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ORIGINAL RESEARCH

# Co-treatment with Gabapentinoid and Japanese Herbal Medicine Goshajinkigan for CIPN is Associated with Longer Duration and Higher Dose of Chemotherapy

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## ABSTRACT

***Introduction***: In Japan, both gabapentinoids and the Japanese traditional herbal medicine goshajinkigan (GJG) are used to manage chemotherapy-induced peripheral neuropathy (CIPN); however, evidence for their effectiveness is inconclusive. Patients with CIPN experience reduced quality of life and often undergo reductions in dose or discontinuation of chemotherapy. Therefore, this retrospective cohort study used a real-world database to examine the efficacy of gabapentinoids and GJG therapy for patients with CIPN by evaluating chemotherapy duration and dose.

***Methods***: Data from 145,384 patients diagnosed with CIPN while receiving platinum- or taxane-based chemotherapy between April 1, 2008 and March 31, 2022 were stratified by CIPN treatment: simultaneous gabapentinoid (mirogabalin or pregabalin) plus GJG (prescription dates overlap); non-simultaneous gabapentinoid plus GJG (prescription dates do not overlap); gabapentinoid alone; GJG alone; and neither gabapentinoids nor GJG. Duration and dose of chemotherapy were the primary outcomes.

***Results***: Treatment with either a gabapentinoid or GJG alone was associated with longer duration and higher doses of chemotherapy versus neither gabapentinoids nor GJG in patients treated with carboplatin, cisplatin, or paclitaxel. Combined gabapentinoid plus GJG treatment elicited further longer duration and higher doses of chemotherapy versus gabapentinoid alone or GJG alone in patients treated with carboplatin,

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oxaliplatin, cisplatin, paclitaxel, or docetaxel. When stratified by cancer type, similar trends were observed regarding combination gabapentinoid plus GJG treatment among patients with colorectal cancer treated with oxaliplatin and patients with gastric, lung, or breast cancer treated with paclitaxel.

***Conclusion*:** Combination treatment with gabapentinoid plus GJG might prevent reductions in dose or discontinuation of chemotherapy, and might be effective for the treatment of CIPN.

**Keywords:** Chemotherapy-induced peripheral neuropathy; Gabapentinoid; Goshajinkigan; Japanese herbal Kampo medicine; Platinum-based chemotherapy; Taxane-based chemotherapy

**Key Summary Points**

*Why carry out this study?*

There are few effective treatment options for chemotherapy-induced peripheral neuropathy (CIPN), which is an adverse event caused by several chemotherapeutic drugs and can result in reduced quality of life and reductions in dose or discontinuation of chemotherapy.

We hypothesised that combination treatment of CIPN with both gabapentinoid (GPN) and the Japanese traditional herbal medicine goshajinkigan (GJG) would result in fewer dose reductions and dose interruptions of platinum- and taxane-based chemotherapy.

*What was learned from the study?*

Among patients treated with carboplatin, those who received either simultaneous or non-simultaneous GPN + GJG had a longer mean chemotherapy duration and a higher mean chemotherapy total dose than those who received GPN alone, GJG alone, or neither GPN/GJG; patients who received GPN alone or GJG alone had a longer duration and a higher total dose than those who received neither.

These results were broadly similar to those for patients who received other platinum-based drugs or taxane-based chemotherapies, with some exceptions to this tendency according to simultaneous versus non-simultaneous administration as well as cancer type.

Physicians may consider treatment with GPN in combination with GJG to prevent dose reductions or chemotherapy discontinuations in patients with CIPN, which may lead to better patient outcomes.

## INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating adverse event (AE) that can be caused by several chemotherapeutic drugs [1]. The rates of CIPN vary by the type of chemotherapeutic drug, with the highest reported rates occurring in patients undergoing treatment with platinum-based drugs (ranging from 70% to 100%) or taxane-based drugs (ranging from 11% to 87%) [2]. Patients with CIPN experience reduced quality of life (QoL) and may undergo reductions in dose or discontinuation of chemotherapy [3, 4]. Effective pain reduction in patients with CIPN is not only expected to improve the affected patients' QoL but also enable maintenance of chemotherapy treatment. However, effective treatment options for CIPN are currently lacking [5–8].

The gabapentinoid (GPN) drug class includes analgesics that are often used for the management of neuropathic pain [9], although there are inconsistent reports regarding their efficacy in the treatment of CIPN [10–14]. In Japan, the traditional herbal Kampo medicine goshajinkigan (GJG) is also used for the treatment of CIPN and other AEs related to anti-cancer treatment; however, its use lacks strong supporting evidence [15, 16]. The phase III GENIUS trial evaluating the efficacy of GJG showed that GJG treatment had no preventive effect on oxaliplatin-associated CIPN, and there was a higher incidence of

neuropathy with the active treatment compared with placebo (hazard ratio: 1.908; $p = 0.007$) [17]. In contrast, several other trials have supported the use of GJG treatment for the treatment of CIPN [18–21].

As the pathological mechanism of CIPN involves multiple pathways [1], it is plausible that combination therapy with multiple analgesic agents targeting different pathways may offer an effective approach to CIPN management. GPNs, including pregabalin and mirogabalin besylate (mirogabalin), selectively bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels to achieve pain relief [22]. In contrast, GJG is believed to exert its analgesic effect via several mechanisms, notably through interacting with cortical astrocytes [23]. Additionally, GJG is thought to suppress the expression of transient receptor potential (TRP) channel genes, including TRP ankyrin subtype 1, TRP vanilloid 4, and TRP melastatin 8 genes, all of which are implicated in the pathogenesis of CIPN [24–26]. Moreover, in a rat model, GJG has been shown to reduce oxaliplatin-induced increases in reactive oxygen species, ameliorate abnormal sensations, and prevent damage to the sciatic nerve [26].

We hypothesised that combination treatment of CIPN with both GPN and GJG would result in fewer dose reductions and dose interruptions of platinum- and taxane-based chemotherapy. Real-world data studies offer a distinct advantage in this context, as they provide a broader perspective by examining these treatments in larger and more diverse populations of patients than typically enrolled in clinical trials, thereby more accurately reflecting actual use in clinical practice [27, 28]. Thus, we conducted this retrospective cohort study using a real-world database to examine the duration of chemotherapy treatment and total chemotherapy doses in patients with cancer and diagnosed with CIPN.

# METHODS

## Study Design

This retrospective cohort study used the EBM Provider® database (Medical Data Vision) and evaluated data from patients with CIPN between April 1, 2008 and March 31, 2022. This Japanese nationwide database includes inpatient and outpatient practices of more than 420 acute care providers.

As this study involved the secondary use of an existing database in which all data were anonymised and no new data were obtained during this study, informed consent was not required. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (No. 2022-1-1128).

## Study Population

Eligible patients were those diagnosed with CIPN while receiving continuous doses of platinum-based (carboplatin, oxaliplatin, cisplatin, or nedaplatin) or taxane-based (paclitaxel, docetaxel, or cabazitaxel) chemotherapy, and had a date of chemotherapy initiation between April 1, 2008 and March 31, 2022. Continuous dosing was defined as chemotherapy administered at intervals of no more than 67 days between doses. Patients with a confirmed diagnosis of CIPN at least 1 day prior to the date of the first prescription of platinum- or taxane-based chemotherapy were excluded.

The EBM Provider database disease codes were used to identify CIPN diagnoses, including peripheral neuritis (3545003), numbness (7820002), numbness of lower extremity (782006), numbness of extremities (7820018), peripheral neuropathy (8840255), peripheral neuropathic pain (8846220 and 8849550), and neuropathic pain (8847489).

The patient background data collected included CIPN treatment (determined by receipt of either GPN or GJG after CIPN diagnosis, and whether these treatments were administered simultaneously), chemotherapy type, cancer type, cancer stage, age, height, weight, sex, hospitalisation status (inpatient or outpatient), and presence/absence of duloxetine prescription. Simultaneous administration of GPN and GJG was defined as cases with the date of GJG

administration during the period of GPN administration. Non-simultaneous administration of GPN and GJG was defined as cases with administration of both drug types after initiation of chemotherapy, but without any overlap in the date of drug administration.

### Study Outcomes

The primary study outcomes were the duration and total dose of chemotherapy. Chemotherapy duration was defined as the period from the first day of platinum- or taxane-based chemotherapy in the month that the patient was initially diagnosed with CIPN to the day of the last dose of continuous chemotherapy administration. Chemotherapy doses within 67 days of the previous dose were considered continuous. The total chemotherapy dose was defined as the cumulative amount of the platinum- or taxane-based chemotherapeutic drug administered during a continuous period of chemotherapy, starting from the day of initial diagnosis of CIPN to the day of last chemotherapy administration.

Data were stratified by the following treatment combinations: simultaneous GPN (mirogabalin or pregabalin) and GJG treatment (GPN + GJG); non-simultaneous GPN + GJG treatment; GPN treatment alone; GJG treatment alone; and neither GPN nor GJG (GPN/GJG) treatment. A further stratification by cancer type (colorectal, gastric, lung, prostate, breast, or other) was also performed. These five cancer types were chosen because of their prevalence as the most common cancers in Japan [28] the definitions for each cancer type are shown in Table S1.

### Sample Size and Statistical Analyses

There was no prespecified sample size for the study, and data from all patients in the database who met the eligibility criteria were included in the analyses. Continuous data were summarised using means and medians, and categorical data were summarised by number and percentage. Missing values were not imputed, and comparisons between subgroups for the study outcomes were conducted using a *t* test. No potential confounders were considered in these analyses. All statistical analyses had a 5% significance level and were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Patients

Data from 145,384 patients with cancer diagnoses, a history of platinum- or taxane-based chemotherapy, and a CIPN diagnosis were evaluated from the EBM Provider database (Fig. 1). Among the patients treated with platinum-based chemotherapy, 18,063 received carboplatin, 12,653 received oxaliplatin, and 6212 received cisplatin, while among patients treated with taxane-based chemotherapy, 28,330 received paclitaxel and 6337 received docetaxel (Table 1). By chemotherapy type, the percentages of female patients were 64% (carboplatin), 38% (oxaliplatin), 33% (cisplatin), 70% (paclitaxel), and 68% (docetaxel). The mean height and weight reflected the proportion of women for each chemotherapy type (carboplatin: 156.5 cm, 57.5 kg; oxaliplatin: 158.9 cm, 58.6 kg; cisplatin: 160.0 cm, 58.8 kg; paclitaxel: 156.8 cm, 57.2 kg; docetaxel: 156.6 cm, 57.7 kg). The duloxetine prescription rates were 3.7% (carboplatin), 4.5% (oxaliplatin), 2.6% (cisplatin), 5.7% (paclitaxel), and 2.1% (docetaxel).

Including patients with multiple cancer diagnoses, patients treated with carboplatin included 378 with colorectal cancer, 300 with gastric cancer, 7921 with lung cancer, 171 with prostate cancer, 485 with breast cancer, and 14,588 with other cancer types. Regarding patients treated with oxaliplatin, 6715 had colorectal cancer, 2310 had gastric cancer, 1103 had lung cancer, 181 had prostate cancer, 135 had breast cancer, and 9717 had other cancer types. Among patients treated with cisplatin, 165, 908, 2054, 112, and 63 had colorectal, gastric, lung, prostate, and breast cancer, respectively, and 4895 had other cancer types. Among patients treated with paclitaxel, 551, 3139, 4786, 220, and 7343, had colorectal, gastric, lung, prostate, and breast cancer, respectively, and 22,444 had other cancer

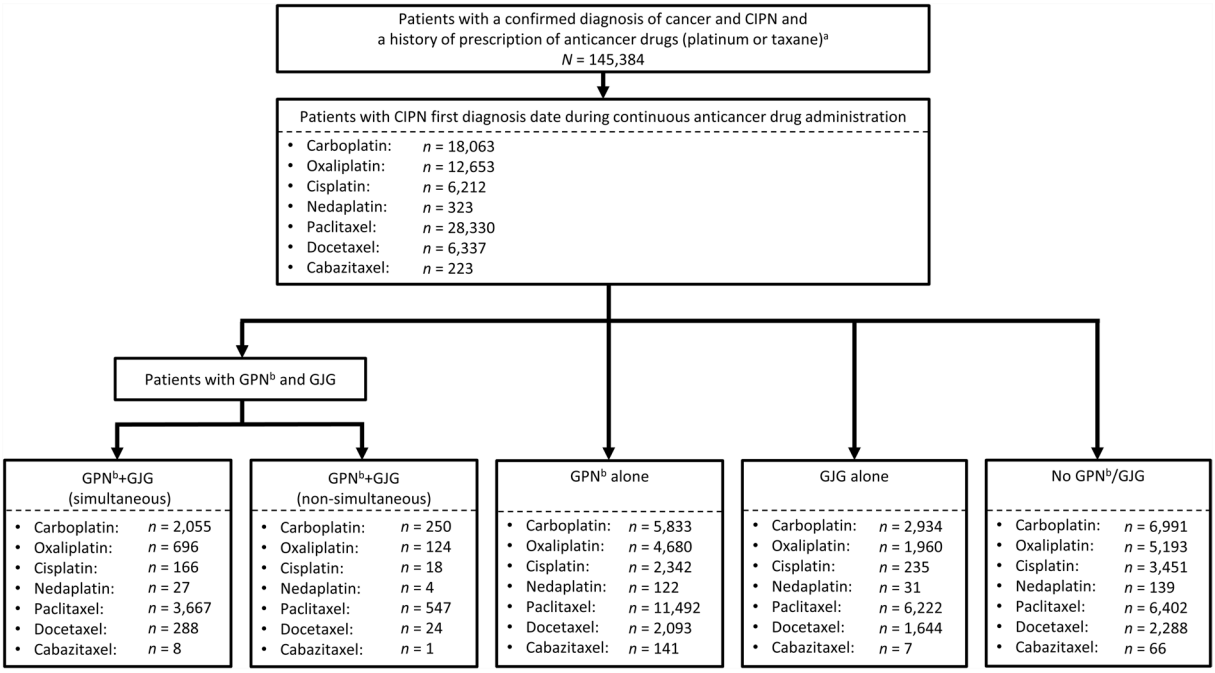


**Fig. 1** Study design and patient disposition. [a]Eligible patients had a diagnosis of CIPN while receiving continuous doses (intervals of no more than 67 days) of platinum- or taxane-based chemotherapy, and initiated chemotherapy between April 1, 2008 and March 31, 2022. [b]Either mirogabalin besylate or pregabalin. *CIPN* chemotherapy-induced peripheral neuropathy, *GPN* gabapentinoid, *GJG* goshajinkigan

types. For those treated with docetaxel, 62 had colorectal cancer, 360 had gastric cancer, 1166 had lung cancer, 708 had prostate cancer, 3375 had breast cancer, and 3416 had other cancer types.

## CIPN Treatment

When grouped by chemotherapeutic regimen (Table 1), most patients received either GPN alone (carboplatin: 32.3%; oxaliplatin: 37.0%; cisplatin: 37.7%; paclitaxel: 40.6%; docetaxel: 33.0%) or received neither GPN/GJG (carboplatin: 38.7%; oxaliplatin: 41.0%; cisplatin: 55.6%; paclitaxel: 22.6%; docetaxel: 36.1%). The percentages who received GJG alone were 16.2% (carboplatin), 15.5% (oxaliplatin), 3.8% (cisplatin), 22.0% (paclitaxel), and 25.9% (docetaxel). Among patients who received GPN + GJG, the percentages of patients who received simultaneous treatment were higher than the percentages of patients who received non-simultaneous treatment (carboplatin: 11.4% vs. 1.4%; oxaliplatin: 5.5% vs. 1.0%; cisplatin: 2.7% vs. 0.3%; paclitaxel: 12.9% and 1.9%; and docetaxel: 4.5% vs. 0.4%, respectively).

## Chemotherapy Dose and Duration by CIPN Treatment

The primary outcomes (chemotherapy dose and duration) were evaluated by GPN and GJG treatment (Table 2) and the statistical analysis results including mean differences and 95% confidence intervals (CIs) are shown in Table S2. Among patients treated with carboplatin, those who received GPN + GJG simultaneously had a longer chemotherapy duration than those who received GPN alone [mean difference 6.4 days (95% CI 2.4–10.3)], GJG alone [18.9 days (15.4–22.4)], or neither GPN/GJG [23.7 days (20.3–27.1)], and a higher chemotherapy total dose than those who received GPN alone [146.3 mg (75.8–216.7)], GJG alone [553.5 mg (490.6–616.3)], or neither

**Table 1** Patient background characteristics

| | All patients | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|---|
| Platinum-based regimens | | | | | | |
| Carboplatin, *n* (%) | 18,063 | 2055 (11.38) | 250 (1.38) | 5833 (32.29) | 2934 (16.24) | 6991 (38.70) |
| Sex, *n* (%) | | | | | | |
| Female | 11,598 (64.21) | 1851 (90.07) | 228 (91.20) | 3526 (60.45) | 2645 (90.15) | 3348 (47.89) |
| Male | 6465 (35.79) | 204 (9.93) | 22 (8.80) | 2307 (39.55) | 289 (9.85) | 3643 (52.11) |
| Age, years | 64.38 ± 11.16 | 61.08 ± 11.17 | 61.24 ± 12.06 | 64.17 ± 11.05 | 61.41 ± 11.44 | 66.88 ± 10.47 |
| Height, cm | 156.54 ± 20.53 | 154.50 ± 19.29 | 156.00 ± 12.24 | 157.57 ± 20.05 | 154.53 ± 17.28 | 157.24 ± 22.80 |
| Weight, kg | 57.48 ± 12.99 | 57.59 ± 13.76 | 56.47 ± 12.09 | 57.91 ± 13.03 | 56.61 ± 12.27 | 57.50 ± 13.05 |
| Cancer stage, *n* | | | | | | |
| I | 336 | 43 | 10 | 90 | 88 | 105 |
| II | 112 | 11 | 2 | 51 | 16 | 32 |
| III | 290 | 33 | 3 | 105 | 47 | 102 |
| IV | 442 | 21 | 3 | 187 | 38 | 193 |
| Cancer type, *n* | | | | | | |
| Colorectal | 378 | 39 | 10 | 138 | 44 | 147 |
| Gastric | 300 | 15 | 1 | 98 | 24 | 162 |
| Lung | 7921 | 265 | 36 | 2586 | 413 | 4621 |
| Prostate | 171 | 4 | 1 | 64 | 8 | 94 |
| Breast | 485 | 89 | 11 | 156 | 95 | 134 |
| Other | 14,588 | 1924 | 227 | 4817 | 2747 | 4873 |
| Hospitalisation status, *n* | | | | | | |
| Inpatient | 6719 | 732 | 96 | 2410 | 1107 | 2374 |
| Outpatient | 11,344 | 1323 | 154 | 3423 | 1827 | 4617 |
| Duloxetine, *n* (%) | 672 (3.7) | 113 (5.5) | 24 (9.6) | 315 (5.4) | 95 (3.2) | 125 (1.8) |
| Oxaliplatin, *n* (%) | 12,653 | 696 (5.50) | 124 (0.98) | 4680 (36.99) | 1960 (15.49) | 5193 (41.04) |
| Sex, *n* (%) | | | | | | |
| Female | 4803 (37.96) | 239 (34.34) | 56 (45.16) | 1713 (36.60) | 773 (39.44) | 2022 (38.94) |
| Male | 7850 (62.04) | 457 (65.66) | 68 (54.84) | 2967 (63.40) | 1187 (60.56) | 3171 (61.06) |

**Table 1** continued

| | All patients | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|---|
| Age, years | 65.21 ± 10.41 | 64.18 ± 10.62 | 65.36 ± 11.35 | 64.84 ± 10.38 | 65.13 ± 10.47 | 65.71 ± 10.35 |
| Height, cm | 158.93 ± 23.66 | 157.82 ± 29.26 | 159.43 ± 17.48 | 159.65 ± 22.30 | 158.73 ± 23.49 | 158.44 ± 24.27 |
| Weight, kg | 58.60 ± 16.75 | 58.01 ± 15.57 | 58.81 ± 13.40 | 58.95 ± 13.94 | 58.40 ± 14.09 | 58.42 ± 20.06 |
| Cancer stage, *n* | | | | | | |
| I | 118 | 1 | 0 | 37 | 16 | 64 |
| II | 370 | 14 | 2 | 138 | 52 | 164 |
| III | 1141 | 47 | 6 | 346 | 202 | 540 |
| IV | 1378 | 65 | 15 | 661 | 131 | 506 |
| Cancer type, *n* | | | | | | |
| Colorectal | 6715 | 367 | 65 | 2256 | 1172 | 2855 |
| Gastric | 2310 | 108 | 28 | 881 | 273 | 1020 |
| Lung | 1103 | 73 | 11 | 461 | 143 | 415 |
| Prostate | 181 | 17 | 2 | 64 | 30 | 68 |
| Breast | 135 | 6 | 3 | 57 | 16 | 53 |
| Other | 9717 | 543 | 92 | 3842 | 1449 | 3791 |
| Hospitalisation status, *n* | | | | | | |
| Inpatient | 2657 | 127 | 16 | 890 | 396 | 1228 |
| Outpatient | 9996 | 569 | 108 | 3790 | 1564 | 3965 |
| Duloxetine, *n* (%) | 571 (4.5) | 42 (6.0) | 3 (2.7) | 265 (5.7) | 52 (2.7) | 209 (4.0) |
| Cisplatin, *n* (%) | 6212 | 166 (2.67) | 18 (0.29) | 2342 (37.70) | 235 (3.78) | 3451 (55.55) |
| Sex, *n* (%) | | | | | | |
| Female | 2029 (32.66) | 83 (50.00) | 7 (38.89) | 735 (31.38) | 135 (57.45) | 1069 (30.98) |
| Male | 4183 (67.34) | 83 (50.00) | 11 (61.11) | 1607 (68.62) | 100 (42.55) | 2382 (69.02) |
| Age, years | 64.00 ± 11.56 | 61.03 ± 12.95 | 63.72 ± 12.11 | 63.34 ± 11.74 | 59.65 ± 14.30 | 64.89 ± 11.02 |
| Height, cm | 160.04 ± 21.86 | 158.85 ± 15.67 | 162.65 ± 9.29 | 160.70 ± 20.85 | 157.23 ± 24.03 | 159.78 ± 22.75 |
| Weight, kg | 58.78 ± 13.38 | 56.98 ± 14.40 | 59.23 ± 12.84 | 59.33 ± 12.96 | 56.96 ± 13.62 | 58.58 ± 13.60 |
| Cancer stage, *n* | | | | | | |
| I | 56 | 4 | 0 | 21 | 4 | 27 |
| II | 61 | 2 | 1 | 31 | 2 | 25 |

**Table 1** continued

| | All patients | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|---|
| III | 90 | 0 | 0 | 37 | 3 | 50 |
| IV | 187 | 3 | 0 | 79 | 7 | 98 |
| Cancer type, *n* | | | | | | |
| Colorectal | 165 | 5 | 0 | 58 | 10 | 92 |
| Gastric | 908 | 38 | 2 | 293 | 43 | 532 |
| Lung | 2054 | 25 | 5 | 685 | 36 | 1303 |
| Prostate | 112 | 2 | 0 | 66 | 2 | 42 |
| Breast | 63 | 1 | 0 | 26 | 3 | 33 |
| Other | 4895 | 153 | 15 | 1914 | 201 | 2612 |
| Hospitalisation status, *n* | | | | | | |
| Inpatient | 2849 | 84 | 9 | 1230 | 97 | 1429 |
| Outpatient | 3363 | 82 | 9 | 1112 | 138 | 2022 |
| Duloxetine, *n* (%) | 161 (2.6) | 8 (4.8) | 0 (0.0) | 102 (4.4) | 10 (4.3) | 41 (1.2) |
| Taxane-based regimens | | | | | | |
| Paclitaxel, *n* (%) | 28,330 | 3667 (12.94) | 547 (1.93) | 11,492 (40.56) | 6222 (21.96) | 6402 (22.60) |
| Sex, *n* (%) | | | | | | |
| Female | 19,826 (69.98) | 2931 (79.93) | 425 (77.70) | 7224 (62.86) | 5179 (83.24) | 4067 (63.53) |
| Male | 8504 (30.02) | 736 (20.07) | 122 (22.30) | 4268 (37.14) | 1043 (16.76) | 2335 (36.47) |
| Age, years | 62.80 ± 11.50 | 61.41 ± 11.29 | 62.10 ± 11.47 | 63.34 ± 11.29 | 61.30 ± 11.69 | 64.13 ± 11.57 |
| Height, cm | 156.75 ± 18.91 | 155.79 ± 18.18 | 156.62 ± 16.52 | 157.67 ± 19.48 | 155.71 ± 16.64 | 156.63 ± 20.50 |
| Weight, kg | 57.21 ± 13.59 | 57.75 ± 18.00 | 56.82 ± 12.18 | 57.46 ± 12.75 | 56.69 ± 12.82 | 56.95 ± 12.79 |
| Cancer stage, *n* | | | | | | |
| I | 469 | 57 | 13 | 184 | 119 | 96 |
| II | 471 | 32 | 7 | 242 | 92 | 98 |
| III | 556 | 54 | 10 | 280 | 86 | 126 |
| IV | 869 | 68 | 11 | 467 | 96 | 227 |
| Cancer type, *n* | | | | | | |
| Colorectal | 551 | 63 | 15 | 250 | 90 | 133 |
| Gastric | 3139 | 272 | 65 | 1536 | 397 | 869 |

**Table 1** continued

| | All patients | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|---|
| Lung | 4786 | 371 | 58 | 2235 | 609 | 1513 |
| Prostate | 220 | 23 | 4 | 118 | 33 | 42 |
| Breast | 7343 | 919 | 161 | 2770 | 2107 | 1386 |
| Other | 22,444 | 3047 | 437 | 9192 | 4874 | 4894 |
| Hospitalisation status, *n* | | | | | | |
| Inpatient | 6712 | 896 | 120 | 2429 | 1612 | 1655 |
| Outpatient | 21,618 | 2771 | 427 | 9063 | 4610 | 4747 |
| Duloxetine, *n* (%) | 1615 (5.7) | 259 (7.1) | 70 (12.8) | 715 (6.2) | 249 (4.0) | 322 (5.0) |
| Docetaxel, *n* (%) | 6337 | 288 (4.54) | 24 (0.38) | 2093 (33.03) | 1644 (25.94) | 2288 (36.11) |
| Sex, *n* (%) | | | | | | |
| Female | 4325 (68.25) | 226 (78.47) | 18 (75.00) | 1152 (55.04) | 1558 (94.77) | 1371 (59.92) |
| Male | 2012 (31.75) | 62 (21.53) | 6 (25.00) | 941 (44.96) | 86 (5.23) | 917 (40.08) |
| Age, years | 61.27 ± 11.96 | 60.40 ± 11.94 | 59.54 ± 13.35 | 62.83 ± 11.54 | 57.11 ± 11.20 | 62.95 ± 12.11 |
| Height, cm | 156.63 ± 20.96 | 155.70 ± 20.16 | 161.59 ± 9.34 | 157.59 ± 23.21 | 155.59 ± 14.18 | 156.40 ± 22.59 |
| Weight, kg | 57.73 ± 14.14 | 58.14 ± 12.21 | 57.24 ± 9.83 | 58.51 ± 13.58 | 56.73 ± 15.53 | 57.53 ± 13.96 |
| Cancer stage, *n* | | | | | | |
| I | 90 | 6 | 0 | 15 | 54 | 15 |
| II | 150 | 4 | 0 | 27 | 97 | 22 |
| III | 61 | 4 | 0 | 21 | 18 | 18 |
| IV | 82 | 2 | 2 | 41 | 13 | 24 |
| Cancer type, *n* | | | | | | |
| Colorectal | 62 | 1 | 0 | 21 | 9 | 31 |
| Gastric | 360 | 15 | 0 | 104 | 29 | 212 |
| Lung | 1166 | 34 | 1 | 527 | 80 | 524 |
| Prostate | 708 | 22 | 3 | 376 | 19 | 288 |
| Breast | 3375 | 153 | 13 | 815 | 1432 | 962 |
| Other | 3416 | 179 | 17 | 1345 | 611 | 1264 |
| Hospitalisation status, *n* | | | | | | |
| Inpatient | 1098 | 56 | 3 | 503 | 118 | 418 |

**Table 1** continued

| | All patients | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|---|
| Outpatient | 5239 | 232 | 21 | 1590 | 1526 | 1870 |
| Duloxetine, *n* (%) | 131 (2.1) | 13 (4.5) | 3 (12.5) | 61 (2.9) | 15 (0.9) | 39 (1.7) |

Data are shown as mean values unless otherwise stated

*GPN* gabapentinoid, *GJG* goshajinkigan, *SD* standard deviation

[a]Either mirogabalin besylate or pregabalin

GPN/GJG [724.7 mg (663.2–786.2)]. Non-simultaneous GPN + GJG was similarly associated with longer duration and higher total dose. Patients who received GPN alone or GJG alone had a longer duration and a higher total dose than patients who received neither GPN/GJG.

Among those who received oxaliplatin, patients treated with GPN + GJG simultaneously or non-simultaneously had a longer chemotherapy duration and a higher total chemotherapy dose than patients who received either GPN alone [mean difference 30.4 days (95% CI 21.9–39.0); 218.6 mg (159.2–277.9)], GJG alone [12.0 days (2.7–21.3); 81.9 mg (17.4–146.4)], or neither GPN/GJG 24.7 days [(16.2–33.2); 174.2 mg (115.2–233.2)]. The chemotherapy duration and total dose was longer and higher in patients treated with GJG alone, and shorter and lower in patients treated with GPN alone, compared with patients who received neither GPN/GJG.

In the cisplatin group, patients treated with GPN + GJG simultaneously had a longer chemotherapy duration and a higher total chemotherapy dose than patients who received GPN alone [mean difference 50.6 days (95% CI 36.4–64.7); 102.4 mg (65.4–139.3)], GJG alone [39.4 days (21.5–57.3); 92.0 mg (45.4–138.7)], or neither GPN/GJG [58.7 days (44.7–72.7); 123.4 mg (86.8–160.0)]. Patients who received GPN or GJG alone had a longer duration and a higher total dose than patients who received neither GPN/GJG.

Regarding patients treated with taxane-based chemotherapy, the paclitaxel and docetaxel groups showed similar results: those who received GPN + GJG simultaneously had a longer chemotherapy duration and a higher total chemotherapy dose than those who received GPN alone [in the paclitaxel group, mean difference 26.6 days (95% CI 21.8–31.4) and 302.7 mg (247.6–357.9); in the docetaxel group, 18.6 days (4.1–33.1) and 117.6 mg (71.5–163.6)], GJG alone [in the paclitaxel group, 19.3 days (14.1–24.5) and 249.9 mg (189.4–310.4); in the docetaxel group, 29.1 days (14.4–43.9) and 77.5 mg (30.7–124.3)], or neither GPN/GJG [in the paclitaxel group, 31.5 days (26.3–36.7) and 439.0 mg (378.8–499.2); in the docetaxel group, 18.5 days (4.1–32.9) and 113.7 mg (67.9–159.5)]. Similar results were also observed for those who received GPN + GJG non-simultaneously. Moreover, in the paclitaxel group, those who received either GPN alone or GJG alone had a longer duration and a higher total dose than those who had neither GPN/GJG. Among patients treated with docetaxel, those who received GJG alone had a shorter duration and a higher total dose than those who had neither GPN/GJG. Results for nedaplatin and cabazitaxel, which had small sample sizes, are reported in Tables S3 and S4.

## Chemotherapy Dose and Duration by Cancer Types

The dose and duration of oxaliplatin for patients with colorectal or gastric cancer, and the dose and duration of paclitaxel for patients with gastric, lung, or breast cancer, are shown in Table 3. The dose/duration of all chemotherapies by cancer type are shown in Table S3 and

**Table 2** Duration and total dose of chemotherapy by GPN and GJG treatment regimen

| | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|
| Platinum-based regimens | | | | | |
| Carboplatin | | | | | |
| Patients, *n* (%) | 2055 (11.38) | 250 (1.38) | 5833 (32.29) | 2934 (16.24) | 6991 (38.70) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 86.6 ± 71.9$^{**,\#\#,++}$ | 100.8 ± 57.6$^{**,\#\#,++}$ | 67.6 ± 70.1$^{++}$ | 80.2 ± 76.3$^{++}$ | 62.8 ± 66.4 |
| Median | 81 | 92 | 57 | 70 | 57 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 2282.9 ± 1451.9$^{**,\#\#,++}$ | 2583.9 ± 1236.5$^{**,\#\#,++}$ | 1729.1 ± 1238.1$^{++}$ | 2136.9 ± 1346.0$^{++}$ | 1557.7 ± 1150.1 |
| Median | 2100 | 2400 | 1450 | 1900 | 1350 |
| Oxaliplatin | | | | | |
| Patients, *n* (%) | 696 (5.50) | 124 (0.98) | 4680 (36.99) | 1960 (15.49) | 5193 (41.04) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 121.4 ± 134.7$^{**,\#,++}$ | 151.7 ± 124.1$^{**,\#\#,++}$ | 91.0 ± 106.7$^{++}$ | 109.4 ± 113.8$^{++}$ | 96.7 ± 101.0 |
| Median | 92 | 121.5 | 64 | 85 | 71 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 1041.2 ± 972.2$^{**,\#,++}$ | 1208.0 ± 774.3$^{**,\#\#,++}$ | 822.7 ± 775.0$^{++}$ | 959.3 ± 760.7$^{++}$ | 867.0 ± 673.6 |
| Median | 805 | 1040 | 600 | 800 | 750 |
| Cisplatin | | | | | |
| Patients, *n* (%) | 166 (2.67) | 18 (0.29) | 2342 (37.70) | 235 (3.78) | 3451 (55.55) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 119.2 ± 145.7$^{**,\#\#,++}$ | 108.0 ± 87.1$^{+}$ | 68.7 ± 89.6$^{++}$ | 79.8 ± 86.4$^{++}$ | 60.5 ± 86.9 |
| Median | 78 | 81 | 43 | 56 | 40 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 410.2 ± 375.5$^{**,\#\#,++}$ | 373.1 ± 183.3 | 307.8 ± 245.2$^{++}$ | 318.1 ± 229.3$^{+}$ | 286.8 ± 218.8 |
| Median | 350 | 387.5 | 240 | 255 | 240 |
| Taxane-based regimens | | | | | |
| Paclitaxel | | | | | |
| Patients, *n* (%) | 3667 (12.94) | 547 (1.93) | 11,492 (40.57) | 6222 (21.96) | 6402 (22.60) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 115.7 ± 149.6$^{**,\#\#,++}$ | 153.4 ± 238.0$^{**,\#\#,++}$ | 89.1 ± 116.9$^{+}$ | 96.4 ± 131.6$^{++}$ | 84.2 ± 119.1 |
| Median | 78 | 93 | 57 | 69 | 52 |
| Total dose[b] of chemotherapy (mg) | | | | | |

**Table 2** continued

| | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|
| Mean ± SD | 1609.5 ± 1785.9$^{**,\#\#,++}$ | 1915.5 ± 2028.5$^{**,\#\#,++}$ | 1306.5 ± 1461.9$^{++}$ | 1359.3 ± 1440.6$^{++}$ | 1170.2 ± 1305.8 |
| Median | 1200 | 1320 | 900 | 1040 | 800 |
| Docetaxel | | | | | |
| Patients, *n* (%) | 288 (4.54) | 24 (0.38) | 2093 (33.03) | 1644 (25.94) | 2288 (36.11) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 95.4 ± 150.7$^{*,\#\#,+}$ | 196.2 ± 257.0$^{**,\#\#,++}$ | 76.8 ± 130.2 | 66.3 ± 72.8$^{++}$ | 76.9 ± 124.2 |
| Median | 63.5 | 64 | 43 | 64 | 45.5 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 485.8 ± 557.5$^{**,\#\#,++}$ | 728.4 ± 628.6$^{**,\#\#,++}$ | 368.3 ± 410.4 | 408.4 ± 257.5$^{++}$ | 372.2 ± 376.9 |
| Median | 361.5 | 420 | 240 | 400 | 280 |

Data are shown as mean values unless otherwise stated. Nedaplatin and cabazitaxel are listed in online supplemental Tables 3 and 4 because of the small sample size

*CIPN* chemotherapy-induced peripheral neuropathy, *GPN* gabapentinoid, *GJG* goshajinkigan, *SD* standard deviation

$^{*}p < 0.05$ vs. GPN alone

$^{**}p < 0.01$ vs. GPN alone

$^{\#}p < 0.05$ vs. GJG alone$^{\#\#}p < 0.01$ vs. GJG alone

$^{+}p < 0.05$ vs. neither GPN/GJG$^{++}p < 0.01$ vs. neither GPN/GJG

[a]Either mirogabalin besylate or pregabalin

[b]Total dose of the chemotherapy drug, defined as the total amount administered from the date of the first administration of the chemotherapy drug after CIPN diagnosis to the date of the last administration of the chemotherapy drug

S4, and statistical analysis results are shown in Table S5.

In patients with colorectal cancer receiving oxaliplatin, patients who received GPN + GJG simultaneously had a longer chemotherapy duration and higher total chemotherapy dose than patients who received GPN alone [mean difference 31.9 days (95% CI 20.2–43.5); 215.8 mg (136.1–295.5)] or neither GPN/GJG [21.0 days (95% CI 9.5–32.5); 127.1 mg (48.6–205.6)]. Patients who received GPN + GJG non-simultaneously also had a longer duration and higher total dose than patients who received GPN alone or neither GPN/GJG. Additionally, patients who received non-simultaneous GPN + GJG had a longer duration than those who received GJG alone. Patients who received GJG alone had a longer duration, and those who received GPN alone had a shorter duration, than those who received neither GPN/GJG. Compared with those who received neither GPN/GJG, those who received GJG alone had a higher total dose, and those who received GPN alone had a lower total dose.

Among patients receiving oxaliplatin for gastric cancer, those who received GPN + GJG non-simultaneously had longer chemotherapy duration and higher total chemotherapy dose than patients who received GPN alone, GJG alone, or neither GPN/GJG. However, patients who received GPN + GJG simultaneously did not have longer duration or higher total dose than patients who received GPN alone, GJG alone,

**Table 3** Duration and total dose of oxaliplatin and paclitaxel by GPN and GJG treatment regimen and cancer type

| | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|
| Oxaliplatin | | | | | |
| Colorectal cancer | | | | | |
| Patients, *n* (%) | 367 (5.47) | 65 (0.97) | 2256 (33.60) | 1172 (17.45) | 2855 (42.52) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 120.2 ± 116.3$^{**,++}$ | 145.9 ± 126.6$^{**,\#\#,++}$ | 88.3 ± 103.0$^{++}$ | 109.4 ± 111.5$^{++}$ | 99.2 ± 103.4 |
| Median | 92 | 113 | 64 | 85 | 77 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 1026.4 ± 771.2$^{**,++}$ | 1129.2 ± 654.6$^{**,+}$ | 810.6 ± 763.6$^{++}$ | 972.8 ± 743.2$^{++}$ | 899.3 ± 673.1 |
| Median | 850 | 1030 | 600 | 800 | 800 |
| Gastric cancer | | | | | |
| Patients, *n* (%) | 108 (4.68) | 28 (1.21) | 881 (38.14) | 273 (11.82) | 1020 (44.16) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 100.1 ± 77.6 | 170.1 ± 132.5$^{**,\#\#,++}$ | 86.7 ± 105.6 | 108.4 ± 118.1$^{++}$ | 88.0 ± 94.8 |
| Median | 90.5 | 148 | 56 | 85 | 64 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 840.5 ± 555.8 | 1221.1 ± 636.6$^{**,\#\#,++}$ | 757.6 ± 713.3 | 876.4 ± 666.6$^{++}$ | 740.2 ± 592.8 |
| Median | 760 | 1125 | 550 | 750 | 600 |
| Paclitaxel | | | | | |
| Gastric cancer | | | | | |
| Patients, *n* (%) | 272 (8.67) | 65 (2.07) | 1536 (48.93) | 397 (12.65) | 869 (27.68) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 154.2 ± 157.6$^{**,\#,++}$ | 281.7 ± 525.3$^{**,\#\#,++}$ | 107.9 ± 141.5 | 128.2 ± 149.7$^{+}$ | 107.9 ± 149.4 |
| Median | 105.5 | 148 | 64 | 85 | 63 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 1908.1 ± 1953.0$^{**,\#\#,++}$ | 2673.7 ± 3366.4$^{**,\#\#,++}$ | 1271.6 ± 1441.0 | 1573.3 ± 1686.5$^{++}$ | 1202.5 ± 1462.0 |
| Median | 1275 | 1560 | 800 | 1040 | 720 |
| Lung cancer | | | | | |
| Patients, *n* (%) | 371 (7.75) | 58 (1.21) | 2235 (46.70) | 609 (12.72) | 1513 (31.61) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 105.9 ± 158.7$^{**,++}$ | 153.0 ± 129.2$^{**,\#\#,++}$ | 72.3 ± 101.3 | 98.3 ± 156.4$^{++}$ | 69.6 ± 112.0 |
| Median | 64 | 102.5 | 45 | 64 | 40 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 1469.0 ± 1678.3$^{**,++}$ | 2093.6 ± 2002.1$^{**,\#\#,++}$ | 1139.8 ± 1280.7$^{+}$ | 1334.6 ± 1558.4$^{++}$ | 1048.7 ± 1188.2 |

**Table 3** continued

| | GPN[a] + GJG (simultaneous) | GPN[a] + GJG (non-simultaneous) | GPN[a] alone | GJG alone | Neither GPN[a]/GJG |
|---|---|---|---|---|---|
| Median | 990 | 1445 | 800 | 940 | 660 |
| Breast cancer | | | | | |
| Patients, *n* (%) | 919 (12.52) | 161 (2.19) | 2770 (37.72) | 2107 (28.69) | 1386 (18.88) |
| Duration of chemotherapy (days) | | | | | |
| Mean ± SD | 120.2 ± 188.7$^{**,\#\#,++}$ | 157.0 ± 229.6$^{**,\#\#,++}$ | 88.9 ± 132.6 | 97.1 ± 147.3 | 91.0 ± 138.3 |
| Median | 64 | 71 | 50 | 64 | 57 |
| Total dose[b] of chemotherapy (mg) | | | | | |
| Mean ± SD | 1658.2 ± 2097.0$^{**,\#\#,++}$ | 1937.7 ± 2174.9$^{**,\#\#,++}$ | 1270.0 ± 1459.2 | 1387.1 ± 1482.5$^{++}$ | 1248.0 ± 1334.2 |
| Median | 1170 | 1300 | 900 | 1130 | 960 |

Data are shown as mean values unless otherwise stated

*CIPN*, chemotherapy-induced peripheral neuropathy; *GPN*, gabapentinoid; *GJG*, goshajinkigan, *SD*, standard deviation

$^{*}p < 0.05$ vs. GPN alone

$^{**}p < 0.01$ vs. GPN alone

$^{\#}p < 0.05$ vs. GJG alone$^{\#\#}p < 0.01$ vs. GJG alone

$^{+}p < 0.05$ vs. neither GPN/GJG$^{++}p < 0.01$ vs. neither GPN/GJG

[a]Either mirogabalin besylate or pregabalin

[b]Total dose of the chemotherapy drug, defined as the total amount administered from the date of the first administration of the chemotherapy drug after CIPN diagnosis to the date of the last administration of the chemotherapy drug

or neither GPN/GJG. Compared with those who received neither GPN/GJG, those who received GJG alone had longer duration and higher total dose, while those treated with GPN alone did not.

Regarding paclitaxel for gastric cancer, patients who received GPN + GJG simultaneously or non-simultaneously had a longer chemotherapy duration and a higher chemotherapy total dose than patients who received GPN alone, GJG alone, or neither GPN/GJG. Compared with those who received neither GPN/GJG, those who received GJG alone had a longer duration and a higher total dose, while those who received GPN alone did not.

Similar trends were also observed for patients who received paclitaxel for lung cancer. Patients who received GPN + GJG simultaneously and non-simultaneously had a longer chemotherapy duration and a higher total chemotherapy dose than patients who received GPN alone or neither GPN/GJG. Patients treated with GPN + GJG non-simultaneously also had a longer duration and a higher total dose than patients who received GJG alone. Compared with patients treated with neither GPN/GJG, those who received GJG alone had a longer duration and a higher total dose, and those treated with GPN alone had a higher total dose.

In patients with breast cancer, patients who received GPN + GJG simultaneously or non-simultaneously had a longer chemotherapy duration and a higher total dose than patients who received GPN alone, GJG alone, or neither GPN/GJG. Compared with patients treated with

neither GPN/GJG, those who received GJG alone had a higher total dose.

## DISCUSSION

This retrospective cohort study, conducted with data from the EBM Provider database, investigated the chemotherapy total dose and duration in patients diagnosed with CIPN, including those who did or did not receive treatment with GPN and/or GJG. We observed that patients who received either GPN or GJG alone tended to have longer chemotherapy durations and higher doses versus those who received neither GPN/GJG, although there were some exceptions to this tendency. Furthermore, patients who received both GPN and GJG, simultaneously or non-simultaneously, had even longer durations and higher total chemotherapy doses than patients who received either GPN or GJG alone. These findings suggest that combination treatment with GPN + GJG may have the potential to reduce the need for dose reductions or chemotherapy discontinuation in patients with cancer and CIPN.

In Japan, Kampo medicines are often used as part of supportive and palliative cancer therapy to treat CIPN and other conditions, including anorexia, cachexia, and oral mucositis [29, 30]. In this study, fewer than 30% of patients with cancer and CIPN received GJG. The proportion of women treated with GJG tended to be higher than the overall male:female ratio for each anticancer drug. Japanese women more often experience peripheral coldness than men [31], and a previous study has reported that *Aconiti tuber*, a component of GJG, could be effective at improving peripheral coldness symptoms in patients with CIPN [32]. It is possible that some of the women treated with GJG in our study may have received GJG prescriptions to treat peripheral coldness, which warrants further investigation.

In this study, the effects of GPN and GJG on peripheral neuropathy could not be analysed. The pharmacological effects of these drugs have been previously reported: GPNs act through voltage-gated calcium channels [22], whereas GJGs act through several mechanisms, including interactions with cortical astrocytes, suppression of TRP channel gene expression, and reduction of oxaliplatin-induced reactive oxygen species [23–26]. This suggests that GPNs and GJG achieve their pain relief and analgesic effects through different mechanisms. We are currently using an animal model of CIPN to compare the improvement of CIPN with combined GPN + GJG versus GPN or GJG alone, and are investigating whether the effects are additive or synergistic. We also plan to analyse the mechanism of CIPN improvement when GPN and GJG are used in combination.

Duloxetine is also commonly used to treat CIPN [7, 14]. In this study, fewer than 13% of patients in each group received duloxetine. Therefore, we believe that the use of concomitant duloxetine would have had a minimal effect on the observed chemotherapy total dose or duration.

The EBM Provider database did not include information regarding whether GPN or GJG were prescribed for treating CIPN, or any information regarding CIPN severity. Thus, we were unable to evaluate any trends regarding the improvement or worsening of CIPN. Furthermore, the database did not distinguish between chemotherapy prescribed as neoadjuvant, adjuvant, or for advanced recurrence, which can vary greatly in terms of chemotherapy duration. Therefore, we evaluated the chemotherapy duration and total doses from the date of first administration of the chemotherapy drugs after the first CIPN diagnosis, rather than from the start of chemotherapy, and we did not assess whether patients had discontinued chemotherapy or reduced the dose of chemotherapy after the onset of CIPN by comparing with data prior to CIPN diagnosis. Nevertheless, the large population included was made possible by the EBM Provider database and remains a strength of the study.

Many reports have shown that higher chemotherapy dose intensity in patients with cancer is associated with favourable outcomes, such as prolonged overall survival, whereas dose reductions of chemotherapy are associated with poor outcomes [33–35]. Studies of other potential treatments for CIPN, including cooling of hands and feet, have shown variable

results at preventing chemotherapy dose reductions [36–38], although a recent meta-analysis reported that the incidence of taxane dose reduction was decreased with cryotherapy (risk ratio: 0.48, 95% CI 0.24, 0.95; $p = 0.04$) [39]. Although our study did not record the incidence of chemotherapy dose reductions, we found that patients who received either GPN or GJG had longer durations of chemotherapy and higher total chemotherapy doses than patients who did not receive these treatments, including when stratified by cancer type. This may suggest that treatment with GPN, GJG, or both has the potential to support the maintenance of chemotherapy dose intensity and prevent chemotherapy dose reductions in patients with CIPN. Although not assessed in this study, prevention of chemotherapy dose reductions with GPN or GJG treatment may contribute to improved patient outcomes. Furthermore, patients at higher risk of CIPN (those treated with oxaliplatin or paclitaxel) [1, 2] who received GPN + GJG had a higher duration and higher total chemotherapy dose than those who did not receive these treatments, further supporting the use of combination GPN + GJG treatment in these patients. Overall, our findings suggest that combination therapy with GPN and GJG could be a promising candidate for further study.

## LIMITATIONS

This study had several limitations that should be considered when interpreting the results. First, no information on AEs associated with GPN or GJG was collected or assessed in the EBM Provider database; thus, we cannot speculate on the safety of these agents when used in combination as supportive care for cancer patients. However, the AE profile of the GPN drug class is well known [9], and a prior report indicated that GJG is well tolerated without serious adverse reactions in patients with cancer [18]. Second, we did not conduct a multiplicity adjustment. Therefore, the $p$ values provided are for reference only and cannot be used to draw definitive conclusions. Finally, data for other risk factors for neuropathy, such as diabetes, were not collected, and, as such, their effects could not be taken into account in the analysis. To mitigate the impact of this on the study findings, patients with a diagnosis of neuropathy [peripheral neuritis (3545003), numbness (7820002), numbness of lower extremity (782006), numbness of extremities (7820018), peripheral neuropathy (8840255), peripheral neuropathic pain (8846220 and 8849550), or neuropathic pain (8847489)] prior to the administration of anticancer agents were excluded from the analysis. However, we note that patients who developed diabetes after receiving anticancer agents or those who developed diabetes before receiving anticancer agents but did not develop neuropathy until later in the study, would not have been excluded. Focusing on the above points, further investigation is needed to assess the safety and efficacy of combination GPN + GJG therapy in patients with cancer.

## CONCLUSION

The findings of this retrospective study suggest that combination GPN + GJG therapy might be effective for the treatment of CIPN, and could potentially be a suitable supportive care regimen for patients undergoing cancer chemotherapy. Prospective clinical trials are needed to evaluate whether the combined use of GPN + GJG is effective and safe in these patients.

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***Author Contributions.*** All authors contributed to the study conception and design. Material preparation and data collection were performed by Satoshi Komoriya and Wataru Hashimoto. Analysis of the data was performed by Takuhiro Yamaguchi. Kanako Miyano, Yasuhito Uezono, Takuhiro Yamaguchi, Wataru Hashimoto, and Satoshi Komoriya participated in consideration of validity of analysis methods and interpretation of the data. Kanako Miyano, Yasuhito Uezono, Takuhiro Yamaguchi, Wataru Hashimoto, and Satoshi Komoriya read and approved the final manuscript.

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***Data Availability.*** The data that support the findings of this study are available from Medical Data Vision Co., Ltd. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Medical Data Vision Co., Ltd.

### *Declarations*

***Conflict of Interest.*** Kanako Miyano declares no competing interests. Yasuhito Uezono received consulting fees from Daiichi Sankyo Co., Ltd. Takuhiro Yamaguchi received support for the present manuscript from Daiichi Sankyo Co., Ltd. through his institution; grants or contracts through his institution from 3H Medi Solution Inc., A2 Healthcare Corporation, AC Medical Inc., Baseconnect Inc., ClinChoice, Cordis, Hemp Kitchen Inc., Intellim Corporation, Japan Media Corporation, Japan Tobacco Inc., Kyowa Kirin Co., Ltd., Medidata Solutions, Inc., Medrio, Inc., Nipro Corporation, NTT DOCOMO, Inc., Ono Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., PSP Corporation, Puravida Technologies LLC., Solasia Pharma K.K., Tsumura & Co., and Welby Inc.; consulting fees from 3H Clinical Trial Inc., AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., EPS Corporation, Intellim Corporation, Japan Tobacco Inc., Kowa Co., Ltd., Mebix, Inc., Medidata Solutions, Inc., Merck & Co., Inc., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., Public Health Research Foundation, Seikagaku Corporation, and SONIRE Therapeutics Inc.; and payments for participation on a data safety monitoring board or advisory board for Incyte Biosciences Japan G.K. Wataru Hashimoto and Satoshi Komoriya are employees of Daiichi Sankyo Co., Ltd.

***Ethical Approval.*** This study was conducted in accordance with the tenets of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (No. 2022-1-1128). This was a secondary use study of fully anonymised data from an existing database, so informed consent was not required.



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