Treatment Strategy of Oxaliplatin-induced Peripheral Neuropathy: A Retrospective, Nationwide Study

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Abstract

Purpose

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse events of cancer treatment; however, no drug is recommended for the prevention of CIPN. In Japan, several drugs such as Gosha-Jinki-Gan and duloxetine have been frequently administered for the treatment of CIPN. The aim of this study was to elucidate prescription patterns of drugs administered for the treatment of CIPN caused by oxaliplatin and the association between these drugs and the duration of oxaliplatin treatment.

Methods

We conducted a retrospective nationwide study using the JMDC administrative claims database (January 2005–June 2020). Patients newly treated with oxaliplatin were identified, and prescription patterns of CIPN medication including Gosha-Jinki-Gan, pregabalin, duloxetine, mecobalamin, and mirogabalin were investigated. The primary outcome was the duration of oxaliplatin treatment. Multivariable logistic regression analysis was performed to examine the association between CIPN medication and duration of oxaliplatin treatment.

Results

A total of 4,739 patients who newly received oxaliplatin were identified. Of these, 759 (16.0%) had received CIPN medication. Duloxetine was administered in 99 (2.1%) patients. Multivariable logistic regression analysis revealed that CIPN medication was significantly associated with the prolonged duration of oxaliplatin treatment (odds ratio: 2.35, [95% confidence interval: 1.99-2.77]).

Conclusion

Real-world data demonstrated that the administration rate of CIPN medication was higher in patients who underwent oxaliplatin treatment for over 6 months. Increasing administration preference of duloxetine and conducting prospective studies to verify the causal relationship between CIPN medication and prolonged duration of oxaliplatin treatment are needed.

Introduction

Chemotherapy is one of the main treatment methods for cancer. However, adverse events caused by chemotherapy are clinically problematic. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the representative adverse events of cancer treatment; it is observed in most patients treated with neurotoxic anti-cancer drugs such as oxaliplatin, paclitaxel, nab-paclitaxel, vincristine, and bortezomib [1]. Severe CIPN requires a dose reduction or an early cessation of chemotherapy [2]. Currently, there are no therapeutic options available for the prevention of CIPN. Furthermore, few drugs are recommended for the treatment of existing neuropathies [3]. In Japan, several drugs, such as Gosha-Jinki-Gan, pregabalin, duloxetine, vitamin B12 (mecobalamin), have been frequently administered for the treatment of CIPN.

However, pregabalin and mecobalamin were certified to have “unknown effectiveness.” In addition, Gosha-Jinki-Gan was counter-indicated for oxaliplatin-related CIPN [4]. Duloxetine is the only agent that has appropriate evidence to support its use for patients with established painful CIPN [5, 6].

We focused on CIPN associated with oxaliplatin in this study. Oxaliplatin has been administered for colorectal cancer, gastric cancer, and pancreatic cancer, and shows a high effectiveness. However, peripheral neuropathy induced by oxaliplatin is a dose-limiting toxicity that causes for dose reduction and discontinuation of treatment [7, 8]. For patients treated with oxaliplatin, prescription patterns of drugs for treatment of CIPN have been unclear at the broad-scale level. The aim of the present study was to elucidate prescription patterns of drugs administered for the treatment of CIPN and the association between these drugs and duration of oxaliplatin treatment using a widely utilized Japanese public health insurance database.

Methods

Data source

We conducted a retrospective, nationwide study using the JMDC administrative claims database which is a large and chronologically organized Japanese claims database (JMDC Inc., Tokyo, Japan) that uses standardized disease classification and anonymous record linkage [9, 10]. In total, this database (January 2005 – December 2020) includes approximately 12 million insured persons in Japan (JMDC Inc. Available from: https://www.jmdc.co.jp. [Accessed 9 May 2021].), including the following data for each patient: age, sex, dates of hospital or clinic visit, International Statistical Classification of Diseases and Related Health Problems-Tenth Revision (ICD-10) codes, and prescription of drugs categorized according to the Anatomical Therapeutic Chemical (ATC) classification of both the European Pharmaceutical Market Research Association and World Health Organization. An encrypted personal identifier was used to link the claims data from various hospitals, clinics, and pharmacies.

Compliance with ethical standards

This study was approved by the Ethics Committees of the Kindai University School of Pharmacy on April 14, 2018 (approval number, 18-128). Due to the anonymous nature of the data, the requirement for informed consent was waived.

Patient selection

This study used data from January 2005 to June 2020. The inclusion criteria were patients who were diagnosed gastric cancer (C16)、small intestinal cancer (C17), colorectal cancer (C18-C20), and pancreatic cancer (C25), and who were newly administered oxaliplatin. Patients without oxaliplatin dose data, with less than 6 months of run-in period, or treated with paclitaxel, nab-paclitaxel, vincristine, or bortezomib before oxaliplatin initiation were excluded. Among selected patients, we defined the interval between the last month and first month wherein oxaliplatin was administered as the duration of

oxaliplatin treatment. There were patients who were administered oxaliplatin for the treatment of advanced malignancies or for adjuvant chemotherapy.

We selected patients in whom the duration of oxaliplatin treatment met the upper limit (Q3+1.5*[Q3-Q1]) or less of that in all cases; this group comprised approximately 90% of all patients newly treated with oxaliplatin (model 1). A sensitivity analysis was performed to confirm the correctness of the inclusion criteria mentioned above. We also selected patients in whom the duration of oxaliplatin treatment met the upper quartile or less of that in all cases; these patients comprised approximately 75% of all patients newly treated with oxaliplatin (model 2).

The primary outcome of interest was the duration of oxaliplatin treatment. Oxaliplatin-based chemotherapy for advanced or metastatic gastrointestinal cancer is continued until disease progression is defined, while adjuvant chemotherapy consisted of oxaliplatin is continued to completion at 6 months [11-13]. Patients were divided into two groups based on the duration of oxaliplatin treatment: (1) 6 months or longer group (2) less than 6 months group.

Data collection

CIPN medication was defined as treatment with drugs, namely Gosha-Jinki-Gan, pregabalin, duloxetine, mirogabalin, and mecobalamin. These drugs when newly administered during oxaliplatin treatment were identified. Baseline characteristics recorded in the month of the last administration of oxaliplatin included the following: age, sex, cancer type, chemotherapeutic regimen, and adverse drug reaction (anaphylaxis [ICD-10 code: T782/T886/T887], interstitial lung disease [J84], and febrile neutropenia [D70]). We also investigated comorbidities (metastasis [C78/C79], diabetes mellitus [E10-E14], non-alcoholic liver disorder [K71-K77], chronic kidney disease [N18/N19], hypoalbuminemia [E880], anemia [D50-D53], and hypomagnesemia [E834]), and concomitant medication (monoamine reuptake inhibitors excluding for duloxetine [ATC code: N06A], opioid [N02A], and non-steroidal anti-inflammatory drugs (NSAID) [M01A]) within 3 months of the last month of oxaliplatin administration.

Data analysis

Continuous variables were reported as median and interquartile range (IQR) and categorical variables were reported as number and percentage. Binary logistic regression was performed to identify the independent factor for the duration of oxaliplatin treatment (≥6 months). Subsequently, multivariable logistic regression was also conducted. The multivariable model contained variables that were associated with $P<0.1$ in univariate analysis. Using Mann–Whitney tests, continuous variables were compared between the groups that did or did not receive CIPN medication. Data management were performed using Visual Mining Studio software (version 8.7; NTT DATA Mathematical Systems Inc., Tokyo, Japan). All statistical tests were two-sided, with the significance set at 0.05 using JMP Pro 14.2 (SAS Institute Inc., NC, USA).

Results

Figure 1 presents the flow diagram of patient selection for this study. We identified 5,233 patients newly treated with oxaliplatin. Of the 5,233 patients, 3,230 (61.3%) were men, and the median age (IQR) was 57 (50-63). Median duration of oxaliplatin treatment (IQR; Min, Max) was 5 (3-7; 1, 95) months. The upper limit (Q3+1.5*[Q3-Q1]) and upper quartile (Q3) of the duration of oxaliplatin treatment were 13 and 7 months, respectively. We selected patients with a duration of oxaliplatin treatment ≤13 months for model 1 (n=4,739) and those with treatment duration ≤7 months for model 2 (n=4,061). The baseline characteristics of model 1 are shown in Table 1. Of the 4,739 patients, 759 (16.0%) had received CIPN medication. The most used drug was Gosha-Jinki-Gan (n=361, 7.6%). Pregabalin and duloxetine had been administered in 228 (4.8%) and 99 (2.1%) patients, respectively. Of the 759 patients, 629 patients had received monotherapy.

Figure 2 shows the percentage of patients (model 1) receiving CIPN medication among patients newly administered oxaliplatin in each year. The percentage of Gosha-Jinki-Gan and pregabalin users peaked in 2012 and 2013, respectively. Thereafter, the percentage of these users gradually decreased. Contrastingly, the percentage of duloxetine users gradually increased after 2011.

Analysis of model 1 identified 1,927 patients who received oxaliplatin for 6 months or more and 2,812 patients who received oxaliplatin for less than 6 months (Table 2). The percentage of patients who received CIPN medication in the 6 months or more group (22.5%) was higher than in the less than 6 months group (11.6%) in model 1. Multivariable logistic regression model revealed that seven variables, namely CIPN medication (odds ratio [OR]: 2.35, 95% confidence interval [CI]: 1.99-2.77), gastric cancer (OR: 0.76, 95% CI: 0.59-0.98), FOLFOX±molecular-targeted drug therapy (OR: 1.19, 95% CI: 1.02-1.39), metastasis (OR: 0.36, 95% CI: 0.28-0.45), concomitant diabetes mellitus (OR: 0.60, 95% CI: 0.53-0.69), opioid use (OR: 0.58, 95% CI: 0.46-0.73), and NSAID use (OR: 0.53, 95% CI: 0.45-0.63), were significantly associated with the duration of oxaliplatin treatment. In model 2, the number of patients who received oxaliplatin for 6 months or more was 1,249 (Table 3). Multivariable logistic regression model revealed that five variables, namely CIPN medication (OR: 2.09, 95% CI: 1.74-2.52), metastasis (OR: 0.51, 95% CI: 0.40-0.66), concomitant diabetes mellitus (OR: 0.60, 95% CI: 0.51-0.69), opioid use (OR: 0.49, 95% CI: 0.37-0.66), and NSAID use (OR: 0.50, 95% CI: 0.40-0.62), were significantly associated with the duration of oxaliplatin treatment. These five variables were significantly associated with the duration of oxaliplatin treatment in both models 1 and 2.

The median duration of oxaliplatin treatment for patients who received CIPN medication (n=759) was 6 (IQR: 4-7) months, which was significantly longer than that for patients who did not receive CIPN medication (n=3,980) in model 1. The median cumulative dose of oxaliplatin in patients who received CIPN medication was also significantly higher than that for patients who did not receive CIPN medication (1,350 [800-1,750] vs. 1,000 [600-1,500], $p<0.01$) (Table 4).

Discussion

This retrospective study investigated the association between duration of oxaliplatin treatment and CIPN medication (Gosha-Jinki-Gan, pregabalin, duloxetine, mirogabalin, and/or mecobalamin) using a Japanese nationwide claims database. Of the patients treated with oxaliplatin, 16% received CIPN medication, most of whom were treated with monotherapy. The administration rate of the CIPN medication in patients who received oxaliplatin for 6 months or longer was significantly higher than that in patients who received it for less than 6 months. The cumulative dose of oxaliplatin in patients who received CIPN medication was significantly higher than that in patients who did not receive this drug.

Peripheral neuropathy caused by oxaliplatin is a disabling adverse drug reaction that interferes with patients' quality of life. Under the situation of no efficient strategy for CIPN, it is necessary to understand the current state of CIPN medication. The rate of patients manifesting acute peripheral neuropathy after the administration of oxaliplatin was reported to be almost 80% [14], and the incidence rate of persistent peripheral neuropathy was 47% [15]. In this study, the exact incidence rate of CIPN could not be revealed owing to the nature of the database; however, it is assumed that a similar proportion of patients suffered from CIPN. There were 16% patients who received CIPN medication in this study. It has been reported in another country that most of the patients who experienced CIPN did not inform the doctors about CIPN, and very few patients who did, received pharmacological intervention [16]. Our results also suggested that the administration rate of CIPN medication was low. Insufficient patient education and doctor-patient communication may be one of the causes [17]. The administration rate of duloxetine increased for pain and numbness from CIPN in a Japanese questionnaire survey [4]. Contrastingly, real-world data in this study revealed that only 2.1% of patients received duloxetine. It is presumed that duloxetine was difficult to use in Japan because it was not covered by government health insurance for the treatment of peripheral neuropathy. Our results show that pharmacological intervention for oxaliplatin-induced peripheral neuropathy is probably inadequate.

Interestingly, the 6 months or longer groups showed higher administration rate of CIPN medication than the less than 6 months group. The duration of oxaliplatin treatment in patients who received CIPN medication was extended by approximately 2 months than in those who did not receive CIPN medication. The cumulative dose of oxaliplatin in patients who received CIPN medication was 350 mg higher than that in patients who did not receive CIPN medication. Therefore, CIPN medication may have prevented a decrease in the dose intensity of oxaliplatin. Oxaliplatin-based adjuvant chemotherapy administered over 6 months remains the standard adjuvant treatment. However, many patients experience dose reduction or early termination of chemotherapy due to oxaliplatin toxicity, increasing the risk of early recurrence [18]. Although the difference between adjuvant chemotherapy and chemotherapy of advanced cancer is not taken into consideration in this study, the prognosis may have improved in patients who received CIPN medication. Apart from CIPN medication, metastasis, concomitant diabetes mellitus, and administration of opioids/NSAIDs were significantly related to the duration of oxaliplatin treatment (<6 months). Chemotherapy is often changed if metastases are found. Further, the worsening of peripheral neuropathy due to diabetes [19] and decrease in performance status, indicated by administration of opioids/NSAIDs for pain control, were associated with the shortening of the duration of oxaliplatin treatment.

The four drugs: Gosha-Jinki-Gan, pregabalin, duloxetine, and mecobalamin have been preferably administered for CIPN in Japan [4]. Gosha-Jinki-Gan showed some tendency to prevent persistence of CIPN [20] or did not prevent oxaliplatin-associated peripheral neuropathy [21, 22]. Pregabalin was reported not to decrease the incidence of oxaliplatin-associated CIPN [23], and mecobalamin's effectiveness for CIPN is not clear. Mirogabalin was approved for the usage of neuropathic pain relief in 2019; however, there is no obvious evidence for its use in CIPN. Duloxetine is the only drug that has been scientifically proven to be useful for CIPN [24, 25]. We theorize that the administration rate of CIPN medication was higher in the 6 months or longer group in this study because long-term treatment of oxaliplatin might have resulted in CIPN medication. Doctors might have carefully altered the treatment according to patients' symptoms and implemented the Stop and Go strategy [26].

Our study had several limitations that warrant consideration. First, the JMDC claims database did not include patients over 75 years of age. Second, we could not determine whether the chemotherapy performed was for adjuvant chemotherapy or for treatment of advanced malignancies. Third, the characteristics of CIPN, such as pain or numbness and degree of severity, were not considered. Finally, non-pharmacological strategies or complementary and integrative medicine [27] were not considered.

In conclusion, our analysis demonstrated that the administration rate of CIPN medication was significantly higher in patients treated with oxaliplatin-based chemotherapy for 6 months or longer than in those treated with this chemotherapy for less than 6 months. There is a need to increase the administration preference of duloxetine and perform prospective studies to verify the causal relationship between CIPN medication and prolonged duration of oxaliplatin treatment.

Declarations

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Conflict of interest

The authors declare no competing interest.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Code availability

Not applicable

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Satoshi Yokoyama and Chihiro Nakagawa. Analysis and interpretation of data were performed by Satoshi Yokoyama, Chihiro Nakagawa, and Kouichi Hosomi. The first draft of the manuscript was written by Satoshi Yokoyama and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate

Not applicable

Consent for publication

Not applicable

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Tables

Due to technical limitations, table 1, 2, 3 and 4 is only available as a download in the Supplemental Files section.

Figures

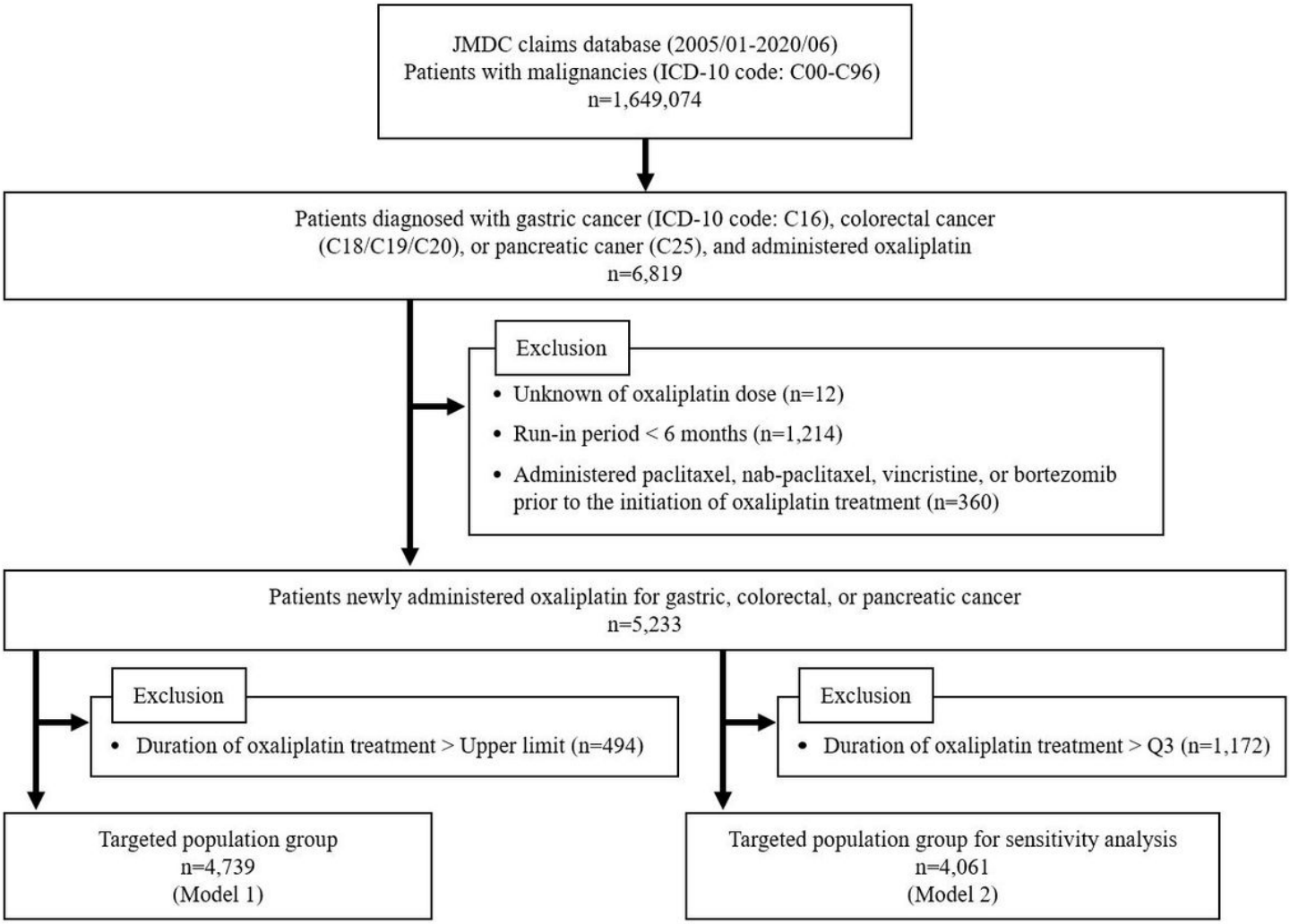

Figure 1

Flow diagram of patient selection. Duration of oxaliplatin treatment: the interval between the last month and first month wherein oxaliplatin was administered, Q3; upper quartile, Upper limit: Q3 + 1.5*(Q3-Q1), CIPN: chemotherapy-induced peripheral neuropathy, ICD-10: International Statistical Classification of Diseases and Related Health Problems-Tenth Revision

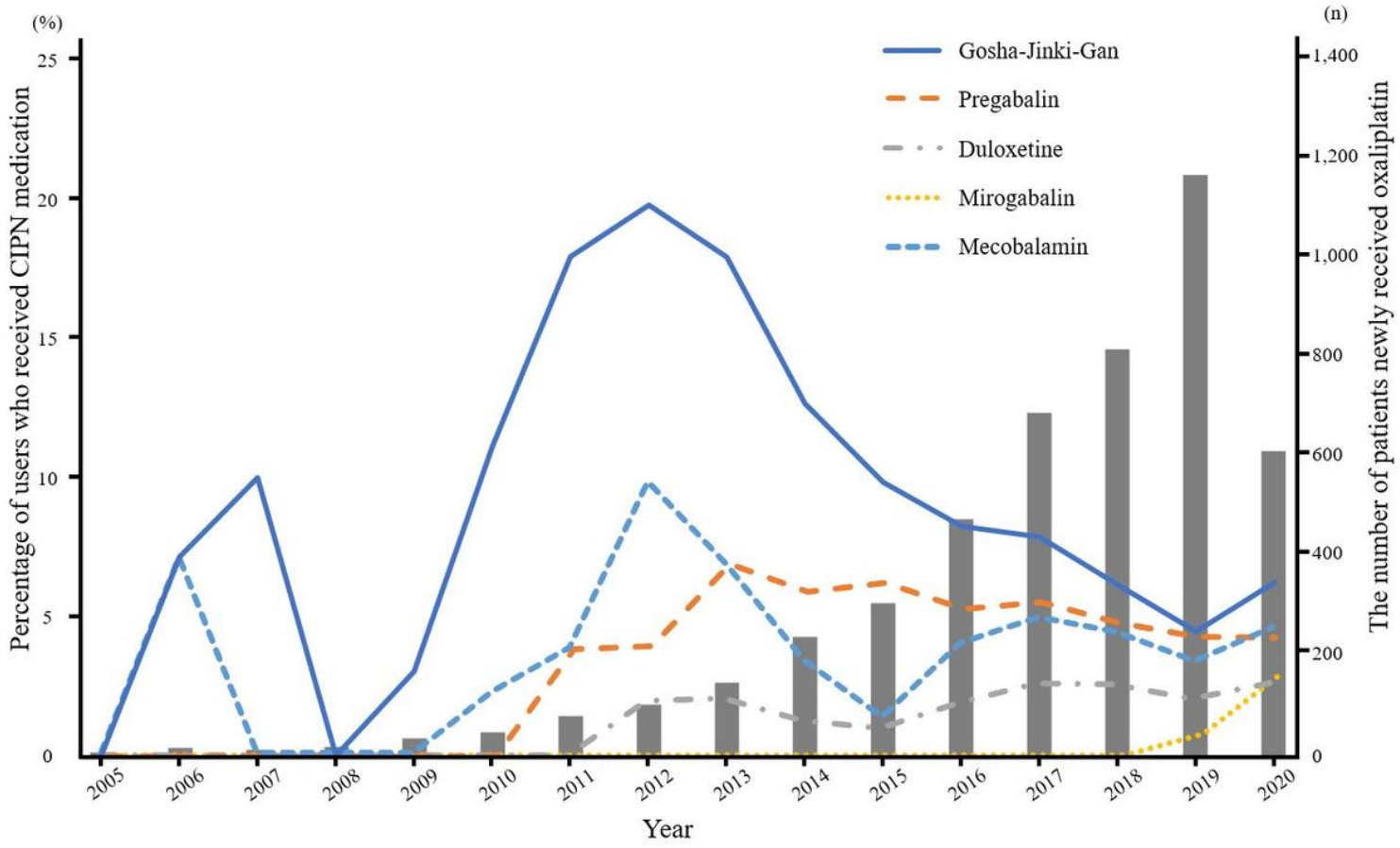

Figure 2

Percentage of users who received chemotherapy-induced peripheral neuropathy medication (Gosha-Jinki-Gan, pregabalin, duloxetine, mecobalamin, and mirogabalin) in each fiscal year.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 03.Table0120210608.xlsx
- 04.Table0220210624.xlsx
- 05.Table0320210624.xlsx
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