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Original Article

Incidence and correlates of high-grade chemotherapy-induced peripheral neuropathy in patients with lung cancer

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Abstract

Background: High-grade chemotherapy-induced peripheral neuropathy (CIPN) represents a dreaded toxicity of cancer treatments. In some cases, it may limit activities of daily living and become permanent. Because many prior studies of CIPN were conducted in breast cancer populations, less is known about CIPN in men. We therefore determined the incidence and correlates of high-grade CIPN in a large cohort of patients with lung cancer.

Methods: We collected data from the ECOG-ACRIN E1594 (comparison of 4 chemotherapy regimens: cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, carboplatin-paclitaxel) and E4599 (carboplatin-paclitaxel ± concurrent and maintenance bevacizumab) clinical trials. We identified cases with grade ≥3 CIPN. Multivariable logistic regression modeling was performed to estimate adjusted odds ratios according to patient characteristics.

Results: Among 1,998 patients included in the study, 167 (8%) developed grade ≥3 CIPN. Grade ≥3 CIPN was associated with higher body mass index (BMI) ($P = .01$), sex (7% for men vs 10% for women; $P = .005$), age (11% for ≥65 years vs 7% for <65 years; $P < .001$), chemotherapy regimen ($P = .01$), and greater number treatment cycles ($P < .001$). In a multivariate model, regimens featuring higher doses of paclitaxel or cisplatin, greater number of chemotherapy cycles, female sex, greater age, and higher BMI remained independently associated with grade ≥3 CIPN.

Conclusions: High-grade CIPN is associated with chemotherapy type and exposure, female sex, greater age, and elevated BMI. Given the ongoing use of cytotoxic agents in established and new (eg, antibody-drug conjugates) treatment regimens, these findings have implications for patient monitoring and treatment selection.

Key words: chemotherapy; neuropathy; nonsmall cell lung cancer; toxicity; CIPN.

Implications for practice

High-grade peripheral neuropathy represents a devastating toxicity of cytotoxic chemotherapy. In this study, almost 10% of patients receiving chemotherapy for lung cancer developed grade ≥3 neuropathy, which implies interference with activities of daily living. We identified elevated BMI, female sex, older age, and chemotherapy type and exposure as independent risk factors for the development of neuropathy. Given the ongoing use of cytotoxic agents in established and new (eg, antibody-drug conjugates) treatment regimens, these findings have implications for patient monitoring and treatment selection.

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Introduction

Despite recent advances in molecularly targeted therapies and immune checkpoint inhibitors, cytotoxic chemotherapy remains a foundational treatment for many cancer types, including nonsmall cell lung cancer (NSCLC). Among chemotherapy-associated toxicities, neuropathy represents a particular challenge, as it cannot be monitored through laboratory or imaging studies, may necessitate treatment reduction or discontinuation, and in severe cases may be debilitating or permanent.[1] This adverse event is also common. Among patients treated with platinum, taxane, or vinca alkaloid chemotherapeutic agents, more than two-thirds of patients experience chemotherapy-induced peripheral neuropathy (CIPN) within 1 month of finishing chemotherapy, with one-third of patients having persistent neuropathy more than 6 months after completing treatment.[2]

Chemotherapy-induced peripheral neuropathy can affect both large and small nerve fibers, resulting in neuropathic pain and motor or autonomic dysfunction.[3] Platinum-based compounds induce neuropathy through accumulation of platinum adducts in dorsal root neurons, leading to apoptosis.[4] Taxanes cause neuropathy via microtubule disruption and dysfunction, axonal degeneration, altered ion exchange and neuron overexcitability, and neuroinflammation.[3] Vinca alkaloids interfere with the neuronal cytoskeleton, which leads to impairment of neuronal transport and axonal degeneration.[5] Notably, peripheral neuropathy is not limited to conventional chemotherapy, as it also occurs in up to 75% of multiple myeloma patients receiving the proteasome inhibitor bortezomib.

It has also become apparent that newer classes of cancer treatment may convey this toxicity. Because tubulin inhibitors are frequently used as cytotoxic payloads for antibody-drug conjugates (ADCs), despite their greater degree of tumor-specific targeting, these agents may cause neuropathy in a substantial proportion of patients. For instance, more than one-third of patients receiving enfortumab vedotin (a nectin 4 antibody conjugated to a monomethyl auristatin E [MMAE] payload approved for bladder cancer treatment in 2019) develop peripheral sensory neuropathy.[6]

Many prior studies of CIPN have been conducted breast cancer clinical trial cohorts, which tend to be exclusively female.[7,8] Even in studies including both sexes, men generally represent less than 20% of patients.[9-11] To identify neuropathy risk factors among a broader demographic, we determined the incidence and correlates of CIPN in a large lung cancer population. We focused on high-grade peripheral neuropathy because these cases have major effects on near-term quality of life and may convey substantial risk of chronic symptoms.[12]

Methods

Patient selection and data source

We analyzed data from the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) E1594 and E4599 clinical trials. E1594 was a phase III randomized trial in advanced NSCLC comparing 4 chemotherapy regimens: (1) cisplatin 75 mg/m^2 on day 2 plus paclitaxel 135 mg/m^2 on day 1 every 3 weeks; (2) cisplatin 100 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on day 1, 8, and 15 every 4 weeks; (3) cisplatin 75 mg/m^2 on day 1 plus docetaxel 75 mg/m^2 on day 1 every 3 weeks; or (4) carboplatin AUC 6 mg/mL/min on day 1 plus paclitaxel 225 mg/m^2 on day 1 every 3 weeks.[13] E4599 (NCT00021060) was a phase III randomized trial in advanced nonsquamous NSCLC that compared carboplatin AUC 6 mg/mL/min plus paclitaxel 200 mg/m^2 with or without bevacizumab 15 mg/kg every 3 weeks for up to a total of 6 cycles, with maintenance bevacizumab continued until progression or intolerable toxicity.[14] Because some studies have identified an association between bevacizumab and peripheral neuropathy, we included this agent as a variable in our analyses.[15] We selected these trials due to their large sample sizes, long duration of follow-up, inclusion of both male and female patients, and availability of demographic and clinical data.

Clinical variables

Clinical and demographic variables available for analysis included age, sex, race/ethnicity, body mass index (BMI), weight loss prior to therapy, tumor histology, and ECOG performance status. We identified patients who experienced treatment-related grade ≥3 CIPN. We selected this threshold because (1) it represents a highly clinically significant event that poses substantial risk for chronicity, and (2) grade <3 non-hematologic adverse events were not recorded in E4599. In E1594, grade of CIPN was determined according to National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 2 (published 1999) as follows: grade 1 (mild paresthesias; loss of deep tendon reflexes), grade 2 (mild or moderate objective sensory loss; moderate paresthesias), grade 3 (severe objective sensory loss or paresthesias that interfere with function), with no grade 4 designation. E4599 used CTCAE version 3 (published 2006): grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia [including tingling] but not interfering with function), grade 2 (sensory alteration or paresthesia [including tingling], interfering with function, but not interfering with ADL), grade 3 (sensory alteration or paresthesia interfering with ADL), grade 4 (disabling). Each of these scales differs slightly from the current CTCAE version 5 (published 2017), in which grade 1 peripheral neuropathy is defined as paresthesias with no limitations in ADLs; grade 2 is defined as moderate to severe paresthesias or mild weakness with mild to moderate limitations to ADLs; grade 3 neuropathy is defined as intolerable paresthesias or marked weakness with severe limitations in ADLs; and events that are life-threatening and/or require urgent intervention are designated grade 4.[16-18]

Each protocol specified dose modifications for CIPN. In E4599, for grade 2 neuropathy, paclitaxel dose should be withheld until toxicity improved to grade 1 and then the dose should be modified to 160 mg/m^2. For grade 3 neuropathy, the paclitaxel dose should be withheld until toxicity improved to grade 1 and then reduced to 140 mg/m^2. The E1594 protocol specified that for grade 2 neurological toxicity, treatment should be withheld until resolved to grade 1 toxicity, then dose reduced to 75% of the original dose. For grade 3 neurological toxicity, treatment should be withheld until improved to grade 1, then dose reduced to 50% of the original dose.

Statistical analysis

We summarized patient demographics and disease characteristics using descriptive statistics. Body mass index was categorized according to median value for the study population. We dichotomized age as <65 or ≥65 years, as this threshold was associated with CIPN risk in earlier studies.[19] We tested differences in the distribution of the incidence of peripheral

neuropathy using Fisher's exact test. All *P*-values are 2-sided, with a significance level of 0.05. Multivariable logistic regression was performed using backwards model selection to estimate adjusted odds ratios. Variables that were found to be significant at the 2-sided 0.20 univariate level were included in the full initial models; variables were removed individually unless they remained significant at the 2-sided 0.10 level. We also conducted landmark analyses of PFS and OS using the Kaplan–Meier method, limiting inclusion to patients with OS and PFS >6 months to limit bias from early deaths or progression. The analyses were not corrected for multiple comparisons.

Results

A total of 1207 patients were enrolled in E1594, of whom 1,139 (94%) had sufficient data available for our analysis. E4599 enrolled 878 patients, with 859 (98%) having sufficient data for inclusion in the present study. Combining both populations, 1,998 patients were included in the analysis, of which 1188 (59%) were <65 years old and 1183 (59%) were male. Additional patient characteristics and treatment regimens are listed in Table 1.

Within the study population, 167 patients (8%) developed grade ≥3 CIPN. We observed significant differences according to chemotherapy regimen, with highest rates for patients receiving carboplatin-paclitaxel (10%) and lowest for cisplatin-paclitaxel (5%) ($P = .01$). Grade ≥3 CIPN was also associated with BMI (10% for ≥25.2 kg/m^2 vs 7% for <25.2 kg/m^2; $P = .01$), sex (10% for women vs 7% for men vs; $P = .005$), and age (11% for ≥65 years vs 7% for <65 years; $P < .001$). Those with grade ≥3 CIPN were more likely to have received more treatment cycles, median 6 vs median 4 ($P < .001$). In landmark analyses, there were no significant differences in PFS or OS according to grade ≥3 CIPN (Supplementary Figure 1).

The final multivariable model included chemotherapy regimen, sex, age, BMI, and number of treatment cycles. For the chemotherapy regimen variable, the reference group combined the cisplatin-paclitaxel and cisplatin-docetaxel arms, as their results were not significantly different from one another. Because both E4599 arms received carboplatin-paclitaxel, we combined these cases with the carboplatin-paclitaxel arm of E1594, recognizing the difference in paclitaxel dosing (200 mg/m^2 in E4599, 225 mg/m^2 in E1594). In this analysis, carboplatin-paclitaxel and cisplatin-gemcitabine regimens, female sex, higher age, and elevated BMI remained independently associated with grade ≥3 CIPN (Table 2).

Because the E1594 study collected data on ≥grade 2 CIPN, we conducted a subgroup analysis focused on these cases (Table 3). This analysis revealed that ≥grade 2 CIPN was associated with female sex, ECOG 0 status, <5% weight loss prior to treatment, cisplatin/gemcitabine and carboplatin/paclitaxel regimens, and greater number of treatment cycles. In multivariate analysis, cisplatin/gemcitabine and carboplatin/paclitaxel regimens, female sex, <5% weight loss prior to treatment, and number of treatment cycles remained associated with ≥grade 2 CIPN (Table 4). In landmark analyses, we observed an increase in survival in patients with ≥grade 2 CIPN in the E1594 study ($P = .001$), although there was no significant difference in PFS (Supplementary Figure 2).

Discussion

Among the numerous and diverse toxicities of systemic cancer therapies, peripheral neuropathy remains a major clinical challenge. No routine laboratory tests or imaging studies contribute to its detection and monitoring. While analgesics and adjuvant analgesics (eg, antidepressants, anticonvulsants) may decrease symptoms, they do not improve nerve damage. In the present study—to our knowledge, the largest analysis of CIPN conducted in a lung cancer population—we found that almost 10% of patients receiving platinum-based chemotherapy for lung cancer developed high-grade neuropathy, comparable to the rate reported in an analysis of over 1400 patients from 23 Southwest Oncology Group (SWOG) clinical trials of taxane-based chemotherapy.[9] Risk of CIPN was greater for women, individuals with higher BMI and age, and with certain chemotherapy regimens and number of cycles received.

Our finding that female sex is associated with heightened risk of noteworthy because multiple earlier studies have either excluded men,[7,8] not reported patient sex,[10] or not identified this relationship.[9] The biological mechanism underlying this observation is unclear, but pharmacokinetic and hormonal differences between men and women may play a role.[20] Indeed, an increased risk of severe toxicity in females has been observed across classes of systemic treatment, including cytotoxic chemotherapy, immunotherapy, and targeted therapy.[21]

Given the increasing rates of overweight and obesity, the observed association between BMI and neuropathy risk has public health considerations. In the present cohort, more than half of all patients were overweight or obese (BMI > 25 kg/m^2). In the multivariable model accounting for other demographic and treatment factors, these individuals had a 50% greater risk of high-grade CIPN, as has been shown in prior studies.[8,11] Body composition has established links with other characteristics, including age, sex, and race. Older adults and females tend to have higher proportions of fat vs muscle.[22] Compared to non-Hispanic white individuals, non-Hispanic blacks have a 35% greater and Hispanics have a 15% greater prevalence of obesity.[23] Although we did not observe an association between race and ethnicity in the present study, small numbers of non-White patients limited our ability to detect such a difference.

These findings raise an additional question. Because elevated BMI appears to be associated with increased risk of high-grade neuropathy, should full body surface area dosing be reconsidered for obese patients? Clinical guidelines generally recommend providing full doses of chemotherapy to patients with elevated BMI to ensure adequate therapeutic activity.[24,25] Furthermore, weight-based dosing of overweight or obese patients with other anticancer therapies such as immune checkpoint inhibitors has been associated with differences in clinical outcomes.[26] However, BMI does not distinguish between fat and muscle,[27] a limitation with practical impact because increased chemotherapy complications are observed in patients with sarcopenia and increased body fat percentages.[28,29] Whether increased BMI has a direct link to neurotoxicity, is an indicator of comorbidities associated with neuropathy (such as diabetes), or both is not clear. With obesity rates more than tripling over the past 60 years,[30] greater understanding of chemotherapy pharmacokinetics and toxicity according to body composition is clearly needed. Given these considerations, as well as the increasing rates of

Table 1. Clinical and demographic characteristics associated with high-grade CIPN.

Characteristic	Overall *N* = 1998 *n* (%)	≥Grade 3 CIPN		*P*-value[a]
		No *N* = 1831 *n* (%)	Yes *N* = 167 *n* (%)	
Age (years)				<.001
<65	1188 (59)	1110 (61)	78 (47)	
≥65	810 (41)	721 (39)	89 (53)	
Sex				.005
Male	1183 (59)	1101 (60)	82 (49)	
Female	815 (41)	730 (40)	85 (51)	
Race				.6
White	1708 (85)	1561 (85)	147 (88)	
Black	150 (8)	140 (8)	10 (6)	
Unknown/Other	140 (7)	130 (7)	10 (6)	
ECOG Performance Status				.2
0	691 (35)	624 (34)	67 (40)	
1	1238 (62)	1141 (63)	97 (58)	
2	63 (3)	60 (3)	3 (2)	
Unknown	6	6	0 (0)	
Weight loss prior to treatment				.13
<5%	1379 (69)	1255 (69)	124 (74)	
≥5%	618 (31)	575 (31)	43 (26)	
Unknown	1 (0)	1 (0)	0 (0)	
Tumor histology				.3
Squamous	225 (11)	210 (11)	15 (9)	
Adenocarcinoma	1239 (62)	1130 (62)	109 (65)	
Large cell	120 (6)	106 (6)	14 (8)	
Other	414 (21)	385 (21)	29 (17)	
BMI (kg/m^2)				.012
<25.2	991 (50)	924 (51)	67 (40)	
≥25.2	1004 (50)	905 (49)	99 (60)	
Unknown	3 (0)	2 (0)	1 (1)	
Chemotherapy regimen				.013
Cisplatin-paclitaxel	287 (14)	274 (15)	13 (8)	
Cisplatin-gemcitabine	280 (14)	254 (14)	26 (16)	
Cisplatin-docetaxel	286 (14)	270 (15)	16 (10)	
Carboplatin-paclitaxel	723 (36)	648 (35)	75 (45)	
Carboplatin-paclitaxel + bevacizumab	422 (21)	385 (21)	37 (22)	
Bevacizumab				.7
No	1576 (79)	1446 (79)	130 (78)	
Yes	422 (21)	385 (21)	37 (22)	
Treatment cycles				<.001
Mean (SD)	5.1 (4.6)	5.0 (4.7)	5.9 (3.8)	
Median (Q1, Q3)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	6.0 (4.0, 6.0)	
(Min, Max)	(0.0, 58.0)	(0.0, 58.0)	(1.0, 23.0)	
Unknown	18	18	0	
Trial				.067
E1594	1139 (57)	1055 (58)	84 (50)	
E4599	859 (43)	776 (42)	83 (50)	

[a]Pearson's chi-squared test; Wilcoxon rank sum test. *P*-values denote the comparisons between with and without high-grade CIPN groups combining treatment arms of the studies.

Table 2. Multivariate model for the overall cohort.

Characteristic	OR	95% CI	*P*-value
Chemotherapy regimen			
Cisplatin-paclitaxel/docetaxel	–	–	
Cisplatin-gemcitabine	1.96	1.11, 3.42	.019
Carboplatin-paclitaxel ± bevacizumab	1.88	1.23, 2.95	.005
Age (years)			
<65	–	–	
≥65	1.74	1.26, 2.40	<.001
Sex			
Male	–	–	
Female	1.61	1.17, 2.23	.004
BMI (kg/m^2)			
<25.2	–	–	
≥25.2	1.49	1.08, 2.08	.017
Treatment cycles	1.03	0.99, 1.05	.093

Abbreviations: CI, confidence interval; OR, odds ratio.

overweight and obesity nationwide, further studies evaluating the association between treatment dose and outcomes in these populations are warranted.

Increased rates of CIPN in older individuals have also been noted in earlier neuropathy studies.[9-11,19] Not only does incidence vary by age, but clinical manifestations as well, as older adults with CIPN report greater differences in light touch, cold, and vibration sensations but less severe pain and interference with daily activities.[31] Older adults appear to be at higher risk of chronic CIPN.[32] Patients with CIPN also face heightened risk of falls, a leading cause of morbidity and mortality in older adults.[33] With increasing age and female sex also associated with reduced bone mineral density, older women with chronic CIPN also have increased risk of fall-related fractures.[34] As a result of these and other neuropathy-related complications, healthcare costs for patients with CIPN are more than 30% greater than for non-CIPN-matched controls.[35]

A large prior study analyzing fatigue and neuropathy from an NSCLC clinical trial (CALGB 9730), including predominantly male patients, showed older age (greater than 65) was associated with increased risk of grade 2 or higher neuropathy.[19] Furthermore, many other prior studies have identified clinical variables associated with risk of neuropathy. First, several studies identified associations between increased body mass and CIPN.[8,11] Increased age has been associated with risk of CIPN in several studies.[9-11,19] History of diabetes and type of chemotherapy was also previously shown to be associated with CIPN.[9] History of neuropathy has been associated with CIPN,[19] as has number of chemotherapy cycles received.[10]

Because some major studies of CIPN have exclusively included taxane-based chemotherapy regimens,[8,9] our study provides useful insight into platinum and antimetabolite agents. Interestingly, patients treated with cisplatin-paclitaxel and cisplatin-docetaxel—regimens in which both drugs may cause neuropathy—had lower rates of neuropathy than did patients treated with cisplatin-gemcitabine and carboplatin-paclitaxel. Relative dosing may account for this observation. Although gemcitabine is not generally associated with neurotoxicity, the cisplatin dose in this regimen was one-third higher than in the taxane-based cisplatin doublets. Similarly, although carboplatin tends not to cause CIPN and is considered better tolerated in general than cisplatin,[36,37] the paclitaxel doses in the carboplatin-paclitaxel arms were 50-65% greater than in the cisplatin-paclitaxel group. These observations serve as a reminder that optimal chemotherapy dosing remains an important consideration even in the era of molecularly targeted therapies and immune checkpoint inhibitors. Some clinicians prefer weekly lower-dose cisplatin to the higher-dose 3 weekly regimen, as it may cause less high-grade CIPN and yield comparable clinical benefit.[38,39] Albumin-bound paclitaxel (*nab*-paclitaxel) caused significantly less grade ≥3 sensory neuropathy than did standard solvent-based paclitaxel in a phase 3 lung cancer trial,[40] but rates appear comparable in breast cancer.[41]

The study has several limitations. A number of prior studies have identified comorbidities associated with CIPN risk, including diabetes and preexisting neuropathy,[9,10,19,42] and lack of these data in the current analysis represents a major limitation. It is known that clinician grading of CIPN is difficult, subjective, and may underreport toxicity compared to patient report.[43,44] However, patient-reported outcomes were not captured in the trials we studied, an important consideration because CIPN has been associated with lower quality of life.[45] We also lacked data on cumulative dose and dose modifications of individual chemotherapy agents. Additionally, due to the timing of trial conduct, different CTCAE versions were used to categorize neuropathy in the studies included in this analysis. Strengths include the inclusion of a range of chemotherapy regimens, the focus on clinically significant (high-grade) CIPN, the data quality inherent in prospective therapeutic clinical trials, and a large sample size relatively balanced according to sex.

In conclusion, high-grade CIPN occurs in almost 10% of patients receiving cisplatin- and/or taxane-containing chemotherapy regimens for lung cancer. Female sex, elevated BMI, and higher paclitaxel or cisplatin doses convey increased risk of this dreaded toxicity. Although taxane- and cisplatin-sparing regimens are now options for a substantial proportion of patients with lung cancer, neuropathy

Table 3. Clinical and demographic characteristics associated with ≥Grade 2 CIPN in E1594.

Characteristic	Overall *N* = 1139 *n* (%)	No *N* = 876 *n* (%)	Yes *N* = 263 *n* (%)	*P*-value[a]
Age (years)				.3
<65	698 (61)	530 (61)	168 (64)	
≥65	441 (39)	346 (39)	95 (36)	
Sex				.008
Male	716 (63)	569 (65)	147 (56)	
Female	423 (37)	307 (35)	116 (44)	
Race				.2
White	972 (85)	741 (85)	231 (88)	
Black	105 (9)	88 (10)	17 (7)	
Unknown/Other	62 (5)	47 (5)	15 (6)	
ECOG Performance Status				.004
0	349 (31)	249 (28)	100 (38)	
1	727 (64)	572 (65)	155 (59)	
2	63 (6)	55 (6)	8 (3)	
Weight loss prior to treatment				<.001
<5%	760 (67)	560 (64)	200 (76)	
≥5%	378 (33)	315 (36)	63 (24)	
Unknown	1 (0)	1 (0)	0	
Tumor histology				>.9
Squamous	224 (20)	172 (20)	52 (20)	
Adenocarcinoma	647 (57)	496 (57)	151 (57)	
Large cell	74 (7)	58 (7)	16 (6)	
Other	194 (17)	150 (17)	44 (17)	
BMI (kg/m^2)				.14
<25.2	587 (52)	462 (53)	125 (48)	
≥25.2	549 (48)	412 (47)	137 (52)	
Unknown	3 (0)	2 (0)	1 (0)	
Chemotherapy regimen				<.001
Cisplatin-paclitaxel	287 (25)	241 (28)	46 (17)	
Cisplatin-gemcitabine	280 (25)	195 (22)	85 (32)	
Cisplatin-docetaxel	286 (25)	236 (27)	50 (19)	
Carboplatin-paclitaxel	286 (25)	204 (23)	82 (31)	
Treatment cycles				<.001
Mean (SD)	4 (3)	4 (2)	5 (3)	
Median (Q1, Q3)	4 (2, 6)	3 (2, 6)	6 (4, 6)	
(Min, Max)	(1, 22)	(1, 22)	(1, 21)	
Unknown	6	6	0	

[a]Pearson's chi-squared test; Wilcoxon rank sum test.
Abbreviations: Q, quartile; SD, standard deviation.

will remain a major clinical and public health concern. Paclitaxel remains widely used for squamous histology. *nab*-paclitaxel costs substantially more than paclitaxel and may not be available in many settings.[41,46,47] With the addition of immune checkpoint inhibitors to platinum-taxane chemotherapy doubling the 5-year survival for advanced squamous NSCLC,[48] more patients with high-grade CIPN may suffer from symptoms chronically. Furthermore, the emerging therapeutic class of ADCs—many of which feature tubulin-targeting cytotoxic payloads—represent a new source of neuropathy. While there is emerging evidence that agents such as metformin and minocycline may protect against CIPN, clinical data is lacking,[49,50] and to date no therapeutic agents have been shown to be effective for preventing CIPN.[51] Until this clinical scenario changes, close attention to CIPN risk, manifestations, and early intervention remain critical to optimal patient care.

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Table 4. Multivariate model for ≥Grade 2 CIPN in E1594.

Characteristic	OR	95% CI	*P*-value
Chemotherapy regimen			
Cisplatin-paclitaxel/docetaxel	–	–	
Cisplatin-gemcitabine	2.81	1.95, 4.04	<.001
Carboplatin-paclitaxel	2.07	1.45, 2.98	<.001
Sex			
Male	–	–	
Female	1.56	1.15, 2.11	.004
ECOG Performance Status			
0	–	–	
1–2	0.78	0.57, 1.07	.12
Weight loss prior to treatment			
<5%	–	–	
≥5%	0.61	0.43, 0.86	.005
Cycle	1.34	1.26, 1.43	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Author contributions

M.S.vI. critically reviewed the analysis, wrote the original manuscript draft, and reviewed and edited the manuscript. S.R. critically reviewed the analysis, wrote the original manuscript draft, and reviewed and edited the manuscript. S.E.D. conducted data curation, performed formal analysis, and reviewed and edited the manuscript. D.E.G. conceived of the current study, provided supervision of the current study, wrote the original manuscript draft, and reviewed and edited the manuscript. A.B.S. provided administrative supervision of the parent E1594 and E4599 clinical trials, and reviewed and edited the manuscript. J.H.S. provided administrative supervision of the parent E1594 and E4599 clinical trials, and reviewed and edited the manuscript. D.H.J. designed and oversaw the parent E1594 and E4599 clinical trials, and reviewed and edited the manuscript. Y.W. conducted data curation, performed formal analysis, and reviewed and edited the manuscript. Z.S. conducted data curation, performed formal analysis, and reviewed and edited the manuscript. S.S.R. provided administrative support, and reviewed and edited the manuscript.

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Conflicts of interest

None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *The Oncologist* online.

References

1. Cheng XL, Liu HQ, Wang Q, et al. Chemotherapy-induced peripheral neurotoxicity and complementary and alternative medicines: progress and perspective. *Front Pharmacol*. 2015;6:234. https://doi.org/10.3389/fphar.2015.00234
2. 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;155:2461-2470. https://doi.org/10.1016/j.pain.2014.09.020
3. Zajaczkowska R, Kocot-Kepska M, Leppert W, et al. Mechanisms of chemotherapy-induced peripheral neuropathy. *Int J Mol Sci*. 2019;20:1451. https://doi.org/10.3390/ijms20061451
4. Kanat O, Ertas H, Caner B. Platinum-induced neurotoxicity: a review of possible mechanisms. *World J Clin Oncol*. 2017;8:329-335. https://doi.org/10.5306/wjco.v8.i4.329
5. Ibrahim EY, Ehrlich BE. Prevention of chemotherapy-induced peripheral neuropathy: a review of recent findings. *Crit Rev Oncol Hematol*. 2020;145:102831. https://doi.org/10.1016/j.critrevonc.2019.102831
6. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med*. 2021;384:1125-1135. https://doi.org/10.1056/NEJMoa2035807
7. Rivera DR, Ganz PA, Weyrich MS, Bandos H, Melnikow J. Chemotherapy-associated peripheral neuropathy in patients with early-stage breast cancer: a systematic review. *J Natl Cancer Inst*. 2018;110:131-140.
8. Bao T, Basal C, Seluzicki C, et al. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res Treat*. 2016;159:327-333. https://doi.org/10.1007/s10549-016-3939-0
9. Hershman DL, Till C, Wright JD, et al. Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in Southwest Oncology Group Clinical Trials. *J Clin Oncol*. 2016;34:3014-3022. https://doi.org/10.1200/JCO.2015.66.2346
10. Molassiotis A, Cheng HL, Leung KT, et al. Risk factors for chemotherapy-induced peripheral neuropathy in patients receiving taxane- and platinum-based chemotherapy. *Brain Behav*. 2019;9:e01312. https://doi.org/10.1002/brb3.1312

11. Mizrahi D, Park SB, Li T, et al. Hemoglobin, body mass index, and age as risk factors for paclitaxel- and oxaliplatin-induced peripheral neuropathy. *JAMA Netw Open*. 2021;4:e2036695. https://doi.org/10.1001/jamanetworkopen.2020.36695
12. Reyes-Gibby CC, Morrow PK, Buzdar A, Shete S. Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated with paclitaxel. *J Pain*. 2009;10:1146-1150. https://doi.org/10.1016/j.jpain.2009.04.006
13. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92-98. https://doi.org/10.1056/NEJMoa011954
14. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542-2550. https://doi.org/10.1056/NEJMoa061884
15. Matsuoka A, Maeda O, Mizutani T, et al. Bevacizumab exacerbates paclitaxel-induced neuropathy: a retrospective cohort study. *PLoS One*. 2016;11:e0168707. https://doi.org/10.1371/journal.pone.0168707
16. Zhang X, Chen WW, Huang WJ. Chemotherapy-induced peripheral neuropathy. *Biomed Rep*. 2017;6:267-271. https://doi.org/10.3892/br.2017.851
17. Burgess J, Ferdousi M, Gosal D, et al. Chemotherapy-induced peripheral neuropathy: Epidemiology, pathomechanisms and treatment. *Oncol Ther*. 2021;9:385-450. https://doi.org/10.1007/s40487-021-00168-y
18. Park SB, Alberti P, Kolb NA, et al. Overview and critical revision of clinical assessment tools in chemotherapy-induced peripheral neurotoxicity. *J Peripher Nerv Syst*. 2019;24:S13-S25. https://doi.org/10.1111/jns.12333
19. Wong ML, Gao J, Thanarajasingam G, et al. Expanding beyond maximum grade: chemotherapy toxicity over time by age and performance status in advanced non-small cell lung cancer in CALGB 9730 (Alliance A151729). *Oncologist*. 2021;26:e435-e444. https://doi.org/10.1002/onco.13527
20. Rakshith HT, Lohita S, Rebello AP, Goudanavar PS, Raghavendra Naveen N. Sex differences in drug effects and/or toxicity in oncology. *Curr Res Pharmacol Drug Discov*. 2023;4:100152. https://doi.org/10.1016/j.crphar.2022.100152
21. Unger JM, Vaidya R, Albain KS, et al. Sex differences in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials. *J Clin Oncol*. 2022;40:1474-1486. https://doi.org/10.1200/JCO.21.02377
22. Bredella MA. Sex differences in body composition. *Adv Exp Med Biol*. 2017;1043:9-27. https://doi.org/10.1007/978-3-319-70178-3_2
23. Petersen R, Pan L, Blanck HM. Racial and ethnic disparities in adult obesity in the United States: CDC's tracking to inform state and local action. *Prev Chronic Dis*. 2019;16:E46. https://doi.org/10.5888/pcd16.180579
24. Lyman GH. Weight-based chemotherapy dosing in obese patients with cancer: back to the future. *J Oncol Pract*. 2012;8:e62-e64. https://doi.org/10.1200/JOP.2012.000606
25. Silvestris N, Argentiero A, Natalicchio A, et al. Antineoplastic dosing in overweight and obese cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Societa Italiana Endocrinologia (SIE)/Societa Italiana Farmacologia (SIF) multidisciplinary consensus position paper. *ESMO Open*. 2021;6:100153. https://doi.org/10.1016/j.esmoop.2021.100153
26. Ahmed M, von Itzstein MS, Sheffield T, et al. Association between body mass index, dosing strategy, and efficacy of immune checkpoint inhibitors. *J ImmunoTher Cancer*. 2021;9:e002349. https://doi.org/10.1136/jitc-2021-002349
27. Iyengar NM, Arthur R, Manson JE, et al. Association of body fat and risk of breast cancer in postmenopausal women with normal body mass index: a secondary analysis of a randomized clinical trial and observational study. *JAMA Oncol*. 2019;5:155-163. https://doi.org/10.1001/jamaoncol.2018.5327
28. Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. *Ann Oncol*. 2018;29:ii1-ii9. https://doi.org/10.1093/annonc/mdx810
29. Surov A, Pech M, Gessner D, et al. Low skeletal muscle mass is a predictor of treatment related toxicity in oncologic patients. A meta-analysis. *Clin Nutr*. 2021;40:5298-5310. https://doi.org/10.1016/j.clnu.2021.08.023
30. DeJesus RS, Croghan IT, Jacobson DJ, Fan C, St Sauver J. Incidence of obesity at 1 and 3 years among community dwelling adults: a population-based study. *J Prim Care Commun Health*. 2022;13:21501319211068632. https://doi.org/10.1177/21501319211068632
31. Wong ML, Cooper BA, Paul SM, et al. Age-related differences in patient-reported and objective measures of chemotherapy-induced peripheral neuropathy among cancer survivors. *Support Care Cancer*. 2019;27:3905-3912. https://doi.org/10.1007/s00520-019-04695-3
32. Bulls HW, Hoogland AI, Kennedy B, et al. A longitudinal examination of associations between age and chemotherapy-induced peripheral neuropathy in patients with gynecologic cancer. *Gynecol Oncol*. 2019;152:310-315. https://doi.org/10.1016/j.ygyno.2018.12.002
33. Gewandter JS, Fan L, Magnuson A, et al. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. *Support Care Cancer*. 2013;21:2059-2066. https://doi.org/10.1007/s00520-013-1766-y
34. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. *J Clin Oncol*. 2017;35:2604-2612. https://doi.org/10.1200/JCO.2016.71.3552
35. Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemother Res Pract*. 2012;2012:913848. https://doi.org/10.1155/2012/913848
36. Adams M, Kerby IJ, Rocker I, et al. A comparison of the toxicity and efficacy of cisplatin and carboplatin in advanced ovarian cancer. The Swons Gynaecological Cancer Group. *Acta Oncol*. 1989;28:57-60. https://doi.org/10.3109/02841868909111182
37. Griesinger F, Korol EE, Kayaniyil S, et al. Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: a meta-analysis. *Lung Cancer*. 2019;135:196-204. https://doi.org/10.1016/j.lungcan.2019.07.010
38. Ramalingam S, Perry MC, La Rocca RV, et al. Comparison of outcomes for elderly patients treated with weekly paclitaxel in combination with carboplatin versus the standard 3-weekly paclitaxel and carboplatin for advanced nonsmall cell lung cancer. *Cancer*. 2008;113:542-546. https://doi.org/10.1002/cncr.23583
39. Kiyota N, Tahara M, Mizusawa J, et al; Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG). Weekly cisplatin plus radiation for postoperative head and neck cancer (JCOG1008): a multicenter, noninferiority, phase II/III randomized controlled trial. *J Clin Oncol*. 2022;40:1980-1990. https://doi.org/10.1200/JCO.21.01293
40. 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;30:2055-2062. https://doi.org/10.1200/JCO.2011.39.5848
41. Dranitsaris G, Cottrell W, Spirovski B, Hopkins S. Economic analysis of albumin-bound paclitaxel for the treatment of metastatic breast cancer. *J Oncol Pharm Pract*. 2009;15:67-78. https://doi.org/10.1177/1078155208098584
42. Gu J, Lu H, Chen C, et al. Diabetes mellitus as a risk factor for chemotherapy-induced peripheral neuropathy: a meta-analysis. *Support Care Cancer*. 2021;29:7461-7469. https://doi.org/10.1007/s00520-021-06321-7

43. Cavaletti G, Frigeni B, Lanzani F, et al. Chemotherapy-induced peripheral neurotoxicity assessment: a critical revision of the currently available tools. *Eur J Cancer*. 2010;46:479-494. https://doi.org/10.1016/j.ejca.2009.12.008
44. 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;17:1483-1491. https://doi.org/10.1007/s00520-009-0613-7
45. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Support Care Cancer*. 2014;22:2261-2269. https://doi.org/10.1007/s00520-014-2255-7
46. Fernandes GDS, Pereira A. Development of new therapies for metastatic pancreatic cancer: are they better than FOLFIRINOX? *ESMO Open*. 2019;4:e000537. https://doi.org/10.1136/esmoopen-2019-000537
47. Gharaibeh M, McBride A, Bootman JL, Patel H, Abraham I. Economic evaluation for the US of nab-paclitaxel plus gemcitabine versus FOLFIRINOX versus gemcitabine in the treatment of metastatic pancreas cancer. *J Med Econ*. 2017;20:345-352. https://doi.org/10.1080/13696998.2016.1269015
48. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the Phase III KEYNOTE-407 Study. *J Clin Oncol*. 2023;41:1999-2006. https://doi.org/10.1200/JCO.22.01990
49. Pereira AF, Pereira LMS, Silva CMP, et al. Metformin reduces c-Fos and ATF3 expression in the dorsal root ganglia and protects against oxaliplatin-induced peripheral sensory neuropathy in mice. *Neurosci Lett*. 2019;709:134378. https://doi.org/10.1016/j.neulet.2019.134378
50. Starobova H, Mueller A, Allavena R, et al. Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. *Front Neurosci*. 2019;13:653. https://doi.org/10.3389/fnins.2019.00653
51. 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;38:3325-3348. https://doi.org/10.1200/JCO.20.01399