 2 OIPN than no statin use (19.8% vs. 28.3%, respectively; $p=0.029$). Our findings indicate that statins may protect against OIPN in patients with CRC.

1 | Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and serious adverse effect of anticancer drugs [1, 2]. CIPN can reduce patient quality of life and lead to dose reduction or premature cessation of chemotherapy, with negative impacts on treatment efficacy [2].

Oxaliplatin is a cytotoxic, platinum-based anticancer agent, most frequently used for the treatment of colorectal cancer (CRC). First-line chemotherapy consisting of oxaliplatin with fluorouracil is offered to patients with initially unresectable microsatellite-stable or proficient mismatch repair CRC [3]. Oxaliplatin is also used to treat pancreatic and gastric cancers. Its most frequent and dose-limiting toxicity is oxaliplatin-induced peripheral neuropathy (OIPN), which affects 20%–50% of patients at conventional doses and almost all patients at high cumulative doses [1, 2]. With respect to the duration of administration, the reported rates of OIPN are 13% and 36% after 3 and 6 months of oxaliplatin-containing chemotherapy, respectively [4]. OIPN occurs in acute and chronic phases, depending on the time of onset [2]. The main symptom of acute peripheral neuropathy is sensory disturbance, which occurs in 85%–94% of patients within 2 days post-administration and is usually temporary and reversible. Chronic neuropathy is predominantly sensory, and the major symptom is tingling [2, 5, 6]. It is dose-dependent and usually occurs at cumulative doses $> 540 \text{ mg/m}^2$ [7]. The acute and chronic forms of OIPN are assumed to have different mechanisms, with acute OIPN attributed to oxalate-induced calcium chelation and altered sodium-channel function, and chronic OIPN caused by reduced cellular metabolism and axonal trafficking in dorsal root ganglion cells [8].

Despite the increased use of CIPN-inducing agents such as oxaliplatin and taxane paclitaxel, supportive care for CIPN remains challenging because of difficulty in determining the efficacies of drug and nondrug therapies [2, 6, 9]. Although some agents, such as gabapentin and vitamin E, have been used to treat and prevent CIPN, no intervention is currently highly recommended [2, 6, 10]. More comprehensive research is therefore needed to develop effective preventive strategies and evidence-based interventions to mitigate CIPN for improving patients' well-being and quality of life [11].

Accumulating evidence suggests that statins, which are commonly used for lowering cholesterol, have multiple pleiotropic effects, including potential neuroprotective benefits against CIPN and OIPN. Preliminary studies indicate that statins, such as simvastatin, atorvastatin, and rosuvastatin, can reduce mechanical allodynia in OIPN animal models [12, 13]. In addition, retrospective studies indicated a reduction in the incidence of peripheral neuropathy in patients administered statins concurrently with oxaliplatin [12]. In contrast, a single-centre retrospective study investigating the impact of statins on CIPN in patients with CRC found that statins did not mitigate peripheral neuropathy [14]. These inconsistent results

warrant further studies to corroborate the findings and ascertain if statins may offer further advantages.

We therefore conducted a large multicentre retrospective study to explore the effect of statins on OIPN in patients treated with oxaliplatin-containing chemotherapy, using propensity score matching. In particular, we examined the effect of statins on OIPN in patients with CRC, since oxaliplatin is most frequently used for this cancer type.

2 | Methods

2.1 | Ethical Considerations

The study was conducted following the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [15]. This study was evaluated by the central institutional review board and adhered to the ethical guidelines for medical research involving human participants. The study was approved by the Ethics Committee of Tokushima University Hospital (approval number: 3275) and conforms to the guidelines of the Declaration of Helsinki. The requirement for informed consent was waived in view of the retrospective nature of the study.

2.2 | Study Period and Participants

A total of 2657 Japanese individuals aged > 18 years, who received oxaliplatin-based chemotherapy at the 13 participating institutions between April 2009 and December 2019, were included in this study. The following exclusion criteria were applied: patients with previous use of oxaliplatin, peripheral neuropathy due to other agents or diseases, and patients who received nerve block therapy.

2.3 | Survey Parameters

The following data were collected from electronic medical records: patient age, sex, body mass index (BMI), medical history, cancer type, chemotherapy regimens, number of doses, initial and cumulative doses of oxaliplatin, estimated glomerular filtration rate (eGFR), alanine transaminase, aspartate aminotransferase, concomitant medications, and medications for peripheral neuropathy and pain relief. The peripheral neuropathy was assessed based on data collected from electronic medical records written by physicians, pharmacists, and nurses; the grading was classified using JCOG, the Japanese translation of the Common Terminology Criteria for Adverse Events (v4.0). The occurrence of chronic peripheral neuropathy (Grade ≥ 2 with symptoms lasting ≥ 1 week) and the timing of the first onset of peripheral neuropathy were analyzed retrospectively. Grade 2 CIPN was defined as pain/numbness or functional movement disorders that limited the instrumental activities of daily living. Patients

Study Highlights

- What is the current knowledge on the topic?
 - Statins possess potential neuroprotective benefits against CIPN and OIPN; however, reports on the impacts of statins on CIPN in patients with CRC are inconsistent.
- What question did this study address?
 - We explored the effects of statins on OIPN in patients treated with oxaliplatin-containing chemotherapy.
- What does this study add to our knowledge?
 - We found that statins reduced the incidence of Grade ≥ 2 OIPN in patients with CRC.
- How might this change clinical pharmacology or translational science?
 - Our findings support the conclusions suggesting statins as neuroprotective agents.

were categorized into 'statin' and 'non-statin' groups based on the continuous use of statins before initiating oxaliplatin treatment. Statin use was continued during chemotherapy.

2.4 | Statistical Analyses

Continuous and categorical patient background variables were analyzed using the Mann–Whitney *U*-test and Fisher's exact test or χ^2 test. The log-rank test for the incidence of peripheral neuropathy was performed using the Kaplan–Meier method. Propensity score matching was used to analyze the incidence of chronic peripheral neuropathy. Propensity score was calculated using age, BMI, eGFR, diabetes mellitus, and the regular use of combination drugs such as angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), and calcium channel blockers as covariates. Matching was performed using logistic regression analysis, with the caliper coefficient set at 0.2. Subsequently, the effect of statin use on CIPN was analyzed. In risk factor analysis with logistic regression, univariate and multivariate regression were performed for CRC patients with $\geq$ Grade 2 OIPN as a response variable and the patient background factors as explanatory variables. Conditional logistic regression was used in the analysis, especially in the CRC patient group after propensity score matching. The odds ratio, 95% confidence interval, and *p* value for each background factor were calculated. We fitted a multivariable logistic regression model including variables of a priori interest (age, diabetes, ACEI, and statin) and included potential explanatory variables found to be significant in bivariate analyses with a *p* value < 0.1 . Statistical significance was set at *p* < 0.05 . EZR (64-bit, v1.55, Saitama Medical Center, Jichi Medical University, Japan) was used for statistical analysis [16].

3 | Results

3.1 | Patient Characteristics

Among 2657 patients treated with oxaliplatin, 368 patients (14%) received statins prior to the initiation of and during the oxaliplatin-containing regimen. The patient characteristics

according to statin use are summarized in Table 1. Patients in the statin group were older and had higher BMI than those in the non-statin group. Patients in the statin group also had a lower eGFR, higher prevalence of diabetes, and significantly higher rates of usage of ARBs, ACEIs, and calcium channel blockers. There was no significant difference in the types of oxaliplatin-containing regimen and initial and cumulative doses of oxaliplatin between the statin and non-statin groups.

3.2 | Incidence of OIPN

Grade 1 peripheral neuropathy is asymptomatic, and the credibility of a Grade 1 assessment was low in a retrospective study. In this study, we targeted Grade ≥ 2 CIPN. The incidence of Grade ≥ 2 OIPN among the 2657 patients receiving oxaliplatin was 24.7%, including 23.0% and 25.0% in the statin and non-statin groups, respectively (*p* = 0.469, Table 2). The incidence of Grade ≥ 3 OIPN was 3.2% (4.3% in the statin group and 3.1% in the non-statin group, *p* = 0.203, Table 2). There were no significant differences in oxaliplatin relative dose or the rate of treatment discontinuation owing to neuropathy between the two groups. The rate of oxaliplatin dose reduction was smaller in the statin group than in the non-statin group. We performed propensity score matching to balance covariates to determine the differences in patient background characteristics that might affect the occurrence of peripheral neuropathy [17]. After propensity score matching, there were no significant differences in age, BMI, cancer type, comorbidity, concomitant drug use, dosage of oxaliplatin, type of chemotherapy regimen, or the proportion of adjuvant chemotherapy between the two groups (Table 1). Similarly, the incidence of OIPN between these matched patients showed no differences (22.0% and 24.9% in the statin and non-statin groups, respectively, *p* = 0.425, Figure 1 and Table 2). The incidence of Grade ≥ 3 OIPN was 3.5%, including 4.4% and 2.5% in the statin and non-statin groups, respectively (*p* = 0.221, Table 2). The severity of neuropathy and the oxaliplatin discontinuation rate owing to peripheral neuropathy were similar in both groups. We examined the relationship between the cumulative oxaliplatin dosage and the incidence of OIPN using the log-rank test and found no significant differences in the cumulative incidence between the statin and non-statin groups.

3.3 | Effects of Statins on OIPN in Patients With CRC

Furthermore, we analyzed the effects of statins in patients with CRC. The clinical characteristics of patients with CRC are presented in Table 3. When restricted to patients with CRC, statin users were significantly older and had significantly higher BMI, lower eGFR, higher prevalence of diabetes, and higher usage rates of ARBs, ACEIs, and calcium channel blockers than nonusers. Similar to the overall patient outcome, there was no significant difference in the occurrence of Grade ≥ 2 OIPN between the statin (21.5%) and non-statin (25.1%) groups for patients with CRC (*p* = 0.244, Figure 1 and Table 2). In addition, we analyzed the association between statin use and OIPN in patients with CRC using propensity score matching and found no significant differences in patient characteristics, including chemotherapy regimens or the proportion of adjuvant chemotherapy, between the two groups; however,

TABLE 1 | Clinical characteristics of patients in the statin and non-statin groups.

Variable	All patients				Propensity score-matched patients		
	Total	Non-statin group	Statin group	<i>p</i>	Non-statin group	Statin group	<i>p</i>
	<i>n</i> = 2657	<i>n</i> = 2289	<i>n</i> = 368		<i>n</i> = 361	<i>n</i> = 361	
Age, years							
Median (IQR)	64 (57.0, 71.0)	64 (55.0, 70.0)	69 (63.8, 74.0)	<0.001	70 (64.0, 74.0)	69 (63.0, 74.0)	0.194
Sex, <i>n</i> (%)							
Male	1566 (58.9)	1351 (59.0)	215 (58.4)	0.864	230 (63.7)	212 (58.7)	0.194
Female	1091 (41.1)	938 (41.0)	153 (41.6)		131 (36.3)	149 (41.3)	
BMI, kg/m ²							
Median (IQR)	21.7 (19.6, 24.0)	21.5 (19.4, 23.7)	23.0 (20.8, 25.7)	<0.001	22.8 (20.8, 25.6)	22.9 (20.7, 25.5)	0.825
Cancer type, <i>n</i> (%)							
Colorectal cancer	1866 (70.2)	1602 (70.0)	264 (71.7)	0.024	253 (70.1)	258 (71.5)	0.758
Gastric cancer	435 (16.4)	374 (16.3)	61 (16.6)		63 (17.5)	60 (16.6)	
Pancreatic cancer	239 (9.0)	202 (8.8)	37 (10.1)		35 (9.7)	37 (10.2)	
Other cancer	117 (4.4)	111 (4.8)	6 (1.6)		10 (2.8)	6 (1.7)	
Comorbidity, <i>n</i> (%)							
Diabetes	389 (14.6)	265 (11.6)	124 (33.7)	<0.001	119 (33.0)	118 (32.7)	1
Herpes zoster	14 (0.5)	11 (0.5)	3 (0.8)	0.428	4 (1.1)	3 (0.8)	1
Autoimmune diseases	42 (1.6)	33 (1.4)	9 (2.4)	0.172	5 (1.4)	9 (2.5)	0.419
Laboratory data, median (IQR)							
eGFR (mL/min/1.73 m ²)	76.7 (65.0, 89.7)	77.6 (66.2, 90.2)	70.8 (58.0, 82.6)	<0.001	70.0 (61.0, 81.1)	70.9 (58.8, 82.7)	0.864
ALT (U/L)	16 (12.0, 26.0)	16 (12.0, 26.0)	17 (12.0, 27.3)	0.077	17 (12.0, 24.0)	18 (12.0, 28.0)	0.079
AST (U/L)	21 (16.5, 28.0)	21 (16.0, 28.0)	21 (17.0, 27.0)	0.192	21 (17.0, 27.0)	21 (17.0, 27.0)	0.493
HbA1c (%)	5.8 (5.5, 6.3)	5.8 (5.4, 6.2)	6.1 (5.8, 7.0)	<0.001	6.1 (5.6, 6.8)	6.1 (5.7, 6.9)	0.314
Concomitant medications, <i>n</i> (%)							
ACEI or ARB	477 (18.0)	316 (13.8)	161 (43.8)	<0.001	144 (39.9)	154 (42.7)	0.496
Ca antagonist	544 (20.5)	386 (16.9)	160 (43.5)	<0.001	141 (39.1)	153 (42.4)	0.405
Opioid	184 (6.9)	162 (7.4)	22 (6.3)	0.577	19 (5.4)	22 (6.4)	0.631
NSAIDs	536 (20.2)	459 (20.9)	77 (22.0)	0.622	73 (20.9)	76 (22.2)	0.712
Antiepileptic drugs	51 (19.2)	40 (1.8)	11 (3.1)	0.102	7 (2.0)	11 (3.2)	0.349
Antidepressants	79 (3.0)	66 (3.3)	13 (4.0)	0.508	15 (4.6)	12 (3.8)	0.696
Oxaliplatin							
Initial dose, mg (range)	150 (47, 290)	150 (47, 290)	150 (47, 277)	0.083	150 (48, 286)	150 (47, 277)	0.907
Cumulative dosage, mg (IQR)	900 (525, 1350)	900 (521, 1350)	890 (550, 1350)	0.786	939 (560, 1410)	880 (550, 1350)	0.158
Course, <i>n</i> (IQR)	6 (4, 9)	6 (4, 9)	6 (4, 9)	0.34	6 (4, 9)	6 (4, 9)	0.183

(Continues)

TABLE 1 | (Continued)

Variable	All patients				Propensity score-matched patients		
	Total <i>n</i> = 2657	Non-statin group <i>n</i> = 2289	Statin group <i>n</i> = 368	<i>p</i>	Non-statin group <i>n</i> = 361	Statin group <i>n</i> = 361	<i>p</i>
Dose reduction, <i>n</i> (%)	398 (14.9)	356 (15.6)	42 (11.4)	0.041	56 (15.5)	42 (11.6)	0.158
Withdrawal, <i>n</i> (%)	391 (14.7)	348 (15.2)	43 (11.7)	0.081	52 (14.4)	41 (11.4)	0.267
Chemotherapy cessation, <i>n</i> (%)	271 (10.2)	237 (11.8)	34 (10.2)	0.459	37 (11.2)	32 (9.8)	0.611
Chemotherapy regimen, <i>n</i> (%)							
FOLFOX	844	738 (32.2)	106 (28.8)	0.342	105 (29.1)	102 (28.3)	0.886
XELOX	1027	869 (38.0)	158 (42.9)		142 (39.3)	154 (42.7)	
SOX	453	394 (17.2)	59 (16.0)		67 (18.6)	59 (16.3)	
FOLFIXIRI	67	60 (2.6)	7 (1.9)		6 (1.7)	7 (1.9)	
FOLFIRINOX	231	195 (8.5)	36 (9.8)		34 (9.4)	36 (10.0)	
Adjuvant chemotherapy, <i>n</i> (%)	953	802 (35.0)	151 (41.0)	0.030	147 (40.7)	148 (41.0)	1.000
Statin use, <i>n</i> (%)	368 (13.8)	0 (0)	368 (100)	—	0 (0)	361 (100)	—
Type of statin, <i>n</i> (%)							
Atorvastatin	118 (31.7)	—	118 (31.7)	—	—	115 (31.8)	—
Rosuvastatin	117 (31.7)	—	117 (31.7)	—	—	115 (31.8)	—
Pitavastatin	61 (16.8)	—	61 (16.8)	—	—	61 (16.9)	—
Pravastatin	60 (16.3)	—	60 (16.3)	—	—	55 (15.2)	—
Fluvastatin	7 (1.9)	—	7 (1.9)	—	—	7 (1.9)	—
Simvastatin	5 (1.4)	—	5 (1.4)	—	—	4 (1.1)	—

Note: FOLFOX included oxaliplatin (85 mg/m²) + 5-FU + leucovorin; XELOX included oxaliplatin (130 mg/m²) + capecitabine; SOX included oxaliplatin (100-130 mg/m²) + S-1; FOLFIXIRI included oxaliplatin (85 mg/m²) + 5-FU + irinotecan; FOLFIRINOX included oxaliplatin (85 mg/m²) + 5-FU + levofolinate calcium + irinotecan. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

the initial oxaliplatin dose was higher in the statin group (Table 3). In addition, we conducted a multivariate analysis to address the potential confounding effect in patients with CRC (Table S1) and propensity score-matched patients with CRC (Table S2). In a multivariate analysis of CRC patients, adjuvant therapy was identified as a protective factor against OIPN. In contrast, when the same analysis was performed on propensity score-matched patients, opioid use emerged as a potential risk factor for OIPN. In this population, the incidence of Grade ≥ 2 OIPN was significantly lower in statin users (19.8% in the statin group vs. 28.3% in the non-statin group, $p = 0.029$, Figure 1 and Table 2), and oxaliplatin dose reduction was more frequent in the non-statin group ($p = 0.038$). The percentage of patients who discontinued oxaliplatin owing to neuropathy was also lower in the statin group (11.5%) than in the non-statin group (14.8%); however, the difference was not significant. Ten patients in the statin group (3.9%) and five in the non-statin group (2.0%) had Grade ≥ 3 OIPN ($p = 0.294$,

Table 2). There was no difference in the incidence of Grade ≥ 2 or 3 OIPN according to the type of chemotherapy regimen. The cumulative incidence of peripheral neuropathy in patients with CRC was examined using the log-rank test. The Kaplan–Meier curve showed that statins tended to reduce the risk of developing peripheral neuropathy; however, the difference was not significant (Figure 2 and Table S3).

3.4 | Comparison Between Patients With and Without Grade ≥ 2 OIPN

We compared the clinical characteristics of patients with and without Grade ≥ 2 OIPN (Table 4). There were no differences in age, sex, BMI, comorbidity, or concomitant drug use; however, antidepressant use differed between the two groups. Patients with Grade ≥ 2 OIPN received less frequent adjuvant

TABLE 2 | Cumulative incidence rates of oxaliplatin-induced peripheral neuropathy in statin and non-statin groups.

Variable	All patients			Propensity score-matched patients			All patients with colorectal cancer			Propensity score-matched patients with colorectal cancer		
	Non-statin group	Statin group	p	Non-statin group	Statin group	p	Non-statin group	Statin group	p	Non-statin group	Statin group	p
	n = 2289	n = 368		n = 361	n = 361		n = 1602	n = 264		n = 255	n = 255	
Grade ≥ 2 (%)	25.0	23.0	0.469	24.9	22.0	0.425	25.1	21.5	0.244	28.3	19.8	0.029
Grade ≥ 3 (%)	3.1	4.3	0.203	2.5	4.4	0.221	3.2	3.8	0.771	2.0	3.9	0.294

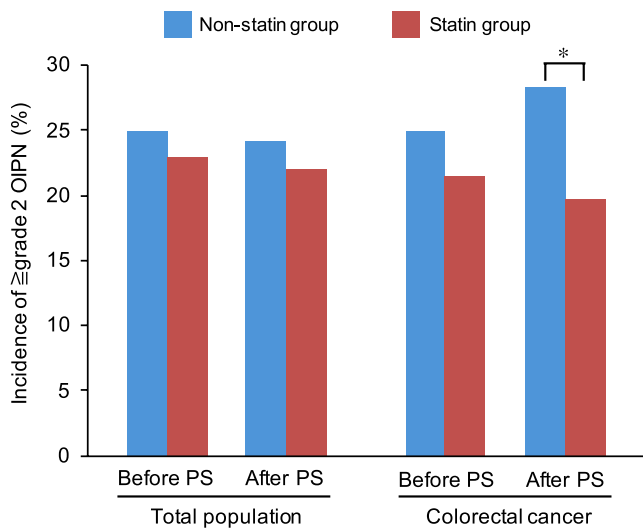


FIGURE 1 | Incidence of Grade ≥ 2 oxaliplatin-induced peripheral neuropathy (OIPN). The incidence of Grade ≥ 2 OIPN in statin and non-statin groups before and after propensity score matching in the total population and patients with colorectal cancer (CRC). OIPN, oxaliplatin-induced peripheral neuropathy; PS, propensity score matching. **p* < 0.03, compared with non-statin groups.

chemotherapy and had a significantly higher cumulative dose of oxaliplatin, more frequent oxaliplatin dose reduction, and treatment cessation.

4 | Discussion

Adverse events occur in most patients undergoing chemotherapy, of which CIPN is among the most frequent and challenging complications in cancer treatment using oxaliplatin [1, 2]. CIPN can negatively interfere with the patient's activities of daily life and can affect their overall quality of life [2]. The dose intensity of cytotoxic agents was related to poor overall survival. Patients with CRC or pancreatic cancer receiving oxaliplatin-containing regimens had a significantly increased risk of mortality at a relative dose intensity level of < 80% versus ≥ 80%, or < 85% versus ≥ 85% [18]. Given the increasing use of CIPN-inducing agents for various cancers and the fact that CIPN is an important dose-limiting factor that can

jeopardize the continuation of chemotherapy, appropriate pharmacological and non-pharmacological management is needed. To date, however, CIPN remains a significant challenge in cancer therapy [2, 6], and the National Cancer Institute has designated it as a priority in translational research [19]. The results of the current retrospective study showed that the occurrence of OIPN was lower in patients with CRC who were taking statins, suggesting a potential neuroprotective effect of statins.

Oxaliplatin is used to treat various cancers, such as CRC, gastric, and pancreatic cancer, with high incidences of acute and chronic CIPN [2, 6, 20]. We therefore conducted a multicentre, institution-based observational study to investigate the effect of statins on peripheral neuropathy in patients receiving oxaliplatin-containing chemotherapy, particularly among patients with CRC. The incidences of ≥ Grade 2 OIPN among all 2657 patients and among 1866 patients with CRC were 24.7% and 24.5%, respectively, consistent with previous reports [5, 21]. In these populations, patients with ≥ Grade 2 OIPN had a higher cumulative oxaliplatin dose, more frequent oxaliplatin dose reduction, and treatment cessation, which were also consistent with previous reports [5, 7, 21]. Although diabetes, obesity, and older age have been reported as risk factors for CIPN, they were not related to the occurrence of ≥ Grade 2 OIPN in this study [22, 23]. Some peripheral neuropathy-associated factors differed between the statin and non-statin groups, and we therefore used propensity score matching to reduce confounding. Following propensity score matching, the incidence of Grade ≥ 2 OIPN in patients with CRC taking statins was significantly lower than that in the non-statin group. Although the initial dose of oxaliplatin was higher, the rate of dose reduction was significantly lower in the statin group. Although the difference was not significant, statins tended to reduce the risk of developing peripheral neuropathy in patients with CRC, according to cumulative oxaliplatin dosage. These results, based on a relatively large cohort of patients, indicate that statins might help to prevent OIPN in patients with CRC. Statins have been widely used for a long time, and their safety profiles are therefore well-known, which strengthens their potential use as a candidate drug for OIPN prevention.

The mechanisms by which statins reduce the occurrence of OIPN, however, are unclear. They may involve upregulation of

TABLE 3 | Clinical characteristics of patients with colorectal cancer in the statin and non-statin groups.

Variable	All patients			Propensity score-matched patients		
	Non-statin group	Statin group	<i>p</i>	Non-statin group	Statin group	<i>p</i>
	<i>n</i> = 1602	<i>n</i> = 264		<i>n</i> = 255	<i>n</i> = 255	
Age, years						
Median (IQR)	63 (55.0, 70.0)	69 (62.0, 74.0)	<0.001	69 (64.0, 74.0)	69 (62.0, 73.0)	0.241
Sex, <i>n</i> (%)						
Male	899 (56.1)	146 (55.3)	0.841	162 (63.5)	140 (54.9)	0.058
Female	703 (43.9)	118 (44.7)		93 (36.5)	115 (45.1)	
BMI, kg/m ²						
Median (IQR)	21.8 (19.7, 24.0)	23.2 (21.1, 26.2)	<0.001	23.1 (21.3, 25.6)	23.1 (21.0, 25.8)	0.759
Comorbidity, <i>n</i> (%)						
Diabetes	167 (10.4)	83 (31.4)	<0.001	76 (29.8)	76 (29.8)	1
Herpes zoster	9 (0.6)	2 (0.8)	0.661	1 (0.4)	2 (0.8)	1
Autoimmune diseases	24 (1.5)	6 (2.3)	0.423	1 (0.4)	6 (2.4)	0.122
Laboratory data, median (IQR)						
eGFR (mL/min/1.73 m ²)	77.6 (66.1, 89.9)	68.9 (58.0, 81.3)	<0.001	69.0 (58.9, 80.0)	69.4 (58.7, 82.1)	0.852
ALT (U/L)	16 (12.0, 25.0)	18 (12.0, 26.3)	0.081	15 (11.0, 22.0)	18 (12.5, 26.5)	0.002
AST (U/L)	20 (16.0, 28.0)	21 (17.0, 27.0)	0.070	20 (16.0, 27.0)	21 (17.0, 27.0)	0.098
HbA1c (%)	5.7 (5.4, 6.1)	6.1 (5.7, 6.9)	<0.001	6.0 (5.6, 6.5)	6.1 (5.7, 6.9)	0.185
Concomitant medications, <i>n</i> (%)						
ACEI or ARB	241 (15.0)	121 (45.8)	<0.001	112 (43.9)	112 (43.9)	> 0.95
Ca antagonist	279 (17.4)	128 (48.5)	<0.001	118 (46.3)	119 (46.7)	> 0.95
Opioid	85 (5.5)	9 (3.6)	0.282	18 (7.3)	8 (3.3)	0.068
NSAIDs	301 (19.5)	48 (19.1)	0.932	55 (22.4)	45 (18.6)	0.314
Antiepileptic drugs	28 (1.8)	7 (2.8)	0.320	5 (2.0)	6 (2.5)	0.771
Antidepressants	44 (3.1)	8 (3.4)	0.839	12 (5.3)	7 (3.1)	0.349
Oxaliplatin						
Initial dose, mg (range)	150 (47, 290)	161 (47, 277)	0.008	145 (48, 260)	160 (47, 277)	0.023
Cumulative dosage, mg (IQR)	960 (570, 1380)	920 (608, 1395)	0.703	960 (553, 1376)	910 (600, 1391)	0.767
Course, <i>n</i> (IQR)	6 (4, 9)	6 (4, 9)	0.243	7 (4, 9)	6 (4, 9)	0.181
Dose reduction, <i>n</i> (%)	259 (16.2)	27 (10.2)	0.013	43 (16.9)	26 (10.2)	0.038
Withdrawal, <i>n</i> (%)	255 (15.9)	33 (12.5)	0.168	43 (16.9)	31 (12.2)	0.166
Chemotherapy cessation, <i>n</i> (%)	184 (12.8)	29 (12.0)	0.834	34 (14.8)	27 (11.5)	0.337
Chemotherapy regimen, <i>n</i> (%)						
FOLFOX	692 (43.2)	99 (37.5)	0.080	119 (46.7)	96 (37.6)	0.084
XELOX	780 (48.7)	151 (57.2)		117 (45.9)	145 (56.9)	
SOX	70 (4.4)	8 (3.0)		13 (5.1)	8 (3.1)	
FOLFOXIRI	53 (3.3)	6 (2.3)		6 (2.4)	6 (2.4)	

(Continues)

TABLE 3 | (Continued)

Variable	All patients		<i>p</i>	Propensity score-matched patients		<i>p</i>
	Non-statin group	Statin group		Non-statin group	Statin group	
	<i>n</i> = 1602	<i>n</i> = 264		<i>n</i> = 255	<i>n</i> = 255	
Adjuvant chemotherapy	657 (41.0)	131 (49.6)	0.011	108 (42.4)	127 (49.8)	0.110
Statin use, <i>n</i> (%)	0 (0)	264 (100)		0 (0)	255 (100)	
Type of statin, <i>n</i> (%)						
Atorvastatin		86 (32.5)			85 (33.3)	
Rosuvastatin		84 (31.8)			80 (31.4)	
Pitavastatin		48 (18.2)			46 (18.0)	
Pravastatin		37 (14.0)			36 (14.1)	
Fluvastatin		4 (1.5)			4 (1.6)	
Simvastatin		5 (1.9)			4 (1.6)	

Note: FOLFOX included oxaliplatin (85 mg/m²) + 5-FU + leucovorin; XELOX included oxaliplatin (130 mg/m²) + capecitabine; SOX included oxaliplatin (100-130 mg/m²) + S-1; FOLFOXIRI included oxaliplatin (85 mg/m²) + 5-FU + irinotecan. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; AR, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

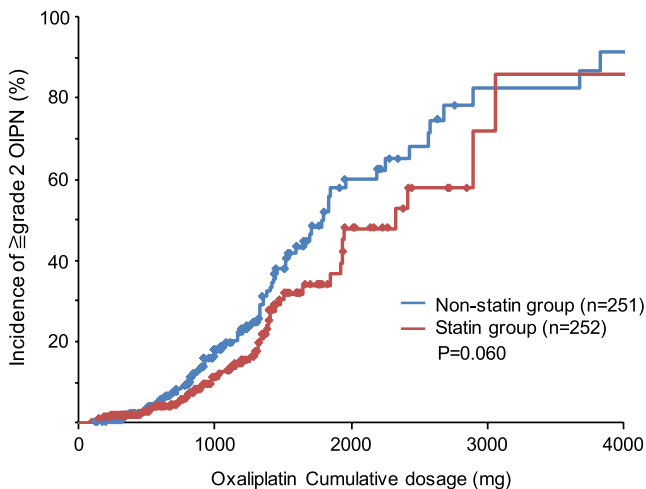


FIGURE 2 | Effect of statin on Grade ≥ 2 OPIN. Kaplan-Meier analysis of the incidence of OPIN in patients with CRC after propensity score matching. OIPN, oxaliplatin-induced peripheral neuropathy.

glutathione S-transferase (GST), an enzyme involved in detoxification of oxidative stress and alleviating reactive compounds in cells, in the dorsal root ganglia of the spinal cord, providing neuroprotection [12]. In an animal model of OIPN, statins increased GSTM1 mRNA expression, which might reduce reactive oxygen species levels in nerve cells [12]. This finding is supported by in vitro studies showing that statins protected PC12 model neuronal cells from oxaliplatin-induced cell death, and this effect was reversed by blockade of GST [12]. Simvastatin inhibited oxaliplatin-induced extracellular signal-regulated kinase 1/2 phosphorylation in the lumbar spinal cord, thereby providing a potential mechanism for its protective effect against OIPN [24]. Daliri et al. suggested that the neuroprotective effect of statins was primarily related to their antioxidant effect [25]. In addition, improved endothelial function, inhibition of thrombogenic

responses, and modulation of the peripheral inflammatory response have been discussed as possible neuroprotective mechanisms of statins [26–28]. Aizawa et al. suggested that statins modulated immune cell activity and activated the GST pathway, which reduced the occurrence of peripheral neuropathy [13]. In addition to pharmacodynamic interactions, oxaliplatin and statins can also interact via pharmacokinetic mechanisms. Stage et al. suggested that CIPN was related to reduced efflux transporter function [29]; and concomitant use of efflux transporter inhibitors may thus increase blood levels of oxaliplatin, causing OIPN. In addition, the efflux transporter, organic cation transporter 3 (OCT3), may be involved in the uptake of oxaliplatin [30]; however, the relationship between OCT3 and OIPN remains to be examined.

Drug repositioning is a process of identifying new uses for existing drugs, outside their original indications [31]. This procedure can reduce the time and costs involved in drug development because the safety profiles and risks of drug–drug interactions have often already been identified, and exploratory phase trials can thus be reduced. Considering these merits, drug repositioning might be a promising strategy, particularly in diseases and conditions with no existing therapeutic drugs. CIPN is a serious adverse event with no recommended prophylaxis and therapeutics, and multifaceted interventions including drug repositioning strategies are thus strongly desirable. Zamami et al. found that statin treatment suppressed the oxaliplatin-induced degeneration of nerve axons in a rat OIPN model [12] and suggested that statins may serve as new agents for OIPN management based on drug repositioning. Recently, Okamoto et al. retrospectively examined the effects of statins on the incidence of OIPN [14], but found no significant effect on the incidence or severity of OIPN; however, this was a single-centre study with a small number of patients, and further studies with larger numbers of patients are needed to elucidate the statin effect. Although this was a retrospective study, the large population showed

TABLE 4 | Comparison of clinical characteristics of patients with and without Grade ≥ 2 neuropathy.

Variable	All patients			CRC patients		
	Patients with Grade <1	Patients with Grade ≥ 2	<i>p</i>	Patients with Grade <1	Patients with Grade ≥ 2	<i>p</i>
	<i>n</i> = 1946	<i>n</i> = 638		<i>n</i> = 1378	<i>n</i> = 448	
Age, years						
Median (IQR)	64.0 (57.0, 71.0)	64.0 (56.0, 71.0)	0.662	64.0 (56.3, 71.0)	64.0 (56.0, 71.0)	0.594
Sex, <i>n</i> (%)						
Male	1149 (59.0)	382 (59.9)	0.745	765 (55.5)	261 (58.3)	0.324
Female	797 (41.0)	256 (40.1)		613 (44.5)	187 (41.7)	
BMI, kg/m ²						
Median (IQR)	21.7 (19.6, 24.0)	21.8 (19.6, 24.1)	0.304	21.9 (19.9, 24.2)	22.1 (19.7, 24.6)	0.667
Cancer type, <i>n</i> (%)						
Colorectal cancer	1378 (70.8)	448 (70.2)	0.020			
Gastric cancer	337 (17.3)	92 (14.4)				
Pancreatic cancer	165 (8.5)	61 (9.6)				
Other cancer	66 (3.4)	37 (5.8)				
Comorbidity, <i>n</i> (%)						
Diabetes	289 (14.9)	89 (13.9)	0.606	185 (13.4)	61 (13.6)	0.937
Herpes zoster	9 (0.5)	5 (0.8)	0.354	7 (0.5)	4 (0.9)	0.480
Autoimmune diseases	32 (1.6)	9 (1.4)	0.855	24 (1.7)	5 (1.1)	0.514
Laboratory data, median (IQR)						
eGFR (mL/min/1.73 m ²)	77.2 (65.5, 90.1)	75.3 (64.4, 87.2)	0.035	77.2 (65.4, 89.6)	74.8 (64.1, 86.5)	0.040
ALT (U/L)	16.0 (12.0, 26.0)	16.5 (12.0, 27.00)	0.946	16.0 (12.0, 25.0)	16.0 (12.0, 26.3)	0.544
AST (U/L)	21.0 (17.0, 29.0)	20.0 (16.0, 27.0)	0.128	20.0 (16.0, 28.0)	20.0 (16.0, 26.3)	0.939
HbA1c (%)	5.9 (5.5, 6.4)	5.7 (5.4, 6.1)	0.007	5.8 (5.4, 6.2)	5.7 (5.4, 6.1)	0.046
Concomitant medications, <i>n</i> (%)						
ACEI or ARB	364 (18.7)	107 (16.8)	0.288	281 (20.4)	78 (17.4)	0.172
Ca antagonist	410 (21.1)	129 (20.2)	0.694	312 (22.6)	92 (20.5)	0.36
Opioid	131 (7.0)	47 (7.6)	0.653	67 (5.1)	25 (5.8)	0.535
NSAIDs	383 (20.6)	139 (22.5)	0.306	249 (18.8)	91 (21.1)	0.294
Antiepileptic drugs	38 (2.0)	12 (1.9)	1	25 (1.9)	9 (2.1)	0.841
Antidepressants	48 (2.9)	28 (5.0)	0.021	32 (2.6)	18 (4.5)	0.068
Oxaliplatin						
Initial dose, mg (range)	150 (47, 290)	150 (48, 286)	0.528	152 (47, 290)	150 (48, 286)	0.182
Cumulative dosage, mg (IQR)	840 (495, 1280)	1140 (735, 1518)	<0.001	901 (560, 1320)	1138 (728, 1525)	<0.001
Course, <i>n</i> (IQR)	6 (4, 8)	8 (5, 11)	<0.001	6 (4, 8)	8 (5, 11)	<0.001

(Continues)

TABLE 4 | (Continued)

Variable	All patients			CRC patients		
	Patients with Grade <1	Patients with Grade ≥ 2	<i>p</i>	Patients with Grade <1	Patients with Grade ≥ 2	<i>p</i>
	<i>n</i> = 1946	<i>n</i> = 638		<i>n</i> = 1378	<i>n</i> = 448	
Dose reduction, <i>n</i> (%)	186 (9.6)	209 (32.8)	<0.001	141 (10.2)	144 (32.1)	<0.001
Withdrawal, <i>n</i> (%)	159 (8.2)	231 (36.3)	<0.001	123 (8.9)	164 (36.6)	<0.001
Chemotherapy cessation, <i>n</i> (%)	53 (3.1)	218 (37.6)	<0.001	47 (3.8)	166 (39.9)	<0.001
Chemotherapy regimen, <i>n</i> (%)						
FOLFOX	574 (29.8)	250 (39.8)	<0.001	547 (39.6)	228 (50.8)	0.001
XELOX	789 (40.9)	223 (35.5)		725 (52.5)	200 (44.5)	
SOX	351 (18.2)	88 (14.0)		63 (4.6)	14 (3.1)	
FOLFIXIRI	52 (2.7)	8 (1.3)		46 (3.3)	7 (1.6)	
FOLFIRINOX	163 (8.4)	59 (9.4)		1 (0.1)	0 (0)	
Treatment setting, <i>n</i> (%)						
Adjuvant chemotherapy	735 (48.4)	191 (37.5)	<0.001	612 (56.8)	157 (44.4)	<0.001
Non-adjuvant chemotherapy	1211 (51.6)	447 (62.5)		766 (43.2)	291 (55.6)	
Statin use, <i>n</i> (%)	278 (14.3)	83 (13.0)	0.469	205 (14.9)	56 (12.5)	0.244
Type of statin, <i>n</i> (%)						
Atorvastatin	97 (34.8)	20 (24.1)	0.485	72 (35.1)	13 (23.2)	0.345
Rosuvastatin	79 (28.4)	33 (39.8)		57 (27.8)	25 (44.5)	
Pitavastatin	48 (17.2)	13 (15.7)		39 (19.0)	8 (14.3)	
Pravastatin	47 (16.9)	13 (15.7)		31 (15.1)	7 (12.5)	
Fluvastatin	4 (1.4)	2 (2.4)		3 (1.5)	1 (1.8)	
Simvastatin	3 (1.1)	2 (2.4)		3 (1.5)	2 (3.6)	

Note: FOLFOX included oxaliplatin (85 mg/m²) + 5-FU + leucovorin; XELOX included oxaliplatin (130 mg/m²) + capecitabine; SOX included oxaliplatin (100-130 mg/m²) + S-1; FOLFIXIRI included oxaliplatin (85 mg/m²) + 5-FU + irinotecan; FOLFIRINOX included oxaliplatin (85 mg/m²) + 5-FU + leucovorin + irinotecan. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; AR, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CRC, colorectal cancer; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

the potential of statins for protecting against OIPN in patients with CRC. Further prospective studies are warranted to elucidate the ability of statins to address this unmet medical need.

In addition to oxaliplatin, various anticancer drugs are neurotoxic and can cause peripheral neuropathy [1, 2]. The pathogenesis and toxicity profiles differ among these agents [9, 32]. Taxanes frequently induce acute, length-dependent distal sensory neuropathy, sometimes with severe pain, with paclitaxel having a higher incidence than docetaxel. Vinca alkaloids induce sensory and motor nerve impairment, which may continue long after treatment cessation. It remains unclear if the protective effect of statins can also be observed in patients treated with other neuropathy-inducing drugs and types of cancer.

Statins can be subgrouped according to their lipophilicity or cholesterol-lowering potency. In this study, patients used six different statins, but the incidence of OIPN was similar in patients receiving the hydrophilic statin pravastatin (with a limited number of patients) compared with patients receiving lipophilic statins. The lipid-lowering potency varies among statins [33], and atorvastatin, rosuvastatin, and pitavastatin are classified as statins with strong lipid-lowering effects. The incidence of OIPN in patients receiving these statins was 19.8%, compared with 20.0% in patients receiving other statins. The protective effect of statins against CIPN might be a pleiotropic, class effect of statins, and the preventive effect may not be related to their lipid-lowering potency. We did not compare the incidence of OIPN according to the doses of the six statins used, and their dose-related effects were therefore unclear.

This study had some limitations. First, it was a retrospective study, and the assessment of CIPN was based on clinical records. The diagnosis of CIPN is based on the patient's clinical records, including the use of neuropathy-inducing drugs and neurological symptoms [2, 6]. Neurological tests can be used to diagnose CIPN, but they are not routinely used and are not usually necessary [6]. Grade 1 peripheral neuropathy is asymptomatic and is characterized by reduced deep tendon reflexes or abnormal sensory perception. The credibility of a Grade 1 CIPN assessment was low in this retrospective study, and we therefore did not include Grade 1 CIPN. We targeted Grade ≥ 2 CIPN, which is based on subjective symptoms, and this assessment is considered reliable and commonly used, even in retrospective studies [34–36]. The incidence of Grade ≥ 2 CIPN was 24.7% in all 2657 patients, consistent with previous reports [5, 20]. Second, most patients used one or multiple cytotoxic agents other than oxaliplatin; however, none of the concomitant agents had peripheral neuropathy-inducing effects, and there was no concomitant use of noncytotoxic agents that can induce peripheral neuropathy, such as ethambutol, isoniazid, metronidazole, and amiodarone. Nevertheless, we cannot exclude the possibility that some information on concomitant drugs was not collected in our survey because of the retrospective nature of the study. Third, the present study analyzed the effect of statins on OIPN, mainly in patients with CRC; however, we did not analyze the efficacy of statins in patients with other carcinomas because of the limited number of cases. The reason for the lower incidence of OIPN in patients with CRC and taking statins remains unknown. Unfortunately, data concerning performance status was lacking. Srivastava et al. showed that performance status was associated with CIPN symptom scores [37]. The impairment of general condition was the major reason for chemotherapy discontinuation; poor performance status may affect treatment response and the development of side effects, including OIPN. It is possible that differences in performance status might have influenced the effectiveness of the statin. Fourth, we only included Japanese patients in this analysis, and the risk of CIPN may differ according to ethnicity. In addition, we did not analyze genetic variations that may be associated with neuropathy [38]. Schneider et al. showed that individuals of Black ethnicity have a higher risk of developing CIPN [39]. The effect of statins on the incidence of OIPN may vary according to racial groups. Future analysis in a multi-ethnic population is warranted. Finally, we used propensity score matching to balance characteristics between the statin and non-statin groups. Although there were no differences in variants after score matching, it is possible that some unidentified confounding factors remained.

In conclusion, the current study found that statin use reduced the incidence of OIPN in patients with CRC. The use of statins might help to prevent OIPN; however, further prospective studies with matched patient backgrounds are warranted to confirm these findings.

Author Contributions

Kenshi Takechi wrote the manuscript. Kenshi Takechi, Takehiro Kawashiri, Keisuke Mine, Soichiro Ushio, Hirofumi Hamano, Noriko Hida, Keisuke Mine, Masanobu Uchiyama, Mami Uchida,

Hideki Yasui, Masahiro Ueda, Ryohei Fujii, Misaki Hashimoto, Yasutaka Sakamoto, Kana Uyama, Takahiro Niimura, Yuki Hanai, Ayaka Tsuboya, Keisuke Suzuki, Naoya Kamiyama, Hiromi Hagiwara, Naoto Okada, and Yoshito Zamami designed the research. Kenshi Takechi, Takehiro Kawashiri, Keisuke Mine, Soichiro Ushio, Hirofumi Hamano, Noriko Hida, Keisuke Mine, Masanobu Uchiyama, Mami Uchida, Mamoru Tanaka, Noriko Hida, Hideki Yasui, Masahiro Ueda, Ryohei Fujii, Misaki Hashimoto, Yasutaka Sakamoto, Kana Uyama, Takahiro Niimura, Yuki Hanai, Ayaka Tsuboya, Keisuke Suzuki, and Naoya Kamiyama performed the research. Kenshi Takechi, Takehiro Kawashiri, Soichiro Ushio, Noriko Hida, Masanobu Uchiyama, Mami Uchida, Hideki Yasui, Masahiro Ueda, Yasutaka Sakamoto, Takahiro Niimura, Yuki Hanai, Ayaka Tsuboya, Keisuke Suzuki, Naoya Kamiyama, Naoto Okada, Yoshito Zamami, and Keisuke Ishizawa analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used in this study are not publicly available due to restrictions regarding the inclusion of information that could compromise the privacy of the research participants.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Univariate and multivariate regression analysis of independent factors associated with grade ≥ 2 OIPN in patients with colorectal cancer. **Table S2:** Univariate and multivariate regression analysis of independent factors associated with grade ≥ 2 OIPN in patients with colorectal cancer after propensity score matching. **Table S3:** Incidence rates of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer after propensity score matching.