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Original Research

Identification of high-risk drugs related to chemotherapy-induced peripheral neuropathy in Cancer Therapy Evaluation Program–sponsored phase I trials

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Paclitaxel;
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Abstract ***Background:*** Chemotherapy-induced peripheral neuropathy (CIPN) is a significant and debilitating side effect. However, there have been no studies of the relative risk of CIPN with known causative agents. We examined the risk of CIPN in patients taking such agents as a part of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program–sponsored phase I trials.

Methods: CIPN events in each patient were graded according to the Clinical Terminology of Common Adverse Effects and compared among several high-risk chemotherapeutic agent groups, adjusting for possible confounding factors. Patients receiving tubulin-targeted agents were analysed separately for specific background factors associated with CIPN.

Results: In 135 phase I clinical trials, 259 of 3614 patients were identified as developing CIPN during chemotherapy. Tubulin-targeting agents and proteasome inhibitors were identified as high-risk agents (hazard ratio 9.04 and 5.01, respectively) for CIPN, whereas platinum-complex agents and thalidomide analogues imparted lower risk (hazard ratio 1.52 and 1.11, respectively). Age, sex and medical history of diabetes were not significantly related to CIPN. CIPN developed over time as the number of chemotherapy cycles increased. Among patients with CIPN, treatment with tubulin-targeting agents resulted in a significantly higher rate of chemotherapy schedule modification compared with treatments with other chemotherapeutic agents.

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Conclusions: Tubulin-targeting agents and proteasome inhibitors were associated with a greatly increased risk of CIPN compared with other agents. CIPN tended to develop in later chemotherapy cycles. These findings will help to minimise the risk of CIPN by encouraging increased surveillance and earlier dose adjustment of high-risk agents in phase I trials.
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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating adverse effect of cancer treatments [1]. The typical clinical presentation is a symmetric, predominantly sensory, distal neuropathy with symptoms of mostly paraesthesia, numbness and impaired balance, although it differs depending on the drug class [1,2]. Chemotherapeutic agents associated with CIPN include platinum-complex agents, tubulin-targeting agents, proteasome inhibitors and thalidomide analogue [3,4]. CIPN is usually diagnosed by oncologists based on subjective complaints from the patient and objective assessment of neuropathic signs with clinical examinations [5]. Although the symptoms are not usually life-threatening, they require prompt medical attention from the earliest stage because they are related to a significant decrease in quality of life [1]. When symptoms worsen, dose adjustment or even discontinuation of a regimen needs to be considered because there is no established gold-standard therapy to prevent or minimise CIPN [6–8]. Therefore, even grade I or II CIPN is noteworthy and occasionally treated prophylactically.

The aim of phase I clinical trials is to identify adverse effects of drugs and establish a safe dose for phase 2 trials. Detailed information on adverse events (AEs) in Cancer Therapy Evaluation Program (CTEP)-sponsored clinical trials is recorded using the Common Terminology Criteria for Adverse Events (CTCAE), to monitor systematically the AEs that are linked to oncology research. By using this standardised AE reporting across clinical trials, direct and reliable comparative risk assessment of drugs is feasible [5].

In this study, we analysed the most recent 10 years of data from phase I clinical studies sponsored by the CTEP at the National Cancer Institute, focussing on four drug classes which are widely known for their neurotoxicity: platinum-complex agents, tubulin-targeting agents, proteasome inhibitors and thalidomide analogues. The analysis examined the frequency of CIPN induced by these drug classes and the impact of CIPN on the conduct of the phase I clinical trials. The findings from this research will help to improve the risk assessment of neurotoxicity and selection of appropriate regimens of chemotherapy.

2. Materials and methods

2.1. Data source

Data were obtained on 3614 patients enrolled in 135 CTEP-sponsored phase I clinical trials involving 103 antineoplastic agents between 2006 and 2016 (See supplementary data Table1). The data source was the Clinical Trial Monitoring System database managed by Theradex Systems (Princeton, NJ). All NCI-sponsored clinical trials used for this analysis were reviewed and approved by the institutional review board where the study was conducted, and written informed consent was obtained from all patients.

2.2. Study population

Patients evaluated in this study were aged >18. The exclusion criteria were primary cancer site in the CNS; ECOG grade >2 and missing data on age, sex, body mass index (BMI) or chemotherapy regimen. With these selection criteria, we could achieve wide coverage of patients with an exclusion rate of about 3.8% (Fig. 1). The database included CTCAE codes for CIPN (peripheral sensory neuropathy, peripheral motor neuropathy, paraesthesia, dysaesthesia and neuralgia) [9], CTCAE grades [1–5] (See supplementary data Tables 2 and 3) and the relationship of CIPN to chemotherapy as assessed by the oncologist (unrelated, unlikely, possible, probable or definite). Cases assessed as unrelated and unlikely were not considered as CIPN.

The regimens were categorised into 5 groups by their regimen: tubulin-targeting agent (paclitaxel, ixabepilone)–containing regimen, platinum-complex (cisplatin, carboplatin and oxaliplatin)–containing regimen, proteasome inhibitors (bortezomib)–containing regimen, thalidomide analogues (lenalidomide)–containing regimen and 'other' in which none of these drugs were included.

2.3. Statistical analysis

Univariate analyses were performed using Fisher's exact tests to compare age, sex, BMI, race, ECOG performance status and recorded diabetes in patients with and without CIPN. Height and weight were compared using

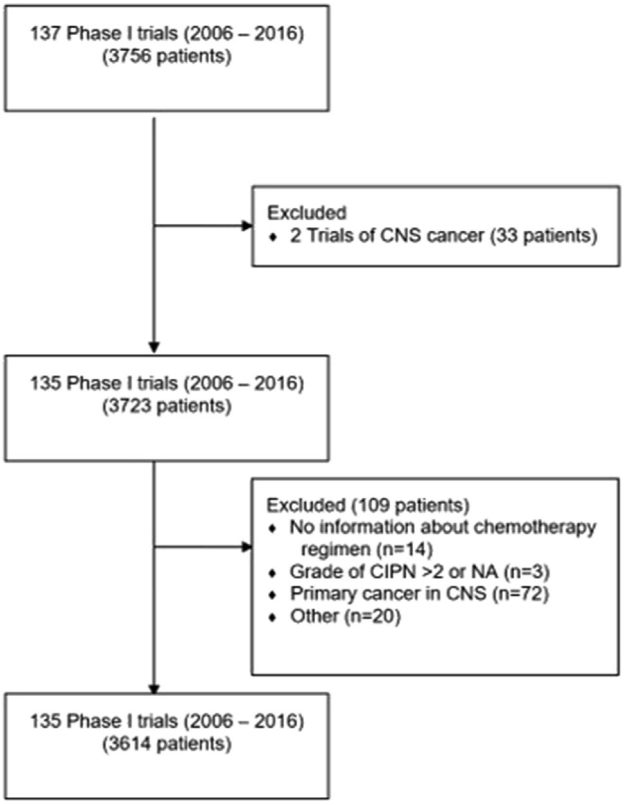

Fig. 1. Selection diagram of patients included in the study. CNS, central nervous system; NA, not available.

t tests. To take drug dose information into consideration by incorporating a time variable in the model, multivariable regression analysis was undertaken using a Cox proportional-hazards model to evaluate the risk of CIPN for each regimen, adjusting for age, sex, ECOG performance status, African American race, BMI and diabetes. The combination therapy of tubulin-targeting agents and platinum-complex agents was separately included in the model, and the number of courses of chemotherapy was considered as time.

The cumulative incidence of CIPN was estimated from 0 to 30 chemotherapy cycles. The time to CIPN was defined as the number of chemotherapy cycles from the first dose of study drug to CIPN occurrence. The earliest report of CIPN was considered as the time of incidence in this analysis. For each patient, the cycle in which they first experienced CIPN was identified as the primary outcome event. All statistical analyses performed done using R version 3.3.1. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Demographic data

From the 135 clinical trials with available data, 3614 patients met the inclusion criteria and were analysed (Table 1). Three hundred twenty-two patients received platinum-complex agents, and 60 received tubulin-targeting agents; 227 were treated with a combination of these regimens. Proteasome inhibitors were administered to 46 patients, and thalidomide analogues, to 98 patients. 'Other' regimens were administered to 2861 patients (See supplementary data Table 4).

3.2. Identification of CIPN

A total of 3463 neurological AEs were reported in the database. CIPN (defined as peripheral sensory neuropathy, peripheral motor neuropathy, paraesthesia, dysaesthesia or neuralgia) was the most frequent neurological AE, totalling 1100 events (31.8%), followed by dysgeusia (23.8%), headache (22.8%) and dizziness (10.4%) (See supplementary data Table S5). Among the CIPN events, peripheral sensory neuropathy was the most common (66.2%), followed by paraesthesia (21.2%), peripheral motor neuropathy (6.5%), dysaesthesia (5.5%) and neuralgia (0.6%) (See supplementary data Table S2). The 1100 CIPN events occurred in 259 patients. Supplementary data Fig. S1 shows the distribution of the number of reported CIPN events in individual patients. Eighty-four patients (32.4%) had 4 or more events.

3.3. Association of CIPN toxicity profile with chemotherapeutic agent class

The 1100 CIPN events were distributed differently in the different chemotherapeutic agent classes (Supplementary data Fig. S2). In patients taking tubulin-targeting agents, 87.7% of the events were peripheral sensory neuropathy, and there was no paraesthesia. In contrast, 35.1% of the events in the 'other' group and 23.1% of the events in patients taking platinum-complex agents were paraesthesia. Events in patients taking both platinum-complex agents and tubulin-targeting agents showed a mixed profile of the two drug classes (peripheral sensory neuropathy: 84.1%, paraesthesia: 6.9%). Events in patients taking thalidomide analogues displayed a higher ratio of dysaesthesia, which is specific for this drug class (40%).

3.4. Cumulative incidence rate

The cumulative incidence rate was estimated as shown in Fig. 2. Patients taking tubulin-targeting agents alone or in combination with platinum-complex agents showed clearly higher cumulative incidence rates than other groups. These two groups had a similar incidence rate until the fifth course of chemotherapy, when the group taking tubulin-targeting agents alone demonstrated a higher incidence rate from that time forward. Patients taking proteasome inhibitors showed a higher cumulative incidence rate than those taking platinum-complex agents alone and thalidomide analogues.

Table 1
Demographic and clinical information on evaluable patients with/without CIPN.

Characteristic		Total	CIPN				*p*
			+	(%)	−	(%)	
Age	−40	344	22	6.4	322	93.6	Ref
	41−60	1711	131	7.7	1580	92.3	0.50
	61−80	1512	104	6.9	1408	93.1	0.81
	81-	47	2	4.3	45	95.7	0.75
Sex	Female	1992	142	7.1	1850	92.9	0.99
	Male	1622	117	7.2	1505	92.8	
BMI	−20	266	20	7.5	246	92.5	0.90
	20−25	1090	80	7.3	1010	92.7	Ref
	25−30	1271	82	6.5	1189	93.5	0.41
	30-	987	77	7.8	910	92.2	0.74
Race	White	2887	213	7.4	2674	92.6	Ref
	Black or African American	373	27	7.2	346	92.8	1.00
	Asian	166	8	4.8	158	95.2	0.28
	American Indian	13	3	23.1	10	76.9	0.07
	Native Hawaiian	11	0	0.0	11	100	1.00
	Others	164	8	4.9	156	95.1	0.28
ECOG	0	1312	130	9.9	1182	90.1	Ref
	1	2139	124	5.8	2015	94.2	>0.001
	2	163	5	3.1	158	96.9	0.002
Recorded diabetes	+	119	8	6.7	111	93.3	1.00
	−	3495	251	7.2	3244	92.8	
Drug class	PC+TT	227	77	33.9	150	66.1	>0.001
	PC	322	20	6.2	302	93.8	0.12
	TT	60	23	38.3	37	61.7	>0.001
	PI	46	8	17.4	38	82.6	>0.001
	TH	98	8	8.2	90	91.8	0.08
	O	2861	123	4.3	2738	95.7	Ref

Age, height, weight and BMI are expressed as mean ± SD. Height and weight were expressed as cm ± SD, kg ± SD, respectively. Age, sex, BMI, race, ECOG and recorded diabetes and treatment regimens sorted by drug classes were compared using a fisher's exact test. Height and weight were compared using a t test.
Ref: reference used in the fisher's exact test.
BMI, body mass index; ECOG, Eastern cooperative oncology group; PC, platinum-complex agents; TT, tubulin-targeting agents; PI, proteasome inhibitors; TH thalidomide analogues; O, others; CIPN, chemotherapy-induced peripheral neuropathy; SD, standard deviation.

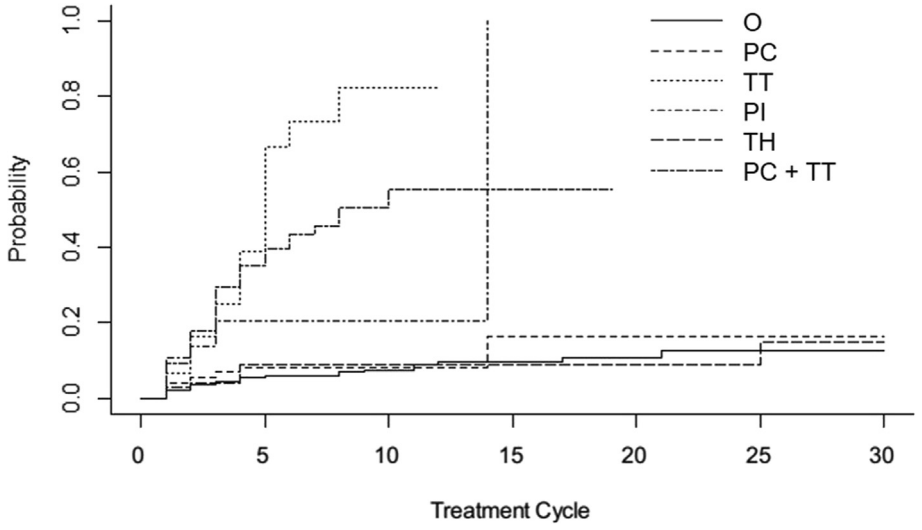

Fig. 2. The cumulative incidence of CIPN. TT+PC, TT and PI groups showed higher cumulative incidence compared with other groups. PC, platinum-complex agents; TT, tubulin-targeting agents; PI, proteasome inhibitors; TH thalidomide analogues; O, others; CIPN, chemotherapy-induced peripheral neuropathy.

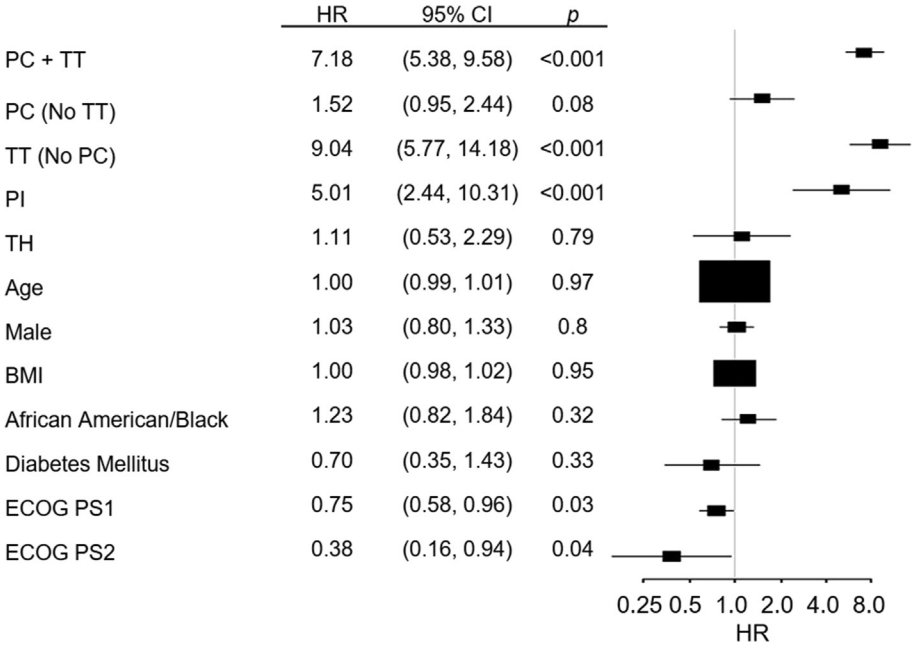

Fig. 3. Risk of CIPN via Cox proportional-hazards regression analysis. CIPN, chemotherapy-induced peripheral neuropathy; PC, Platinum-containing agents; TT, tubulin-targeting agents; PI, proteasome inhibitors; TH thalidomide analogues; BMI, body mass index; ECOG, Eastern cooperative oncology group; HR, hazard ratio; CI, confidence interval.

3.5. Correlates and risk of CIPN

3.5.1. Univariate analysis

We compared the demographic and clinical characteristics of patients with and without CIPN by univariate analysis (Table 1). The differences in age, sex, height, weight, BMI and race were insignificant. ECOG performance status score showed a statistically significant difference in favour of higher scores among patients with CIPN. A medical history of diabetes was also analysed because it is often associated with peripheral neuropathy. However, no statistical difference was detected between those with and without such a history. Regimens containing tubulin-targeting agents, both tubulin-targeting agents and platinum complex agents and proteasome-inhibitors showed a distinctively higher rate of CIPN (38%, 34% and 17%, respectively) than regimens containing platinum complex agents, thalidomide analogues and others (6.2%, 8.2% and 4.3%).

3.5.2. Cox proportional-hazards regression analysis

The data of all 3614 patients were analysed by Cox proportional-hazards regression to identify the risk of CIPN with these four drug classes (Fig. 3). The risk of CIPN with tubulin-targeting agents and proteasome inhibitors was very high (hazard ratio [HR] 9.04 and 5.01, respectively), whereas lower risk of CIPN was observed with platinum-complex regimens (HR 1.52) and thalidomide analogues (HR 1.11). Higher ECOG score was associated with a lower risk of CIPN.

Because patients who received tubulin-targeting agents had a markedly higher rate of CIPN, a subgroup analysis was carried out in patients receiving this regimen (alone or in combination with platinum). None of the covariates were associated with a significant change in the risk of CIPN (See supplementary data Fig. S3).

3.6. Impact of CIPN on regimen modification in phase I trials

The number of chemotherapy cycles received by different groups of patients (total patients [n = 3614], those with non-CIPN AEs [n = 1824] and those with CIPN [n = 259]) was determined (Fig. 4). The median number of chemotherapy cycles was greater in CIPN patients than in total patients, suggesting that CIPN tends to develop in patients with longer treatment period. Twenty-eight of 259 patients who developed CIPN (10.8%) were reported to need a regimen modification such as reduced/interrupted dosing or therapy discontinuation (Table 2). A significantly higher rate of patients who were treated with tubulin-targeting agents needed such clinical interventions compared with patients in other groups (15.0% versus 4.8% in patients on the combination regimen and 0.3% in patients taking platinum-complex agents alone).

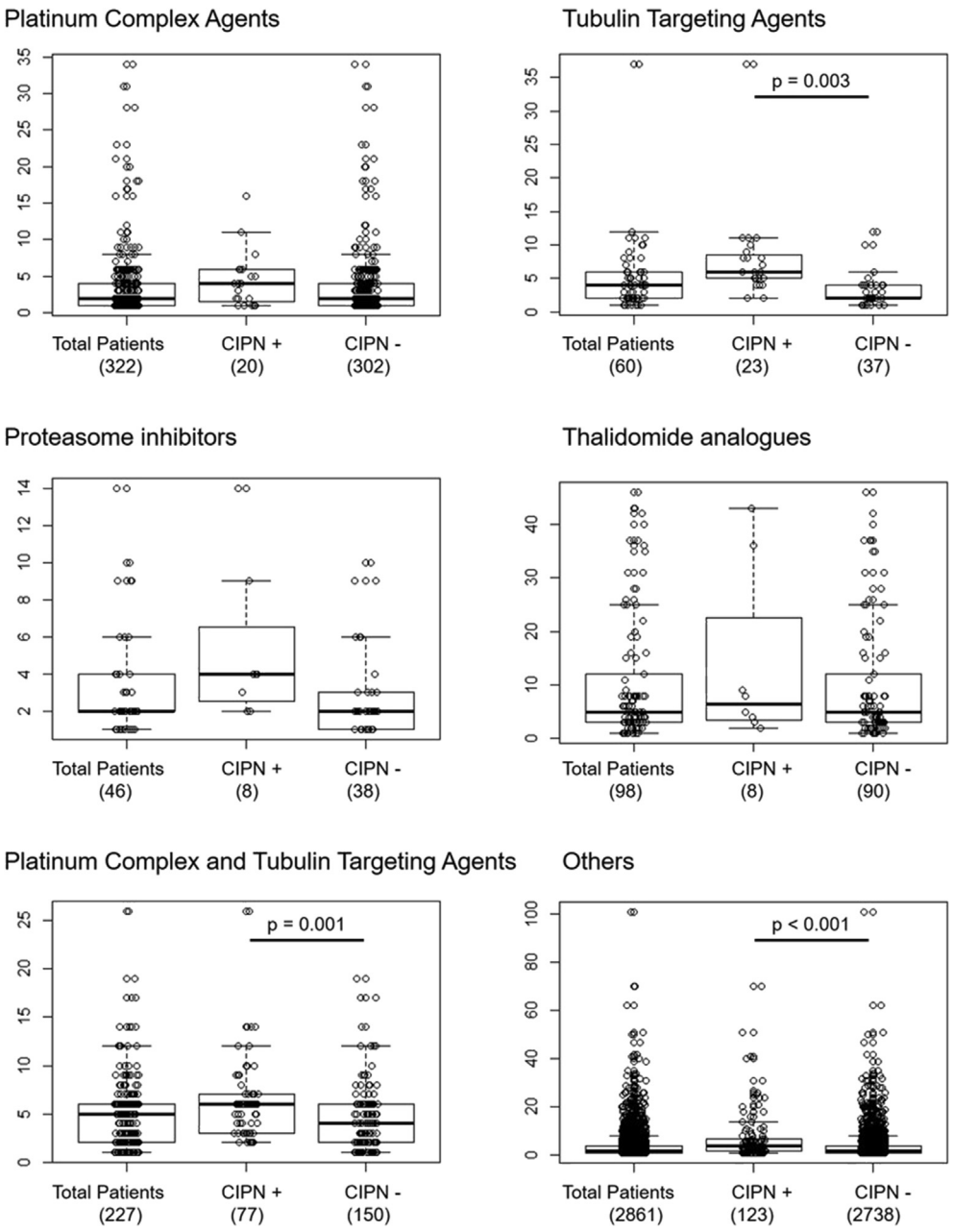

Fig. 4. Comparison of number of chemotherapy cycles between total patients, patients with CIPN and patients without CIPN, sorted by groups. CIPN, chemotherapy-induced peripheral neuropathy.

4. Discussion

When evaluating the risk of CIPN using phase I clinical trial database in which many of the patients included in this study received very few number of cycles, it was important to account for the influence of the number of treatment cycles. As it is known that CIPN develops with accumulated dose [1,8,17], the incidence rate of CIPN in patients receiving fewer cycles might be underestimated. In this study, we avoided the potential underestimation by using Cox proportional-hazard model in which the number of treatment cycles was accounted for.

Our findings revealed that tubulin-targeting agents are a high-risk drug for CIPN and platinum-complex agents are not. Several reasons were considered as the cause of this disparity in risk. The regimen of chemotherapy in phase I trials, which focus mainly on adverse effects, might be related to the low risk of CIPN with platinum-complex agents. The dose of each agent is not controlled in phase I trials because it is determined based on the toxicity of the therapy [18]. Because neurotoxicity is caused by an accumulation of administered drugs [1,8,17], it is possible that other types of AEs limited the dose of platinum-complex agents before they reached a neurotoxic level. The fact that the median

Table 2
Proportion of patients who required regimen modifications, sorted by treatment group.

Drug class	Number of patients	Patients with adverse event requiring regimen modification	(%)	Patients with CIPN requiring regimen modification	(%)
PC+TT	227	171	75.3	11	4.8
PC	322	103	32.0	1	0.3
TT	60	41	68.3	9	15.0
PI	46	26	56.5	1	2.2
TH	98	60	61.2	0	0.0
Others	2861	1435	50.2	6	0.2
Total	3614	1836	50.8	28	0.8

PC, Platinum-containing agents; TT, tubulin-targeting agents; PI, proteasome inhibitors; TH thalidomide analogues; CIPN, chemotherapy-induced peripheral neuropathy.

number of chemotherapy cycles of all patients was lower than that of CIPN patients supports this viewpoint (Fig. 4). In patients taking platinum-complex agents, 103 experienced AEs requiring regimen modification and CIPN was only one of them. In patients taking tubulin-targeting agents, 41 experienced AEs requiring regimen modification and CIPN contributed 9 of them (Table 2). This finding suggests that, unlike in the tubulin-targeting group, non-CIPN AEs tended to limit the dose accumulation in the platinum-complex group.

The difference in clinical presentation between the drug classes might also be partially responsible for the low CIPN risk of platinum-complex agents. In supplementary data Fig. S2, compared with tubulin-targeting agents, platinum-complex agents were associated with a significantly lower ratio of motor neuropathy (3.6% versus 14.0%), which is likely to be noticeable to patients and examiners. In contrast, paraesthesia in patients taking platinum-complex agents might have been underestimated because paraesthesia does not necessarily evoke an uncomfortable sensation like numbness or pain.

This study also identified proteasome inhibitors as imparting a high risk of developing CIPN (HR = 5.01) and thalidomide analogues as not (HR = 1.11). Proteasome inhibitors induced a high incidence rate of peripheral sensory neuropathy (100%), and thalidomide analogues demonstrated the highest rate of dysaesthesia among all the drug classes (40%). The high rate of dysaesthesia in the thalidomide-analogue group implies that axonopathy caused by thalidomide analogues has an unknown mechanism different from other axonopathy-causing agents such as tubulin-targeting agents or proteasome inhibitors.

Another interesting finding was that a higher ECOG grade was associated with a lower risk of developing CIPN. CTCAE scoring is performed by a medical examiner interviewing a patient for restrictions in their activities of daily living (ADL). As both patients' and examiners' subjective judgements are involved in the grading, the neurological complications might be underestimated in patients who are already with lower ADL, because CIPN events are not life-threatening in most cases [19].

Several background characteristics associated with paclitaxel-induced CIPN were documented in previous reports. Gogas *et al.* [20] reported that the likelihood of neuropathy was higher in patients who have other contributing predispositions to neuropathy such as diabetes. Although it was not statistically significant, low risk of CIPN was observed in patients with a medical history of diabetes in the present study, in contrast to previous reports [20–22]. This finding might be because of the interference of the correct diagnosis of CIPN by concurrent diabetic neuropathy. Rowinsky *et al.* [23,24] reported that patients who are obese and older are at greater risk of CIPN. A recent study also suggested that African American patients might be at a higher risk for paclitaxel-induced CIPN (HR = 2.1) [2]. Cox analysis on the subgroup of patients taking tubulin-targeting agents (alone or in combination; n = 287) was carried out with adjustment for African American race, resulting in African American race as a not statistically significant risk factor for CIPN in our study (HR = 1.77, p = 0.089).

The cumulative incidence rate gives insights into CIPN induced by the high-risk drug classes. The rate increased linearly until the fifth cycle of chemotherapy. This is a different profile from other AEs, such as allergic reaction, which occurs mostly in the first or second chemotherapy cycles or haematological toxicity, which is cumulative to a degree but attenuated by dose adjustments or use of colony-stimulafting factors [25–27]. This finding underscores the impact of dose dependency on developing CIPN, as described in previous studies [8,13]. Such toxicity might be underestimated in phase I trials because the regimen of phase I trials is more suitable for exploring acute toxicity, resulting in the low diagnostic rate of CIPN in this study.

By analysing the patients who required a regimen modification such as reduced/interrupted dose or therapy discontinuation, tubulin-targeting agents were

identified as the highest risk among the other drug classes. Platinum-complex agents were comparatively unlikely to require a regimen modification to avoid exacerbation of CIPN during phase I trials. However, careful medical attention is still required because all platinum agents are known to share the 'coasting' phenomenon that involves worsening of the severity of symptoms for weeks following treatment withdrawal [28].

There are several limitations in the current analyses. Because patients enrolled in phase I clinical trials tend to be heavily treated with other chemotherapeutics before the trial, the occurrence of AEs with the investigational drugs can be influenced by the prior treatments, which is a factor not accounted for in this evaluation. In this study, 808 patients were diagnosed as CIPN at the beginning of phase I trials. These cases were not counted as CIPN occurrence in the analysis. When the existence of previous CIPN was included in the Cox model, this parameter was not statistically significant (HR = 1.01), suggesting preexisting CIPN did not impact the CIPN development in the current analyses. It should also be noted that we used the number of chemotherapy cycles administered as a proxy for drug exposure. The actual doses of drugs were not taken into consideration in the risk assessment analyses because patients in phase I trials involving multiple agents received various drug doses and it was technically difficult to include the actual doses in the model [18]. This approach could potentially lead to inaccuracies in drug exposure assessment. The validity of the database may also affect the results. Non-randomised trial including phase I trials may have certain biases, such as reporting bias on the patients' end and experimenter bias on the clinicians' end.

5. Conclusions

Although platinum-complex agents and thalidomide analogues are well known for their neurotoxicity, they were not identified as significantly high-risk causative agents for CIPN in phase I clinical trials conducted under CTEP from 2006 to 2016. Tubulin-targeting agents were identified as high-risk for CIPN, along with proteasome-inhibitors. The combination therapy of tubulin-targeting agent and platinum-complex agent did not show an enhanced risk of CIPN. Patients treated with tubulin-targeting agents should be closely monitored for CIPN and may require a higher rate of regimen modification due to its occurrence.

Conflict of interest statement

The authors have no conflict to declare.

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S.K., M.C.K. and N.T. conceived and designed the study. M.R. was responsible for the collection and assembly of data, and S.K. and N.O. performed statistical analyses of the data. S.K. and N.T. drafted the manuscript. All authors discussed the results and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.04.023.

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