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Cost of peripheral neuropathy in patients receiving treatment for multiple myeloma: a US administrative claims analysis

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Abstract

Background: Peripheral neuropathy (PN) is a common consequence of multiple myeloma (MM) among those commonly treated with older-generation proteasome inhibitors (PIs). In this study, we evaluated the economic burden attributable to PN among MM patients in real-world practice settings in the US.

Methods: Adults diagnosed with MM and first treated (index event) between 1 July 2006 and 28 February 2017 were identified from MarketScan® Commercial and Medicare claim databases. Continuous enrollment for at least 12 months without treatment and PN diagnoses were required pre-index. Patients were followed for at least 3 months until inpatient death or end of data. The International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and ICD-10-CM diagnosis codes were used to identify PN. Propensity-score matching was applied to match every patient with PN to two MM patients without a PN diagnosis (controls). Healthcare utilization and expenditures per patient per month (PPPM) in the postindex period were estimated.

Results: Of 11,851 patients meeting the study criteria, 15.5% had PN. After matching 1387 patients with PN and 2594 controls were identified. Baseline characteristics were well balanced between cohorts; mean follow up was 23–26 months. PPPM total costs were significantly higher by $1509 for patients with PN than controls, driven by higher hospitalization (PN 77.4%, controls 67.2%; $p < 0.001$) and emergency department rates (PN 67.8%, controls 58.4%; $p < 0.001$) and more outpatient hospital-based visits PPPM (PN 13.5 $\pm$ 14.7, controls 11.5 $\pm$ 18.0; $p < 0.001$).

Conclusions: PN is a prevalent MM treatment complication associated with a significant economic burden adding to the complexity and cost of MM treatment. Highly effective novel treatments such as carfilzomib may reduce the overall disease burden.

Keywords: chemotherapy-induced neuropathy, healthcare costs, line of therapy, multiple myeloma, peripheral neuropathy

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Introduction

Multiple myeloma (MM) is a systemic malignancy of plasma cells in bone marrow, with approximately 30,280 incident cases estimated to be diagnosed in the United States in 2017 (17,940 men and 12,790 women). MM primarily affects the elderly population since the median age at incidence is 69 years.[1,2] For several decades, the standard treatment approach has been induction therapy followed by autologous stem-cell transplantation for transplant-eligible patients and high-dose chemotherapy for other patients. While the recent introduction of many novel therapies such as immunomodulating agents, proteasome inhibitors (PIs), monoclonal antibodies, and histone deacetylase inhibitor have shown improved response, progression-free survival[3–9] and survival rates[10] in clinical trials, MM remains an incurable malignancy for the majority of patients.[11]

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Peripheral neuropathy (PN) is a common complication of MM and one of the main dose-limiting iatrogenic toxicities associated with some antimyeloma treatments, including older-generation PIs such as bortezomib.[12–16] The incidence of PN associated with MM treatments during the course of the disease and treatment has been estimated to range between 21% and 70% depending on the treatment and PN severity.[15] MM treatment options are often limited by the likelihood of therapies causing or exacerbating neuropathies with significant negative impacts on patient quality of life.[14,16] Treatment-induced PN, although usually reversible, can cause severe pain and affect the patient's activities of daily living, as well as causing serious problems, such as loss of sensation, balance issues, muscle weakness, and organ failure.[15–18]

Management of PN is an ongoing challenge for healthcare providers. Actions to mitigate the incidence and effects of PN may include dosage and dosing-schedule adjustments of PIs, PI treatment discontinuation, other modalities (e.g. electrical nerve stimulation, physical therapy, acupuncture, other), and medications to address the pain (e.g. topical analgesics, antidepressants, antiepileptics, opioids).[16,19] These treatment measures for managing the effects of PN also carry an economic burden for the healthcare system (e.g. increased visits to monitor or treat the PN, costs of PN treatment), as well as significant financial and lifestyle repercussions for the MM patient.

The impact of PN on healthcare utilization and costs for MM patients treated in real-world practice settings is not well understood. The purpose of this study was to use real-world data to examine the healthcare resource utilization and costs associated with PN in patients being treated for MM, comparing those diagnosed with PN to a matched control cohort without PN.

Methods

Study design and data source

This retrospective, observational cohort study was based on administrative healthcare claims data from 1 January 2006 to 28 February 2017 from the IBM® MarketScan Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits (Medicare) databases. These databases include inpatient medical, outpatient medical, and outpatient pharmacy claims data, as well as insurance enrollment and demographic information collected from a wide variety of health plans across the US. The Commercial database includes information for over 20 million individuals annually who are under the age of 65 years with employer-sponsored health insurance, including the primary insured, spouses and dependents. The Medicare Supplemental database includes both the Medicare-paid and supplemental-paid components of reimbursed insurance claims information for over 2 million individuals annually with both traditional and supplemental Medicare coverage. The study databases satisfy Sections 164.514 (a)–(b)(1)(ii) of the Health Insurance Portability and Accountability Act of 1996 privacy rule (HIPAA) regarding the determination and documentation of statistically de-identified data. This study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, and therefore institutional review board approval was not required.

Patient identification

Selected adult patients, 18 years of age and older, had at least one inpatient or two outpatient claims (from 30 to 365 days of the first found outpatient claim) with a diagnosis of MM based on International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) diagnosis codes 203.0x or ICD-10-CM (tenth revision) diagnosis codes C9000, C9001 and C9002 between 1 July 2006 and 28 February 2017, and at least one claim indicating the administration or prescription of an MM therapy (bendamustine, bortezomib, carfilzomib, cisplatin, cyclophosphamide, doxorubicin, doxorubicin liposomal, lenalidomide, melphalan, panobinostat, pomalidomide, thalidomide) on or after the date of the first MM diagnosis. Claims associated with a diagnostic workup such as laboratory tests or diagnostic X-rays were not used for patient selection. To ensure that patients were newly diagnosed and newly treated, a 12-month period with no diagnosis of MM prior to the first found (initial) MM diagnosis and a 12-month period with no MM therapy prior to the initial MM therapy was required. The index date was the date of the first claim for one of the MM therapies on or after the initial MM diagnosis.

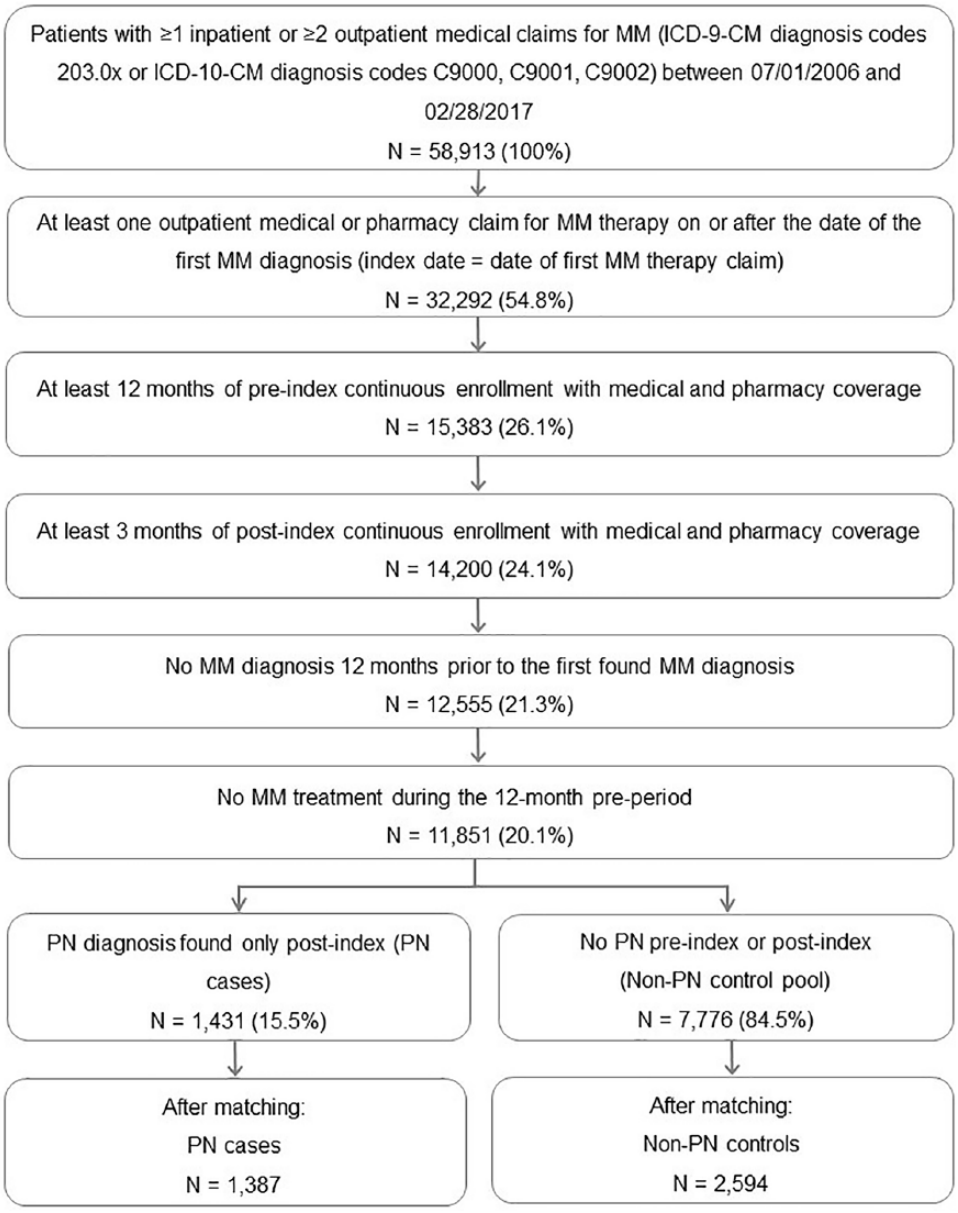

Figure 1. Patient selection flowchart.
ICD-9-CM, International Classification of Diseases, ninth revision, Clinical Modification; ICD-10-CM, tenth revision; MM, multiple myeloma; PN, peripheral neuropathy.

Continuous medical and prescription coverage was required for at least 12 months prior to the index date (preperiod), and for at least 3 months after the index date (postperiod). Patients were followed from the index date until the earliest evidence of inpatient death (*via* discharge status), end of continuous enrollment, or end of study period (28 February 2017). This process is described in Figure 1.

Identification of peripheral neuropathy cases and matched controls

Due to the lack of diagnosis code specificity for disease-related or treatment-induced PN, PN was identified using an algorithm from previously published studies.[20,21] PN cases were identified by a medical claim with a diagnosis for PN (codes in Table A.1) during the 9 months following their initial MM therapy and without evidence of PN

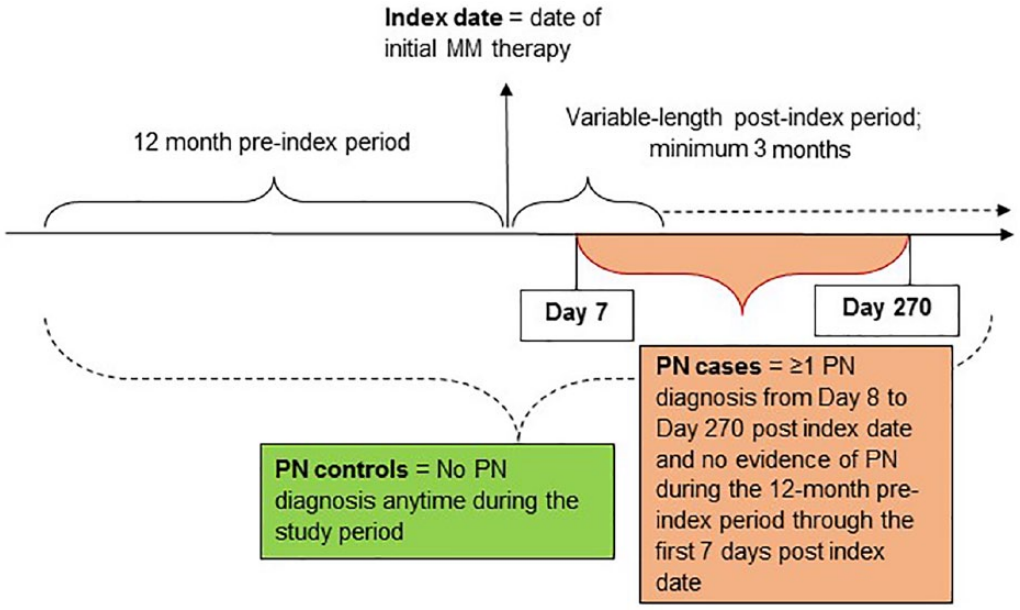

Figure 2. PN definition at the patient level.
MM, multiple myeloma; PN, peripheral neuropathy.

during the 12-month preperiod through the 7 days following the initial MM treatment (Figure 2). Controls had no medical claims with a diagnosis of PN anytime during the 12-month preperiod and throughout the follow-up period.

To adjust for imbalances in demographics and clinical characteristics, patients with PN were matched to a pool of patients without PN in a ratio of 1:2 (PN:without PN) using propensity-score modeling with nearest-neighbor matching. Matching factors included patients' demographic characteristics [age, sex, geographic region of residence, payer (Commercial or Medicare), health-plan type] and baseline clinical characteristics (Deyo–Charlson Comorbidity Index, DCI)[22] and specific preindex comorbidities including cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, chronic kidney disease, skeletal-related events, coagulopathies, hematologic disease, hypertension, and the index MM medication). Standardized differences in matching factors between patients with PN and patients without PN were calculated before and after the matching to examine the quality of the match.

Lines of therapy

This study used a previously published MM treatment algorithm to identify the number of lines of therapy.[21] The first line started on the date of the first MM chemotherapy or immunotherapy treatment with bendamustine, bortezomib, carfilzomib, cisplatin, cyclophosphamide, doxorubicin, doxorubicin liposomal, lenalidomide, melphalan, panobinostat, pomalidomide, or thalidomide. A treatment regimen was defined as consisting of one or more chemotherapy with or without immunotherapy agents administered within 90 days of the start of the line of therapy. A line of therapy ended at the earliest occurrence of a 90-day gap in all MM treatments in a regimen comprising the line of therapy, initiation of a different MM treatment $>$ 90 days after the start of current line of therapy, inpatient discharge status of death, end of enrollment, or end of data. Note that lenalidomide monotherapy initiated within 60 days of the last drug administration in the line of therapy was classified as 'maintenance therapy'. Maintenance therapy was considered to be a continuation of the line of therapy and not a new line of therapy. Moreover, any MM therapy received within 90 days following a stem-cell transplant date was considered to be 'consolidation therapy' within the current line and not the start of a new line of therapy. All subsequent lines of therapy were identified using the same approach as for the first line (with the noted exception above regarding first-line maintenance). Figure 3 describes two examples of changes in treatment regimen and how lines of therapy were defined.

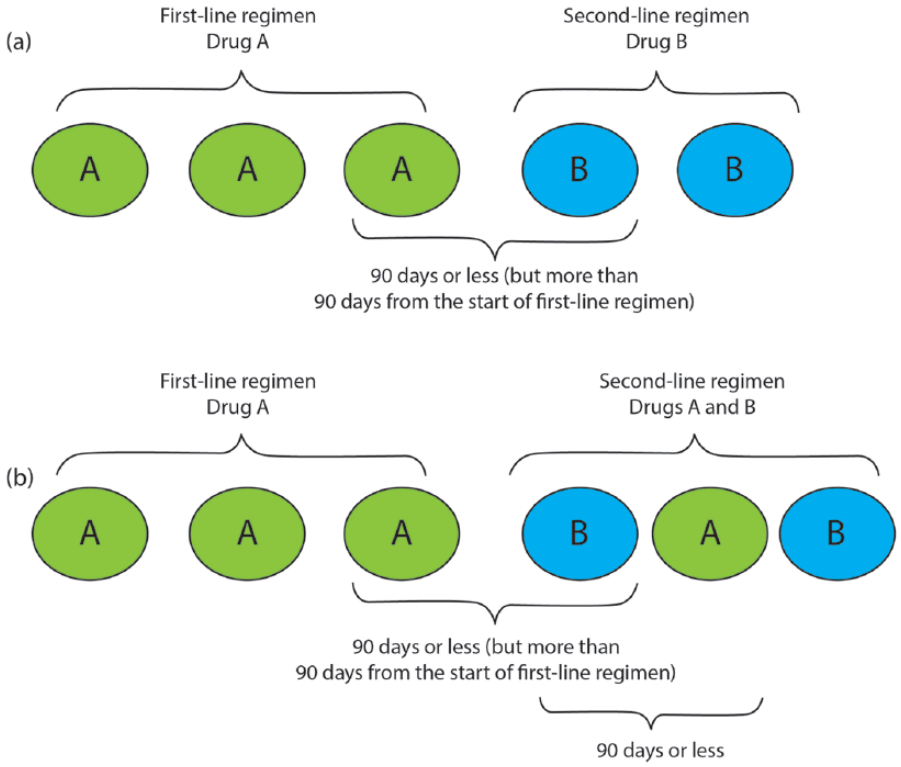

Figure 3. Examples of switching in regimens.
(a) Switch in treatment regimen; (b) addition to treatment regimen.

Patients with and without PN were identified during each line of therapy. Because of the small number of patients with more than three lines of therapy with PN, the third line and subsequent lines were combined in reporting.

Covariates and study outcomes

Demographics data extracted on the index date, included age, sex, US Census Bureau geographic region, payer (Commercial insurance or Medicare), healthplan type, and index year. Baseline clinical characteristics, measured throughout the 12-month pre-index period, included the DCI (an aggregate measure of comorbidity expressed as a numeric score based on the presence of various diagnoses), specific conditions contained in the DCI, other primary cancers, and other disease-related complications.[22]

Study outcomes included all-cause healthcare utilization and costs measured during the at-least-3-month follow-up period and stratified for occurrence during the first, second, or third (or higher) lines of therapy. Healthcare utilization and costs were categorized as inpatient medical, emergency department/room (ER), office visits, outpatient hospital-based visits, other outpatient services, and outpatient pharmacy. Due to the variable length of follow up for patients overall and during lines of therapy, healthcare utilization and costs were reported in per-patient-per-month units (PPPM). Costs used the total paid amounts from all payers to all providers, including plan-paid, patient-paid, and coordinated benefit payments. All dollar amounts were inflation adjusted to 2017 US dollars using the Medical Care component of the Consumer Price Index.[23]

The incidence rate of PN was calculated using the unmatched sample of all treated MM patients as the number of patients with PN divided by the person-time from the index date to the first PN diagnosis for PN patients, plus the person-time from the index date to the end of follow up for patients without PN.

Statistical considerations

Pairwise descriptive statistics were used to compare demographics, comorbid conditions, healthcare utilization and costs between patient cohorts with and without PN after propensity-score matching. Descriptive statistics also evaluated these differences between the comparator cohorts during first line, second line, and third-plus-subsequent lines of therapy. Chi-squared tests were conducted for differences in dichotomous or categorical variables and *t* tests were conducted for comparisons of continuous variables. A p value $<$ 0.05 was set as the threshold for statistically significant differences. Following propensity-score matching of PN patients and patients without PN, statistically significant postindex differences in results between cohorts were presumed to be associated with the effects of the key independent variable, the incidence of PN. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, US).

Results

A total of 9207 patients comprising the case and control pool; 15.5% (1431 patients) were identified as having PN; 7776 had no PN diagnosis anytime during the study period (Figure 1). The incidence rate for a mean (standard deviation) duration of 624 (594) days after an initial MM diagnosis until PN was identified or end of follow up was estimated as 9.1 PN cases per 100 person-years.

Following matching, the study cohorts consisted of 1387 MM patients with PN and 2594 patients without any PN diagnosis during the study period. These matched study cohorts were well balanced with no statistically significant differences in demographics or baseline clinical characteristics (Tables 1). Mean patient age was 64 years, with 60–61% males, and 43–44% covered by Medicare. The length of follow up was longer for PN patients at a mean (SD) of 788 (580) days and 693 (571) days for non-PN patients (Table 1). Among the 1387 MM patients with PN, the mean (SD) and median duration from index date to PN diagnosis was 129 (68) days and 125 days, respectively.

The most common baseline comorbid conditions included hypertension (60–63%), skeletal-related events (48%), diabetes (26–30%), renal disease (21–23%), and ischemic vascular conditions (22%). At index, approximately 50–53% received bortezomib; 37–38% received lenalidomide; 10% received cyclophosphamide, and 5–6% received thalidomide as their initial MM therapy, with the remaining MM therapies received as index medications in less than 3% of patients (Table 1). Of the 3981 matched patients, 1267 (32%) had a PN diagnosis and 2687 (68%) had no PN diagnosis during their first-line therapy. There were 27 patients whose PN diagnosis occurred after the end of the first line but before the start of second-line therapy. A total of 1974 patients had a second-line therapy, of which 280 patients (15%) had PN during their second line, while 1532 patients (85%) had no PN during their second line, with the remaining patients having PN during the first line, thus not eligible for the PN analysis during the second line. Of the 1103 patients with a third or subsequent line of therapy, 75 patients (7%) had a PN diagnosis and 1028 patients (93%) had no PN during their third or subsequent line. Demographic and baseline clinical characteristics measured during first-line, second-line, and third/subsequent-line therapy were similar between PN patients and patients without PN (Tables A.2–A.4).

All-cause healthcare utilization

Healthcare utilization was significantly higher in most healthcare use categories among patients with PN compared with patients with no PN. Significantly more PN patients had a hospitalization during follow up (77.4%) compared with patients without PN (67.2%; $p < 0.001$), however, their length of stay was similar [PN 0.60 (0.87) days PPPM *versus* non-PN 0.66 (0.96) days PPPM; $p = 0.052$]. More patients with PN had an ER visit (67.8% *versus* 58.4%; $p < 0.001$), had significantly more outpatient hospital-based visits [mean 13.5 (14.7) visits PPPM *versus* 11.5 (18.0) visits PPPM; $p < 0.001$], fewer laboratory tests [mean 4.1 (5.1) tests PPPM *versus* 4.7 (5.6) tests PPPM; $p < 0.001$], and outpatient prescriptions [4.7 (2.5) prescription claims PPPM *versus* 4.2 (2.4) prescription claims PPPM; $p < 0.001$] compared with patients without PN (Table 2).

Use of narcotic pain medication was common and also higher among patients with PN compared with patients with no PN (during first-line therapy: 82% *versus* 72%; $p < 0.001$).

Table 1. Demographic and baseline clinical characteristics.

	PN cases	Non-PN controls	*p* value	Standard difference
	n = 1387	*n* = 2594		×100*
Age, mean (SD) years	63.9 (10.8)	64.2 (11.6)	0.314	3.39
18–44	0.4%	0.3%	0.395	2.75
45–54	2.7%	3.7%	0.084	5.89
55–64	16.4%	15.9%	0.692	1.31
65–74	37.1%	37.8%	0.670	1.42
75+	25.5%	20.7%	0.001	11.38
Sex, %				
Male	60.6%	60.1%	0.725	1.17
Female	39.4%	39.9%	0.725	1.17
Payer, %				
Commercial	55.6%	57.0%	0.399	2.80
Medicare	44.4%	43.0%	0.399	2.80
Insurance plan type, %				
Preferred-provider organization	55.7%	56.2%	0.740	1.10
Comprehensive	19.6%	19.0%	0.623	1.63
Health-maintenance organization	11.6%	11.7%	0.945	0.23
Point of service	5.3%	5.4%	0.818	0.77
Other	7.9%	7.7%	0.867	0.55
Geographic region, %				
Northeast	17.8%	17.8%	0.975	0.11
North central	28.8%	27.9%	0.552	1.97
South	35.4%	37.6%	0.166	4.62
West	17.2%	15.3%	0.114	5.22
Unknown	0.7%	1.3%	0.109	5.55
Length of follow up, mean (SD) days	788 (580)	693 (571)	<0.001	16.52
Median follow up (days)	642	522		
Deyo–Charlson Comorbidity Index, mean (SD)	4.5 (2.9)	4.4 (2.8)	0.999	3.69
Comorbid conditions[$]				
Hypertension	62.5%	59.9%	0.109	5.34
Skeletal-related events	48.4%	48.4%	0.980	0.08

(Continued)

Table 1. (Continued)

	PN cases	Non-PN controls	*p* value	Standard difference
	n = 1387	*n* = 2594		×100*
Diabetes	30.1%	25.9%	0.004	9.43
Renal disease	23.0%	21.0%	0.155	4.71
Ischemic vascular condition‡	22.5%	22.4%	0.922	0.32
Chronic kidney disease	19.4%	18.6%	0.532	2.07
Anemia or anemia treatment	57.0%	56.1%	0.569	1.89
Chronic pulmonary disease	16.4%	15.4%	0.435	2.59
Hypercalcemia	14.0%	13.3%	0.523	2.12
GI bleeding	5.0%	5.2%	0.871	0.54
Pneumonia	9.4%	9.6%	0.847	0.64
Congestive heart failure	7.8%	8.1%	0.732	1.14
Cerebrovascular disease	6.8%	6.6%	0.860	0.59
Thrombocytopenia	7.8%	6.9%	0.282	3.55
End-stage renal disease/renal failure	6.3%	6.5%	0.802	0.84
Venous thromboembolism	5.3%	5.7%	0.593	1.79
Prior primary cancer				
Solid tumor	24.4%	24.0%	0.805	0.82
Hematologic cancer	12.4%	13.5%	0.331	3.25
Days from diagnosis to treatment, mean (SD)	158 (355)	163 (360)	0.623	1.64
Median (days)	26	27		
Stem-cell transplant prior to index treatment, %	0.8%	1.0%	0.588	1.83
Index MM therapy, %				
Bendamustine	0.2%	0.6%	0.081	6.22
Bortezomib	52.5%	50.0%	0.135	4.98
Carfilzomib	0.1%	0.2%	0.722	2.01
Cisplatin	0.4%	0.4%	0.902	0.41
Cyclophosphamide	9.9%	10.3%	0.733	1.14
Doxorubicin	1.7%	1.7%	0.937	0.26
Doxorubicin liposomal	0.2%	0.2%	1.000	0.32

Table 1. (Continued)

	PN cases	Non-PN controls	*p* value	Standard difference
	***n* = 1387**	***n* = 2594**		**×100***
Lenalidomide	37.1%	37.9%	0.620	1.65
Melphalan	2.1%	2.8%	0.190	4.45
Panobinostat	0.0%	0.0%	–	–
Pomalidomide	0.1%	0.1%	1.000	0.18
Thalidomide	4.7%	5.6%	0.244	3.93

GI, gastrointestinal; MM, multiple myeloma; PN, peripheral neuropathy; SD, standard deviation.
*The standardized differences were multiplied by 100 to facilitate readers' viewing results.
$Comorbid condition occurring during the preperiod in <5% patients are not shown.
‡Ischemic vascular conditions include unstable angina, stable angina, ischemic stroke, transient ischemic event, and other chronic ischemic heart disease, including coronary revascularization.

Table 2. Per-patient-per-month all-cause healthcare utilization over the entire follow-up period.

	Entire follow-up period		
	PN cases	Non-PN controls	*p* value
	***n* = 1387**	***n* = 2594**	
All-cause healthcare utilization (PPPM)			
Patients with an inpatient admission, %	77.4%	67.2%	<0.001
Admissions PPPM, mean (SD)	0.11 (0.14)	0.10 (0.15)	0.019
Patients with an admission, mean (SD)	0.14 (0.14)	0.15 (0.16)	0.373
Patients with an ER visit, %	67.8%	58.4%	<0.001
ER visits PPPM, mean (SD)	0.13 (0.33)	0.11 (0.22)	0.015
Patients with a visit, mean (SD)	0.19 (0.39)	0.19 (0.26)	0.629
Patients with an outpatient office visit, N%	97.9%	96.6%	0.024
Outpatient office visits PPPM, mean (SD)	1.7 (1.2)	1.6 (1.2)	0.142
Patients with a visit, mean (SD)	1.7 (1.2)	1.7 (1.1)	0.342
Patients with outpatient hospital-based visits, %	98.7%	96.3%	<0.001
Outpatient hospital-based visits PPPM, mean (SD)	13.3 (14.7)	11.1 (17.8)	<0.001
Patients with a visit, mean (SD)	13.5 (14.7)	11.5 (18.0)	<0.001
Patients with a laboratory test, %	90.9%	87.9%	0.003
Laboratory tests PPPM, mean (SD)	3.7 (5.0)	4.1 (5.5)	0.018
Patients with a test, mean (SD)	4.1 (5.0)	4.7 (5.6)	0.001

(Continued)

Table 2. (Continued)

	Entire follow-up period		
	PN cases	Non-PN controls	*p* value
	n = 1387	*n* = 2594	
Patients filling an outpatient prescription, %	97.2%	97.1%	0.941
Outpatient prescriptions PPPM, mean (SD)	4.6 (2.6)	4.0 (2.5)	<0.001
Patients with a prescription, mean (SD)	4.7 (2.5)	4.2 (2.4)	<0.001

ER, emergency department (room); PN, peripheral neuropathy; PPPM, per patient per month; SD, standard deviation.

Table 3. Per-patient-per-month all-cause healthcare costs over the entire follow-up period.

	Entire follow-up period		
	PN cases	Non-PN controls	*p* value
	n = 1387	*n* = 2594	
All-cause healthcare costs (PPPM)			
Inpatient-admission costs, mean (SD)	$4750 ($9944)	$4002 ($8993)	0.016
Outpatient medical costs, mean (SD)	$8100 ($8,341)	$7408 ($8,007)	0.010
ER costs, mean (SD)	$126 ($620)	$92 ($374)	0.029
Outpatient office-visit costs, mean (SD)	$216 ($302)	$203 ($329)	0.214
Outpatient hospital-based visit costs, mean (SD)	$4906 ($6410)	$4076 ($6280)	<0.001
Laboratory-testing costs, mean (SD)	$144 ($309)	$140 ($290)	0.687
Outpatient prescription costs, mean (SD)	$3749 ($3312)	$3681 ($3596)	0.555
Total costs, mean (SD)	$16,600 ($14,450)	$15,090 ($13,399)	0.001
Quarterly healthcare costs (PPPM)			
0–90 days postindex, *n*	1381	2583	
Total costs, mean (SD)	$22,777 ($19,074)	$19,460 ($16,064)	<0.001
91–180 days postindex, *n*	1299	2286	
Total costs, mean (SD)	$24,402 ($24,760)	$19,235 ($19,769)	<0.001
181–270 days postindex, *n*	1168	1986	
Total costs, mean (SD)	$15,766 ($21,032)	$14,052 ($18,286)	0.008
271–360 days postindex, *n*	1026	1682	
Total costs, mean (SD)	$11,955 ($15,774)	$11,518 ($15,756)	0.404

ER, emergency department (room); PN, peripheral neuropathy; PPPM, per patient per month; SD, standard deviation.

All-cause healthcare costs

Healthcare costs were also higher among patients with PN compared with control patients with no PN and increased as patients proceeded to higher lines of therapy (Table 3). Mean total costs for PN patients exceeded those of patients without PN by $1509 PPPM [PN $16,600 (SD $14,450) *versus* non-PN $15,090 (SD $13,399); $p = 0.001$] over the entire follow-up period. This difference was primarily attributable to the first 180 days postindex, where PN patients' mean PPPM costs exceeded those of the non-PN cohort by $3317 during the first 90 days ($p < 0.001$), and by $5167 during the period 91–180 days postindex ($p < 0.001$).

Table 4 contrasts the PPPM costs for patients who had a PN diagnosis during a particular line of therapy with patients who did not have a PN diagnosis during that same line. The PN patients' total costs were significantly higher during the first line of therapy ($23,183 (SD $22,243) *versus* $20,790 (SD $27,748); $p = 0.007$) and second line ($37,880 (SD $58,007) *versus* $29,694 (SD $103,457); $p = 0.198$) compared with patients without a PN diagnosis during those lines. This difference was primarily driven by outpatient medical costs, and particularly by outpatient hospital-based visits.

Discussion

This study found significantly higher healthcare resource utilization and costs in patients with a post-treatment diagnosis for PN during their follow up compared with a matched group of patients without PN. Patients with PN were significantly more likely to be hospitalized, had an ER visit, had an outpatient hospital-based visit, and filled more outpatient prescriptions than matched patients without a PN diagnosis. This increased use of healthcare resource was associated with $1509 higher PPPM total costs, amounting to $36,216 over PN patients' mean 2-year follow-up time. Pike and colleagues, in a similar study using administrative US claims data (1999–2006), estimated the costs for chemotherapy-induced PN in a matched cohort comparison of cancer patients (not MM) with and without post-treatment PN, finding that PN patients had higher mean total healthcare costs by $17,344 during the 12-month study period than comparable patients without PN. They further found that more PN cases were hospitalized, had an ER visit, and had other outpatient visits.[24] In a 2001 pilot study of chemotherapy-induced toxicity in ovarian cancer patients, Calhoun and colleagues found indirect costs, such as the cost of caregiver time and lost wages, to be a substantial contributor to the total burden of chemotherapy-induced toxicity.[25] The estimated marginal healthcare expenditure of $1509 PPPM attributable to PN in our study using direct medical and prescription expenditures derived from paid healthcare claims represents only a portion of the overall societal cost. Due to the lack of information, costs associated with caregiver burden, indirect costs, or the quality of life impact were not examined.

In our study, the rate of PN in MM patients was 15.5%, which appears low compared with other studies where PN rates ranged from over 20% to as high as 70%[15,16,26,27] This may be attributable to several contributing factors. The diagnosis of PN may be under-reported in claims, as healthcare providers may only include the diagnosis when the presentation of PN is severe or substantially affecting disease management. Patients expecting drug side effects may not seek treatment for mild PN. This was confirmed by the finding of Yong et al. using chart review data. Yong and colleagues found that although more than 45% of MM patients had PN, less than 4% had grade 3 or 4 PN during the first four lines of therapy.[27] Clinical trials have also reported a much lower PN rate of grade 3–4 than PN rate of grade 1–2.[16] Some patients indexing in the latter years of the study may have experienced PN after the end of their available data. The incidence rate reported in our study of 9.1 PN cases per 100 person-years may likewise reflect a similar underestimate. In addition, it was estimated that 3.2% of MM patients have baseline PN.[21] In the current study, patients with baseline PN who later had another PN diagnosis post-treatment were excluded from the PN rate calculation, which may further lower the estimated PN rate. This exclusion was applied so as not to overestimate PN.

Our cohorts were demographically similar to the US MM population in terms of age and sex based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program's reporting most patients diagnosed between 65 and 74 years of age, median age 69 at initial diagnosis, and the SEER and American Cancer Society's estimate of 59% male–41% female

Table 4. Per-patient-per-month all-cause healthcare costs by line of therapy stratified by patients with and without PN.

	Line of therapy		
	First-line therapy		
	PN in first line	No PN first line	*p* value
	n = 1267	*n* = 2687	
Inpatient-admission costs, mean (SD)	$6158 ($18,095)	$5000 ($24,001)	0.127
Outpatient medical costs, mean (SD)	$12,598 ($11,306)	$10,949 ($11,319)	<0.001
ER costs, mean (SD)	$180 ($798)	$129 ($766)	0.055
Outpatient office-visit costs, mean (SD)	$318 ($659)	$281 ($522)	0.062
Outpatient hospital-based visits, mean (SD)	$7687 ($10,244)	$6049 ($9927)	<0.001
Laboratory-testing costs, mean (SD)	$212 ($552)	$197 ($454)	0.376
Outpatient prescription costs, mean (SD)	$4427 ($4103)	$4841 ($6715)	0.043
Total costs, mean (SD)	$23,183 ($22,243)	$20,790 ($27,748)	0.007
	Second-line therapy		
	PN second line	No PN second line	*p* value
	n = 280	*n* = 1532	
Inpatient-admission costs, mean (SD)	$15,726 ($51,561)	$11,468 ($99,972)	0.487
Outpatient medical costs, mean (SD)	$15,807 ($22,951)	$11,277 ($18,854)	<0.001
ER costs, mean (SD)	$271 ($2811)	$133 ($879)	0.119
Outpatient office-visit costs, mean (SD)	$244 ($325)	$240 ($483)	0.889
Outpatient hospital-based visits, mean (SD)	$11,250 ($21,747)	$7176 ($17,414)	0.001
Laboratory-testing costs, mean (SD)	$173 ($546)	$149 ($441)	0.428
Outpatient prescription costs, mean (SD)	$6348 ($6,192)	$6950 ($9282)	0.297
Total costs, mean (SD)	$37,880 ($58,007)	$29,694 ($103,457)	0.198
	Third and subsequent lines of therapy		
	PN third+ line	No PN third+ line	*p* value
	n = 75	*n* = 1028	
Inpatient-admission costs, mean (SD)	$7228 ($19,480)	$6488 ($27,591)	0.820
Outpatient medical costs, mean (SD)	$9803 ($12,438)	$10,563 ($15,657)	0.681
ER costs, mean (SD)	$148 ($347)	$126 ($784)	0.812
Outpatient office-visit costs, mean (SD)	$235 ($256)	$224 ($351)	0.787
Outpatient hospital-based visits, mean (SD)	$7414 ($11,805)	$6240 ($13,760)	0.472
Laboratory-testing costs, mean (SD)	$70 ($174)	$147 ($440)	0.132
Outpatient prescription costs, mean (SD)	$8563 ($7307)	$7777 ($11,021)	0.543
Total costs, mean (SD)	$25,594 ($26,656)	$24,827 ($34,532)	0.851

ER, emergency department (room); PN, peripheral neuropathy; PPPM, per patient per month; SD, standard deviation.

incidence. The population in this study is slightly younger overall due to larger representation from commercial carriers than from Medicare data providers.[1,2]

Obtaining optimal clinical efficacy requires carefully balancing treatment effectiveness with the potential for negative consequences on the patient's quality of life. The dosage reductions, treatment switches, or discontinuation of MM therapies to manage PN may ultimately affect response to therapy.[28] Thalidomide and bortezomib are associated with higher rates of PN.[12,13,15,16] Recent approval of novel therapies[29–32] hold promise for antimyeloma efficacy with reduced incidence of PN.

Limitations

There are several limitations associated with this study. Use of diagnosis coding from administrative claims data may be subject to misclassification errors, where the extent of undercoding for the selected conditions or comorbidities is unknown, and without the availability of patient charts or physician attestations. PN diagnoses may not be included on administrative claims unless the impairment significantly affects patient management, thereby under-reported or biased toward more severe cases. PN could not be identified directly in claims data because of the lack of diagnosis codes specific to disease-related and treatment-induced PN. Consequently, PN identification used an algorithm from a previously published study that has not been validated, and the PN could be due to other causes. This study used propensity-score matching to ensure cohorts had similar baseline demographic and clinical characteristics, increasing the likelihood that differences between cohorts were associated with PN. However, there is always the potential of unmeasured confounders outside of this study's data sources. In addition, the incremental healthcare utilization and costs in the PN cohort may not be directly linked to PN; it could also be due to PN treatment, PN complications, and other conditions that could not be controlled or adjusted for in the claims data. Pharmacological treatments that were based on pharmacy prescription claims only indicated that prescriptions were received, not necessarily how the patients took the medications. This is not an issue for medications administered in the physician's office and billed through a medical claim. Several drugs (carfilzomib, pomalidomide, panobinostat) entered the US market more recently (since 2012), resulting in limited sample sizes for these agents, so PN rates specific to individual medications were not examined. MarketScan® Commercial and Medicare databases are convenience samples of employees, retirees, and dependents with US Commercial and Medicare health-insurance coverage, therefore results from these databases may not be generalizable to populations with other healthcare coverage (e.g. Medicaid), or those lacking coverage.

Conclusion

PN was observed in 15.5% of MM patients, and was associated with a significant economic burden, adding an average of $1509 monthly per patient to the cost of MM treatment, as well as adding to the complexity of treatment with detrimental impact to patients. These results suggest that utilization of newer, more effective novel treatments might ease the economic and disease burden for MM associated with PN.

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Conflict of interest statement

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References

1. Howlader N, Noone AM, Krapcho M, *et al. SEER cancer statistics review, 1975–2011*. Bethesda, MD: National Cancer Institute, 2014, http://seer.cancer.gov/csr/1975_2011/ (accessed 14 March 2019).
2. American Cancer Society. *What are the key statistics about multiple myeloma?*, http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics (2016, accessed 1 April 2018).

3. Avet-Loiseau H, Fonseca R, Siegel D, *et al*. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. *Blood* 2016; 128: 1174–1180.
4. Dimopoulos MA, Moreau P, Palumbo A, *et al*. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; 17: 27–38.
5. Dimopoulos MA, Oriol A, Nahi H, *et al*. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 1319–1331.
6. Lonial S, Dimopoulos M, Palumbo A, *et al*. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015; 373: 621–631.
7. Palumbo A, Chanan-Khan A, Weisel K, *et al*. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 754–766.
8. San-Miguel JF, Hungria VT, Yoon SS, *et al*. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol* 2014; 15: 1195–1206.
9. San-Miguel JF, Hungria VT, Yoon SS, *et al*. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. *Lancet Haematol* 2016; 3: e506–e515.
10. Siegel DS, Oriol A, Rajnics P, *et al*. Updated results from ASPIRE and ENDEAVOR, randomized, open-label, multicenter phase 3 studies of carfilzomib in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *Clin Lymphoma Myeloma Leuk* 2017; 17: e142.
11. National Comprehensive Cancer Network. *National comprehensive cancer network: multiple myeloma*, http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf (2013, accessed 18 August 2018).
12. THALOMID®. Prescribing information: Thalomid (thalidomide). Summit, NJ: Celgene Corporation, https://media.celgene.com/content/uploads/thalomid-pi.pdf (2017, accessed 14 March 2019).
13. VELCADE®. Prescribing information: Velcade (bortizumib). Cambridge, MA: Millennium Pharmaceuticals, Inc., http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021602s042lbl.pdf (2015, accessed 5 October 2018).
14. Boland E, Eiser C, Ezaydi Y, *et al*. Living with advanced but stable multiple myeloma: a study of the symptom burden and cumulative effects of disease and intensive (hematopoietic stem cell transplant-based) treatment on health-related quality of life. *J Pain Symptom Manage* 2013; 46: 671–680.
15. Delforge M, Bladé J, Dimopoulos MA, *et al*. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. *Lancet Oncol* 2010; 11: 1086–1095.
16. Mohty B, El-Cheikh J, Yakoub-Agha I, *et al*. Peripheral neuropathy and new treatments for multiple myeloma: background and practical recommendations. *Haematologica* 2010; 95: 311–319.
17. American Cancer Society. *Peripheral neuropathy caused by chemotherapy*, https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/peripheral-neuropathy.html (2015, accessed 1 April 2018).
18. Grisold W, Cavaletti G and Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro Oncol* 2012; 14(Suppl. 4): iv45–iv54.
19. Trivedi MS, Hershman DL and Crew KD. Management of chemotherapy-induced peripheral neuropathy. *Am J Hematol Oncol* 2015; 11: 4–10.
20. Cavaletti G, Cornblath DR, Merkies IS, *et al*. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Ann Oncol* 2013; 24: 454–462.
21. Song X, Cong Z and Wilson K. Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. *Curr Med Res Opin* 2016; 32: 95–103.
22. Deyo RA, Cherkin DC and Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45: 613–619.
23. United States Bureau of Labor Statistics. Consumer price index, http://www.bls.gov/cpi/ (2018, accessed 1 June 2018).

24. Pike CT, Birnbaum HG, Muehlenbein CE, *et al*. 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.

25. Calhoun EA, Chang C-H, Welshman EE, *et al*. Evaluating the total costs of chemotherapy-induced toxicity: results from a pilot study with ovarian cancer patients. *Oncologist* 2001; 6: 441–445.

26. 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.

27. Yong K, Delforge M, Driessen C, *et al*. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol* 2016; 175: 252–264.

28. Martin III TG, Panjabi S, Kerr J, *et al*. Association of treatment induced peripheral neuropathy (TIPN) with treatment patterns and outcomes in patients (pts) with newly diagnosed multiple myeloma (NDMM). *Blood* 2013; 122: 1750.

29. POMALYST®. Prescribing information: Pomalyst (pomalidomide). Summit, NJ: Celgene Corporation, http://www.celgene.com/content/uploads/pomalyst-pi.pdf (2018, accessed 18 April 2018).

30. KYPROLIS®. Prescribing information: Kyprolis (carfilzomib). Thousand Oaks, CA: Amgen Inc., http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/kyprolis/kyprolis_pi.ashx (2018, accessed 18 April 2018).

31. DARZALEX®. Prescribing information: Darzalex (daratumumab), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761036s004lbl.pdf (2016, accessed 18 April 2018).

32. EMPLICITI®. Prescribing information: Empliciti (elotuzumab). Princeton, NJ: Bristol-Myers Squibb Company, http://packageinserts.bms.com/pi/pi_empliciti.pdf?&utm_source=bing&utm_medium=cpc&utm_campaign=managementbnd&utm_term=prescribinginformation&utm_content=managementbnd_sitelink_pi_empliciti.pdf_text (2017, accessed 18 April 2018).

Appendix

Table A.1. ICD-9 and ICD-10 diagnosis codes of peripheral neuropathy.

ICD-9-CM diagnosis code	Description
337.20	Reflex sympathetic dystrophy, unspecified
337.21	Reflex sympathetic dystrophy of the upper limb
337.22	Reflex sympathetic dystrophy of the lower limb
337.29	Reflex sympathetic dystrophy of other specified site
353.0	Brachial plexus lesions
353.2	Cervical root lesions, not elsewhere classified
353.4	Lumbosacral root lesions, not elsewhere classified
355.71	Causalgia of lower limb
355.79	Other mononeuritis of lower limb
355.9	Mononeuritis of unspecified site
357.0	Acute infective polyneuritis
357.1	Polyneuropathy in collagen vascular disease
357.2	Polyneuropathy in diabetes
357.3	Polyneuropathy in malignant disease
357.4	Polyneuropathy in other diseases classified elsewhere
357.5	Alcoholic polyneuropathy
357.6	Polyneuropathy due to drugs
357.7	Polyneuropathy due to other toxic agents
357.81	Chronic inflammatory demyelinating polyneuritis
357.82	Critical illness polyneuropathy
357.89	Other inflammatory and toxic neuropathy
357.9	Unspecified inflammatory and toxic neuropathies
377.34	Toxic optic neuropathy
729.2	Neuralgia, neuritis, and radiculitis, unspecified
782.0	Disturbance of skin sensation
ICD-10-CM diagnosis code	**Code description**
G9050	Complex regional pain syndrome I, unspecified
G90513	Complex regional pain syndrome I of upper limb, bilateral
G90511	Complex regional pain syndrome I of right upper limb
G90512	Complex regional pain syndrome I of left upper limb

Table A.1. (Continued)

ICD-9-CM diagnosis code	Description
G90519	Complex regional pain syndrome I of unspecified upper limb
G90521	Complex regional pain syndrome I of right lower limb
G90529	Complex regional pain syndrome I of unspecified lower limb
G90522	Complex regional pain syndrome I of left lower limb
G90523	Complex regional pain syndrome I of lower limb, bilateral
G9059	Complex regional pain syndrome I of other specified site
G540	Brachial plexus disorders
G55	Nerve root and plexus compressions in diseases classified elsewhere
G542	Cervical root disorders, not elsewhere classified
G544	Lumbosacral root disorders, not elsewhere classified
E0841	Diabetes mellitus due to underlying condition with diabetic mononeuropathy
E0941	Drug or chemical-induced diabetes mellitus with neurological complications with diabetic mononeuropathy
E1041	Type 1 diabetes mellitus with diabetic mononeuropathy
E1141	Type 2 diabetes mellitus with diabetic mononeuropathy
E1341	Other specified diabetes mellitus with diabetic mononeuropathy
G5770	Causalgia of unspecified lower limb
G5771	Causalgia of right lower limb
G5772	Causalgia of left lower limb
G5773	Causalgia of bilateral lower limbs
G59	Mononeuropathy in diseases classified elsewhere
G5780	Other specified mononeuropathies of unspecified lower limb
G5781	Other specified mononeuropathies of right lower limb
G5782	Other specified mononeuropathies of left lower limb
G5783	Other specified mononeuropathies of bilateral lower limbs
G588	Other specified mononeuropathies
G589	Mononeuropathy, unspecified
G64	Other disorders of peripheral nervous system
G610	Guillain–Barré syndrome
M0550	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder

(Continued)

Table A.1. (Continued)

ICD-9-CM diagnosis code	Description
M05512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M0559	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
E0840	Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified
E0842	Diabetes mellitus due to underlying condition with diabetic polyneuropathy
E0940	Drug or chemical-induced diabetes mellitus with neurological complications with diabetic neuropathy, unspecified
E0942	Drug or chemical-induced diabetes mellitus with neurological complications with diabetic polyneuropathy
E1040	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E1042	Type 1 diabetes mellitus with diabetic polyneuropathy
E1140	Type 2 diabetes mellitus with diabetic neuropathy, unspecified

Table A.1. (Continued)

ICD-9-CM diagnosis code	Description
E1142	Type 2 diabetes mellitus with diabetic polyneuropathy
E1340	Other specified diabetes mellitus with diabetic neuropathy, unspecified
E1342	Other specified diabetes mellitus with diabetic polyneuropathy
G130	Paraneoplastic neuromyopathy and neuropathy
G131	Other systemic atrophy primarily affecting central nervous system in neoplastic disease
A3683	Diphtheritic polyneuritis
A5215	Late syphilitic neuropathy
G63	Polyneuropathy in diseases classified elsewhere
M3483	Systemic sclerosis with polyneuropathy
G621	Alcoholic polyneuropathy
G611	Serum neuropathy
G620	Drug-induced polyneuropathy
G622	Polyneuropathy due to other toxic agents
G6282	Radiation-induced polyneuropathy
G6181	Chronic inflammatory demyelinating polyneuritis
G6281	Critical illness polyneuropathy
G6189	Other inflammatory polyneuropathies
G6289	Other specified polyneuropathies
G619	Inflammatory polyneuropathy, unspecified
G629	Polyneuropathy, unspecified
H463	Toxic optic neuropathy
M5410	Radiculopathy, site unspecified
M5418	Radiculopathy, sacral and sacrococcygeal region
M792	Neuralgia and neuritis, unspecified
R200	Anesthesia of skin
R201	Hypoesthesia of skin
R202	Paresthesia of skin
R203	Hyperesthesia
R208	Other disturbances of skin sensation
R209	Unspecified disturbances of skin sensation

ICD-9-CM, International Classification of Diseases, ninth revision, Clinical Modification; ICD-10, tenth revision.

Table A.2. Demographic and baseline clinical characteristics of first-line therapy.

Demographic characteristics	First-line therapy				*p* value
	With PN		Without PN		
	n = 1267		*n* = 2687		
	n/mean	%/SD	*n*/mean	%/SD	
Age (mean, SD)	64.0	10.81	64.2	11.61	0.661
Age group (*n*, %)					
18–34	4	0.3%	9	0.3%	1.000
35–44	36	2.8%	95	3.5%	0.255
45–54	204	16.1%	429	16.0%	0.914
55–64	459	36.2%	1021	38.0%	0.283
65–74	333	26.3%	555	20.7%	0.000
75+	231	18.2%	578	21.5%	0.017
Sex (*n*, %)					
Male	761	60.1%	1621	60.3%	0.874
Female	506	39.9%	1066	39.7%	0.874
Payer (*n*, %)					
Commercial	690	54.5%	1536	57.2%	0.110
Medicare	577	45.5%	1151	42.8%	0.110
Insurance plan type (*n*, %)					
Comprehensive	259	20.4%	503	18.7%	0.200
Exclusive-provider organization	4	0.3%	19	0.7%	0.131
Health-maintenance organization	141	11.1%	321	11.9%	0.455
Point of service (POS)	66	5.2%	147	5.5%	0.734
Preferred-provider organization	704	55.6%	1508	56.1%	0.742
POS with capitation	8	0.6%	14	0.5%	0.663
Consumer-driven healthplan	60	4.7%	116	4.3%	0.552
High-deductible healthplan	25	2.0%	59	2.2%	0.651
Unknown	0	0.0%	0	0.0%	
Geographic region (*n*, %)					
Northeast	217	17.1%	488	18.2%	0.428
North central	372	29.4%	744	27.7%	0.276
South	448	35.4%	1011	37.6%	0.168

Table A.2. (Continued)

Demographic characteristics	First-line therapy				*p* value
	With PN		Without PN		
	n = 1267		*n* = 2687		
	n/mean	%/SD	*n*/mean	%/SD	
West	221	17.4%	410	15.3%	0.080
Unknown	9	0.7%	34	1.3%	0.116
Population density (*n*, %)					
Urban	1086	85.7%	2276	84.7%	0.406
Rural	172	13.6%	379	14.1%	0.654
Unknown	9	0.7%	32	1.2%	0.164
Duration of line of therapy (mean, SD)	234.9	219.9	244.6	241.2	0.222
DCI (mean, SD)	4.5	2.84	4.5	2.86	0.581
DCI (*n*, %)					
0	11	0.9%	21	0.8%	0.777
1	12	0.9%	13	0.5%	0.086
2	402	31.7%	900	33.5%	0.270
3+	842	66.5%	1753	65.2%	0.452
DCI components (*n*, %)					
Myocardial infarction	46	3.6%	87	3.2%	0.523
Congestive heart failure	100	7.9%	217	8.1%	0.843
Peripheral vascular disease	53	4.2%	112	4.2%	0.983
Cerebrovascular disease	87	6.9%	179	6.7%	0.810
Dementia	2	0.2%	7	0.3%	0.727
Chronic pulmonary disease	206	16.3%	417	15.5%	0.551
Rheumatologic disease	30	2.4%	60	2.2%	0.791
Peptic ulcer disease	19	1.5%	50	1.9%	0.418
Mild liver disease	10	0.8%	15	0.6%	0.392
Diabetes (mild to moderate)	286	22.6%	561	20.9%	0.225
Diabetes with chronic complications	93	7.3%	144	5.4%	0.014
Hemiplegia or paraplegia	5	0.4%	11	0.4%	0.946
Renal disease	285	22.5%	573	21.3%	0.405
Moderate or severe liver disease	2	0.2%	5	0.2%	1.000

(Continued)

Table A.2. (Continued)

Demographic characteristics	First-line therapy				*p* value
	With PN		Without PN		
	n = 1267		*n* = 2687		
	n/mean	%/SD	*n*/mean	%/SD	
Human immunodeficiency virus	3	0.2%	6	0.2%	1.000
Any malignancy, including lymphoma and leukemia	1094	86.3%	2339	87.0%	0.542
Metastatic solid tumor	190	15.0%	417	15.5%	0.670
Prior primary cancer (*n*, %)					
Solid tumor	309	24.4%	647	24.1%	0.832
Hematologic cancer	157	12.4%	363	13.5%	0.332
Preperiod events of interest (*n*, %)					
Chronic kidney disease	243	19.2%	503	18.7%	0.730
End-stage renal disease/renal failure	84	6.6%	170	6.3%	0.717
Skeletal-related events	610	48.1%	1303	48.5%	0.838
Hypercalcemia	172	13.6%	361	13.4%	0.904
Venous thromboembolism	52	4.1%	120	4.5%	0.603
Neutropenia	42	3.3%	93	3.5%	0.813
Pneumonia	123	9.7%	251	9.3%	0.713
Major bleeding	26	2.1%	52	1.9%	0.805
GI bleeding	63	5.0%	141	5.2%	0.715
Anemia	718	56.7%	1504	56.0%	0.681
Anemia or anemia treatment	720	56.8%	1514	56.3%	0.776
Thrombocytopenia	95	7.5%	188	7.0%	0.568
Amyloidosis	49	3.9%	88	3.3%	0.342

DCI, Deyo–Charlson Comorbidity Index; GI, gastrointestinal; PN, peripheral neuropathy; SD, standard deviation.

Table A.3. Demographic and baseline clinical characteristics of second-line therapy.

Demographic characteristics	Second-line therapy				*p* value
	With PN		Without PN		
	n = 280		*n* = 1532		
	n/mean	%/SD	*n*/mean	%/SD	
Age (mean, SD)	62.8	10.35	62.3	11.09	0.418
Age group (*n*, %)					

Table A.3. (Continued)

Demographic characteristics	Second-line therapy				*p* value
	With PN		Without PN		
	n = 280		*n* = 1532		
	n/mean	%/SD	*n*/mean	%/SD	
18–34	4	1.4%	6	0.4%	0.054
35–44	5	1.8%	60	3.9%	0.078
45–54	47	16.8%	309	20.2%	0.190
55–64	110	39.3%	617	40.3%	0.756
65–74	74	26.4%	281	18.3%	0.002
75+	40	14.3%	259	16.9%	0.277
Sex (*n*, %)					
Male	178	63.6%	926	60.4%	0.324
Female	102	36.4%	606	39.6%	0.324
Payer (*n*, %)					
Commercial	164	58.6%	981	64.0%	0.081
Medicare	116	41.4%	551	36.0%	0.081
Insurance plan type (*n*, %)					
Comprehensive	46	16.4%	260	17.0%	0.824
Exclusive-provider organization	2	0.7%	16	1.0%	1.000
Health-maintenance organization	43	15.4%	188	12.3%	0.155
Point of service (POS)	17	6.1%	96	6.3%	0.901
Preferred-provider organization	150	53.6%	854	55.7%	0.501
POS with capitation	2	0.7%	9	0.6%	0.682
Consumer-driven health plan	12	4.3%	76	5.0%	0.629
High-deductible health plan	8	2.9%	33	2.2%	0.467
Unknown	0	0.0%	0	0.0%	
Geographic region (*n*, %)					
Northeast	51	18.2%	256	16.7%	0.537
North central	70	25.0%	431	28.1%	0.281
South	107	38.2%	582	38.0%	0.943
West	50	17.9%	249	16.3%	0.506
Unknown	2	0.7%	14	0.9%	1.000

(Continued)

Table A.3. (Continued)

Demographic characteristics	Second-line therapy				*p* value
	With PN		Without PN		
	n = 280		*n* = 1532		
	n/mean	%/SD	*n*/mean	%/SD	
Population density (*n*, %)					
Urban	242	86.4%	1,294	84.5%	0.400
Rural	36	12.9%	224	14.6%	0.439
Unknown	2	0.7%	14	0.9%	1.000
Duration of line of therapy (mean, SD)	171.2	199.7	201.0	249.9	0.059
DCI (mean, SD)	4.7	2.95	4.3	2.78	0.03
DCI (*n*, %)					
0	1	0.4%	18	1.2%	0.340
1	1	0.4%	8	0.5%	1.000
2	96	34.3%	547	35.7%	0.648
3+	182	65.0%	959	62.6%	0.444
DCI components (*n*, %)					
Myocardial infarction	11	3.9%	43	2.8%	0.310
Congestive heart failure	16	5.7%	92	6.0%	0.850
Peripheral vascular disease	7	2.5%	53	3.5%	0.409
Cerebrovascular disease	19	6.8%	92	6.0%	0.617
Dementia	0	0.0%	4	0.3%	
Chronic pulmonary disease	44	15.7%	225	14.7%	0.657
Rheumatologic disease	3	1.1%	32	2.1%	0.255
Peptic ulcer disease	7	2.5%	28	1.8%	0.452
Mild liver disease	1	0.4%	6	0.4%	1.000
Diabetes (mild to moderate)	66	23.6%	311	20.3%	0.215
Diabetes with chronic complications	20	7.1%	70	4.6%	0.068
Hemiplegia or paraplegia	0	0.0%	9	0.6%	
Renal disease	73	26.1%	334	21.8%	0.115
Moderate or severe liver disease	0	0.0%	2	0.1%	
Human immunodeficiency virus	0	0.0%	6	0.4%	
Any malignancy, including lymphoma and leukemia	247	88.2%	1,434	93.6%	0.001

Table A.3. (Continued)

Demographic characteristics	Second-line therapy				*p* value
	With PN		Without PN		
	n = 280		*n* = 1532		
	n/mean	%/SD	*n*/mean	%/SD	
Metastatic solid tumor	50	17.9%	244	15.9%	0.421
Prior primary cancer (*n*, %)					
Solid tumor	59	21.1%	325	21.2%	0.957
Hematologic cancer	40	14.3%	189	12.3%	0.367
Preperiod events of interest (*n*, %)					
Chronic kidney disease	59	21.1%	250	16.3%	0.052
End-stage renal disease/renal failure	14	5.0%	76	5.0%	0.978
Skeletal-related events	138	49.3%	738	48.2%	0.732
Hypercalcemia	41	14.6%	222	14.5%	0.947
Venous thromboembolism	13	4.6%	64	4.2%	0.723
Neutropenia	7	2.5%	50	3.3%	0.501
Pneumonia	22	7.9%	129	8.4%	0.754
Major bleeding	5	1.8%	22	1.4%	0.595
GI bleeding	15	5.4%	77	5.0%	0.817
Anemia	163	58.2%	825	53.9%	0.178
Anemia or anemia treatment	163	58.2%	829	54.1%	0.205
Thrombocytopenia	29	10.4%	100	6.5%	0.022
Amyloidosis	10	3.6%	34	2.2%	0.177

DCI, Deyo–Charlson Comorbidity Index; GI, gastrointestinal; PN, peripheral neuropathy; SD, standard deviation.

Table A.4.

Demographic characteristics	Third and subsequent line of therapy				*p* value
	With PN		Without PN		
	n = 75		*n* = 1028		
	n/mean	%/SD	*n*/mean	%/SD	
Age (mean, SD)	62.0	9.57	61.2	10.72	0.517
Age group (*n*, %)					
18–34	0	0.0%	7	0.7%	
35–44	2	2.7%	44	4.3%	0.764

(Continued)

Table A.4. (Continued)

Demographic characteristics	Third and subsequent line of therapy				*p* value
	With PN		Without PN		
	n = 75		*n* = 1028		
	n/mean	%/SD	*n*/mean	%/SD	
45–54	14	18.7%	227	22.1%	0.490
55–64	31	41.3%	408	39.7%	0.779
65–74	19	25.3%	210	20.4%	0.312
75+	9	12.0%	132	12.8%	0.833
Sex (*n*, %)					
Male	50	66.7%	617	60.0%	0.256
Female	25	33.3%	411	40.0%	0.256
Payer (*n*, %)					
Commercial	45	60.0%	671	65.3%	0.356
Medicare	30	40.0%	357	34.7%	0.356
Insurance plan type (*n*, %)					
Comprehensive	11	14.7%	176	17.1%	0.585
Exclusive-provider organization	0	0.0%	7	0.7%	
Health-maintenance organization	9	12.0%	130	12.6%	0.871
Point of service (POS)	7	9.3%	74	7.2%	0.494
Preferred-provider organization	42	56.0%	547	53.2%	0.640
POS with capitation	0	0.0%	5	0.5%	
Consumer-driven health plan	4	5.3%	66	6.4%	1.000
High-deductible health plan	2	2.7%	23	2.2%	0.685
Unknown	0	0.0%	0	0.0%	
Geographic region (*n*, %)					
Northeast	11	14.7%	188	18.3%	0.431
North central	13	17.3%	283	27.5%	0.054
South	30	40.0%	356	34.6%	0.347
West	21	28.0%	195	19.0%	0.057
Unknown	0	0.0%	6	0.6%	
Population density (*n*, %)					
Urban	64	85.3%	900	87.5%	0.577

Table A.4. (Continued)

Demographic characteristics	Third and subsequent line of therapy				*p* value
	With PN		Without PN		
	n = 75		*n* = 1028		
	n/mean	%/SD	*n*/mean	%/SD	
Rural	11	14.7%	122	11.9%	0.472
Unknown	0	0.0%	6	0.6%	0.507
Duration of line of therapy (mean, SD)	244.0	275.6	196.2	239.1	0.099
DCI (mean, SD)	4.3	2.84	4.0	2.55	0.274
DCI (*n*, %)					
0	0	0.0%	15	1.5%	0.292
1	0	0.0%	0	0.0%	NA
2	29	38.7%	399	38.8%	0.98
3+	46	61.3%	614	59.7%	0.784
DCI components (*n*, %)					
Myocardial infarction	0	0.0%	16	1.6%	
Congestive heart failure	2	2.7%	32	3.1%	1.000
Peripheral vascular disease	3	4.0%	27	2.6%	0.452
Cerebrovascular disease	6	8.0%	66	6.4%	0.625
Dementia	0	0.0%	2	0.2%	
Chronic pulmonary disease	12	16.0%	150	14.6%	0.739
Rheumatologic disease	2	2.7%	13	1.3%	0.272
Peptic ulcer disease	0	0.0%	16	1.6%	
Mild liver disease	3	4.0%	4	0.4%	0.009
Diabetes (mild to moderate)	13	17.3%	210	20.4%	0.519
Diabetes with chronic complications	2	2.7%	54	5.3%	0.581
Hemiplegia or paraplegia	1	1.3%	1	0.1%	0.131
Renal disease	14	18.7%	218	21.2%	0.602
Moderate or severe liver disease	0	0.0%	2	0.2%	
Human immunodeficiency virus	0	0.0%	1	0.1%	
Any malignancy, including lymphoma and leukemia	74	98.7%	1000	97.3%	0.716
Metastatic solid tumor	13	17.3%	140	13.6%	0.369
Prior primary cancer (*n*, %)					

(Continued)

Table A.4. (Continued)

Demographic characteristics	Third and subsequent line of therapy				*p* value
	With PN		Without PN		
	n = 75		*n* = 1028		
	n/mean	%/SD	*n*/mean	%/SD	
Solid tumor	19	25.3%	215	20.9%	0.366
Hematologic cancer	11	14.7%	125	12.2%	0.524
Preperiod events of interest (*n*, %)					
Chronic kidney disease	11	14.7%	168	16.3%	0.704
End-stage renal disease/renal failure	2	2.7%	48	4.7%	0.573
Skeletal-related events	42	56.0%	486	47.3%	0.144
Hypercalcemia	10	13.3%	115	11.2%	0.571
Venous thromboembolism	1	1.3%	38	3.7%	0.512
Neutropenia	2	2.7%	28	2.7%	1.000
Pneumonia	5	6.7%	84	8.2%	0.644
Major bleeding	2	2.7%	13	1.3%	0.272
GI bleeding	3	4.0%	46	4.5%	1.000
Anemia	36	48.0%	550	53.5%	0.357
Anemia or anemia treatment	36	48.0%	554	53.9%	0.323
Thrombocytopenia	7	9.3%	62	6.0%	0.224
Amyloidosis	0	0.0%	18	1.8%	0.248

DCI, Deyo–Charlson Comorbidity Index; GI, gastrointestinal; NA, not applicaple; PN, peripheral neuropathy; SD, standard deviation.