Patient-Reported and Clinician-Reported Chemotherapy-Induced Peripheral Neuropathy in Patients With Early Breast Cancer: Current Clinical Practice

Kirsten A. Nyrop, PhD [1,2]; Allison M. Deal, MS[2]; Kathryn E. Reeder-Hayes, MD, MBA [1,2]; Shlomit S. Shachar, MD[3]; Bryce B. Reeve, PhD [4]; Ethan Basch, MD[1,2]; Seul Ki Choi, MPH[5]; Jordan T. Lee, MA[6]; William A. Wood, MD[1,2]; Carey K. Anders, MD[7]; Lisa A. Carey, MD[1,2]; Elizabeth C. Dees, MD[1,2]; Trevor A. Jolly, MD[1,2]; Gretchen G. Kimmick, MD, MS[7]; Meghan S. Karuturi, MD[8]; Raquel E. Reinbolt, MD [9]; JoEllen C. Speca, MD[1]; and Hyman B. Muss, MD[1,2]

BACKGROUND: In the current study, the authors investigated the incidence of moderate to severe chemotherapy-induced peripheral neuropathy (CIPN) for chemotherapy regimens commonly used in current clinical practice for the treatment of patients with early breast cancer. Patient-reported and clinician-assessed CIPN severity scores were compared, and risk factors for CIPN severity were identified. **METHODS:** Patients completed a Patient-Reported Symptom Monitoring form and oncologists completed a Common Terminology Criteria for Adverse Events form. CIPN reports were collected prospectively during regularly scheduled infusion visits throughout the duration of chemotherapy. **RESULTS:** The sample included 184 women with a mean age of 55 years; approximately 73% were white. The 4 chemotherapy regimens used were doxorubicin and cyclophosphamide plus paclitaxel (60 patients); docetaxel and cyclophosphamide (50 patients); docetaxel, carboplatin, and anti–human epidermal growth factor receptor 2 (HER2) (24 patients); and doxorubicin and cyclophosphamide plus paclitaxel and carboplatin (18 patients). All patients treated with doxorubicin and cyclophosphamide plus paclitaxel and doxorubicin and cyclophosphamide plus paclitaxel and carboplatin received paclitaxel; all patients treated with docetaxel and cyclophosphamide and docetaxel, carboplatin, and anti-HER2 received docetaxel. The chemotherapy dose was reduced in 52 patients (28%); in 15 patients (29%), this reduction was due to CIPN. Chemotherapy was discontinued in 26 patients (14%), 8 because of CIPN. Agreement between patient-reported and clinician-assessed CIPN severity scores was minimal (weighted Cohen kappa, $P = .34$). Patient-reported moderate to severe CIPN was higher for paclitaxel (50%) compared with docetaxel (17.7%) ($P < .001$). Pretreatment arthritis and/or rheumatism (relative risk [RR], 1.58; 95% CI, 1.06-2.35 [$P = .023$]) and regimens containing paclitaxel (RR, 2.88; 95% CI, 1.72-4.83 [$P < .0001$]) were associated with higher CIPN severity. Being married (RR, 0.57; 95% CI, 0.37-0.887 [$P = .01$]) was found to be associated with lower CIPN severity. **CONCLUSIONS:** The discrepancy between patient-reported and clinician-assessed CIPN underscores the need for both patient and clinician perspectives regarding this common, dose-limiting, and potentially disabling side effect of chemotherapy. ***Cancer* 2019;125:2945-2954**.

KEYWORDS: breast, cancer, chemotherapy, neuropathy, peripheral.

INTRODUCTION

Peripheral neuropathy is a common, dose-limiting, and potentially disabling side effect of cancer chemotherapy, with varying evidence regarding its incidence, severity, persistence, and risk factors. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)[1] toxicity grades determined by clinicians during chemotherapy trials have provided initial estimates of chemotherapy-induced peripheral neuropathy (CIPN). For example, in patients receiving doxorubicin and cyclophosphamide triweekly and then a taxane, CIPN was observed in 27% of patients treated with paclitaxel weekly, 20% of patients treated with paclitaxel every 3 weeks, 20% of patients treated with weekly docetaxel, and 16% of patients treated with docetaxel every 3 weeks.[2] Other trials similarly have documented higher CTCAE toxicity in paclitaxel-based compared with docetaxel-based regimens.[3] CIPN toxicity is a key concern for clinicians and patients, with long-term follow-up in drug trials documenting the persistence of CIPN years after the completion of chemotherapy.[4,5]

Corresponding author: Kirsten A. Nyrop, PhD, University of North Carolina School of Medicine, CB 7305, Chapel Hill, NC 27599-7305; kirsten_nyrop@med.unc.edu

[1]Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina; [2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [3]Rambam Health Campus, Haifa, Israel; [4]Department of Population Health Sciences, Duke University School of Medicine, Durham, North Carolina; [5]Department of Health Behavior, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina; [6]Department of Exercise and Sport Science, University of North Carolina, Chapel Hill, North Carolina; [7]Department of Medicine, Duke University School of Medicine, Durham, North Carolina; [8]Department of Breast Medical Oncology, MD Anderson Cancer Center, University of Texas, Houston, Texas; [9]Department of Internal Medicine, Ohio State University Comprehensive Cancer Center, Columbus, Ohio.

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With regard to CIPN in clinical practice, retrospective chart reviews of clinician notes have identified the percentage of patients whose CIPN toxicity warranted dose reduction or treatment discontinuation.[6-8] In addition, cross-sectional, retrospective studies have surveyed patients at varying time periods after treatment regarding their recall of symptoms during chemotherapy[9-12] and the persistence of CIPN after treatment.[13-16] However, to the best of our knowledge, there are few prospective data regarding possible discrepancies in patient-reported CIPN toxicity experience compared with clinician-assessed CIPN severity gathered continuously throughout active treatment.

The current study addressed this question in a sample of women who received chemotherapy for early-stage breast cancer and who completed symptom severity reports at regularly scheduled treatment visits. At the same visit, their oncology providers independently completed a CTCAE form for grading symptom severity. Patient-reported and clinician-reported CIPN severity are compared, with a focus on reports of moderate, severe, or very severe toxicity.[17] We also assessed CIPN severity in patients treated with paclitaxel compared with docetaxel regimens, compared individual chemotherapy regimens commonly used in current clinical practice, and analyzed patient characteristics for potential CIPN risk factors.

MATERIALS AND METHODS

Study Participants

The current study is an ancillary data analysis of patients enrolled in 2 prospective nonrandomized studies of the effect of self-directed walking during chemotherapy on a biomarker of aging, p16INK4a.[18] The chemotherapy regimens were selected by clinicians who were treating the patients and represent commonly used regimens recommended for the (neo)adjuvant treatment of early breast cancer.[19-21] The 2 studies enrolled women with stage I to stage III breast cancer (according to the seventh edition of the American Joint Committee on Cancer staging system), with 1 study enrolling women aged <65 years (ClinicalTrials.gov identifier NCT02167932) and the other study enrolling women aged ≥65 years (ClinicalTrials.gov identifier NCT02328313). Participants provided written informed consent. The studies were approved by the University of North Carolina at Chapel Hill Lineberger Comprehensive Cancer Center Protocol Review Committee and the institutional review boards of each study site.

Measures

CIPN severity measures

At regularly scheduled infusion visits, study participants completed the Patient-Reported Symptom Monitoring (PRSM) system form.[22] The PRSM is very similar to the patient-reported outcome version of the CTCAE (PRO-CTCAE),[23,24] which was not available to the general community when we launched the walking trials. Two questions pertaining to CIPN symptom experience within "the past 7 days" inquired about "numbness or tingling in your hands or feet." With regard to CIPN symptom "severity," rating options were 0 (indicating none), 1 (indicating mild), 2 (indicating moderate), 3 (indicating severe), or 4 (indicating very severe). With regard to "interference," the item inquired how much the CIPN "keeps you from doing things you usually do," with the response options of 0 (indicating not at all), 1 (indicating a little bit), 2 (indicating somewhat), 3 (indicating quite a bit), or 4 (indicating very much).

At the same clinic visit, the patients' oncology clinicians independently completed a CTCAE form to rate "peripheral sensory neuropathy" toxicity as follows: 0 (indicating none), 1 (indicating asymptomatic on examination only), 2 (indicating moderate symptoms), 3 (indicating severe symptoms limiting self-care), or 4 (indicating life threatening). Patient scores were not shared with the clinicians. For the purpose of comparing the PRSM and CTCAE scores for major toxicity, PRSM scores for moderate, severe, and very severe were treated similarly to CTCAE grades 2, 3, and 4.

For the 9 patients (5%) receiving both neoadjuvant and adjuvant chemotherapy, CIPN symptom reports were collected only during receipt of neoadjuvant chemotherapy. For patients who received anti–human epidermal growth factor receptor 2 (HER2) therapy, toxicity reports were collected only during chemotherapy. PRSM and CTCAE forms were collected every other week for infusion schedules that were weekly (paclitaxel or paclitaxel and carboplatin segment), so that all data points were either biweekly or triweekly.

Research staff–assessed physical function

Prior to the first chemotherapy infusion (study baseline), research staff assessed the physical function of the participants using 2 measures: the Timed Up and Go test[25,26] and the Short Physical Performance Battery.[27,28]

Additional patient-reported measures

At baseline, study participants completed questionnaires for patient-reported measures of function and quality

of life: the patient-reported Karnofsky performance status,[29] Medical Outcomes Survey (MOS) of physical function,[30] Functional Assessment of Cancer Therapy–General (FACT-G; version 4),[31] Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F; version 4),[32] and Mental Health Index-13 (MHI-13).[33] For the FACT-G (possible score of 0-108) and FACIT-F (possible score of 0-52), higher scores indicate a higher quality of life. Study participants also completed the Health Behaviors Questionnaire[34] and provided information regarding their demographics, comorbidities, and number of falls within the past 6 months.

Electronic medical records

Research staff abstracted electronic health records for data pertaining to the participants' breast cancer stage (according to the seventh edition of the American Joint Committee on Cancer)[35] and phenotype, chemotherapy regimen, and body mass index (BMI). Health records also were reviewed regarding adverse events such as dose reduction or treatment discontinuation.

Statistical Analysis

Descriptive statistics were used to summarize study participant characteristics, prechemotherapy treatment assessments and questionnaires, breast cancer diagnosis and treatment, and adverse events. A weighted kappa statistic[36] measured agreement between PRSM and CTCAE CIPN scores, with off-diagonal cells containing weights indicating the extent of disagreement. The cumulative incidence of the development of moderate, severe, or very severe CIPN was estimated using the Kaplan-Meier method, and was compared between patients and clinicians using a log-rank test. A modified Poisson regression model with robust variance was used to evaluate the association between patient and clinical characteristics and the incidence of moderate or higher CIPN, and relative risks (RRs) were reported.[37] A multivariable model was fit based on significant unadjusted results in combination with subject matter expertise. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina) and a 2-sided $P < .05$ was considered to be statistically significant.

RESULTS

Study Participants

Patient characteristics are summarized in Table 1. Among 184 participants, the mean age was 55 years and the majority of participants (73%) were white. Details regarding the timing and order of chemotherapy drugs are provided in Supporting Table 1 for the 4 primary regimens: doxorubicin and cyclophosphamide plus paclitaxel (AC-T; 60 patients); docetaxel and cyclophosphamide (TC; 50 patients); docetaxel, carboplatin, and anti-HER2 (TCH; 24 patients); and doxorubicin and cyclophosphamide plus paclitaxel and carboplatin (AC-TC; 18 patients). With regard to taxane-based chemotherapy, a majority of patients received paclitaxel (56%) compared with docetaxel (44%). All patients treated with AC-T and AC-TC received paclitaxel; all patients treated with TC and TCH received docetaxel. In addition to the patients receiving AC-T or AC-TC (78 patients), 13 patients received other anthracycline-based regimens, 7 of whom also received paclitaxel and 1 of whom received docetaxel. In addition to the patients treated with TC or TCH (74 patients), 19 patients received other taxane-based regimens, 15 of whom received paclitaxel and 4 of whom received docetaxel. The docetaxel and carboplatin and AC regimens were uniformly administered with growth factors (pegfilgrastim).

Patient-reported and physician-assessed CIPN

Figure 1 illustrates maximum patient and clinician-reported CIPN scores at any time during chemotherapy. Overall, 35% of patients (64 patients) rated their CIPN toxicity as moderate (50 patients), severe (12 patients), or very severe (2 patients). Approximately 24% of patients reported moderate or greater CIPN symptom interference with daily activities.

There was minimal agreement (weighted Cohen kappa = 0.34) between patient-reported and clinician-assessed CIPN toxicity scores. Figure 2 shows that patient-provider agreement was highest for grade 0; of the 47 patients who rated their CIPN as grade 0, 41 clinicians (87%) similarly scored their patient's CIPN as grade 0. Patient-clinician agreement was 46% (30 of 65 patients) for grade 1 and 48% (23 of 47 patients) for grade 2. For 13 patients who rated their CIPN as grade 3, a total of 4 clinicians rated their CIPN as grade 1 and 9 rated it as grade 2.

Individual chemotherapy regimens

The percentage of patients rating their CIPN toxicity as moderate or higher varied significantly ($P < .0001$) among the most frequent chemotherapy regimens: TC (10%), TCH (25%), AC-T (48%), and AC-TC (50%). Figure 3 illustrates the percentage of patient-reported maximum scores of none, mild, moderate, or severe/very severe for each of these regimens.

TABLE 1. Study Participants (N = 184)

Variable	No. (%)
Mean age, y	55 (SD 12.9, range 24-83)
≥65	65 (35%)
White race	135 (73%)
Educational level ≤high school	67 (37%)
Married	99 (55%)
Living alone	35 (21%)
Employed >32 h/wk	61 (36%)
Mean BMI, kg/m^2	29 (SD 6.8, range 17-65)
Underweight (BMI, <18.5)	3 (2%)
Normal weight (BMI, 18.5-24.9)	47 (26%)
Overweight (BMI, 25-29.9)	60 (33%)
Obese I (BMI, 30-34.9)	41 (23%)
Obese II/III (BMI, ≥35)	33 (18%)
Prechemotherapy patient-reported comorbidities	
Arthritis or rheumatism	53 (31%)
High blood pressure	51 (30%)
Depression	30 (18%)
Diabetes	19 (11%)
Osteoporosis	16 (9%)
Prechemotherapy assessments	
Timed Up and Go test of ≥14 s/cannot complete	24 (13%)
Short Physical Performance Battery score of <11 (suboptimal)	54 (34%)
Prechemotherapy patient-reported measures	
Patient-reported KPS (suboptimal <80)	18 (10%)
≥1 falls within the past 6 mo	17 (10%)
HBQ regarding vigorous physical activity, min/wk	
Never/a few times per mo	75 (44%)
1-2 times/wk	36 (21%)
3-4 times/wk	40 (24%)
≥5 times/wk	18 (11%)
Physical function score of low function ≤20 (suboptimal)[a]	107 (63%)
FACT-G total score (range, 0-108)[b]	89 (SD, 15.4; range, 36-108)
FACT-G Physical Well-being (range, 0-28)	25 (SD, 4.3)
FACT-G Social/Family Well-being (range, 0-28)	24 (SD, 5.1)
FACT-G Emotional Well-being (range, 0-24)	19 (SD, 3.9)
FACT-G Functional Well-being (range, 0-28)	21 (SD 5.9)
FACIT-F (range, 0-52)[b]	42 (SD, 8.9; range, 4-52)
Mental Health Index–Depression score ≥12 (depressed)[c]	46 (27%)
Mental Health Index–Anxiety score ≥6 (anxious)[c]	80 (46%)
Breast cancer diagnosis and treatment	
Breast cancer AJCC stage	
I	40 (22%)
II	92 (51%)
III	49 (27%)
Anti–HER2 therapy	43 (23%)
Surgery	
None	4 (2%)
Lumpectomy	81 (44%)
Mastectomy	99 (54%)
Radiotherapy	124 (70%)
Timing of chemotherapy	
Neoadjuvant	82 (45%)
Adjuvant	102 (55%)
Duration of chemotherapy, d	100 (SD, 32.9; range, 40-187)
Chemotherapy regimen	
Doxorubicin plus cyclophosphamide → paclitaxel plus carboplatin	18 (10%)
Doxorubicin plus cyclophosphamide → paclitaxel	60 (33%)
Other doxorubicin	13 (7%)
Docetaxel plus carboplatin plus anti–HER2 treatment	24 (13%)
Docetaxel plus cyclophosphamide (plus anti–HER2 treatment [N = 4])	50 (27%)
Other taxane (plus anti–HER2 treatment [N = 13])	19 (10%)
Chemotherapy regimen I	
Anthracycline based	91 (49%)
Not anthracycline based	93 (51%)
Chemotherapy regimen II	
Paclitaxel (including nab-paclitaxel)	100 (56%)
Docetaxel	79 (44%)

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy–General; HBQ, Health Behavior Questionnaire; HER2, human epidermal growth factor receptor; KPS, Karnofsky performance status.

[a]Lower score indicates lower function and less support.

[b]Higher score indicates a higher quality of life and less fatigue.

[c]Higher score indicates more depression, anxiety, deficits, and limitations.

Paclitaxel compared with docetaxel

Overall, throughout chemotherapy including, but not limited to, taxane treatment, patients who received paclitaxel reported moderate or higher CIPN more often than those who received docetaxel (50% vs 17.7%; $P < .0001$). Figure 4 illustrates the cumulative incidence of patient-reported moderate or higher CIPN toxicity during the taxane period only from the initiation of taxane treatment through the next 100 days of chemotherapy.

Dose reduction and treatment discontinuation

The chemotherapy dose was reduced in 52 of the full sample of 184 patients (28%): 33% of the patients receiving AC-T/TC (26 of 78 patients) and 18% of the patients receiving TC/TCH (13 of 74 patients). Among patients treated with AC-T/TC, approximately 77% of dose reductions (20 of 26 patients) occurred during the T/TC component. Clinician notes indicated that dose reductions were due to CIPN in 15 of 52 patients (29%). The mean time to the first or only dose reduction due to clinician-noted CIPN was 8 weeks (SD, 5.3 weeks): 7 weeks (SD, 5.3 weeks) for patients receiving paclitaxel (12 patients receiving AC-T or TC) and 13 weeks (SD, 1.8 weeks) for patients receiving docetaxel (3 patients receiving TC or TCH).

Chemotherapy treatment was discontinued in 26 patients (14%). Among patients treated with AC-T or TC, approximately 80% of treatment discontinuations occurred during the T/TC component. Clinician notes indicated that treatment discontinuations were due to CIPN in 8 of 26 patients (31%). The mean time to treatment discontinuation due to CIPN was 8.7 weeks (SD, 3.2 weeks).

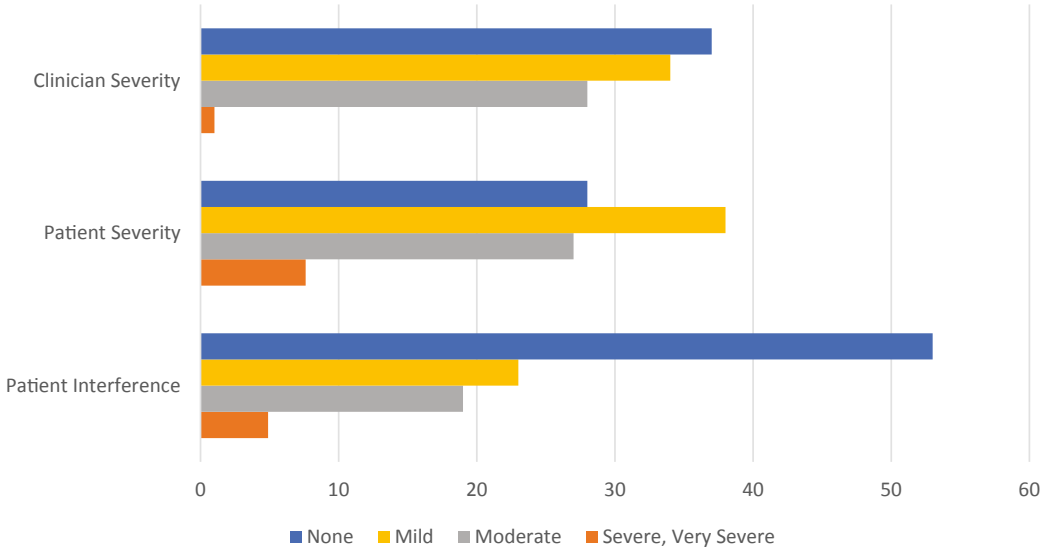

Figure 1. Severity of chemotherapy-induced peripheral neuropathy (CIPN) (as reported by patients and clinicians) and interference (as reported by patients), shown as a percentage.

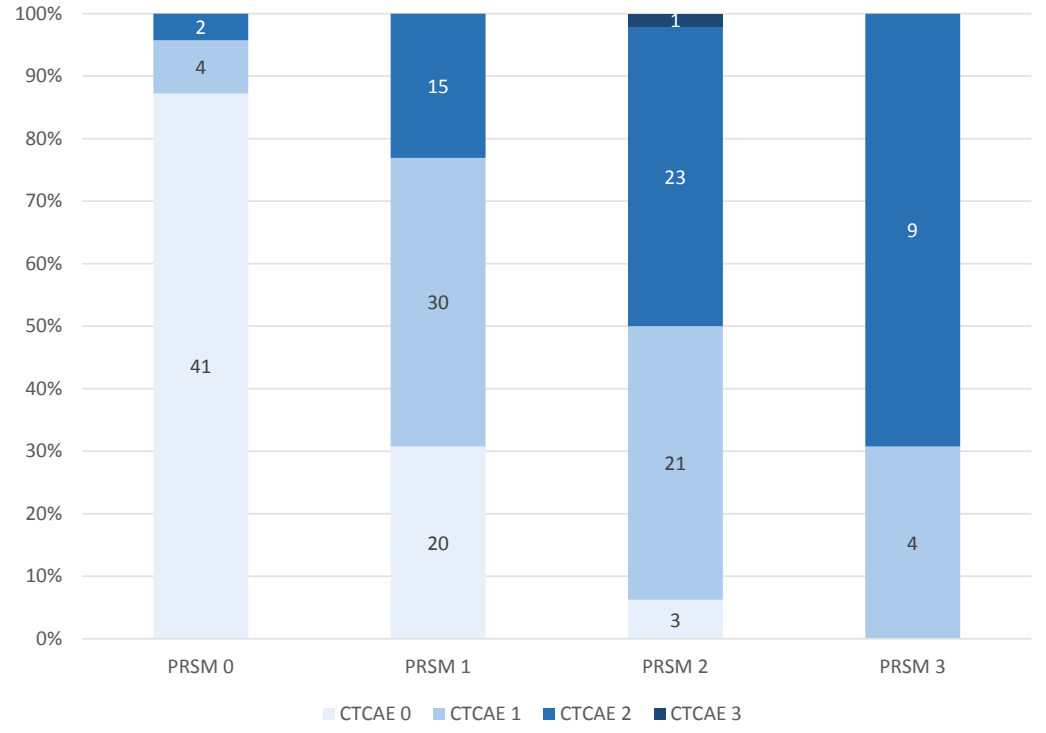

Figure 2. Patient-Reported Symptom Monitoring (PRSM) compared with clinician-reported (Common Terminology Criteria for Adverse Events [CTCAE]) chemotherapy-induced peripheral neuropathy (CIPN) (shown as the number).

RR for patient-reported moderate or higher CIPN

In unadjusted analysis (Table 2), several variables were found to be associated with a greater likelihood of patient-reported moderate or higher CIPN severity at any time during chemotherapy: living alone ($P = .049$), higher BMI ($P = .003$), baseline arthritis or rheumatism ($P = .005$), duration of chemotherapy ($P < .0001$), paclitaxel regimen (compared with

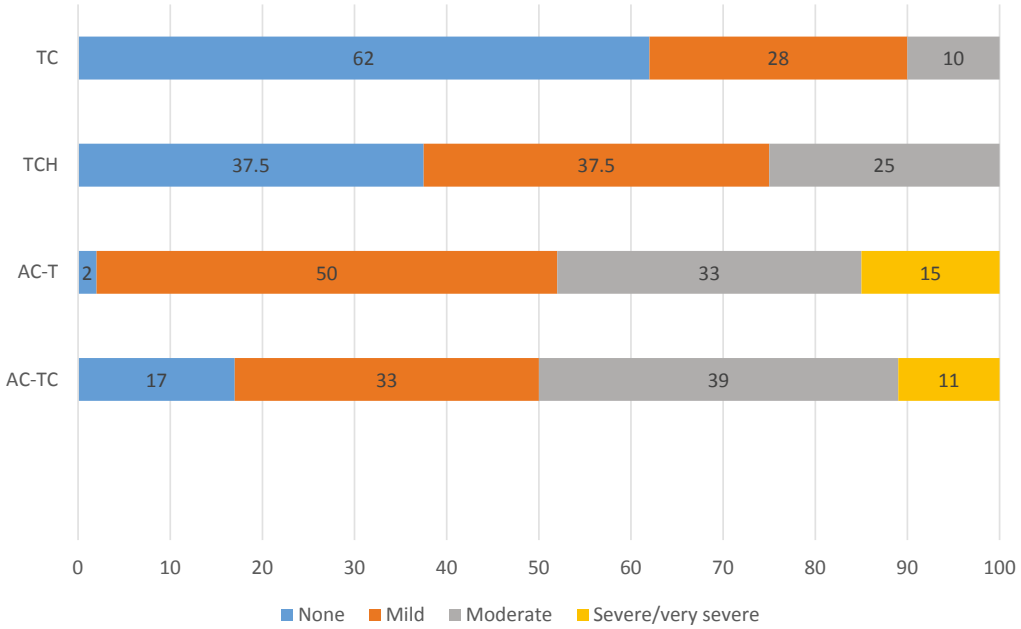

Figure 3. Severity of chemotherapy-induced peripheral neuropathy (CIPN) by chemotherapy regimen, shown as the percentage. AC-T indicates doxorubicin and cyclophosphamide plus paclitaxel; AC-TC, doxorubicin and cyclophosphamide plus paclitaxel and carboplatin; TC, docetaxel and cyclophosphamide; TCH, docetaxel, carboplatin, and anti-human epidermal growth factor receptor 2 (HER2).

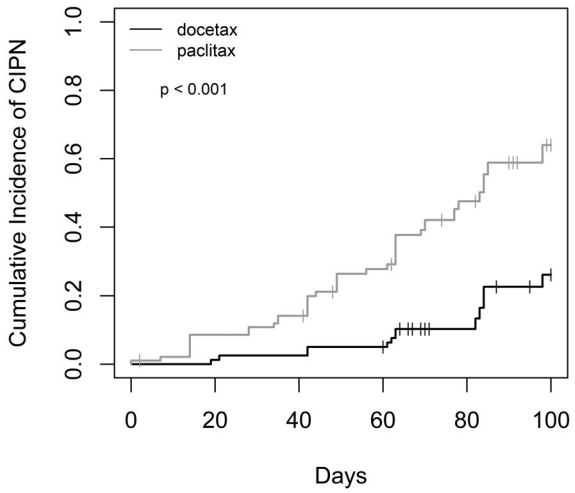

Figure 4. Cumulative incidence of chemotherapy-induced peripheral neuropathy (CIPN). Docetax indicates docetaxel; paclitax, paclitaxel.

docetaxel) ($P < .0001$), and anthracycline-based regimen ($P = .002$). Variables found to be associated with a lower likelihood of moderate or higher CIPN severity were white race ($P = .011$), being married ($P = .009$), and higher scores for health-related quality of life measures (FACT-G overall score [$P = .006$], FACT-G Physical Well-being score [$P < .0001$], FACT-G Functional Well-being score [$P = .027$], and FACIT-Fatigue [$P = .001$]).

On multivariable analysis (Table 2), pretreatment arthritis or rheumatism (RR, 1.58; 95% CI, 1.06-2.35 [$P = .023$]) and paclitaxel regimen (RR, 2.88; 95% CI, 1.72-4.83 [$P < .0001$]) were associated with a greater risk of moderate or higher CIPN, whereas being married (RR, 0.57; 95% CI, 0.37-0.887 [$P = .010$]) was associated with a lower risk. Given the limitations of the sample size in the current study, a limited set of covariates was selected for the multivariable model based on clinical judgement as well as results from the unadjusted analyses; therefore, the FACT-G Physical Well-being and FACT-G Functional Well-being scales were included in the multivariable model because these 2 subdomains of the FACT-G were significantly associated with risk. Conversely, chemotherapy duration and anthracycline-based regimen were not included in the multivariable model to avoid collinearity with paclitaxel regimen.

DISCUSSION

The current study investigated CIPN severity in women with early breast cancer who were receiving

TABLE 2. RR for Patient-Reported Moderate, Severe, or Very Severe Peripheral Neuropathy

Variable	RR (95% CI)	Unadjusted P[a]	RR (95% CI)	Adjusted P[a]
Age	1.01 (0.99-1.02)	.393		
White race	0.60 (0.41-0.89)	**.011**	0.81 (0.53-1.24)	.810
Educational level ≤high school	1.45 (0.98-2.15)	.063		
Married	0.58 (0.39-0.87)	**.009**	0.57 (0.37-0.87)	**.010**
Living alone	1.52 (1.00-2.32)	**.049**		
Employed full time	1.08 (0.72-1.63)	.709		
BMI	1.03 (1.01-1.05)	**.003**		
BMI dichotomized normal/overweight/obese I versus obese II				
Normal/overweight/obese I	0.60 (0.40-0.91)	**.015**	1.00 (0.98-1.02)	.986
Prechemotherapy patient-reported comorbidities				
Arthritis or rheumatism	1.78 (1.19-2.66)	**.005**	1.58 (1.06-2.35)	**.023**
High blood pressure	1.11 (0.72-1.72)	.644		
Depression	1.31 (0.82-2.10)	.264		
Diabetes	0.89 (0.45-1.79)	.752		
Osteoporosis	0.70 (0.29-1.68)	.424		
Prechemotherapy assessments				
Timed Up and Go test of ≥14 s/cannot complete	1.38 (0.85-2.25)	.192		
Short Physical Performance Battery score <11 (suboptimal)	0.93 (0.83-1.04)	.184		
Prechemotherapy patient-reported measures				
Patient-reported KPS (suboptimal <80)	1.45 (0.87-2.42)	.150		
≥1 falls within the past 6 mo	0.85 (0.40-1.84)	.689		
HBQ: engagement in vigorous physical activity (min/wk)				
Few times/mo	1.09 (0.62-1.93)	.763		
1-2 times/week	0.97 (0.54-1.74)	.920		
3-4 times/week	0.94 (0.53-1.67)	.834		
≥5 times/week	0.75 (0.32-1.73)	.495		
Physical function score of low function <20[b]	1.32 (0.85-2.06)	.218		
FACT-G score[c]	0.98 (0.97-0.99)	**.006**		
FACT-G Physical Well-being (range, 0-28)	0.94 (0.91-0.97)	**<.0001**	0.82 (0.66-1.03)	**.084**
FACT-G Social/Family Well-being (range, 0-28)	0.97 (0.94-1.00)	.059		
FACT-G Emotional Well-being (range, 0-24)	0.97 (0.93-1.01)	.187		
FACT-G Functional Well-being (range, 0-28)	0.97 (0.94-1.00)	**.027**	0.91 (0.80-1.05)	.195
FACIT-F[c]	0.97 (0.96-0.99)	**.001**	1.03 (0.89-1.20)	.651
Mental Health Index–Depression score ≥12[d]	1.35 (0.89-2.04)	.160		
Mental Health Index–Anxiety score ≥6[d]	1.01 (0.68-1.51)	.950		
Breast cancer treatment				
Timing of chemotherapy (referent: adjuvant)				
Neoadjuvant	1.24 (0.84-1.83)	.278		
Chemotherapy duration	1.01 (1.01-1.02)	**<.0001**		
Taxane-based chemotherapy regimen (referent: docetaxel)				
Paclitaxel (including nab-paclitaxel)	2.82 (1.69-4.72)	**<.0001**	2.88 (1.72-4.83)	**<.0001**
Chemotherapy regimen (referent: nonanthracycline)	1.95 (1.27-2.99)	**.002**		
Anti–HER2 therapy	1.09 (0.70-1.72)	.699		
Chemotherapy regimen				
Doxorubicin plus cyclophosphamide → paclitaxel plus carboplatin	5.00 (1.93-12.94)	**.009**		
Doxorubicin plus cyclophosphamide → paclitaxel	4.83 (2.02-11.56)	**.0004**		
Docetaxel plus carboplatin plus anti–HER2 treatment	2.50 (0.85-7.38)	.097		
Docetaxel plus cyclophosphamide	Referent			

Abbreviations: BMI, body mass index; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy–General; HBQ, Health Behavior Questionnaire; HER2, human epidermal growth factor receptor; KPS, Karnofsky performance status; RR, relative risk.
[a]Bold type indicates statistical significance.
[b]Lower score indicates lower function and less support.
[c]Higher score indicates a higher quality of life and less fatigue.
[d]Higher score indicates more depression, anxiety, and deficits.

standard-of-care chemotherapy regimens. We observed only minimal congruence between patient-reported and clinician-assessed CIPN severity, with nonagreement increasing as patient-perceived severity increased. A prior study similarly reported physician-assessed CIPN toxicity grades that were lower than patient-reported scores.[38] The findings of the current study corroborate other studies[2,3,8,39,40] reporting higher CIPN toxicity in patients treated with paclitaxel compared with docetaxel.

The larger literature pertaining to chronic pain and marital function may provide some insight into the current study finding of an association between marital status and patient perceptions of CIPN severity.[41-43]

In that literature, marital satisfaction, spousal support, and spousal responses to pain reportedly can contribute to psychological distress (depressive symptoms, anxiety symptoms, and mood disorders) which, in turn, is associated with pain dimensions, including symptom severity. The current study did not explore the quality of marital status, and we did not find significant associations between CIPN symptom severity and the FACT-G Emotional Well-being score, MHI–Depression score, or MHI–Anxiety score. In our multivariable model, these quality-of-life measures were collected before, not after, neurotoxic chemotherapy was received. In general, the association between marital status and social supports and the severity of CIPN warrants further investigation.

Whereas some studies have identified older age as a risk factor for CIPN,[4,5,39] other studies[7,11] including our study have not identified age as a significant factor. The evidence regarding diabetes prior to chemotherapy as a risk factor for CIPN is mixed, with the results of the current study not identifying this disease as a significant factor.[4,11,14] In the current study, BMI overall and BMI dichotomized to compare patients who were obese II with all other patients were found to be significant on unadjusted analysis, but not on multivariable analysis. In the larger literature, the evidence regarding BMI and obesity is mixed.[4,11,39,40,44] In the current study, a history of vigorous exercise prior to chemotherapy was not identified as a factor in the development of CIPN, although other studies have shown significantly reduced CIPN in women who were physically active prior to receiving chemotherapy.[45,46]

A strength of the current study is that patient reports of CIPN severity were collected prospectively throughout the duration of chemotherapy using toxicity reporting that is similar in structure and content to that of the PRO-CTCAE, which we believe now should be used for patient-reported symptom monitoring in both clinical trials and clinical practice.[23,24,47,48] For comparison, clinician-assessed CIPN toxicity was collected using CTCAE. Second, the chemotherapy regimens in the current study sample reflect current clinical practice in patients with early breast cancer, and CIPN toxicity was reported separately for each treatment regimen. Detailed information regarding individual chemotherapy regimens can be important for shared decision making between patients and oncology clinicians as they consider chemotherapy options.[49]

In light of the potentially long-lasting and debilitating effects of CIPN, the findings of the current study underscore the need for continuous monitoring of both patient and clinician perspectives of CIPN severity. Ongoing monitoring of patient-reported symptoms can provide opportunities for patient-centered communication, timely interventions such as dose reduction or treatment discontinuation, and improved clinical outcomes,[50-52] as well as essential data for CIPN prevention trials.[53] The current study findings regarding CIPN toxicity are especially important for the administration of highly efficacious sequential regimens that include both anthracycline and paclitaxel, pointing to the need for extra vigilance in monitoring the existence and progression of CIPN in patients receiving these regimens and timely interventions as warranted.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Kirsten A. Nyrop, **Allison M. Deal**, and **Hyman B. Muss:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Kathryn E. Reeder-Hayes**, **Shlomit S. Shachar**, **Bryce B. Reeve**, **Ethan Basch**, **Seul Ki Choi**, **Jordan T. Lee**, **William A. Wood**, **Carey K. Anders**, **Lisa A. Carey**, **Elizabeth C. Dees**, **Trevor A. Jolly**, **Gretchen G. Kimmick**, **Meghan S. Karuturi**, **Raquel E. Reinbolt**, and **JoEllen C. Speca:** Writing–review and editing.

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