Original Article

Identification of risk factors related to problematic peripheral neuropathy development in gemcitabine and nab-paclitaxel treatment for pancreatic cancer

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ABSTRACT

Purpose

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect in patients treated with gemcitabine (GEM) and nanoparticle albumin-bound paclitaxel (nab-PTX) for pancreatic cancer, negatively impacting their quality of life. This study aimed to identify risk factors for significant CIPN development in a real-world setting of GEM + nab-PTX treatment to inform effective management strategies.

Methods

Patients with unresectable pancreatic cancer who received GEM + nab-PTX (n=140) were retrospectively assessed. The primary endpoint was to identify the risk factor(s) associated with the development of problematic grade ≥2 CIPN within six months of treatment initiation. We also evaluated factors associated with all-grade CIPN and compared CIPN incidence across specific patient groups.

Results

The incidence of grade ≥2 CIPN was 35.0%, with 63.6% of patients experiencing symptoms of any grade. Multivariate Cox proportional hazard regression analysis identified baseline preexisting neuropathy as an independent risk factor for developing grade ≥2 CIPN (adjusted hazard ratio 4.03, 95% confidence interval 1.82–8.96,

P=0.0006). Conversely, dose modification of nab-PTX at or within four weeks of treatment initiation emerged as a protective factor (0.45, 0.22–0.91, *P*=0.03). Additionally, the cumulative incidence of grade ≥2 CIPN was significantly lower and delayed in patients who underwent dose modification within four weeks compared to those who did not in the population with preexisting neuropathy (*P*=0.01).

Conclusion

Baseline preexisting neuropathy significantly increases the risk, while early dose modification of nab-PTX serves as a protective factor against developing grade ≥2 CIPN in patients receiving GEM + nab-PTX treatment for pancreatic cancer.

Key words: gemcitabine; nab-paclitaxel; peripheral neuropathy; chemotherapy-induced peripheral neuropathy; risk factor; pancreatic cancer

Introduction

The prevalence of pancreatic cancer is increasing and most patients are in advanced stages at the time of diagnosis due to the difficulty in detection [1]. Chemotherapy is the main treatment strategy for locally advanced or metastatic pancreatic cancer [2, 3]. However, the treatment of pancreatic cancer presents challenges as it is less responsive to anti-cancer agents compared to other malignancies, and the 5-year survival rate among metastatic patients is less than 5% [4]. Therefore, it is important to focus on maintaining the quality of life (QOL) of patients as well as treatment efficacy.

The combination of gemcitabine (GEM) and nanoparticle albumin-bound paclitaxel (nab-PTX) is one of the most effective chemotherapeutic regimens for the treatment of locally advanced or metastatic pancreatic cancer [5, 6]. However, this treatment induces adverse effects such as neutropenia, thrombocytopenia, rash, fever, edema, and peripheral neuropathy. Notably, chemotherapy-induced peripheral neuropathy (CIPN) caused by nab-PTX occurs in over 50% of treated patients, including approximately 20% with severe cases, significantly reducing their activities of daily living (ADL) and QOL and necessitating dosage adjustments of nab-PTX [5–8]. The most common presentation of CIPN includes sensory symptoms such as numbness, paresthesia, ongoing/spontaneous pain, and hypersensitivity to mechanical stimuli in their hands and

feet [9].

The dose and duration of chemotherapy, treatment schedule, and combination therapy are treatment-associated CIPN risk factors [10]. Individual factors such as being female, old, having anemia, a higher body mass index (BMI), complications of diabetes mellitus, a history of smoking, alcohol intake, hypoalbuminemia, hypomagnesemia, concurrent exposure to other neurotoxic agents, and pre-existing neuropathy, as well as diseases/deficiencies that predispose to neuropathy such as renal insufficiency, hypothyroidism, vitamin deficiencies, infections, and autoimmune rheumatologic conditions are also associated with CIPN development [10–17]. Catalano et al. reported that patient age and the number of treatment cycles are associated with all-grade CIPN development in this regimen [18]. However, as grade 1 CIPN generally does not require pharmacotherapy, it is meaningful that grade ≥2 symptoms, which definitely require medication or dose modification of the suspected drug, are evaluated for their risk factors for early detection and intervention.

In this study, we aimed to assess risk factors related to the development of grade ≥2 CIPN in a real-world setting of GEM + nab-PTX treatment of pancreatic cancer.

Patients and Methods

1. Patients

Patients with unresectable pancreatic cancer receiving GEM + nab-PTX treatment at Hokkaido University Hospital from March 2015 to May 2023 were enrolled in this retrospective observational study. The baseline inclusion criteria were: (1) age ≥20 years; (2) Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 to 2; (3) absolute neutrophil count $\geq 1.5 \times 10^3$ cells/μL and platelet count $\geq 7.0 \times 10^4$ cells/μL; (4) sufficient liver and renal function for the treatment induction; and (5) comprehensive patient information available from medical records. We did not consider the presence or absence of postoperative recurrence. Patients were excluded if they had grade ≥2 neuropathy at baseline, had received taxanes prior to this treatment, were transferred to another hospital during the treatment, were unable to complete the first cycle of treatment, or had a first cycle treatment schedule that deviated from the original regimen. We estimated a sample size of 140–150 based on an anticipated 40% incidence of grade ≥2 CIPN, which is the primary symptom studied, and the inclusion of approximately six covariates in the multivariate analysis, guided by previous studies and our clinical experience [5, 7, 18, 19].

This study was approved by the Ethical Review Board for Life Science and Medical Research of Hokkaido University Hospital (approval number: 023-0360) and was

conducted in accordance with the Declaration of Helsinki and the STROBE statement. Due to the retrospective nature of this study, the requirement for informed consent was waived by the Ethical Review Board for Life Science and Medical Research of Hokkaido University Hospital.

2. Treatment methods

GEM (1000 mg/m²) and nab-PTX (125 mg/m²) were intravenously administered on days 1, 8, and 15 of each 4-week cycle [5, 6]. Prior to chemotherapy, intravenous palonosetron (0.75 mg) and dexamethasone (9.9 mg) were typically administered in line with national antiemetic guidelines [20]. Treatment adjustments, including deferrals or discontinuations, were made based on adverse effects, according to the criteria outlined in the medical package insert [21]. Additional treatments for neuropathy, such as duloxetine, pregabalin, and mirogabalin, were used in monotherapy or combination therapy to alleviate symptoms.

3. Evaluation of CIPN

All necessary data were collected from the participants' medical records. The incidence and severity of neuropathic symptoms were assessed by physicians or pharmacists using the treatment diaries, patients' complain records, and medical interviews. These assessments followed the Common Terminology Criteria for Adverse

127 Events (CTCAE), version 5.0, at each visit, and the highest grade of symptoms noted
128 was recorded. Peripheral neuropathy in this study was defined as the development of
129 new neuropathic symptoms in the extremities in patients without baseline neuropathy
130 and symptom worsening post GEM + nab-PTX treatment in those with baseline
131 neuropathy, referencing prior study and guidelines [22, 23]. The primary endpoint was
132 identifying risk factors for the development of CTCAE grade ≥2 CIPN. Secondary
133 endpoints included the assessment of factors associated with defined CIPN and the
134 comparison of CIPN incidence among specific patient groups. By referring to previous
135 studies, the evaluation period for this study was set for 6 months from the initiation of
136 treatment [18, 24].
137 4. Statistical analysis
138 Univariate and multivariate Cox proportional hazard regression analyses were
139 conducted to identify independent risk factors associated with the development of CIPN
140 within 6 months. The potential baseline clinical variables considered included sex, age,
141 prior treatment history, previous oxaliplatin administration, body surface area (BSA),
142 BMI, anemia, hypoalbuminemia, liver dysfunction (grade 2 or higher elevation in
143 aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels), renal
144 dysfunction (creatinine clearance less than 60 mL/min calculated by the Cockcroft-

Gault formula), smoking history, regular alcohol consumption (≥5 days per week), complications of cardiovascular disease and diabetes mellitus (requiring pharmacotherapy), presence of baseline peripheral neuropathy, regular use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, and dose modification of nab-PTX within 4 weeks from treatment initiation (dose reductions either within 4 weeks from the start or from the initiation of treatment), aligning with previous reports [5, 7, 10, 11, 18, 19]. Variables that demonstrated potential associations in the univariate analysis (P<0.20) were included in the multivariate model. Differences in baseline clinical characteristics between patients with and without grade ≥2 CIPN during GEM + nab-PTX were compared using Fisher's exact probability test for categorical variables and the Mann–Whitney U test for continuous variables. The incidence of CIPN across specific patient groups was compared using the log-rank test.

All analyses were performed using JMP version 16.1 statistical software (SAS Institute Japan, Tokyo, Japan). Differences were considered statistically significant at P-values <0.05.

Results

1. Patient characteristics

In total, 140 patients with unresectable pancreatic cancer were enrolled based on the eligibility criteria of this study (Fig. 1). The baseline characteristics of the patients are detailed in Table 1. Approximately 40% of the patients were female, and 27.1% had received prior treatment, including 13.6% who had received oxaliplatin. The median serum albumin level was 3.8 g/dL (range: 2.3–4.9 g/dL). Patients with a complication of diabetes mellitus accounted for 27.9%, and those with baseline peripheral neuropathy made up 17.1%, with 6 out of these 24 patients receiving medication such as pregabalin or mirogabalin. Patients regularly taking NSAIDs or opioids were 38.6% and 27.1%, respectively. A dose reduction from the initiation of treatment was noted in 10.7% of patients (this included a reduction in nab-PTX at the same rate).

2. Incidence of CIPN

The incidence of grade ≥2 CIPN was 35.0%, and defined symptoms were confirmed in 63.6% of the patients, as shown in Table 2. Patients experiencing grade 3 symptoms accounted for 4.3%, and no cases of grade 4 were observed. The median onset time for defined and grade ≥2 symptoms was 43 days (range: 1–180 days) and 84 days (range: 14–155 days), respectively. The median cumulative nab-PTX dose at the development of defined and grade ≥2 CIPN was 500 (range; 100–2,625) and 1,125 (125–2,875) mg/m^2, respectively. Treatment for CIPN was administered to 35.0% of patients. Dose

modification of nab-PTX during the 6-month period was noted in 73.6% of patients, including 22.1% where the modification was due to CIPN.

3. Risk factor analyses for CIPN development

Multivariate Cox proportional hazard regression analyses indicated that baseline preexisting neuropathy (all symptoms were grade 1) was an independent risk factor for the development of grade ≥2 CIPN in treatments involving GEM and nab-PTX, with an adjusted hazard ratio of 4.03 (95% confidence interval [CI]: 1.82–8.96, *P*=0.0006, Table 3A). Conversely, dose modification of nab-PTX, either from treatment initiation or within 4 weeks from the start, was identified as a preventive factor (adjusted hazard ratio: 0.45, 95% CI: 0.22–0.91, *P*=0.03). Additionally, risk factors for the development of defined CIPN were evaluated, revealing baseline diabetes complication as a singular risk factor (adjusted hazard ratio: 1.96, 95% CI: 1.23–3.11, *P*=0.004, Table 3B). Although not statistically significant, baseline preexisting neuropathy showed a tendency toward association with defined symptom development (*P*=0.08). Previous oxaliplatin administration did not affect the incidence of both defined and grade ≥2 CIPN.

4. Effect of nab-PTX dose modification within 4 weeks of treatment initiation on the development of CIPN in patients with baseline preexisting neuropathy

199 The impact of dose modification of nab-PTX within 4 weeks from treatment initiation
200 on the development of CIPN in patients with preexisting neuropathy was further
201 assessed. The cumulative incidence of grade ≥2 CIPN was significantly lower and
202 delayed in patients who underwent dose modification compared to those who did not
203 (median days with 95% CI: not reached with 49 days–not reached for patients with the
204 modification, and 63 days with 29–96 days in those without; *P*=0.01). However, the
205 incidence of defined all-grade CIPN did not show significant differences between the
206 two groups (70 days with 95% CI of 7 days–not reached and 39 days with 16–63 days,
207 respectively; *P*=0.11).
208 5. Detailed baseline preexisting neuropathy and treatment-induced grade ≥2 CIPN
209 As described previously, baseline preexisting neuropathy was identified as a risk
210 factor for grade ≥2 CIPN. Baseline neuropathy was caused by previously administered
211 oxaliplatin (50.0%), orthopedic factors (33.3%), diabetes mellitus (12.5%), and cancer-
212 related pain (4.2%). As oxaliplatin is occasionally administered prior to GEM + nab-
213 PTX, we additionally assessed the incidence of the grade ≥2 CIPN between those with
214 and without oxaliplatin-induced CIPN in the population with baseline neuropathy. As a
215 result, median onset time of grade ≥2 CIPN did not differ between neuropathic patients
216 with and without oxaliplatin origin (median onset time [95% CI]; 77 [42–105] days and

83 [29–not reached] days, respectively, *P*=0.65).

Discussion

The development of CIPN in patients undergoing GEM and nab-PTX treatment not only decreases their QOL and ADL during the treatment period but also affects subsequent therapies. The emergence of CIPN is influenced by a complex interplay of treatment-associated and individual factors, and its characteristics vary between different chemotherapeutic agents [25]. Given that CIPN can persist for a period after the cessation of the causative treatment and often becomes irreversible, it is crucial to identify high-risk individuals early for appropriate intervention. This study aimed to identify factors associated with problematic CIPN development in GEM + nab-PTX treatment for pancreatic cancer in a real-world setting.

Our findings indicate that baseline-existing neuropathy is an independent risk factor for the development of grade ≥2 CIPN, while dose modification of nab-PTX within the first 4 weeks of treatment serves as a preventive factor. Additionally, the presence of diabetes mellitus was identified as a risk factor for defined CIPN. To the best of our knowledge, this is the first report that evaluates risk factors for problematic grade ≥2 CIPN specifically in GEM + nab-PTX treatment.

All patients with baseline neuropathy who developed problematic CIPN induced by nab-PTX exhibited symptoms at the same site as in their baseline symptoms. Additionally, onset time of grade ≥2 CIPN did not differ between neuropathic patients with and without oxaliplatin origin. Therefore, we can infer that patients with baseline neuropathy from any cause are at higher risk for problematic CIPN with this regimen. In contrast, pretreatment with oxaliplatin was not identified as a risk factor for nab-PTX-induced CIPN. The incidence of GEM + nab-PTX-induced grade ≥2 CIPN was similar between oxaliplatin-induced CIPN and other baseline neuropathy in patients with baseline neuropathy, which suggests patients with oxaliplatin-induced baseline neuropathy are at high risk for grade ≥2 CIPN in GEM + nab-PTX. In contrast, in the population without baseline neuropathy, the incidence of grade ≥2 CIPN in patients receiving prior oxaliplatin was lower than that in those without prior oxaliplatin administration (14.3% and 30.3%, respectively), although this difference was not statistically significant owing to less power. Consequently, we consider that patients with less oxaliplatin-induced CIPN may be less likely to develop nab-PTX-induced CIPN, although detailed mechanisms of taxane- or platinum-induced CIPN differ [25]. However, as there was less power to assess, further studies with sufficient number of participants are required. As for diabetes, we additionally assessed the impact of insulin

253 use considering the severity in the diabetic population, which resulted in non-influence
254 (data not shown). However, we were unable to assess symptom duration owing to data
255 unavailability, requiring further evaluation.
256 The dose-limiting toxicities of this regimen are sepsis and neutropenia [27], with
257 severe neutropenia often necessitating dose reductions or suspension of treatment [28].
258 We have previously reported that 47% of patients required a treatment suspension due
259 to severe neutropenia during the first cycle, leading to early dose modifications [28].
260 Consequently, we evaluated the impact of nab-PTX dose modification during the first
261 cycle on the development of problematic CIPN. This modification was made in 37.1%
262 of patients and resulted in a decrease in the incidence of grade ≥2 symptoms due to
263 early nab-PTX dose reduction. Additionally, we assessed the effect of this modification
264 on grade ≥2 CIPN development in patients with preexisting neuropathy, which revealed
265 an attenuation of symptoms in dose-modified patients. However, it remains unclear how
266 dose or schedule modifications affect cumulative CIPN, necessitating further evaluation
267 of the administration methods of nab-PTX on CIPN.
268 Interestingly, the risk factors identified for defined all-grade and grade ≥2 CIPN
269 differed. While the reasons for these differences are unknown, we speculate that early
270 treatment for CIPN or adjustments to the nab-PTX dose or treatment schedule might

have influenced the outcomes. Additionally, baseline peripheral neuropathy was identified as a risk factor for grade ≥2 CIPN but not for all-grade symptoms. This shows that patients with preexisting neuropathy can experience mild symptom degradation as well as those without the symptoms, but can develop significantly higher grade ≥2 problematic symptoms. We consider that the results were derived from the fact that most of the patients receiving this treatment regimen develop at least grade 1 symptoms or less power. Regarding diabetes, as only 7.7% of the patients with diabetes had baseline neuropathy, very slight baseline asymptomatic neuropathy in patients with diabetes may have contributed to all-grade symptom development but not grade ≥2 symptom development. Furthermore, our findings regarding defined all-grade CIPN differed from those of a previous study [18]; differences in study populations, including pretreatment factors, ethnic variations, or the prevalence of diabetes, might explain these results. Therefore, we should consider CIPN incidence and severity separately and remain cognizant of the differences between studies.

The only recommended treatment for CIPN in the guidelines is duloxetine, although gabapentin, pregabalin, and mirogabalin are also considered viable options [10, 22, 23, 29–32]. Early interventions, such as adjusting the dosage of the suspected drug or administering medication, may mitigate symptoms, leading to long and less burdensome

289 treatment. Therefore, further evaluation of these treatments, particularly in terms of
290 combining medications or improving administration methods with few adverse effects
291 like sleepiness, dizziness, and nausea, is essential for enhancing treatment quality.
292 This study has several limitations. First, it was conducted retrospectively and involved
293 a relatively small patient population from a single institution. Second, patients with
294 early-stage cancer were excluded, and the evaluation period was limited to six months
295 from treatment initiation, indicating that our findings were derived from a restricted
296 dataset. Additionally, this study included patients with prior surgery or chemotherapy.
297 Therefore, we additionally assessed factors in chemotherapy-naïve patients without
298 recurrence, which resulted in the same outcomes although power was less than the
299 initial evaluation (data not shown). Further evaluation in the selected population with
300 sufficient power will provide better comprehension. Third, characteristics of CIPN
301 induced by taxanes or platinums are different owing to differing mechanisms [25, 33].
302 Additionally, combination therapy is also a potential risk factor for CIPN [10] and the
303 dose of nab-PTX varies in each treatment [21]. Thus, present results can differ from
304 those in other treatment regimens, which requires further evaluation. Finally, while we
305 employed an objective-based evaluation of CIPN in this retrospective study, a
306 subjective assessment by patients using the Numerical Rating Scale (NRS) or Visual

Analogue Scale (VAS) could provide new findings. Consequently, these preliminary findings need to be confirmed in future studies.

In conclusion, we found that baseline preexisting neuropathy is a risk factor and that dose modification of nab-PTX within the first 4 weeks of treatment initiation serves as a preventive factor for problematic grade ≥2 CIPN development in GEM + nab-PTX treatment for pancreatic cancer. Further evaluation of CIPN management strategies is necessary to provide less burdensome treatment.

Statements and Declarations

Funding: None.

Conflict of Interest: YS, YT, and MS have no conflicts of interest. YK reports grants and personal fees from Ono, Taiho, Chugai, Eli Lilly, Daiichi Sankyo, Nippon Kayaku, and MSD; personal fees from Bayer and Yakult; and grants from IQVIA, Astellas, Nippon Zoki, Shionogi, EPS, Eisai, and the National Cancer Center outside of the submitted work.

Ethical approval: All procedures involving human participants performed in this study were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was waived by the Ethical Review Board for Life Science and Medical Research of the Hokkaido University Hospital.

Consent to participate: For this type of study, formal consent was not required.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Authors' contributions:

Participated in research design: YS.

Conducted experiments: YS.

Performed data analysis: YS.

Wrote the paper: YS.

All authors have read and approved the manuscript.

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469 **Table 1** Patient characteristics

	All patients (n=140)	Without grade ≥2 CIPN (n=91)	With grade ≥2 CIPN (n=49)	*P*-value
Sex (male/female)	88/52	61/30	27/22	0.20
Age (median, range)	69 (38–81)	69 (38–81)	69 (42–80)	0.59
Performance status (ECOG)				
0-1	140	91	49	-
Location of primary tumor (n, %)				
Pancreatic head	57 (40.7%)	38 (41.8%)	19 (38.8%)	
Pancreatic body	47 (33.6%)	30 (33.0%)	17 (34.7%)	
Pancreatic tail	29 (20.7%)	17 (18.7%)	12 (24.5%)	
Others	7 (5.0%)	6 (6.6%)	1 (2.0%)	-
Staging (n, %)				
IIB	1 (0.7%)	0 (0%)	1 (2.0%)	-
III	9 (6.4%)	5 (5.5%)	4 (8.2%)	-
IV	110 (78.6%)	70 (76.9%)	40 (81.6%)	-
Recurrence	20 (14.3%)	16 (17.6%)	4 (8.2%)	0.20
Treatment line (n, %)				
First line	102 (72.9%)	67 (73.6%)	35 (71.4%)	
Second or later line	38 (27.1%)	24 (26.4%)	14 (28.6%)	0.84

History of oxaliplatin administration (n, %)	19 (13.6%)	10 (11.0%)	9 (18.4%)	0.30
BSA (m^2) (median, range)	1.58 (1.19–2.18)	1.59 (1.19–2.18)	1.57 (1.24–2.14)	0.77
BMI (kg/m^2) (median, range)	21.16 (14.81–34.99)	21.4 (14.8–35.0)	20.8 (17.1–31.2)	0.64
Neutrophil (/μL) (median, range)	4,003 (1,705–9,984)	4,008 (1,705–9,856)	3,858 (1,881–9,984)	0.97
Number of less than LLN (n, %)	3 (2.1%)	1 (1.1%)	2 (4.1%)	0.28
Hb (g/dL) (median, range)	12.2 (7.4–17.6)	12.0 (7.4–17.6)	12.2 (8.0–16.6)	0.72
Number of less than LLN (n, %)	85 (60.7%)	57 (62.6%)	28 (57.1%)	0.59
Plt ($\times 10^3/\mu L$) (median, range)	217 (72–584)	203 (72–543)	235 (82–584)	0.40
Number of less than LLN (n, %)	26 (18.6%)	17 (18.7%)	9 (18.4%)	1.00
Albumin (g/dL) (median, range)	3.8 (2.3–4.9)	3.8 (2.3–4.9)	3.9 (2.4–4.6)	0.72
Number of less than LLN (n, %)	93 (66.4%)	59 (64.8%)	34 (69.4%)	0.71
Liver dysfunction (n, %)	7 (5.0%)	4 (4.4%)	3 (6.1%)	0.70
Creatinine clearance (mL/min) (median, range)	76.4 (31.9–251.6)	75.7 (31.9–186.1)	78.9 (33.3–251.6)	0.54
Cardiovascular disease (n, %)	57 (40.7%)	35 (38.5%)	22 (44.9%)	0.48
Diabetes mellitus (n, %)	39 (27.9%)	23 (25.3%)	16 (32.7%)	0.43
Peripheral neuropathy (n, %)	24 (17.1%)	9 (9.9%)	15 (30.6%)	0.004**
Administration of regular NSAIDs (n, %)	54 (38.6%)	34 (37.4%)	20 (40.8%)	0.72
Administration of regular opioids (n, %)	38 (27.1%)	24 (26.4%)	14 (28.6%)	0.84
Smoking history (n, %)				
Never	54 (38.6%)	36 (39.6%)	18 (36.7%)	
Current or former smoker	86 (61.4%)	55 (60.4%)	31 (63.3%)	0.86
Regular alcohol intake (5 days/week) (n, %)	51 (36.4%)	36 (39.6%)	15 (30.6%)	0.36
Dose reduction of nab-PTX from the initiation	15 (10.7%)	13 (14.3%)	2 (4.1%)	0.09

(n, %)				

**P <0.01

ECOG, Eastern Cooperative Oncology Group; BSA, body surface area; BMI, body mass index; LLN, lower limit of normal; Hb, hemoglobin; Plt, platelets; NSAIDs, non-steroidal anti-inflammatory drugs; nab-PTX, nanoparticle albumin-bound paclitaxel.
Liver dysfunction: grade 2 aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels

476 **Table 2** Incidence and severity of CIPN

Incidence of grade ≥2 CIPN (n, %)	49 (35.0%)
Defined all-grade CIPN (n, %)	89 (63.6%)
Severity of CIPN (n, %)	
Grade 1	40 (28.6%)
Grade 2	43 (30.7%)
Grade 3	6 (4.3%)
Appearance time of grade ≥2 CIPN (days, median, range)	84 (14–155)
Onset time of grade ≥2 CIPN (n, %)	
Week 1–4	0 (0%)
Week 5–8	11 (7.9%)
Week 9–12	15 (10.7%)
Week 13 or later	23 (16.4%)
Appearance time of defined CIPN (days, median, range)	43 (1–180)
Onset time of defined CIPN (n, %)	
Week 1–4	28 (20.0%)
Week 5–8	23 (16.4%)
Week 9–12	23 (16.4%)
Week 13 or later	15 (10.7%)
Median cumulative dose of nab-PTX (mg/m^2) at CIPN onset (range)	
Defined all-grade	500 (100–2,625)
Grade ≥2	1,125 (125–2,875)
Additional anti-CIPN treatment (n, %)	49 (35.0%)
Mirogabalin	27 (19.3%)
Pregabalin	21 (15.0%)
Duloxetine	15 (10.7%)

477 CIPN, chemotherapy-induced peripheral neuropathy

478 Anti-CIPN treatment includes duplications.

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Table 3 Univariate and multivariate Cox proportional hazard regression analyses of the risk factors associated with (A) grade ≥2 and (B) defined CIPN

	Univariate analysis		Multivariate analysis	
(A)	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Sex				
Female/Male	1.61 (0.92–2.83)	0.10	1.55 (0.82–2.94)	0.17
Age (years)				
≥65/<65	0.74 (0.41–1.34)	0.32	Excluded	-
Prior treatment				
Present/Absent	1.47 (0.79–2.75)	0.22	Excluded	-
Previous oxaliplatin administration				
Present/Absent	3.06 (1.46–6.38)	0.003**	1.31 (0.51–3.35)	0.58
BSA (m^2)				
≥1.6/<1.6	0.92 (0.53–1.62)	0.78	Excluded	-
BMI (kg/m^2)				
≥25.0/<25.0	1.48 (0.69–3.17)	0.31	Excluded	-
Anemia				
Present/Absent	0.86 (0.49–1.51)	0.59	Excluded	-
Hypoalbuminemia				
Present/Absent	1.14 (0.62–2.08)	0.68	Excluded	-
Liver dysfunction				
Present/Absent	1.42 (0.44–4.56)	0.56	Excluded	-

Renal dysfunction				
Present/Absent	0.84 (0.41–1.72)	0.63	Excluded	-
Smoking history				
Current or former/Never	0.98 (0.55–1.76)	0.96	Excluded	-
Alcohol intake (≥5 days in a week)				
Yes/No	0.61 (0.33–1.13)	0.12	0.65 (0.33–1.31)	0.23
Cardiovascular disease				
Present/Absent	1.17 (0.66–2.05)	0.59	Excluded	-
Diabetes mellitus				
Present/Absent	1.13 (0.62–2.05)	0.69	Excluded	-
Presence of preexisting neuropathy				
Present/Absent	3.75 (2.03–6.92)	<0.0001**	4.03 (1.82–8.96)	0.0006**
NSAID administration				
Present/Absent	1.30 (0.74–2.31)	0.36	Excluded	-
Opioid administration				
Present/Absent	1.21 (0.65–2.26)	0.54	Excluded	-
Dose modification of nab-PTX within 4 weeks from treatment initiation				
Present/Absent	0.53 (0.28–1.02)	0.06	0.45 (0.22–0.91)	0.03*

(B)	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Sex				
Female/Male	1.42 (0.93–2.17)	0.10	1.33 (0.76–2.31)	0.32
Age (years)				
≥65/<65	0.83 (0.53–1.29)	0.41	Excluded	-
Prior treatment				
Present/Absent	1.32 (0.83–2.11)	0.24	Excluded	-
Previous oxaliplatin administration				
Present/Absent	1.22 (0.66–2.25)	0.52	Excluded	-
BSA (m^2)				
≥1.6/<1.6	0.87 (0.57–1.32)	0.52	Excluded	-
BMI (kg/m^2)				
≥25.0/<25.0	1.27 (0.72–2.26)	0.42	Excluded	-
Anemia				
Present/Absent	0.72 (0.47–1.09)	0.12	0.76 (0.49–1.18)	0.22
Hypoalbuminemia				
Present/Absent	1.06 (0.68–1.66)	0.79	Excluded	-
Liver dysfunction				
Present/Absent	1.42 (0.62–3.26)	0.41	Excluded	-
Renal dysfunction				
Present/Absent	0.85 (0.50–1.47)	0.57	Excluded	-
Smoking history				

Current or former/Never	0.67 (0.44–1.04)	0.07	0.66 (0.39–1.11)	0.11
Alcohol intake (≥5 days in a week)				
Yes/No	0.75 (0.49–1.17)	0.21	Excluded	-
Cardiovascular disease				
Present/Absent	1.32 (0.87–2.02)	0.19	1.42 (0.90–2.24)	0.13
Diabetes mellitus				
Present/Absent	1.81 (1.17–2.80)	0.008**	1.96 (1.23–3.11)	0.004**
Presence of preexisting neuropathy				
Present/Absent	1.48 (0.87–2.51)	0.15	1.61 (0.94–2.76)	0.08
NSAID administration				
Present/Absent	0.96 (0.62–1.49)	0.86	Excluded	-
Opioid administration				
Present/Absent	0.83 (0.51–1.34)	0.45	Excluded	-
Dose modification of nab-PTX within 4 weeks from treatment initiation				
Present/Absent	0.92 (0.59–1.43)	0.72	Excluded	-

*P <0.05, **P <0.01

CI, confidence interval; BSA, body surface area; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; nab-PTX, nanoparticle albumin-bound paclitaxel.

Liver dysfunction: grade ≥2 aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels

Renal dysfunction: creatinine clearance of less than 60 mL/min

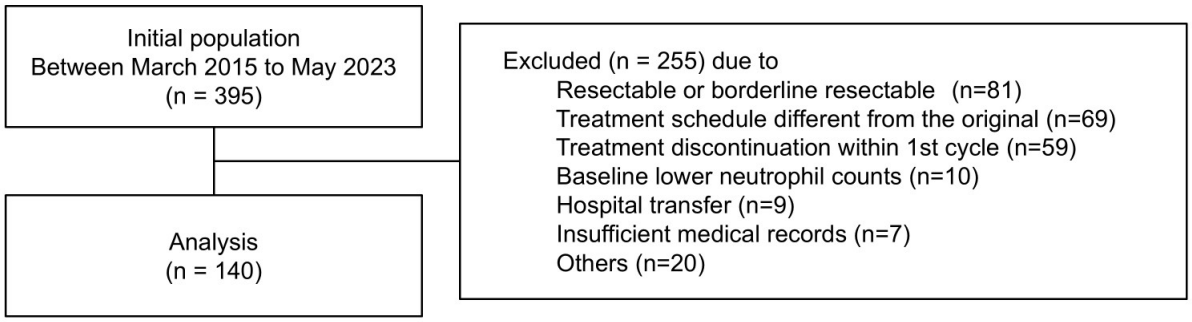

Fig. 1 Study population