Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy Among Participants 65 Years or Older in Southwest Oncology Group Clinical Trials

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ABSTRACT

Background

Neuropathy is a debilitating toxicity associated with various chemotherapy agents. We evaluated the association between common comorbid conditions and the development of peripheral neuropathy in patients treated with taxane-based chemotherapy.

Methods

We examined the Southwest Oncology Group database to identify phase II and III trials that included taxane therapy from 1999 to 2011. We linked the Southwest Oncology Group clinical records to Medicare claims data according to Social Security number, sex, and date of birth. The following disease conditions potentially associated with peripheral neuropathy were evaluated: diabetes, hypothyroidism, hypercholesterolemia, hypertension, varicella zoster, peripheral vascular disease, and autoimmune diseases. Multivariate logistic regression was used to model the odds of experiencing grade 2 to 4 neuropathy.

Results

A total of 1,401 patients from 23 studies were included in the analysis. Patients receiving paclitaxel were more likely to experience grade 2 to 4 neuropathy compared with docetaxel (25% v 12%, respectively; OR, 2.20; 95% CI, 1.52 to 3.18; $P < .001$). The inclusion of a platinum agent was also associated with greater neuropathy (OR, 1.68; 95% CI, 1.18 to 2.40; $P = .004$). For each increase in age of 1 year, the odds of neuropathy increased 4% ($P = .006$). Patients with complications from diabetes had more than twice the odds of having neuropathy (OR, 2.13; 95% CI, 1.31 to 3.46; $P = .002$) compared with patients with no diabetes. In contrast, patients with autoimmune disease were half as likely to experience neuropathy (OR, 0.49; 95% CI, 0.24 to 1.02; $P = .06$). The other conditions were not associated with neuropathy.

Conclusion

We found that in addition to drug-related factors, age and history of diabetes were independent predictors of the development of chemotherapy-induced peripheral neuropathy. Interestingly, we also observed that a history of autoimmune disease was associated with reduced odds of neuropathy. Patients with diabetic complications may choose to avoid paclitaxel or taxane plus platinum combination therapies if other efficacious options exist.

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INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating toxicity associated with various agents that are widely used in the treatment of cancer. These toxicities have a significant impact on quality of life. Clinical trials with taxanes have shown grade 2 to 4 neuropathy rates ranging from 15% to 23%, as graded by the Common Terminology Criteria Adverse Events system, with higher rates related to the specific

drug, dose, schedule, and therapy duration.¹⁻³ Patients with grade 2 neuropathy have interference with function (eg, difficulty buttoning a shirt), those with grade 3 have interference with activities of daily living (eg, brushing teeth), and those with grade 4 have permanent and disabling symptoms.

There are a paucity of effective therapies for the treatment and prevention of CIPN.⁴ Identifying patients at risk for CIPN is important for multiple reasons. First, it can assist with personalizing regimens on the basis of toxicity risk.

Also, understanding factors that contribute to risk may point to potential underlying mechanisms that can be targeted for CIPN treatment or prevention trials.

The majority of studies evaluating risk factors for CIPN have been retrospective, from a single institution, or with inconsistent definitions of CIPN. Initial studies suggested that race, age, and obesity are risk factors for CIPN; however, other studies have not confirmed these findings.⁵⁻¹¹ It also may be that a history of other conditions that predispose patients to peripheral neuropathy may result in an increased risk of developing CIPN. A comprehensive evaluation of preexisting diseases or disorders associated with peripheral neuropathy, such as hypothyroidism, varicella zoster, and autoimmune disease, has not been reported.

Using a novel linkage between elderly patients enrolled in Southwest Oncology Group (SWOG) and Medicare claims data, we examined whether specific demographic, clinical, treatment, and comorbid disease conditions at the start of therapy predicted the development of CIPN among patients age 65 years or older enrolled in clinical trials containing taxane-based therapy.

METHODS

The study data were from SWOG, a national clinical trials consortium. We systematically identified all phase II and phase III trials that included taxane therapy in one or more treatment arms from 1999 to 2011 (inclusive) and that had already published their primary study report. Patients in trials for lung, prostate, breast, head and neck, bladder, and ovarian cancer were included. Patients who did not receive taxane therapy were excluded.

Demographic, Clinical, Treatment, and Neuropathy Data

Patient demographic characteristics, such as age, self-reported race and ethnicity, and sex, were based on questionnaires administered at the time of initial trial enrollment. A prognostic risk variable for survival outcomes was created on the basis of the clinical risk factors identified for each study (Appendix Table A1, online only). Within each study, an outcomes risk score was calculated for each patient as the sum of the number of study-specific adverse risk factors. The risk score was then split at the median, creating an indicator variable for high risk versus low risk. This allowed for risk adjustment for clinical prognosis in a uniform manner across the diverse panel of studies.

Baseline predictors of interest for CIPN were the type of taxane therapy, the planned duration of therapy, and the receipt of any platinum treatment on the basis of protocol-specified planned treatment. The actual observed amount of taxane therapy was examined separately, although it was not included as a model covariate because patients who develop CIPN may stop therapy prematurely. Time of initial registration, split at the halfway point through the period, and observed time on taxane treatment (split at the median) were collected as part of the study protocol. Clinical neuropathy was collected for each study as part of study protocol acute treatment toxicity reporting. Toxicity grades were defined by Common Terminology Criteria Adverse Events (version 2.0). Neuropathy may have occurred at any time during the study. The highest grade reported was the one retained as the neuropathy outcome.

Comorbid Disease Conditions Associated With CIPN

Comorbid disease conditions prevalent at the time of cancer diagnosis are rarely collected as part of baseline trial data. Therefore, to identify noncancer baseline disease conditions, we linked the SWOG clinical records to Medicare claims data according to Social Security

number, sex, and date of birth. We required that patients had at least 6 months of continuous Medicare Parts A and B coverage before study registration to ensure a sufficient minimum amount of coverage to identify potential baseline comorbid conditions. Also, because health maintenance organization providers do not submit claims records to Centers for Medicare & Medicaid Services, patients must simultaneously have had no health maintenance organization coverage. Medicare records were used to identify disease conditions on the basis of Part B, hospital outpatient, and hospital inpatient claims. Events were determined using the International Classification of Diseases (9th revision, clinical modification) diagnosis codes. Only patients who were ≥ 65 years of age at 6 months before enrollment were included.

A comorbid disease condition was identified as any hospital claim—or two or more physician or outpatient claims at least 30 days apart—for diabetes, liver disease, hypothyroidism, hypercholesterolemia, hypertension, varicella zoster, kidney disease, peripheral vascular disease, and autoimmune disease (Appendix Table A2, online only). These conditions are known to be associated with the development of peripheral neuropathy.¹²

Statistical Methods

Multivariate logistic regression was used to model the odds of experiencing clinically meaningful (grade 2 or greater) neuropathy. Separate models were conducted to examine moderate or worse neuropathy (grades 2 to 4) and severe or worse neuropathy (grades 3 to 4). Only one patient in this study population reported grade 4 neuropathy; therefore, grade 4 neuropathy was not examined as a separate outcome. Each predictor was analyzed in a separate model, and all odds ratios and *P* values were adjusted for age, race, sex, prognostic risk, date of initial enrollment, and planned treatment time according to the protocol. Additionally, because of heterogeneity due to separate studies, all analyses were stratified by treatment type as defined in the study protocol (docetaxel v paclitaxel) and the inclusion of platinum treatment as part of the treatment course. To assess whether patients with diabetes may have been already predisposed toward clinical neuropathy, we examined the neuropathy rates in a control set of patients from treatment arms for the studies included in this analysis who received no taxane or platinum treatment. *P* values with $\alpha < .05$ were reported as statistically significant, with no adjustments for multiple comparisons.

RESULTS

Twenty-three studies were included in the analysis (Table 1): nine studies were in lung cancer, five were in genitourinary cancer, four were in breast cancer, three were in head and neck cancer, and two were in gynecologic cancer. Fifteen of the studies were phase II, and eight were phase III. We identified 2,573 patients from these trials age 65 years or older. After restricting to patients with ≥ 6 months of continuous Medicare baseline data, 1,401 patients (55%) were included in the analysis. The number of patients per study ranged from 11 to 408. Fifteen studies comprising 68% of total patients had protocol eligibility criteria, excluding patients with preexisting neuropathy.

Patient Characteristics

Patients with a linkage to Medicare claims data were more likely to be non-Hispanic and male, have registered earlier in the period, have received docetaxel, have prostate cancer, have low-risk cancers, and not have received platinum therapy (Table 2). Among Medicare-linked patients, the median age was 72 years (range, 65.5 to 92 years). Although 9% of patients were black, roughly in line with cancer population rates, only 2% were Hispanic. The majority of

Table 1. Studies Included in Analysis

Study No.	Cancer Site	Cancer Stage	Treatment	Phase	Enrollment Years	Prior Neuropathy Exclusion Level	No.
S9712	Lung	Poor-risk stage III NSCLC	Concurrent carboplatin+VP-16 and radiation followed by paclitaxel	II	1999-2000	None	11
S9900	Lung	Clinical stages IB-IIIA NSCLC	Surgery alone or surgery plus preoperative paclitaxel plus carboplatin	III	2000-2004	Grade $\geq$ 1	38
S9902	H&N	Metastatic/recurrent squamous cell carcinoma	Docetaxel plus carboplatin	II	2000	Grade $\geq$ 2	12
S9912	GYN	Optimally debulked stage II epithelial ovarian, primary peritoneal, or fallopian tube cancer	Intravenous paclitaxel, intraperitoneal cisplatin, intravenous liposomal doxorubicin, and intraperitoneal paclitaxel	II	1999-2005	Grade $\geq$ 2	13
S9914	Lung	Extensive small-cell lung cancer	Paclitaxel, carboplatin, and topotecan with G-CSF	II	1999-2001	Grade $\geq$ 1	21
S9916	GU	Advanced, hormone refractory prostate cancer	Docetaxel and estramustine v mitoxantrone and prednisone	III	2000-2003	None	188
S0003	Lung	Advanced NSCLC	Cisplatin, paclitaxel, tirapazamine v cisplatin, paclitaxel	III	2001-2002	Grade $\geq$ 2	101
S0007	H&N	Advanced/recurrent squamous cell carcinoma	Paclitaxel plus cisplatin and fluorouracil	II	2001-2003	Grade $\geq$ 2	16
S0009	GYN	Stage III and IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	Neoadjuvant paclitaxel plus carboplatin v IV plus IP paclitaxel plus carboplatin	II	2002-2005	Grade $\geq$ 2	20
S0012	Breast	Inflammatory and locally advanced breast cancer	Standard doxorubicin and cyclophosphamide followed by weekly paclitaxel v weekly doxorubicin and daily oral cyclophosphamide plus G-CSF followed by weekly paclitaxel	III	2001-2005	None	23
S0022	Lung	Stage IIIB NSCLC	Concurrent cisplatin plus docetaxel and radiotherapy followed by consolidation docetaxel	II	2001-2002	Grade $\geq$ 1	12
S0023	Lung	Inoperable locally advanced stage III NSCLC	Cisplatin plus etoposide plus radiotherapy with consolidation docetaxel followed by maintenance therapy with ZA1839 or placebo	III	2002-2005	Grade $\geq$ 1	89
S0027	Lung	Advanced NSCLC in patients $\geq$ 70 years	Sequential vinorelbine and docetaxel	II	2001-2003	Grade $\geq$ 2	69
S0028	GU	Metastatic urothelial cancer in patients $\geq$ 70 years	Gemcitabine and paclitaxel	II	2001-2006	None	44
S0029	Breast	Metastatic breast cancer in patients $\geq$ 70 years	Single-agent docetaxel	II	2002-2005	None	12
S0032	GU	High-risk metastatic adenocarcinoma	Early oral estramustine, oral etoposide, and intravenous paclitaxel in combination with hormone therapy	II	2002-2005	None	11
S0102	Breast	HER-2 negative, stage IV	Docetaxel and vinorelbine plus filgrastim	II	2001-2003	Grade $\geq$ 2	13
S0219	GU	Nonmetastatic carcinoma of the bladder	Neoadjuvant gemcitabine, paclitaxel, and carboplatin with molecular correlates	II	2003-2006	None	31
S0221	Breast	Node-positive or high-risk node negative	Continuous schedule AC+G v 2-week schedule AC, followed by paclitaxel administered either every 2 weeks or weekly for 12 weeks	III	2003-2011	None	127
S0329	H&N	Recurrent/metastatic squamous cell carcinoma	Gemcitabine and paclitaxel combination administered every 2 weeks	II	2005-2006	Grade $\geq$ 2	23
S0421	GU	Advanced hormone refractory prostate cancer	Docetaxel and atrasentan v docetaxel and placebo	III	2006-2010	Grade $\geq$ 2	408
S0536	Lung	Advanced NSCLC	Combination carboplatin, paclitaxel, cetuximab and bevacizumab followed by cetuximab and bevacizumab	II	2006-2007	Grade $\geq$ 2	33
S0819	Lung	Advanced NSCLC	Carboplatin plus paclitaxel or carboplatin plus paclitaxel plus bevacizumab with or without concurrent cetuximab	III	2009-2011	Grade $\geq$ 2	86

Abbreviations: AC, adriamycin and cytoxan; G; G-CSF; G-CSF, granulocyte colony-stimulating factor; GU, genitourinary; GYN, gynecologic; H&N, head and neck; IV+IP, intravenous and intraperitoneal; NSCLC, non-small-cell lung cancer; VP-16, etoposide.

Table 2. Patient Characteristics

Characteristic	Medicare-Linked Patients (N = 1,401)		Patients Without Medicare Link (n = 1,172)		P*	Characteristic	Medicare-Linked Patients (N = 1,401)	
	No. or Median	% or Range	No. or Median	% or Range			No. or Median	%
Demographic and treatment factors						Baseline comorbid diseases		
Age, years (median or range)	72	65-92	72	65-89	.65	Diabetes with chronic complications	110	8
Race					.08	Diabetes with or without chronic complications	368	26
Asian	22	2%	18	2%		Hypothyroidism	231	16
Black	129	9%	74	6%		Peripheral vascular disease	130	9
Native	7	< 1%	3	< 1%		Autoimmune diseases*	79	6
Unknown	20	1%	18	2%		Sjögren's syndrome	12	< 1
White	1,223	87%	1,059	90%		Lupus	2	< 1
Ethnicity					.05	Rheumatoid arthritis	49	3
Not Hispanic	1,371	98%	1,132	97%		Scleroderma	27	2
Hispanic	30	2%	40	3%		Mixed connective tissue disease	0	—
Sex					.01	Dermatomyositis	0	—
Female	388	28%	377	32%		Polymyositis	0	—
Male	1,013	72%	795	68%		Vasculitis	0	—
Time of initial registration					< .001	Giant cell arteritis	0	—
< 2004	588	42%	294	25%		HIV	0	—
2004 or later	813	58%	878	75%		Varicella zoster	37	3
Kind of taxane					< .001	Hypertension	956	68
Docetaxel	803	57%	486	41%		Hypercholesterolemia	673	48
Paclitaxel	598	43%	686	59%				
Planned time receiving treatment according to protocol, days (median or range)	126	42-252	126	42-252	.002			
Observed time on treatment, days (median or range)	108	1-1,776	105	1-864	.01			
Type of cancer					< .001			
Bladder	31	2%	15	1%				
Breast	175	12%	116	10%				
Head & neck	51	4%	9	1%				
Lung	460	33%	639	55%				
Ovarian	33	2%	6	1%				
Prostate	651	46%	387	33%				
Cancer stage/high risk					.001			
Low	781	56%	577	49%				
High	620	44%	594	51%				
Total time of Medicare coverage prior to registration, years (median or range)	3.7	0.5-13	—	—				
Platinum therapy as part of protocol	483	34%	645	55%	< .001			
Total time of Medicare coverage prior to registration, years (median or range)	3.7	0.5-13	—	—				

* P value uses t tests for continuous variables and χ^2 tests for categorical variables to compare those patients linked to Medicare claims data with those patients not linked to Medicare claims data.

*P value uses *t* tests for continuous variables and χ^2 tests for categorical variables to compare those patients linked to Medicare claims data with those patients not linked to Medicare claims data.

patients were male (72%), due in part to the predominance of patients with prostate cancer (46%). The median observed time on treatment (108 days) was 14% less than the median planned time on treatment (126 days). The most common comorbid disease conditions were hypertension (68%), hypercholesterolemia (48%), and diabetes (26%).

Predictors of Neuropathy

In total, 251 of 1,401 patients (18%) had grade 2 or worse neuropathy, and 121 (9%) had grade 3 or worse neuropathy. (For

comparison, among patients who were younger than 65 years in these trials and not included in this analysis, the rate of grade 2 to 4 CIPN was 15%, and the rate of grade 3 to 4 CIPN was 9%.) Demographic, clinical, and treatment predictors of neuropathy are listed in Table 3. Patients who received paclitaxel were more likely to experience grade 2 to 4 neuropathy (25% v 12%; OR, 2.20; 95% CI, 1.52 to 3.18; $P < .001$) and grade 3 to 4 neuropathy (13% v 5%; OR, 2.86; 95% CI, 1.70 to 4.80; $P < .001$) than were those who received docetaxel. Patients who received platinum treatment with a taxane were more likely to

Table 3. Neuropathy Rates According to Demographic, Clinical, and Treatment Characteristics

Characteristic	Grades 2-4 Neuropathy				Grades 3-4 Neuropathy			
	No, No. (%)	Yes, No. (%)	OR (95% CI)*	P*	No, No. (%)	Yes, No. (%)	OR (95% CI)*	P*
Total	1,150 (82)	251 (18)			1,280 (91)	121 (9)		
Mean age (years)	72.5	73.0	1.04 (1.01 to 1.07)	.006	72.6	73.1	1.04 (1.00 to 1.08)	.03
Age, categories (years)								
< 75	806 (82)	172 (18)	Reference		898 (92)	80 (8)	Reference	
≥ 75	344 (81)	79 (19)	1.28 (0.94 to 1.75)	.12	382 (90)	41 (10)	1.46 (0.97 to 2.22)	.07
Race								
Asian/Pacific Islander	16 (73)	6 (27)	2.00 (0.75 to 5.29)	.16	17 (77)	5 (23)	3.63 (1.26 to 10.50)	.02
Black	112 (87)	17 (13)	0.84 (0.49 to 1.44)	.52	121 (94)	8 (6)	0.86 (0.41 to 1.84)	.70
Native	7 (100)	0			7 (100)	0		
Unknown	16 (80)	4 (20)	0.99 (0.32 to 3.07)	.99	18 (90)	2 (10)	1.16 (0.26 to 5.16)	.85
White	999 (82)	224 (18)	Reference		1,117 (91)	106 (9)	Reference	
Ethnicity								
Not Hispanic	1,123 (82)	248 (18)	Reference		1,252 (91)	119 (9)	Reference	
Hispanic	27 (90)	3 (10)	0.46 (0.13 to 1.61)	.23	28 (93)	2 (7)	0.61 (0.13 to 2.75)	.52
Sex								
Female	311 (80)	77 (20)	Reference		343 (88)	45 (12)	Reference	
Male	839 (83)	174 (17)	1.06 (0.74 to 1.50)	.76	937 (92)	76 (8)	0.82 (0.52 to 1.29)	.39
Time of initial registration								
< 2004	475 (81)	113 (19)	Reference		526 (89)	62 (11)	Reference	
2004 or later	675 (83)	138 (17)	0.97 (0.72 to 1.31)	.87	754 (93)	59 (7)	0.63 (0.42 to 0.94)	.02
Kind of taxane								
Docetaxel	704 (88)	99 (12)	Reference		761 (95)	42 (5)	Reference	
Paclitaxel	446 (75)	152 (25)	2.20 (1.52 to 3.18)	< .001	519 (87)	79 (13)	2.86 (1.70 to 4.80)	< .001
Cancer stage/high risk								
Low	643 (82)	138 (18)	Reference		713 (91)	68 (9)	Reference	
High	507 (82)	113 (18)	1.00 (0.75 to 1.33)	1.00	567 (91)	53 (9)	0.89 (0.60 to 1.32)	.56
Planned treatment time in protocol, days								
< 126	389 (83)	82 (17)	Reference		430 (91)	41 (9)	Reference	
≥ 126	761 (82)	169 (18)	1.05 (0.71 to 1.55)	.79	850 (91)	80 (9)	1.34 (0.81 to 2.22)	.26
Platinum treatment								
No	793 (86)	125 (14)	Reference		855 (93)	63 (7)	Reference	
Yes	357 (74)	126 (26)	1.68 (1.18 to 2.40)	.004	425 (88)	58 (12)	1.08 (0.67 to 1.74)	.77

*Odds ratios and *P* values adjusted for age, race (black/white/other), sex, cancer stage/risk, date of initial enrollment, and planned treatment time according to the protocol (at or above v below the median), and stratified by treatment type (docetaxel v paclitaxel) and platinum treatment (yes/no).

experience grade 2 to 4 neuropathy (26% v 14%; OR, 1.68; 95% CI, 1.18 to 2.40; *P* = .004) than were those who did not. For each increase in age of 1 year, the odds of neuropathy increased by 4% (*P* = .006).

Compared with patients without diabetes, grade 2 to 4 neuropathy was observed more often in patients with diabetes with complications (16% v 25%, respectively) and in patients with diabetes with or without complications (16% v 22%, respectively; Fig 1A; Appendix Table A3, online only). In contrast, patients with autoimmune disease were less likely to have grade 2 to 4 neuropathy compared with those without autoimmune disease (11% v 18%, respectively). Similarly, grade 3 to 4 neuropathy was most common in patients with diabetes with complications (8% v 12% respectively) and least common in patients with autoimmune disease (9% v 4%, respectively; Fig 1B).

In a multivariable logistic regression model controlling for clinical and demographic factors (Fig 2), patients with diabetic complications had twice the odds of having grade 2 to 4 neuropathy (OR, 2.13; 95% CI, 1.31 to 3.46; *P* = .002) compared with those without. Similarly, patients with diabetes with or without complications had two thirds greater odds of having neuropathy (OR, 1.67; 95% CI, 1.23 to 2.27; *P* = .001). In contrast, patients with autoimmune disease were half as likely to experience grade 2 to 4 neuropathy (OR, 0.49; 95% CI, 0.24 to 1.02; *P* = .06) and one third as likely to

experience grade 3 to 4 neuropathy (OR, 0.32; 95% CI, 0.10 to 1.03; *P* = .06) compared with those without autoimmune disease. There was no evidence that the other disease conditions associated with neuropathy were associated with neuropathy in this set of studies.

CIPN Rates in Non-Taxane-Treated Patients

Among the 23 studies included in the analysis, two phase III trials (S9900 and S9916) included treatment arms with no taxane or platinum treatment, comprising 227 control patients (Appendix Table A4, online only). Among these, 12 had diabetes with complications, 47 had diabetes with or without complications, and five had an autoimmune disease. None of these control patients with these baseline conditions reported neuropathy while in the study. In patients with diabetes, with or without complications, there were much higher rates of grade 2 to 4 neuropathy (22% v 0%; *P* < .001) and grade 3 to 4 neuropathy (11% v 0%; *P* = .02) among those on taxane therapy. Results were similar but less extreme (likely due to smaller samples) for patients who had diabetes with complications (25% v 0%, *P* = .05, and 12% v 0%, *P* = .21, respectively) and for patients with an autoimmune disease (11% v 0%, *P* = .42, and 4% v 0%, *P* = .66, respectively). These findings are consistent with the hypothesis that it was the use of taxane therapy in patients with

Fig 1. Grade 2 to 4 (A) and grade 3 to 4 (B) neuropathy rates by comorbid disease category. Each bar represents the proportion with neuropathy for patients with the specified condition (blue) or without the specified condition (gold). The *P* values shown above each set of bars show the statistical significance for the covariate representing whether a patient had the specified condition (ie, with v without condition) from the multivariable logistic regression analyses. The comorbid disease categories are sorted in descending order of the odds ratio for having grade 2 to 4 neuropathy, derived from multivariable regression analyses. *P* values were derived from multivariable logistic regression models adjusting for age, race (black/white/other), sex, cancer stage/risk, date of initial enrollment, and planned treatment time according to the protocol (at or above v below the median), and stratified by treatment type (docetaxel v paclitaxel) and platinum treatment (yes/no). For the analysis of diabetes with chronic complications, the comparison is between patients with diabetes plus complications versus patients with no diabetes. Patients with diabetes without complications are excluded from this analysis. Autoimmune diseases include Sjögren's syndrome, lupus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, vasculitis, and giant cell arteritis. VD, vascular disease.

diabetes or autoimmune diseases, rather than the disease conditions themselves, that resulted in different CIPN rates.

Sensitivity Analyses

In sensitivity analysis, we considered a longer, 1-year prestudy window for continuous Medicare coverage to identify comorbid

conditions. Results were similar (data not shown). There were also no substantive changes to the results when planned treatment time was considered as a continuous variable (data not shown). In the subset of studies that excluded patients with preexisting neuropathy, patients with autoimmune disease were less likely to have grade 2 to 4 or 3 to 4 neuropathy, but the strength of the association was diminished. Finally, with diabetes included as a baseline

Fig 2. Forest plot of the association of neuropathy grade with each comorbid condition, controlling for demographic, clinical, and treatment characteristics. Each box represents the odds ratio, and each line represents the 95% CI around the estimated odds ratio. The vertical line shows the line of equal odds. Odds ratios to the right of the vertical line indicate that patients with the specified condition had higher odds of grade 2 to 4 or grade 3 to 4 neuropathy, and odds ratios to the left of the vertical line indicate that patients with the specified condition had lower odds of grade 2 to 4 or grade 3 to 4 neuropathy. The comorbid disease categories are sorted in descending order of the odds ratio for having grade 2 to 4 neuropathy in multivariable regression. Odds ratios and *P* values were derived from multivariable logistic regression models, adjusting for age, race (black/white/other), sex, cancer stage and risk, date of initial enrollment, and planned treatment time according to the protocol (at or above v below the median), and stratified by treatment type (docetaxel v paclitaxel) and platinum treatment (yes/no). For the analysis of diabetes with chronic complications, the comparison is between patients with diabetes plus complications versus patients with no diabetes. Patients with diabetes without complications were excluded from this analysis. Autoimmune diseases include Sjögren's syndrome, lupus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, vasculitis, and giant cell arteritis. Each square represents an odds ratio, and each horizontal line is the 95% CI. The vertical line is the line of equal odds.

covariate, the association of autoimmune status and grade 2 to 4 and grade 3 to 4 neuropathy was statistically significant ($P = .04$). Minimal other changes were evident when diabetes and autoimmune disease were included as covariates.

DISCUSSION

Using a novel linkage between a large cohort of elderly patients enrolled in SWOG clinical trials and Medicare claims, we found that patients with a baseline history of diabetes and, in particular, those with a history of complications from diabetes, have a substantially higher risk of developing CIPN. We also observed that patients with autoimmune disease may have a lower risk of developing CIPN. In addition, compared with docetaxel, patients receiving paclitaxel had more than double the risk, and those who had the addition of a platinum agent had more than two thirds increased odds of developing CIPN.

Diabetic peripheral neuropathy is the most common complication in patients with diabetes and the most common cause of neuropathy worldwide.¹³ Early metabolic abnormalities in the nerves are thought to be due to the direct exposure of nerve tissue or its vascular bed to high concentrations of glucose.¹⁴ The presence and severity increases over time with poor glycemic control. Much of the prior research evaluating the association between diabetes and CIPN has come from retrospective trials in which it is difficult to determine what component of the neuropathy is from the diabetes and what is from the exposure.^{10,11,15} To

estimate the association of diabetes with CIPN, investigators evaluated the development of hyperglycemia as a surrogate for diabetes. They found that patients who developed hyperglycemia while receiving taxane therapy had an odds ratio of 1.47 for developing grade 2 to 4 CIPN.⁸ Prospective trials that include agents that are known to cause CIPN typically exclude patients with severe neuropathy; in this study, more than two thirds of patients were from trials that excluded patients with preexisting neuropathy. Furthermore, we found no neuropathy in a control set of patients who received no taxane therapy. Thus, we feel confident that the neuropathy observed in patients with diabetes developed while receiving taxane therapy.

In addition to diabetes, peripheral neuropathy is caused by a number of other diseases and disorders. Underproduction of thyroid hormone can slow metabolism and lead to fluid accumulation, which can exert pressure on peripheral nerves.¹² Vasculitis can impair blood flow to nerves, which decreases oxygen supply to the peripheral nerves, resulting in subsequent nerve damage.¹² Infections such as herpes varicella zoster and HIV can damage sensory nerves. In addition, medications that are commonly used to treat hypertension and high cholesterol can also result in peripheral neuropathy. We did not see an increased risk of CIPN among patients who had a history of these conditions.

Other than age, we did not find other demographic factors such as gender, ethnicity, or self-reported race to be associated with the development of CIPN. Our sample only included patients age 65 years and older who received Medicare. Other studies evaluating the association between age and CIPN have reported conflicting

results; however, the mean age in those studies was significantly younger than our cohort.^{8,15,16} The association between black race and the development of CIPN has also been inconsistent. An analysis of patients with early-stage breast cancer did not show an association between self-reported black race and CIPN; however, a genome-wide association study of patients in the same study found an association between genetically determined African ancestry and taxane-induced CIPN.⁷ Similarly, in an analysis from a SWOG adjuvant breast cancer trial, an African American–specific haplotype was associated with an almost threefold increase in risk of CIPN.¹⁷ These studies did not have information on baseline diabetes. Because racial minorities have higher prevalence rates of diabetes, worse diabetes control, and higher rates of diabetes-associated complications, it has been difficult to ascertain an independent effect of black race.¹⁸ The current analysis provides a detailed assessment of the risk associated with diabetes.

We were intrigued by the borderline, significant, protective effect of a history of autoimmune disease with the development of CIPN. Sjögren's syndrome, rheumatoid arthritis, and lupus can result in autoantibodies that directly cause nerve damage.¹⁹ Although the mechanism contributing to the development of CIPN is poorly understood, there may be a relationship among the immune system, inflammation, and peripheral neuropathy.^{20,21} If so, it is possible that prior anti-inflammatory treatment may have been protective against the development of CIPN in these patients. It has been hypothesized that inflammatory cascade activation, proinflammatory cytokine upregulation, and neuroimmune communication pathways may play essential roles in the initiation and progression of CIPN.²² Paclitaxel-induced CIPN was found to be associated with the activation of microglia following the expression and release of proinflammatory cytokines in the spinal dorsal horn.²³ If these pathways are already active in patients with autoimmune disease, chemotherapy may have a less dramatic effect.

We acknowledge several limitations of our study and of the Medicare database in general. All the patients were older than 65 years of age, and elderly patients are often not accrued to clinical trials. Patients were also required to have 6 or more months of continuous Medicare claims before study registration. This may influence the generalizability of the findings. Although we required patients to have two claims to reduce misclassification bias, a process routinely performed in seeking diagnoses, it is still possible that not all patients with Medicare claims had the comorbid condition we assigned.²⁴⁻²⁶ Other factors known to be associated with neuropathy, such as medication, obesity, and

history of alcohol use, were not available. Also, some comorbid conditions were rare; therefore, power to identify their relationship with neuropathy was limited. It is possible that our results are not generalizable to younger patients. All the patients were enrolled in a clinical trial; therefore, these results may not be generalizable to all patients who did not meet eligibility criteria for one of the SWOG trials, because the majority of patients had a performance status of 0 or 1 and did not have end-organ damage or any medical condition that was uncontrolled at the time of enrollment. Finally, our goal was to identify potential predictors of neuropathy for future examination; therefore, no adjustments for multiple comparisons were made. However, in some instances (eg, taxane type, diabetes), the strength of the association between the predictor and neuropathy would have remained statistically significant, even under conservative multiple comparisons approaches.

In summary, we have shown that in addition to drug-related factors and duration of therapy, age and history of diabetes are independent predictors of the development of CIPN. Interestingly, we also found a suggestion that a prior history of an autoimmune disease was associated with lower rates of neuropathy. Future studies should be performed to understand the role of the immune system and cytokine activation in the development and prevention of CIPN. In the meantime, patients with diabetic complications should consider avoiding paclitaxel or taxane plus platinum combination therapies, if other options exist.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy Among Participants 65 Years or Older in Southwest Oncology Group Clinical Trials

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Appendix

Table A1. Definitions of Adverse Risk Levels for Construction of Prognostic Risk Score

Study No.	Cancer Site	Study-Specific Prognostic Factors	Adverse (ie, Poor Prognosis) Risk Levels	No. of Risk Factors to Be Considered High Risk
S9712	Lung	Weight loss (< 5% v ≥ 5%) T stage (T1/T2 v T3/T4) N stage (N0/N1 v N2/N3) LDH (≤ IULN v > IULN)	Weight loss ≥ 5% T stage T3/T4 N stage N2/N3 LDH > IULN	≥ 2
S9900	Lung	Clinical stage (IB/IIA v IIB/IIA)	Clinical stage IIB/IIIA	1
S9902	H&N	Disease type (metastatic v nonmetastatic)	Metastatic disease	1
S9912	GYN	Stage (IIIA/IIIB v IIIC/IV)	Stage IIIC/IV	1
S9914	Lung	Weight loss (< 5% v ≥ 5%) LDH (≤ IULN v > IULN)	Weight loss ≥ 5% LDH > IULN	≥ 1
S9916	GU	Type of progression (PSA only v measurable/evaluable) Bone pain (grade < 2 v ≥ 2) Performance status (0/1 v 2/3)	Measurable/evaluable disease Bone pain grade ≥ 2 Performance status 2-3	≥ 2
S0003	Lung	Weight loss (< 5% v ≥ 5%) Stage (IIIB v IV) LDH (≤ IULN v > IULN)	Weight loss ≥ 5% Stage IV LDH > IULN	≥ 2
S0007	H&N	Performance status (0/1 v 2) Disease type (nonmetastatic v metastatic)	Performance status 2 Metastatic disease	≥ 1
S0009	GYN	Stage (III v IV) Performance status (0/1 v 2)	Stage IV Performance status 2	≥ 1
S0012	Breast	Inflammatory disease (no v yes)	Inflammatory disease, yes	1
S0022	Lung	Weight loss (< 5% v ≥ 5%) T stage (T1/T2/T3 v T4) N stage (N0/N1/N2 v N3) LDH (≤ IULN v > IULN)	Weight loss ≥ 5% T stage T4 N stage N3 LDH > IULN	≥ 2
S0023	Lung	T stage (T1/T2 v T3/T4) N stage (N0/N1 v N2/N3) Histologic/cytologic subtype (nonsquamous v squamous)	T stage T3/T4 N stage N2/N3 Squamous histologic/cytologic subtype	≥ 2
S0027	Lung	Age (< 70 v ≥ 70) Performance status (0/1 v 2)	Age ≥ 70 Performance status 2	2
S0028	GU	Age (< 60 v ≥ 70)	Age ≥ 70	1
S0029	Breast	Age (< 60 v ≥ 70)	Age ≥ 70	1
S0032	GU	Bone metastases (no v yes) Bone pain (< 2 v ≥ 2)	Bone metastases, yes Bone pain ≥ 2	2
S0102	Breast	ER/PR status (either or both positive or borderline or unknown v both negative)	ER/PR status both negative	1
S0219	GU	T stage (T2 v T3/T4a) Performance status (0-1 v 2)	T stage T3/T4a Performance status 2	≥ 1
S0221	Breast	Nodal status (0-3 v ≥ 4) HER2, ER, PR status (negative v positive)	Nodal status ≥ 4 nodes HER2- and ER and/or PR+: score = 0 HER2+ and ER and PR either - or +: score = 1 HER2- and ER- and PR-: score = 2	≥ 2
S0329	H&N	Disease type (nonmetastatic v metastatic)	Metastatic disease	1
S0421	GU	Type of progression (PSA only v measurable/evaluable) Prior use of bisphosphonates (no v yes) Worst pain (< 4 v ≥ 4) Extraskeletal metastases (no v yes)	Measurable/evaluable disease Prior use of bisphosphonates, yes Worst pain ≥ 4 Extraskeletal metastases, yes	≥ 3
S0536	Lung	Stage (IIIB v IV) Smoking history (former/never v current)	Stage IV Current smoker	2
S0819	Lung	Bevacizumab status (appropriate v inappropriate) Smoking history (former/never v current) M stage (M1a v M1b)	Bevacizumab, inappropriate Current smoker M stage M1b	≥ 2

Abbreviations: ER, estrogen receptor; GU, genitourinary; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; H&N, head and neck; IULN, institutional upper limit of normal; LDH, lactate dehydrogenase; PR, progesterone receptor; PSA, prostate-specific antigen.

Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy

Table A2. Codes for Comorbid Conditions

Comorbid Condition	ICD9 Code
Diabetes with chronic complications	250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.90, 250.91, 250.92, 250.93
Diabetes with or without chronic complications	249.00, 249.01, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.90, 250.91, 250.92, 250.93
Hypothyroidism	246.9, 794.5, V77.0, 240.9, 243, 244.0, 244.1, 244.2, 244.3, 244.8, 244.9, 246.1, 246.8
Hypercholesterolemia	272.2, 272.4
Hypertension	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91
Varicella zoster	053.0, 053.10, 053.11, 053.14, 053.19, 053.20, 053.21, 053.22, 053.29, 053.71, 053.79, 053.8, 053.9
Peripheral vascular disease	093.0, 437.3, 440.0, 440.1, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.9, 441.00, 441.01, 441.02, 441.03, 441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, 441.9, 443.1, 443.21, 443.22, 443.23, 443.24, 443.29, 443.81, 443.82, 443.89, 443.9, 447.1, 557.1, 557.9, V43.4
Autoimmune diseases	
Sjögren's syndrome	370.33
Lupus	373.34, 695.4, 71.0
Rheumatoid arthritis	V82.1, 446.0, 446.1, 446.20, 446.21, 446.29, 446.3, 446.4, 446.5, 446.6, 446.7, 701.0, 710.0, 710.1, 710.2, 710.3, 710.4, 710.8, 710.9, 711.20, 711.21, 711.22, 711.23, 711.24, 711.25, 711.26, 711.27, 711.28, 711.29, 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 714.4, 714.81, 714.89, 714.9, 719.30, 719.31, 719.32, 719.33, 719.34, 719.35, 719.36, 719.37, 719.38, 719.39, 720.0, 720.1, 720.2, 720.81, 720.89, 720.9, 725, 728.5, 728.89, 729.30, 729.31, 729.39
Scleroderma	701.0, 701.1, 517.2
Mixed connective tissue disease	710.8
Dermatomyositis	710.3
Polymyositis	710.4
Vasculitis	362.18
Giant cell arteritis	446.5
Kidney disease	250.40, 250.41, 250.42, 250.43, 285.21, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 580.89, 580.9, 581.89, 581.9, 582.89, 582.9, 583.6, 583.7, 585.1, 585.2, 585.3, 585.4, 585.5, 585.9, 794.4
Liver disease	571.2, 571.3, 571.5, 571.8, 571.9, 572.8, 573, 573.8, 573.9

Abbreviation: ICD9, International Classification of Diseases (9th revision, clinical modification).

Table A3. Adjusted Association Between Baseline Conditions and Chemotherapy-Induced Peripheral Neuropathy

	Grades 2-4 Neuropathy				Grades 3-4 Neuropathy			
	No, No. (%)	Yes, No. (%)	OR (95% CI)*	P*	No, No. (%)	Yes, No. (%)	OR (95% CI)*	P*
Diabetes with chronic complications†	1,150 (82)	251 (18)			1,280 (91)	121 (9)		
No	864 (83.7)	169 (16.3)	Reference		952 (92.2)	81 (7.8)	Reference	
Yes	82 (74.5)	28 (25.5)	2.13 (1.31 to 3.46)	.002	97 (88.2)	13 (11.8)	1.73 (0.90 to 3.32)	.10
Diabetes with or without chronic complications								
No	864 (83.6)	169 (16.4)	Reference		952 (92.2)	81 (7.8)	Reference	
Yes	286 (77.7)	82 (22.3)	1.67 (1.23 to 2.27)	.001	328 (89.0)	40 (11.0)	1.61 (1.07 to 2.42)	.02
Liver Disease								
No	1,005 (83)	212 (17)	Reference		1,112 (91)	105 (9)	Reference	
Yes	145 (79)	39 (21)	1.27 (0.85 to 1.89)	.24	168 (91)	16 (9)	0.98 (0.56 to 1.73)	.95
Hypothyroidism								
No	966 (82.6)	204 (17.4)	Reference		1,072 (91.6)	98 (8.4)	Reference	
Yes	184 (79.7)	47 (20.3)	1.12 (0.77 to 1.63)	.56	208 (90.0)	23 (10.0)	1.05 (0.64 to 1.74)	.84
Hypercholesterolemia								
No	604 (83.0)	124 (17.0)	Reference		671 (92.2)	57 (7.8)	Reference	
Yes	546 (81.1)	127 (18.9)	1.07 (0.80 to 1.43)	.66	609 (90.5)	64 (9.5)	1.23 (0.83 to 1.84)	.30
Hypertension								
No	365 (82.0)	80 (18.0)	Reference		410 (92.1)	35 (7.9)	Reference	
Yes	785 (82.1)	171 (17.9)	0.97 (0.71 to 1.31)	.83	870 (91.0)	86 (9.0)	1.15 (0.75 to 1.77)	.51
Varicella zoster								
No	1,119 (82.0)	245 (18.0)	Reference		1,247 (91.4)	117 (8.6)	Reference	
Yes	31 (83.8)	6 (16.2)	0.82 (0.33 to 2.03)	.67	33 (89.2)	4 (10.8)	1.18 (0.40 to 3.48)	.77
Kidney disease								
No	979 (81)	224 (19)	Reference		1,093 (91)	110 (9)	Reference	
Yes	171 (86)	27 (14)	0.73 (0.46 to 1.14)	.16	187 (94)	11 (6)	0.65 (0.34 to 1.25)	.19
Peripheral vascular disease								
No	1,040 (81.8)	231 (18.2)	Reference		1,158 (91.1)	113 (8.9)	Reference	
Yes	110 (84.6)	20 (15.4)	0.71 (0.43 to 1.19)	.19	122 (93.8)	8 (6.2)	0.62 (0.29 to 1.31)	.21
Autoimmune diseases‡								
No	1,080 (81.7)	242 (18.3)	Reference		1,204 (91.1)	118 (8.9)	Reference	
Yes	70 (88.6)	9 (11.4)	0.49 (0.24 to 1.02)	.06	76 (96.2)	3 (3.8)	0.32 (0.10 to 1.03)	.06

*Odds ratios and *P* values adjusted for age, race (black/white/other), sex, cancer stage/risk, date of initial enrollment, and planned treatment time according to the protocol (at or above v below the median), and stratified by treatment type (docetaxel v paclitaxel) and platinum treatment (yes/no).

†The comparison is between patients with diabetes plus complications versus patients with no diabetes. Patients with diabetes without complications are excluded from this analysis.

‡Includes Sjögren's syndrome, lupus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, vasculitis, and giant cell arteritis.

Table A4. CIPN Rates in Taxane- Versus Non-Taxane-Treated Patients

	Grades 2-4 Neuropathy			Grade 3-4 Neuropathy		
	No, No. (%)	Yes, No. (%)	P*	No, No. (%)	Yes, No. (%)	P*
Diabetes with chronic complications						
Taxane	82 (75)	28 (25)		97 (88)	13 (12)	
No taxane	12 (100)	0 (0)	.05	12 (6)	0 (0)	.21
Diabetes with or without chronic complications						
Taxane	286 (78)	82 (22)		328 (89)	40 (11)	
No taxane	47 (100)	0 (0)	< .001	47 (100)	0 (0)	.02
Autoimmune diseases†						
Taxane	70 (89)	9 (11)		76 (96)	3 (4)	
No taxane	5 (100)	0 (0)	.42	5 (100)	0 (0)	.66

Abbreviation: CIPN, chemotherapy-induced peripheral neuropathy.

**P* value from χ^2 test.

†Autoimmune diseases include Sjögren's syndrome, lupus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, vasculitis, and giant cell arteritis.