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A randomized trial to evaluate the preventive effect of lafutidine on chemotherapy-induced peripheral neuropathy in patients treated with carboplatin and paclitaxel for lung cancer

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) has a significant impact on the therapeutic efficacy of chemotherapy and patients' quality of life. The aim of this study was to assess the preventive effect of lafutidine on CIPN.

Methods: Patients were randomly assigned (1:1) to carboplatin and paclitaxel chemotherapy with lafutidine 10 mg twice daily (lafutidine group) or without lafutidine (control group). Peripheral neuropathy in both groups was assessed with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and two patient-based questionnaires, the Patient Neurotoxicity Questionnaire (PNQ) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx). The primary outcome was the incidence of grade 2 or higher peripheral neuropathy in CTCAE version 5.0. The target number of cases was set at approximately 40.

Results: In total, 18 patients were screened, and 16 patients were assigned to the lafutidine group (n=9) or control group (n=7) between January 2021 and January 2023. Due to poor recruitment, the target number of cases was not reached. Grade 2 or higher neuralgia was 22.2% in the lafutidine group and 14.3% in the control group. Grade 2 or higher peripheral sensory neuropathy was 100% in the lafutidine group and 71.4% in the control group (P=0.175). Grade 3 or higher peripheral neuropathy was not detected in either group. There was no significant difference in PNQ scores between the two groups. Median FACT/GOG-Ntx scores after the fourth cycle tended to be lower in the lafutidine group than in the control group. There was no statistically significant difference in progression free survival (PFS) between the two groups. There were no adverse events due to lafutidine administration.

Conclusions: Although the preventive effect of lafutidine on CIPN could not be demonstrated statistically, lafutidine FACT/GOG-Ntx scores showed a trend toward decreased neurotoxicity as chemotherapy proceeded. More reliable studies using lafutidine on the prevention of CIPN should be conducted.

Trial Registration: Japan Registry of Clinical Trials, identifier: jRCTs021200031.

Keywords: Chemotherapy-induced peripheral neuropathy (CIPN); lafutidine; lung cancer

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Introduction

In recent years, there have been remarkable advances in the treatment of unresectable or postoperative recurrent non-small cell lung cancer, and indications for molecularly targeted agents and immune checkpoint inhibitors have expanded. Meanwhile, cytotoxic agents continue to play an important role. Paclitaxel is a standard cytotoxic agent and is also a leading cause of chemotherapy-induced peripheral neuropathy (CIPN) (1,2). In the treatment of lung cancer, paclitaxel is administered with platinum drugs and is given every 3 weeks at a standard dose of 200 mg/m^2. This regimen has been associated with a high frequency of CIPN. Although weekly divided dosing has been tried in the past as a means to reduce CIPN, it has not become the standard therapy (3). According to the international phase III CA031 trial comparing carboplatin plus nab-paclitaxel therapy with carboplatin plus paclitaxel (control arm) in untreated advanced non-small cell lung cancer patients, the frequency of all grades of peripheral neuropathy in Japanese patients assigned to the control arm was 81.3% (4). However, paclitaxel administration every 3 weeks is still the standard for some combination therapies with immunotherapy. The frequency of CIPN has been reported in several publications: a systematic review and meta-analysis of 31 trials and 4,179 patients reported that 68.1% of patients developed CIPN within 1 month after completion of chemotherapy (5). Prevention and treatment for CIPN is important because of its significant impact on patient quality of life, outcomes, and treatment completion rates (6-9). Several studies have been conducted on the prevention of CIPN (10-15), but there is no significant evidence for the prevention of CIPN (6).

Lafutidine is an H_2-receptor antagonist. It has been suggested that lafutidine indirectly activates Transient Receptor Potential Vanilloid subtype 1 (TRPV1) receptors and improves peripheral neuropathy by sensory nerve desensitization that occurs sequentially (16-18). There are several reports of improvement of CIPN after paclitaxel treatment with lafutidine administration (17,19,20). Although lafutidine is expected to have a certain effect on CIPN, there are no prospective studies concerning its preventive effect. The purpose of this study was to assess the prophylactic effect of lafutidine on CIPN during chemotherapy with carboplatin and tri-weekly PTX. We present this article in accordance with the CONSORT reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-90/rc).

Highlight box

Key findings

- No significant preventive effect of lafutidine on chemotherapy-induced peripheral neuropathy (CIPN) was observed in this underpowered study.

What is known and what is new?

- There was no statistically significant effect of lafutidine on the prevention of CIPN.
- To the best of our knowledge, this is the first study to prospectively assess the preventive effect of lafutidine on CIPN.

What is the implication, and what should change now?

- More reliable studies using lafutidine on the prevention of CIPN should be conducted.

Methods

Study design

This study was a randomized, open-label, prospective, interventional study. Patients were randomly assigned (1:1) to paclitaxel chemotherapy with lafutidine (lafutidine group) or without lafutidine (control group). Randomization was stratified by sex, age (≤75 or >75 years), and Eastern Cooperative Oncology Group performance status. The lafutidine group received lafutidine 10 mg twice a day, after breakfast and dinner, from the day of paclitaxel administration. Peripheral neuropathy was assessed before treatment (baseline), before each paclitaxel dose, and at 3–4 weeks after the fourth cycle of paclitaxel (Figure S1). There are several reports that paclitaxel administered in a single dose is more likely to cause peripheral neuropathy than divided doses (3,21). In this study, paclitaxel was administered to all patients in a single dose so as to make it easier to evaluate the effect of lafutidine.

Patients

Eligible patients were at least 18 years old; had histologically or cytologically confirmed non-small cell lung cancer; had no indications for surgery, curative radiotherapy or chemoradiotherapy; and were scheduled to receive paclitaxel every 3 or 4 weeks. Patients were collected from lung cancer patients treated at Iwate Medical University. Treatments were allowed in combination with carboplatin, bevacizumab, and immune checkpoint inhibitors. If patients

assigned to the lafutidine group were taking other anti-ulcer drugs, they were switched to lafutidine. The study excluded patients with a history of allergy to lafutidine and paclitaxel, pregnant or lactating women, and patients with Grade 2 or higher peripheral neuropathy in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 before study treatment. Written informed consent was obtained from all patients after they had been informed of the study procedures and possible risks. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Certified Review Board of Iwate Medical University (No. SCR2020-101).

Assessment

Peripheral neuropathy was assessed with CTCAE version 5.0, a physician-based instrument, in terms of "Neuralgia" and "Peripheral sensory neuropathy". In addition, we used two patient-based questionnaires, the Patient Neurotoxicity Questionnaire (PNQ) Japanese version and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) Japanese version. The PNQ comprises two items to identify incidence and severity of sensory and motor disturbances. Patients rated their subjective responses to each item of the PNQ on a five-point scale from A (0: no neuropathy) to E (4: severe neuropathy). Several validation studies have been conducted on the PNQ, including the Japanese version (22-24). The FACT/GOG-Ntx was designed to assess the severity of CIPN with sensory, motor, and functional impairments and its impact on patients' quality of life (24). This questionnaire has been validated in several studies on CIPN (25-27). According to one systematic review, the use of FACT/GOG-Ntx to assess CIPN in research settings has the most supporting evidence (28). The FACT/GOG-Ntx consists of 11 items related to neurotoxicity, each rated on a 5-point scale [0–4], with scores ranging from 0 to 44, with lower scores indicating less neurotoxicity. Category D or E on the PNQ and grade 2 or higher on the CTCAE indicate that peripheral neuropathy is interfering with daily life.

Outcomes

The primary outcome was the incidence of grade 2 or higher peripheral neuropathy in CTCAE version 5.0 JCOG Japanese version. Secondary outcomes were the incidence of grade 3 or higher peripheral neuropathy, the distribution of peripheral neuropathy scores in PNQ Japanese version and FACT/GOG-Ntx Japanese version, the timing of the appearance of grade 2 or higher peripheral neuropathy, the ratio of discontinuing or decreasing paclitaxel due to adverse events, progression free survival (PFS), response rate (RR) and safety.

Statistical analysis

According to the CA031 study, the frequency of all grades of peripheral neuropathy in Japanese patients receiving paclitaxel was 81.3% (4). In a Japanese phase II study of paclitaxel in ovarian cancer, the overall Grade I frequency of peripheral neuropathy was 79.4% (29). Based on these reports, the frequency of peripheral neuropathy in the control group without any specific prophylactic intervention is assumed to be about 80%. Although there are no reports on the preventive effect of lafutidine on peripheral neuropathy caused by paclitaxel administration, there is a prospective study on the therapeutic effect of lafutidine after the appearance of peripheral neuropathy, in which 9 of 20 patients (45%) showed moderate or greater symptomatic improvement (20). In the present study, since the prophylactic intervention was performed before the appearance of peripheral neuropathy, we assumed that an improvement of 45% or more could be expected, that the intervention group would show efficacy in more than 60% of patients who develop peripheral neuropathy, and that the frequency of peripheral neuropathy would be 30%. We assumed a frequency of 80% and 30% for peripheral neuropathy in the control group and lafutidine group, respectively, with an alpha error of 0.05 and beta error of 0.80. Using the chi-square test to calculate the sample size, we calculated that nineteen cases in each group were needed, for a total of 38 cases. Considering the possibility of discontinuation of the study, the target sample size was set at 40 cases.

We performed statistical analyses using the EZR statistical software version 1.61 (30). Peripheral neuropathy in CTCAE was analyzed using Fisher's exact test. Measurement data analyzed by the *t*-test were expressed as median ± standard deviation. Kaplan-Meier curves were constructed for day to progressive disease and compared using a stratified log-rank test. Tumor responses were compared between two groups using the chi-square test. Statistical significance was set at $P<0.05$.

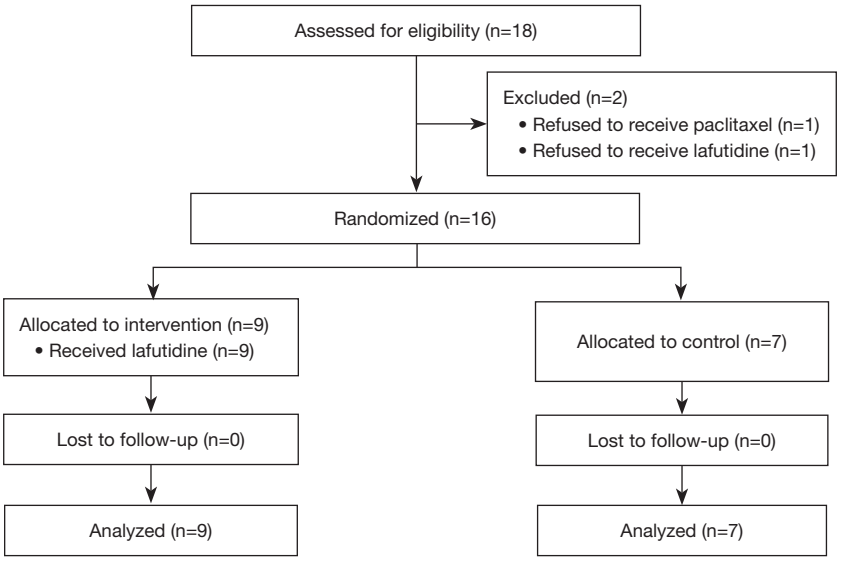

Figure 1 Participant flow.

Results

Baseline characteristics

In total, 18 patients were screened, and 16 were randomly assigned to one of the groups between January 2021 and January 2023 (*Figure 1*). Nine were assigned to lafutidine group and 7 to the control group. The baseline patient characteristics are shown in *Table 1*. The median age was 68 years in the lafutidine group and 73 years in the control group. Fifteen patients (93.8%) were male and ECOG PS of all patients was 1 or 2. Only 1 patient in the control group harbored the EGFR mutation. All patients received the combination of carboplatin and paclitaxel, not in combination with bevacizumab or immune checkpoint inhibitors. Overall, 7 patients (43.8%) had stage IV disease, and 9 (56.3%) stage III or less. Total dose (median) of paclitaxel was 1,143 mg in both groups.

Outcomes

Peripheral neuropathy in CTCAE version 5.0 is shown in *Table 2*. There was no significant difference between the two groups in grade 2 or higher neuralgia (22.2% *vs.* 14.3%, P>0.99). Grade 2 or higher peripheral sensory neuropathy was 100% in the lafutidine group and 71.4% in the control group (P=0.18). Grade 3 or higher peripheral neuropathy was not observed in either group. *Table 3* shows the median score ± standard deviation of each time in terms of sensory and motor disturbances in PNQ. The scores in the control group tended to be slightly higher than those in the lafutidine group, but there was no significant difference. Median FACT/GOG-Ntx values are shown in *Table 4* and *Figure 2*. *Table 4* shows median scores with ± standard deviation respectively. In *Figure 2*, it appears that as the number of paclitaxel doses increases, the score of the control group increases more than that of the lafutidine group. Especially, the median FACT/GOG-Ntx score after the fourth cycle was higher in the control group than in the lafutidine group, but the difference was not significant (P=0.17). No patients were taken off paclitaxel due to adverse events, and 3 patients in the two groups had the paclitaxel dose reduced. The median time to the appearance of grade 2 or higher neuralgia was 3.0 cycles in the lafutidine group and 3.5 cycles in the control group (P=0.67). The median time to the appearance of grade 2 or higher peripheral sensory neuropathy was 3.22 cycles in lafutidine group and 3.20 cycles in the control group (P=0.97). Median PFS in lafutidine group tended to be shorter than that in the control group, but the difference was not statistically significant (147 *vs.* 217.5 days, P=0.71; *Figure 3*). However, the median RR was 78% in the lafutidine group and 85% in the control group, which was not significantly different (P>0.99). There were no adverse events due to lafutidine administration.

Table 1 Baseline characteristics

Characteristics	All (n=16)	Lafutidine group (n=9)	Control group (n=7)
Age, years, median [range]	71 [62–77]	68 [64–74]	73 [69–77]
Sex, n (%)			
Male	15 (93.8)	9 (100.0)	6 (85.7)
Female	1 (6.3)	0	1 (14.3)
ECOG performance status, n (%)			
0	11 (68.8)	6 (66.7)	5 (71.4)
1	5 (31.3)	3 (33.3)	2 (28.6)
Smoking status, n (%)			
Current or former	15 (93.8)	9 (100.0)	6 (85.7)
Never	1 (6.3)	0	1 (14.3)
Histologic features, n (%)			
Squamous	10 (62.5)	6 (66.7)	4 (66.7)
Adeno	1 (6.3)	0	1 (14.3)
Undetermined NSCLC	5 (31.3)	3 (33.3)	2 (28.6)
Activating mutation (driver gene), n (%)			
EGFR	1 (6.3)	0	1 (14.3)
PD-L1 expression, n (%)			
<1%	6 (37.5)	4 (44.4)	2 (28.6)
1–49%	2 (12.5)	2 (22.2)	0
≥50%	4 (25.0)	2 (22.2)	2 (28.6)
Not inspected	4 (25.0)	1 (11.1)	3 (33.3)
Post-operative recurrence, n (%)	2 (12.5)	1 (11.1)	1 (14.3)
Disease stage, n (%)			
I	1(6.3)	0	1 (14.3)
II	4 (25.0)	1 (11.1)	3 (42.9)
III	4 (25.0)	3 (33.3)	1 (14.3)
IV	7 (43.8)	5 (55.6)	2 (28.6)
Total dose (median), mg			
Carboplatin	2,157	2,087	2,247
Paclitaxel	1,143	1,143	1,143
Total cycles, n			
1 cycle/2 cycles/3 cycles/4 cycles	1/2/0/13	0/2/0/7	1/0/0/6
Dose reduction, n (%)	6 (37.5)	3 (33.3)	3 (42.9)
Metastatic site, n (%)			
Brain	2 (12.5)	2 (22.2)	0
Bone	2 (12.5)	2 (22.2)	0
Liver	0	0	0
Adrenal	1 (6.3)	0	0
Pleura	5 (31.3)	3 (33.3)	2 (28.6)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death ligand 1.

Table 2 Comparison of peripheral neuropathy in CTCAE version 5.0 between lafutidine and control groups

Peripheral neuropathy	Lafutidine group (n=9)	Control group (n=7)	P value
Grade ≥2 neuralgia, n (%)	2 (22.2)	1 (14.3)	>0.99
Grade ≥2 peripheral sensory neuropathy, n (%)	9 (100.0)	5 (71.4)	0.18

CTCAE, Common Terminology Criteria for Adverse Events.

Table 3 Comparison of the median peripheral neuropathy score on PNQ between lafutidine and control groups

Peripheral neuropathy	Lafutidine group	Control group	*t*	P value
PNQ sensory				
Baseline	0.22±0.44	0.14±0.38	0.38	0.71
Cycle 2	0.75±0.46	0.50±0.55	0.93	0.37
Cycle 3	1.89±0.93	1.17±0.98	1.44	0.17
Cycle 4	1.17±0.41	1.50±1.05	−0.73	0.48
After cycle 4	1.33±0.82	1.60±1.14	−0.45	0.66
PNQ motor				
Baseline	0.11±0.33	0.57±0.79	−1.59	0.13
Cycle 2	0.50±0.53	0.50±0.84	0	>0.99
Cycle 3	0.78±0.83	0.50±0.84	0.63	0.54
Cycle 4	0.67±0.52	1.17±1.17	−0.96	0.36
After cycle 4	0.50±0.84	0.80±0.84	−0.59	0.57

Median scores are shown with ± standard deviation respectively. PNQ, Patient Neurotoxicity Questionnaire.

Table 4 Comparison of median peripheral neuropathy scores on FACT/GOG-Ntx between lafutidine and control groups

Peripheral neuropathy	Lafutidine group	Control group	*t*	P value
FACT/GOG-Ntx				
Baseline	1.11±0.93	1.57±1.81	−0.66	0.52
Cycle 2	2.38±2.32	3.50±2.81	−0.82	0.43
Cycle 3	6.00±4.63	4.67±4.37	0.55	0.59
Cycle 4	4.33±3.72	7.00±4.73	−1.08	0.30
After cycle 4	4.67±4.46	9.60±6.50	−1.50	0.17

Median scores are shown with ± standard deviation respectively. FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity.

Discussion

Our study was a randomized, open-label, prospective, interventional study. To the best of our knowledge, this is the first study to prospectively evaluate the preventive effect of lafutidine on CIPN. According to the results of the FACT/GOG-Ntx in our study, administration of lafutidine may have some effect in preventing CIPN, but this effect could not be proven statistically.

Lafutidine is an H_2 blocker that stimulates sensory neurons for capsaicin to release calcitonin gene-related peptide (CGRP), which increases blood flow to the gastric mucosa and protects and repairs the gastric mucosa by producing nitric oxide (NO) (18). Unlike other H_2 blockers,

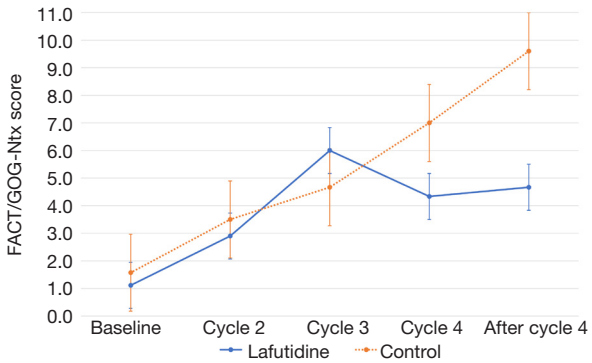

Figure 2 FACT/GOG-Ntx median score. The lafutidine group is shown by the blue line. The control group had higher median scores of FACT/GOG-Ntx than the lafutidine group after cycle 4. There was no significant difference in the scores between the two groups during the entire period. FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity.

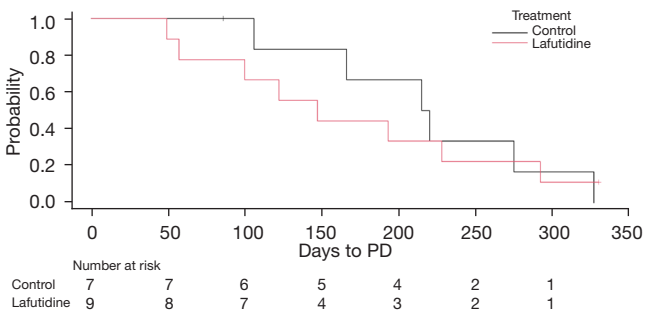

Figure 3 PFS analysis of the two groups using Kaplan-Meier curves. The lafutidine group is shown by the red line. PFS was assessed according to version 1.1 of the RECIST. There was no significant difference in PFS between the two groups. PD, progressive disease; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

lafutidine indirectly induces the TRPV1 receptor, and continued desensitization can block the sensory nerve excitatory response and hyperalgesia (18). As an example of the effects mediated by TRPV1, topical capsaicin showed some efficacy in analgesia of chronic nerve pain in adults (31,32). A study of 20 patients with peripheral neuropathy induced by taxane drugs during treatment of gynecological malignancies, administered orally with lafutidine, found that the drug was effective in 45% of patients (20). Since lafutidine is already available under health insurance in Japan and has been administered, is inexpensive, and has few side effects, if it is effective for CIPN then it may be widely adopted as a prophylactic drug for CIPN.

The results of this study, especially on the CTCEA and PNQ, did not show a statistically superior effect of lafutidine on prevention of CIPN. Rather, grade 2 or higher peripheral sensory neuropathy in CTCAE was more common in the lafutidine group than in the control group. On the other hand, FACT/GOG-Ntx tended to show less peripheral neuropathy in the lafutidine group than in the control group but this did not reach statistical significance possibly due to the study being underpowered as only 16 patients of the planned for 40 patients were recruited. Since the FACT/GOG-Ntx questions were more relevant to daily life than the CTCAE and PNQ questions, it is possible that the FACT/GOG-Ntx scores were more likely to reflect severity of peripheral neuropathy. Lafutidine did not delay the development of CIPN and did not affect the efficacy of chemotherapy in this study. We expected lafutidine to have a favorable effect on chemotherapy and its antitumor effect, but the small number of cases did not enable us to evaluate the effect of lafutidine on efficacy of chemotherapy.

This study had some limitations. The study did not use placebo and was not blinded in the assessment of peripheral neuropathy. The lack of placebo may have influenced the assessment of peripheral neuropathy. Our study had a small sample size and the number of patients included in the analysis fell short of the target number. One of the reasons for the difficulty in enrolling patients was the development of nab-paclitaxel. Nab-paclitaxel is a paclitaxel conjugated to human serum albumin, which eliminates the need for ethanol or other solvents. The combination of carboplatin and nab-paclitaxel is known to cause less peripheral neuropathy than the combination of carboplatin and paclitaxel (4). The KEYNOTE 407 study in patients with stage IV squamous non-small cell lung cancer and the IMpower130 study in patients with stage IV non-small cell lung cancer showed the efficacy of the treatment as first-line therapy and nab-paclitaxel was used in both studies (33,34). The increased use of nab-paclitaxel-based chemotherapy may be reducing the opportunity for clinicians to select paclitaxel-based chemotherapy for patients predisposed to developing peripheral neuropathy.

Conclusions

Although this study was not able to recruit the target number of patients, it did reveal the possibility that

lafutidine may reduce chemotherapy-induced neurotoxicity. CIPN has a significant impact on the quality of life and treatment efficacy of patients receiving chemotherapy, and more reliable studies using lafutidine on the prevention of CIPN should be conducted.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-23-90/rc

Trial Protocol: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-90/tp

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-90/dss

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-90/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-90/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Certified Review Board of Iwate Medical University (No. SCR2020-101). Patients and their families were informed of the study, and all participants provided written informed consent before the study commenced.

References

1. Loprinzi CL, Reeves BN, Dakhil SR, et al. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. J Clin Oncol 2011;29:1472-8.
2. Loprinzi CL, Maddocks-Christianson K, Wolf SL, et al. The Paclitaxel acute pain syndrome: sensitization of nociceptors as the putative mechanism. Cancer J 2007;13:399-403.
3. Sakakibara T, Inoue A, Sugawara S, et al. Randomized phase II trial of weekly paclitaxel combined with carboplatin versus standard paclitaxel combined with carboplatin for elderly patients with advanced non-small-cell lung cancer. Ann Oncol 2010;21:795-9.
4. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012;30:2055-62.
5. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain 2014;155:2461-70.
6. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol 2020;38:3325-48.
7. Mols F, Beijers T, Vreugdenhil G, et al. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. Support Care Cancer 2014;22:2261-9.
8. Bonhof CS, van de Poll-Franse LV, Vissers PAJ, et al. Anxiety and depression mediate the association between chemotherapy-induced peripheral neuropathy and fatigue: Results from the population-based PROFILES registry. Psychooncology 2019;28:1926-33.
9. Battaglini E, Goldstein D, Grimison P, et al. Chemotherapy-Induced Peripheral Neurotoxicity in Cancer Survivors: Predictors of Long-Term Patient Outcomes. J Natl Compr Canc Netw 2021;19:821-8.
10. Campone M, Berton-Rigaud D, Joly-Lobbedez F, et al. A

double-blind, randomized phase II study to evaluate the safety and efficacy of acetyl-L-carnitine in the prevention of sagopilone-induced peripheral neuropathy. Oncologist 2013;18:1190-1.
11. Greenlee H, Crew KD, Capodice J, et al. Randomized sham-controlled pilot trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in women with early stage breast cancer. Breast Cancer Res Treat 2016;156:453-64.
12. Guo Y, Jones D, Palmer JL, et al. Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. Support Care Cancer 2014;22:1223-31.
13. Jordan B, Jahn F, Beckmann J, et al. Calcium and Magnesium Infusions for the Prevention of Oxaliplatin-Induced Peripheral Neurotoxicity: A Systematic Review. Oncology 2016;90:299-306.
14. Glimelius B, Manojlovic N, Pfeiffer P, et al. Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx(®)): a placebo-controlled randomised phase II study (PLIANT). Acta Oncol 2018;57:393-402.
15. Chow R, Novosel M, So OW, et al. Duloxetine for prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN): systematic review and meta-analysis. BMJ Support Palliat Care 2023;13:27-34.
16. Tominaga M. TRPV1 in gastrointestinal organs. Nihon Yakurigaku Zasshi 2006;128:78-81.
17. Mita A, Yamana J, Kodo M. A case of paclitaxel-induced peripheral neuropathy successfully treated with lafutidine and tocoferol nicotinate. Palliative Care Research 2015;10:548-51.
18. Numazaki M, Tominaga T, Takeuchi K, et al. Structural determinant of TRPV1 desensitization interacts with calmodulin. Proc Natl Acad Sci U S A 2003;100:8002-6.
19. Matsumura T, Imamura H, Kishimoto T, et al. A case of paclitaxel-induced peripheral neuropathy successfully treated by H2-blocker, lafutidine. Gan To Kagaku Ryoho 2009;36:1565-8.
20. Nagano H, Sanai H, Muraoka M, et al. Efficacy of lafutidine, a histamine H2-receptor antagonist, for taxane-induced peripheral neuropathy in patients with gynecological malignancies. Gynecol Oncol 2012;127:172-4.
21. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008;26:468-73.
22. Hausheer FH, Schilsky RL, Bain S, et al. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. Semin Oncol 2006;33:15-49.
23. Shimozuma K, Ohashi Y, Takeuchi A, et al. Feasibility and validity of the Patient Neurotoxicity Questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02. Support Care Cancer 2009;17:1483-91.
24. Kuroi K, Shimozuma K, Ohashi Y, et al. Prospective assessment of chemotherapy-induced peripheral neuropathy due to weekly paclitaxel in patients with advanced or metastatic breast cancer (CSP-HOR 02 study). Support Care Cancer 2009;17:1071-80.
25. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 2003;13:741-8.
26. Huang HQ, Brady MF, Cella D, et al. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer 2007;17:387-93.
27. Castellino SM, Rodday AM, Pei Q, et al. Performance of FACT-GOG-Ntx to assess chemotherapy-induced peripheral neuropathy (CIPN) in pediatric Hodgkin lymphoma (HL) patients. J Clin Oncol 2019;37:10064.
28. Li T, Park SB, Battaglini E, et al. Assessing chemotherapy-induced peripheral neuropathy with patient reported outcome measures: a systematic review of measurement properties and considerations for future use. Qual Life Res 2022;31:3091-107.
29. Noda K, Ikeda M, Kudo R, et al. Phase II study of paclitaxel (BMS-181339) in patients with ovarian cancer by 3-hour intravenous infusion. Gan To Kagaku Ryoho 1996;23:317-25.
30. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-8.
31. Derry S, Lloyd R, Moore RA, et al. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2009;(4):CD007393.
32. Derry S, Sven-Rice A, Cole P, et al. Topical capsaicin (high

concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2013;(2):CD007393.
33. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924-37.
34. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.

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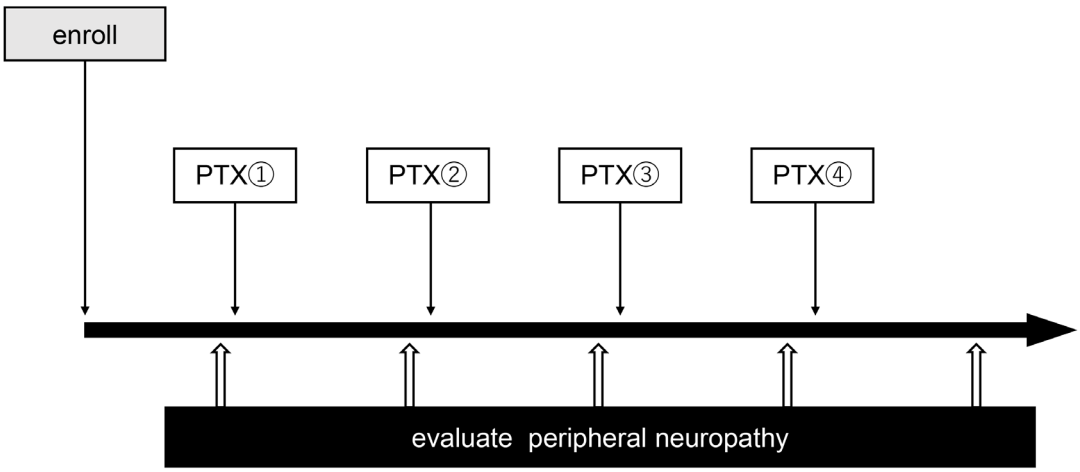

Figure S1 Timing of peripheral neuropathy assessment. Peripheral neuropathy was assessed five times: before treatment (baseline), before each paclitaxel dose, and 3–4 weeks after the fourth cycle of paclitaxel. All patients received carboplatin in addition to paclitaxel. PTX, paclitaxel.

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