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Long-term Peripheral Neuropathy in Breast Cancer Patients Treated With Adjuvant Chemotherapy: NRG Oncology/NSABP B-30

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Abstract

Background: The long-term effects of chemotherapy are sparsely reported. Peripheral neuropathy (PN) is one of the most frequent toxicities associated with taxane use for the treatment of early-stage breast cancer. We investigated the impact of the three different docetaxel-based regimens and patient characteristics on long-term, patient-reported outcomes of PN and the impact of PN on long-term quality of life (QOL).

Methods: The National Surgical Adjuvant Breast and Bowel Project Protocol B-30 was a randomized trial comparing sequential doxorubicin (A) and cyclophosphamide (C) followed by docetaxel (T) (AC→T), concurrent ACT, or AT in women with node-positive, early-stage breast cancer. The AC→T group had a higher cumulative dose of T. PN was one of the symptoms assessed in a QOL substudy. Statistical methods included simple and mixed ordinal logistic regression and general linear models. All statistical tests were two-sided.

Results: Of 1512 patients, 41.9% reported PN two years after treatment initiation. Treatment with AT and ACT was associated with less severe long-term PN compared with AC→T (odds ratio [OR] = 0.45, 95% confidence interval [CI] = 0.35 to 0.58; OR = 0.59, 95% CI = 0.46 to 0.75). Preexisting PN, older age, obesity, mastectomy, and greater number of positive nodes were also associated with higher risk of long-term PN. Patients who reported worse PN symptoms at 24 months had statistically significantly worse QOL ($P_{trend} < .001$).

Conclusions: The administration of docetaxel is associated with long-term PN. The lower rate of long-term PN in AT and ACT patients might be an important consideration in supporting choosing these therapies for individuals with preexisting neuropathic symptoms or other risk factors for neuropathy.

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Peripheral neuropathy (PN) is one of the most frequently occurring toxicities associated with taxane use for the treatment of patients with early-stage breast cancer. It usually arises during treatment and continues to burden patients for many years (1). Even though it is a well-known adverse effect of this class of drugs, the long-term effects of chemotherapy are rarely reported, and investigations about the duration or persistence of PN are limited (2–5), especially including patient-reported outcomes (PROs). Neuropathy is a common complication that could result in chemotherapy dose reduction, but there is no evidence that this toxicity is associated with a higher risk of recurrence or inferior survival (6). At the same time, however, chemotherapy-induced PN may adversely affect long-term quality of life (QOL) (2,7).

The co-authors of this article conducted a systematic review to investigate the long-term effects of commonly used breast cancer adjuvant chemotherapy regimens on PN (8). Of 360 articles identified for potential inclusion, only five reported at least one year of post-treatment data (2–4,9,10).

The persistence and severity of docetaxel-induced patient-reported PN were investigated by Eckhoff et al. (2) using mail-in questionnaires, with the timing of the assessment ranging from 12.7 to 38.8 months from random assignment. Hershman et al. (3) reported on the prevalence and severity of long-term patient-reported PN in a cross-sectional study among patients who were within six and 24 months of completing adjuvant taxane therapy and in a small prospective study in patients initiating taxane therapy with longitudinal assessment up to 12 months after completing therapy. Pereira et al. (9) focused on evaluating the incidence of chemotherapy-induced PN during the first year after diagnosis. Fontes et al. (4), in the updated analyses of the same cohort, reported on the one- and three-year prevalence of PN. PN was quantified using the Common Terminology Criteria for Adverse Events (CTCAE). In another phase III clinical trial, the prevalence of persisting PN was reported as part of the toxicity profile of the investigational chemotherapy regimens (10).

The findings of the review clearly demonstrated a lack of information about PN persistence in early-stage breast cancer patients beyond the initial treatment period. Our review noted this important gap in the literature and called for additional well-conducted research to evaluate the prevalence of PN beyond the acute phase of treatment to better understand the nature and mechanisms of persistent chemotherapy-induced PN as well as potential factors associated with it.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-30, a multicenter randomized trial (Clinical Trials registration: NCT00003782 [11]), compared the effects of three different chemotherapy regimens: adjuvant doxorubicin (A) and cyclophosphamide (C) followed by docetaxel (T) (AC→T); doxorubicin and docetaxel (AT); or doxorubicin, cyclophosphamide, and docetaxel (ACT) on disease-free survival (DFS) and overall survival (OS) in patients with node-positive, early-stage breast cancer (12). The superiority of the sequential AC→T in terms of DFS compared with AT and concurrent ACT regimens was established (hazard ratio [HR] = 0.80, P = .001, and HR = 0.83, P = .01, respectively). Sequential administration of AC and T provided a statistically significant reduction in mortality over AT (HR = 0.83, P = .03). The reduction in OS with AC→T compared with ACT was not statistically significant (HR = 0.86, P = .09). Patients on AC→T reported worse QOL and overall severity of symptoms at six months (13). The treatment differences in QOL and overall symptom severity resolved by 12-month assessment. However, all patients continued to report worse symptoms compared with the baseline assessment for the duration of follow-up.

In the study reported here, we used data collected in B-30 to investigate the impact of three docetaxel-based chemotherapy regimens, which varied in duration and composition, on PROs of PN. We evaluated the prevalence and severity of PN over time and the impact of PN on long-term QOL, and we examined the factors associated with long-term PN.

Methods

Patients

Women participating in NSABP B-30 had node-positive operable breast cancer. Endocrine therapy was planned for all patients whose tumors were ER positive and/or PgR positive. If indicated, radiotherapy was administered after chemotherapy. The random assignment was performed in 1:1:1 fashion to either four cycles of doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every three weeks, followed by four cycles of docetaxel 100 mg/m^2 every three weeks (AC→T), or four cycles of doxorubicin 60 mg/m^2 plus docetaxel 60 mg/m^2 every three weeks (AT), or four cycles of doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 plus docetaxel 60 mg/m^2 every three weeks (ACT). After the study had been open for accrual for approximately a year and a half, the dosages for AT and ACT were modified to the following: doxorubicin 50 mg/m^2 and docetaxel 75 mg/m^2 (AT); doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 and docetaxel 75 mg/m^2 (ACT). The same total dose of docetaxel was planned for AT and concurrent ACT, with a higher total dose of docetaxel for sequential AC→T.

The QOL substudy was conducted in a subset of consecutively enrolled B-30 patients (13). Women were assessed for QOL and symptom severity at baseline (prior to administration of chemotherapy), during chemotherapy (day 1 of cycle 4), and then at 6, 12, 18, and 24 months. QOL was measured with the Functional Assessment of Cancer Therapy–Breast Trial Outcome Index (FACT-B-TOI) (14), which ranges from 0 to 92, with a higher score being better. A five-point difference in FACT-B-TOI score is considered to be clinically meaningful (15). Symptoms were assessed using items from the Breast Cancer Prevention Trial symptom checklist and other treatment toxicity questions (16). Responses, based on a symptom experienced in the past seven days, were recorded on a five-point scale (from a "bother" rating of 0 [zero] = "not at all" to 4 = "very much"). At each assessment point, patients were asked to indicate how much they were bothered by numbness or tingling in hands or feet. The severity of PN was quantified based on the patients' responses to this questionnaire item. The presence of PN was defined as any "bother" level. Data on all B-30-eligible patients who submitted the baseline QOL questionnaire and at least one follow-up questionnaire with nonmissing assessment of PN were included in this report.

The B-30 study was approved by the ethics committees or institutional review boards of all participating centers, in accordance with an assurance filed with and approved by the Department of Health and Human Services. All participants provided written informed consent.

Statistical Analysis

The severity of PN symptoms over time (day 1 of cycle 4, and 6, 12, 18, and 24 months) was analyzed using a mixed effects

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ordinal logistic regression with patients' random effects (PROC GLIMMIX). Treatment, PN at baseline, and assessment point were considered categorical covariates. Presence of time-by-treatment interaction was investigated. A statistical significance level of .05 was used. All statistical tests were two-sided. Ordinal logistic regression modeling was used to evaluate the association of different factors with the severity of neuropathy 24 months after random assignment (PROC LOGISTIC). A stepwise selection approach was used to identify a subset of potentially influential covariates. Items with a univariate *P* value of .2 or less were entered into the model in the order of their *P* values, starting with the most statistically significant. Those with a *P* value of .1 or less were retained in the model. Then, a step-down elimination process removed the covariates, starting with the least statistically significant, keeping those with a *P* value of .05 or less. The estimates of the odds ratios (ORs), which quantify the ratio of odds of experiencing a more severe PN vs a less severe PN, and corresponding 95% confidence intervals (95% CIs), were obtained from the final multivariable model. Differences in the FACT-B-TOI at the 24-month assessment point were compared among patients reporting different levels of PN by means of the general linear model applying the linear test of trend (PROC GLM). All analyses were performed with SAS software (Version 9.4, Cary, NC).

Results

Patient Characteristics

A total 5351 patients were randomly assigned to treatment groups in B-30. Among these, 2156 were included in the QOL substudy (13). A total of 2051 were eligible for the current analyses. Patient and tumor characteristics of these QOL substudy participants are presented in Table 1. There were no statistically significant differences observed among the treatment groups. Women who participated in the QOL substudy and were included in the current analyses were somewhat younger (<50 years; 50.1% vs 42.2%) and less obese (37.5% vs 32.4% with normal body mass index [BMI]) than the rest of the patients in the trial. Slightly more white women had data that were included in these analyses (86.2% vs 81.0%).

Longitudinal Analysis

Approximately 15.8%, 19.1%, and 20.7% of women in the AC→T, AT, and ACT treatment groups, respectively, presented with some level of PN at baseline (Table 1), with 10.7%, 13.3%, and 13.6% reporting a "bother" rating of 1: "a little bit." The percentage of patients reporting any level of PN increased to 18.6%, 22.3%, and 25.7% for the on-treatment assessment (day 1 of cycle 4; occurred before the AC→T group had received any T), and to 68.2%, 33.3%, and 37.7% for the 6-month assessment, respectively. For patients on AT and ACT, the percentages of those with PN remained approximately at the same level later on, up to 24 months. The percentage of patients on AC→T who reported having PN decreased to 56.4% at 12 months and to 49.8% at 24 months, remaining higher than either of the two other treatment groups. The effect of treatment on the severity of PN was statistically significantly different over time (overall time-by-treatment $P_{interaction} < .001$). Women treated with sequential AC→T had higher odds of having a symptom of greater severity at six months or later than did patients on the other two regimens (ORs for AT and ACT vs AC→T ranged from 0.06 to 0.40). The relationship was reversed for the on-treatment assessment, with AT and ACT patients having higher odds of experiencing PN of greater severity than patients on the sequential regimen (OR = 1.40, 95% CI = 0.94 to 2.09, and OR = 1.85, 95% CI = 1.24 to 2.74, respectively) (Table 2, Figure 1).

Long-term PN

The 24-month assessment was available for 1512 patients. Overall, 41.9% experienced PN at 24 months, with 10.3% reporting a severe symptom ("quite a bit"/"very much" "bother" level). Factors associated with the severity of PN at 24 months in univariate analysis included chemotherapy regimen, PN symptoms at baseline, age, BMI, menopausal status, type of surgery, receipt of radiotherapy, and nodal status. The final set of characteristics independently associated with long-term PN is presented in Table 3. Treatment with AT and ACT was associated with less severe long-term PN compared with AC→T (OR = 0.45, 95% CI = 0.35 to 0.58; OR = 0.59, 95% CI = 0.46 to 0.75, respectively). Presenting with PN symptoms before receiving chemotherapy statistically significantly increased the odds of having neuropathy of greater severity at two years (OR = 2.67, 95% CI = 2.08 to 3.43, $P < .001$). Among patients with no PN symptoms at baseline, 46.9%, 28.7%, and 36.1% of AC→T, AT, and ACT patients, respectively, reported having symptoms at 24 months, with 15.2%, 4.3%, and 6.1% having severe symptoms. At the same time, among patients who reported having symptoms at baseline, 65.4%, 62.2%, and 63.0% of patients in the AC→T, AT, and ACT groups reported having PN symptoms at 24 months, with 25.6%, 12.2%, and 17.0% having severe symptoms. Older, overweight women who had mastectomy as definitive surgery and more than three positive nodes were at higher risk of being bothered by PN symptoms 24 months postsurgery.

PN and QOL

Patients who reported long-term PN symptoms of greater severity had statistically significantly lower QOL ($P_{trend} < .001$) (Figure 2). The average reported TOI scores ranged from 57.98 in patients who reported they were "very much" bothered by the symptom to 76.79 in patients without PN symptoms present. The adjustment for treatment and other clinically important factors did not change the conclusions (results not shown).

Discussion

Taxanes are effective chemotherapeutic agents for patients with early-stage breast cancers. However, the administration of this class of drugs can cause a myriad of side effects, with chemotherapy-induced PN being the most common toxicity experienced. This potentially debilitating toxicity arises during treatment, and although it gradually subsides after treatment cessation (17), symptoms may continue to persist beyond treatment in a substantial percentage of patients. Even though it is a standard practice of clinical trials to formally evaluate toxicities while patients are on treatment, the reporting of long-term assessments is usually very limited (8).

The data collected in NSABP B-30 provided us with an opportunity to add to the limited knowledge on PN persistence after treatment with docetaxel-based chemotherapy regimens. The rigorous design of this randomized phase III clinical trial ensured a consistent evaluation of patient and tumor characteristics and a uniform PROs data collection from all patients included in the QOL substudy at baseline and at up to two years of follow-up.

Table 1. Demographic and tumor characteristics of patients eligible for the current analysis: NSABP B-30 Quality of Life substudy

Characteristic	AC→T (n = 684) No.(%)	AT (n = 685) No.(%)	ACT (n = 682) No.(%)	Total (n = 2051) No.(%)	P*
Age at study entry, y					.10
<50	341 (49.9)	364 (53.1)	323 (47.4)	1028 (50.1)	
≥50	343 (50.1)	321 (46.9)	359 (52.6)	1023 (49.9)	
Race					.40
White	581 (84.9)	588 (85.8)	599 (87.8)	1768 (86.2)	
Black	63 (9.2)	52 (7.6)	51 (7.5)	166 (8.1)	
Other	40 (5.8)	45 (6.6)	32 (4.7)	117 (5.7)	
PN at baseline†					.06
No	576 (84.2)	554 (80.9)	541 (79.3)	1671 (81.5)	
Yes	108 (15.8)	131 (19.1)	141 (20.7)	380 (18.5)	
No. of positive nodes					.98
Unknown	4 (0.6)	3 (0.4)	2 (0.3)	9 (0.4)	
1–3	442 (64.6)	442 (64.5)	444 (65.1)	1328 (64.7)	
≥4	238 (34.8)	240 (35.0)	236 (34.6)	714 (34.8)	
Tumor size, cm					.82
Unknown	5 (0.7)	7 (1.0)	3 (0.4)	15 (0.7)	
0–2	300 (43.9)	296 (43.2)	305 (44.7)	901 (43.9)	
2.1–4	281(41.1)	269 (39.3)	269 (39.4)	819 (39.9)	
≥4.1	98 (14.3)	113 (16.5)	105 (15.4)	316 (15.4)	
Receptor status					.65
Negative	163 (23.8)	156 (22.8)	170 (24.9)	489 (23.8)	
Positive	521 (76.2)	529 (77.2)	512 (75.1)	1562 (76.2)	
Endocrine therapy					.98
No	142 (20.8)	141 (20.6)	143 (21.0)	426 (20.8)	
Yes	542 (79.2)	544 (79.4)	539 (79.0)	1625 (79.2)	
Type of surgery					.88
Lumpectomy	351 (51.3)	343 (50.1)	349 (51.2)	1043 (50.9)	
Mastectomy	333 (48.7)	342 (49.9)	333 (48.8)	1008 (49.1)	
Menopausal status					.29
Unknown	4 (0.6)	1 (0.1)	5 (0.7)	10 (0.5)	
Premenopausal	340 (49.7)	364 (53.1)	333 (48.8)	1037 (50.6)	
Postmenopausal	340 (49.7)	320 (46.7)	344 (50.4)	1004 (49.0)	
Radiotherapy					.86
No radiotherapy	156 (22.8)	159 (23.2)	150 (22.0)	465 (22.7)	
Radiotherapy	528 (77.2)	526 (76.8)	532 (78.0)	1586 (77.3)	
Body mass index, kg/m^2					.88
Normal, <25	261 (38.2)	259 (37.8)	250 (36.7)	770 (37.5)	
Overweight, 25–30	212 (31.0)	221 (32.3)	230 (33.7)	663 (32.3)	
Obese, ≥30	211 (30.8)	205 (29.9)	202 (29.6)	618 (30.1)	

*P value for treatment group comparison is based on the two-sided Pearson chi-square test; unknowns were excluded. AC→T = doxorubicin and cyclophosphamide → docetaxel; ACT = doxorubicin, cyclophosphamide, and docetaxel; AT = doxorubicin and docetaxel; NSABP = National Surgical Adjuvant Breast and Bowel Project; PN = peripheral neuropathy.

†Presence of patient-reported peripheral neuropathy at baseline was defined based on the patients' responses on how much they were bothered by numbness or tingling in hands or feet in the past seven days. "No" = "bother" rating of 0 ("not at all"); "yes" = "bother" rating ranging from 1 ("a little bit") to 4 ("very much").

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Forty-two percent of B-30 patients reported PN two years after treatment initiation. This is consistent with Eckhoff et al. (2), who reported that 43% of patients on adjuvant docetaxel experienced symptoms of PN one to three years after treatment. Treatment with AC→T, having PN symptoms before chemotherapy, older age, obesity, mastectomy, and greater number of positive nodes were identified as having independent association with long-term PN in our sample. Although age is a known risk factor for PN in general populations (18), older breast cancer patients also were reported as being at higher risk for having PN (2). In general, paresthesia, other symptoms of PN, and sensory disturbances are frequent complications of breast cancer surgery and axillary lymph node dissection (ALND) (19–22). Because all B-30 patients were required to have undergone ALND, the increased risk of long-term PN in patients who presented with a larger number of positive nodes might be expected. Even one year after the surgery, mastectomy patients continue to report statistically significantly more numbness in the operated breast region or in the ipsilateral arm than lumpectomy patients (23), which might predispose them to the greater level of long-term PN observed in our study. Still, the relationship between surgery and long-term PN are contradictory in the literature (9,22,24). Obesity was also associated with higher risk for long-term PN in another recent observational cohort study of breast cancer patients (25). The reports on whether the patients with a history of diabetes are predisposed to the development of chemotherapy-induced PN are also inconsistent (9,26). Comorbidity data were not collected in our trial and were not able to investigate this association.

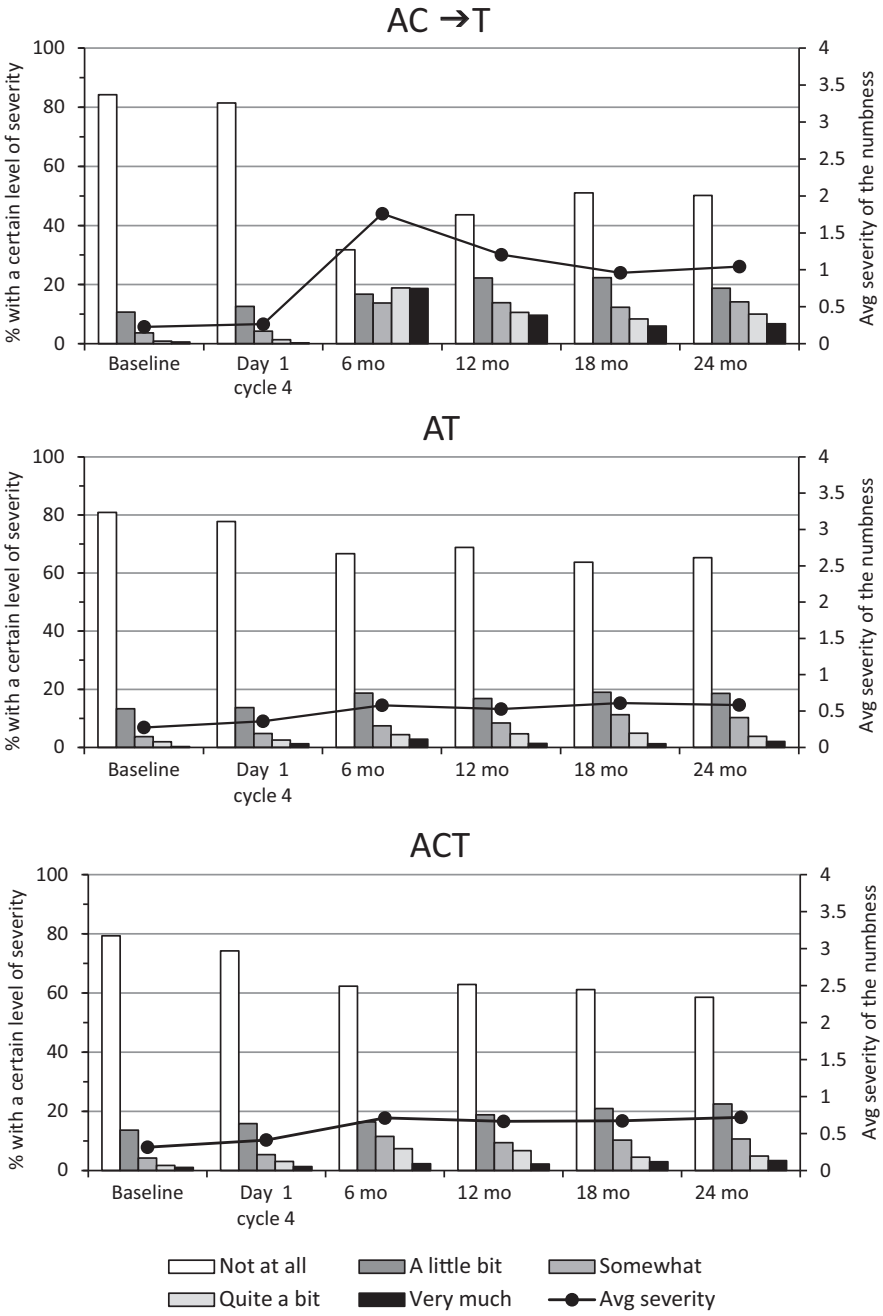

Figure 1. The severity of the peripheral neuropathy symptom by time and treatment as reported by patients enrolled in the NSABP B-30 Quality of Life substudy. Patients were asked to indicate how much they were bothered by numbness or tingling in hands or feet. Responses, based on a symptom experienced in the past seven days, were recorded on a five-point scale (from a "bother" rating of 0 = "not at all" to 4 = "very much"). A = doxorubicin; C = cyclophosphamide; T = docetaxel.

The onset of chemotherapy-induced PN generally depends on the cumulative dose of the taxane agent (17). In B-30, patients on AC→T received a regimen with a higher cumulative dose of docetaxel (400 mg/m^2) than did the other two groups (300 mg/m^2 or 240 mg/m^2 before dose modification) (12). This and the longer duration of treatment, 24 weeks for AC→T vs 12 weeks for AT and ACT, are likely the causes for the greater severity of neuropathy at the 6-month assessment and thereafter. This dose relationship with long-term neurotoxicity was also observed in Pereira et al. (9).

Based on the self-report, the prevalence of PN in B-30 patients at baseline was elevated but within the expected range for the study's patient population (3). The timing of baseline assessment in our study, before initiation of chemotherapy but after the completion of surgery with ALND, could potentially explain these higher numbers. In our study, when patients rated their symptoms at baseline, they could have been considering both preexisting neuropathic symptoms (eg, numbness in the feet) from diabetes or from their recent surgery (eg, numbness in the hand). When they rated their symptoms subsequently, they could have been reflecting completely new symptoms or an exacerbation of their prior symptoms. These types of assessments did not ask for

Table 2. Comparison of peripheral neuropathy (PN) symptom severity between treatment groups over time: NSABP B-30 Quality of Life substudy

Time point	AC→T OR* (95% CI)	AT OR* (95% CI)	ACT OR* (95% CI)
Day 1 of cycle 4 (on treatment)	1.00 (reference)	1.40 (0.94 to 2.09)	1.85 (1.24 to 2.74)
6 mo	1.00 (reference)	0.06 (0.04 to 0.08)	0.08 (0.06 to 0.12)
12 mo	1.00 (reference)	0.17 (0.12 to 0.24)	0.24 (0.17 to 0.33)
18 mo	1.00 (reference)	0.37 (0.26 to 0.53)	0.38 (0.27 to 0.54)
24 mo	1.00 (reference)	0.27 (0.19 to 0.39)	0.40 (0.28 to 0.56)

*The relative odds of experiencing a greater severity rating for a PN symptom adjusted for the presence of a PN symptom at baseline. PN symptom was evaluated by patients on a five-point scale (from a "bother" rating of 0 = "not at all" to 4 = "very much"). AC→T = doxorubicin and cyclophosphamide → docetaxel; ACT = doxorubicin, cyclophosphamide, and docetaxel; AT = doxorubicin and docetaxel; CI = confidence interval; OR = odds ratio.

Table 3. Final multivariable model of characteristics associated with long-term peripheral neuropathy (PN) as evaluated at 24 months after random assignment: NSABP B-30 Quality of Life substudy

Characteristic	No. of patients (n = 1504)*	No. (%) of patients with PN	Average level of PN severity†	OR‡ (95% CI)	P§
PN at baseline‖					
No	1239	462 (37.3)	0.69	1.00 (reference)	<.001
Yes	265	167 (63.0)	1.23	2.67 (2.08 to 3.43)	
Treatment					
AC→T	496	246 (49.6)	1.04	1.00 (reference)	<.001
AT	503	175 (34.8)	0.59	0.45 (0.35 to 0.58)	
ACT	505	208 (41.2)	0.72	0.59 (0.46 to 0.75)	
Age, y					
<50	740	272 (36.8)	0.67	1.00 (reference)	.005
≥50	764	357 (46.7)	0.89	1.34 (1.10 to 1.65)	
Nodal status					
1–3	992	391 (39.4)	0.71	1.00 (reference)	.01
≥4	512	238 (46.5)	0.92	1.32 (1.07 to 1.63)	
Surgery					
Lumpectomy	757	296 (39.1)	0.67	1.00 (reference)	.002
Mastectomy	747	333 (44.6)	0.90	1.39 (1.13 to 1.71)	
Body mass index, kg/m^2					
<25	582	198 (34.0)	0.62	1.00 (reference)	<.001
25–30	476	211 (44.3)	0.79	1.46 (1.14 to 1.87)	
≥30	446	220 (49.3)	0.98	1.92 (1.50 to 2.45)	

*The nodal status was unknown for eight women. AC→T = doxorubicin and cyclophosphamide → docetaxel; ACT = doxorubicin, cyclophosphamide, and docetaxel; AT = doxorubicin and docetaxel; CI = confidence interval; NSABP = National Surgical Adjuvant Breast and Bowel Project; OR = odds ratio.
†PN symptom was evaluated by patients on a five-point scale (from a "bother" rating of 0 = "not at all" to 4 = "very much").
‡Odds ratio of experiencing greater severity of numbness symptom.
§Two-sided *P* value based on the likelihood-ratio test.
‖Presence of patient-reported peripheral neuropathy at baseline defined based on the patients' responses on how much they were bothered by numbness or tingling in hands or feet in the past seven days. "No" = "bother" rating of 0 ("not at all"); "yes" = "bother" rating ranging from 1 ("a little bit") to 4 ("very much").

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attribution but evaluated whether a symptom existed and its severity.

The lack of any objective measurement of PN could be considered a potential limitation of our study. However, even though quantitative sensory testing (QST) and other techniques can be used for the objective assessment of neurotoxicity (3,27), their application in clinical trials and, particularly, in the general practice setting can be labor intensive and costly in terms of time and resources. At the same time, there is an evidence that PROs could be successfully used in identifying patients with PN. Hershman et al. (3) used both QST and PROs to quantify the severity of PN and showed that the changes over time in the PROs were statistically significantly associated with the changes in vibration threshold testing. The standard approach for evaluating treatment-related symptoms in cancer clinical trials by physicians uses the National Cancer Institute's CTCAE. However, it has been recognized that physicians underreport and underestimate symptom severity compared with patients' assessments (28). Several PRO scales to evaluate PN exist (29–33). Recently, a PROs version of the CTCAE measurement system (PRO-CTCAE) was developed as a companion to CTCAE (34). Two items in PRO-CTCAE assess the severity of PN and its interference with daily activities. The item used to evaluate PN symptoms in our trial was very similar to the severity item in PRO-CTCAE. Either of these can be easily implemented in the clinic to identify patients experiencing symptoms at baseline and therefore more likely to be bothered by a long-term PN.

Currently, no effective agents have been recommended for the prevention of chemotherapy-induced PN (35). Therefore, it is important to identify patients before the administration of chemotherapy who are potentially more susceptible to the development of this adverse event. Several studies have identified

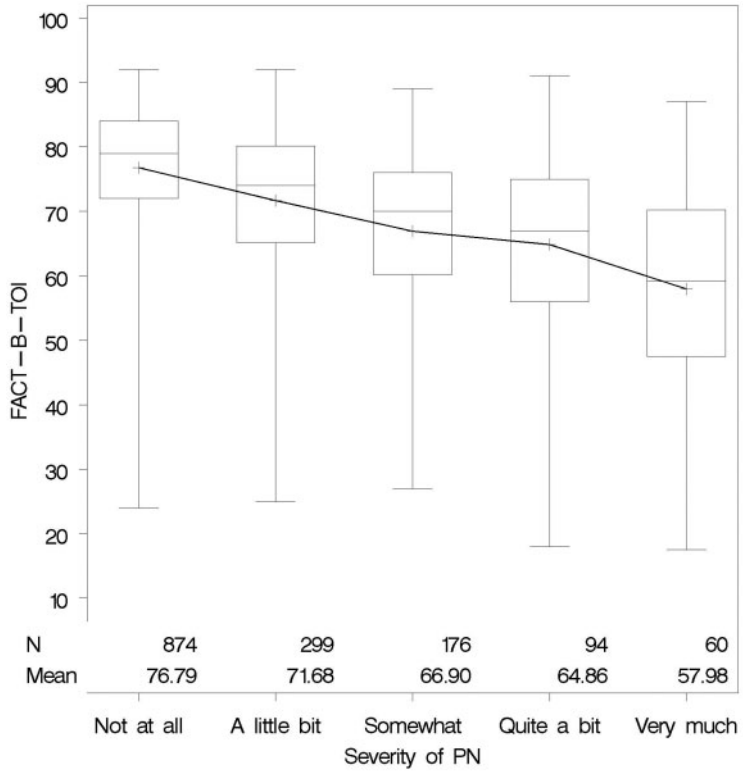

Figure 2. Comparison of quality of life as measured by the Functional Assessment of Cancer Therapy–Breast Trial Outcome Index (FACT-B-TOI) score at 24 months among patients reporting different levels of peripheral neuropathy (PN) symptom severity: NSABP B-30 Quality of Life Sub study. Patients were asked to indicate how much they were bothered by numbness or tingling in hands or feet. Responses, based on a symptom experienced in the past seven days, were recorded on a five-point scale (from a "bother" rating of 0 = "not at all" to 4 = "very much"). The ends of the whiskers in the box and whisker plots represent the minimum and maximum values of the group.

single nucleotide polymorphisms that correlate with taxane-induced neuropathy in breast cancer patients (36–39); however, independent validation of these biomarkers is required.

Cumulative taxane dose was strongly associated with higher rates of long-term chemotherapy-induced PN. The lower rate of PN in patients who received adjuvant doxorubicin and docetaxel (AT) or concurrent doxorubicin, cyclophosphamide, and docetaxel (ACT), both of which employed lower cumulative doses of docetaxel, might be an important factor to support the choice of these therapies for individuals with preexisting neuropathic symptoms or other risk factors for neuropathy because the differences in survival and disease-free trial outcomes for these regimens were of modest magnitude compared with the higher-dose taxane-containing regimen (12). The choice of chemotherapy regimen should include consideration of long-term adverse effects and informed decision-making that involves patients in the process.

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References

1. Ganz PA, Dougherty PM. Painful hands and feet after cancer treatment: Inflammation affecting the mind-body connection. *J Clin Oncol*. 2016;34(7):649–652.
2. Eckhoff L, Knoop AS, Jensen MB, Ewertz M. Persistence of docetaxel-induced neuropathy and impact on quality of life among breast cancer survivors. *Eur J Cancer*. 2015;51:292–300.

3. Hershman DL, Weimer LH, Wang A, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast Cancer Res Treat*. 2011;125:767–774.
4. Fontes F, Pereira S, Castro-Lopes JM, Lunet N. A prospective study on the neurological complications of breast cancer and its treatment: Updated analysis three years after cancer diagnosis. *Breast*. 2016;29:31–38.
5. Ewertz M, Qvortrup C, Eckhoff L. Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. *Acta Oncologica*. 2015;54:587–591.
6. Schneider BP, Zhao F, Wang M, et al. Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. *J Clin Oncol*. 2012;30(25):3051–3057.
7. Mols F, Beijers T, Vreugdenhil G, et al. Chemotherapy-induced peripheral neuropathy and its association with quality of life: A systematic review. *Support Care Cancer*. 2014;22:2261–2269.
8. Rivera DR, Ganz PA, Weyrich MS, Bandos H, Melnikow J. Chemotherapy-associated peripheral neuropathy in patients with early-stage breast cancer: A systematic review. *J Natl Cancer Inst*. 2018:110(2):131–140.
9. Pereira S, Fontes F, Sonin T, et al. Chemotherapy-induced peripheral neuropathy after neoadjuvant or adjuvant treatment of breast cancer: A prospective cohort study. *Support Care Cancer*. 2016;24(4):1571–1581.
10. Nitz U, Gluz O, Huober J, et al. Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: Efficacy and predictive value of Ki67 expression. *Ann Oncol*. 2014;25:1551–1557.
11. Clinical Trials registration: NCT00003782. https://clinicaltrials.gov/ct2/show/NCT00003782. Accessed January 13, 2017.
12. Swain SM, Jeong JH, Geyer CE Jr, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med*. 2010;362(22):2053–2065.
13. Ganz PA, Land SR, Geyer CE Jr, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. *J Clin Oncol*. 2011;29(9):1110–1116.
14. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol*. 1997;15(3):974–986.
15. Eton DT, Cella D, Yost KJ, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. *J Clin Epidemiol*. 2004;57:898–910.
16. Cella D, Land S, Chang CH, et al. Symptom measurement in the Breast Cancer Prevention Trial (BCPT) (P-1): Psychometric properties of a new measure of symptoms for midlife women. *Breast Cancer Res Treat*. 2008;109:515–526.
17. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol*. 2006;24(10):1633–1642.
18. Anish L, Nagappa M, Mahadevan A, Taly AB. Neuropathy in elderly: Lessons learnt from nerve biopsy. *Age Ageing*. 2015;44:312–317.
19. Shimozuma K, Ganz PA, Petersen L, Hirji K. Quality of life in the first year after breast cancer surgery: Rehabilitation needs and patterns of recovery. *Breast Cancer Res Treat*. 1999;56:45–57.
20. Erickson VS, Pearson ML, Ganz PA, et al. Arm edema in breast cancer patients. *J Natl Cancer Inst*. 2001;93:96–111.
21. Maunsell E, Brisson J, Deschenes L. Arm problems and psychological distress after surgery for breast cancer. *Can J Surg*. 1993;36:315–320.
22. Gärtner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*. 2009;302(18):1985–1992. Erratum in: *JAMA*. 2012;308(19):1973.
23. Tasmuth T, von Smittten K, Kalso E. Pain and other symptoms during the first year after radical and conservative surgery for breast cancer. *Br J Cancer*. 1996;74:2024–2031.
24. Bozentka DJ, Beredjiklian PK, Chan PSH, et al. Hand related disorders following axillary dissection for breast cancer. *U Penn Orthopaed J*. 2001;14:35–37.
25. Greenlee H, Hershman DL, Shi Z, et al. Body mass index, lifestyle factors, and taxane-induced neuropathy in women with breast cancer: The Pathways study. *J Clin Oncol*. 2016;34(15_suppl).
26. Hershman DL, Till C, Wright JD, et al. Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in Southwest Oncology Group clinical trials. *J Clin Oncol*. 2016;34(25):3014–3022.
27. Sharma S, Venkitaraman R, Vas PRJ, Rayman G. Assessment of chemotherapy-induced peripheral neuropathy using the LDI_{FLARE} technique: A novel technique to detect neural small fiber dysfunction. *Brain Behav*. 2015;5(7):e00354.
28. Stephens RJ, Hopwood P, Girling DJ, Machin D. Randomized trials with quality of life endpoints: Are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? *Qual Life Res*. 1997;6:225–236.
29. Calhoun EA, Fishman DA, Roland PY. Validity and sensitivity of the functional assessment of cancer therapy/Gynecologic Oncology Group-neurotoxicity (FACT/GOG-Ntx). *Proc Am Soc Clin Oncol*. 2000;19:2000.
30. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. Measuring the side effects of taxane therapy in oncology: The functional assessment of cancer therapy-taxane (FACT-Taxane). *Cancer*. 2003;98(4):822–831.
31. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. *Eur J Cancer*. 2005;41:1135–1139.
32. Shimozuma K, Ohashi Y, Takeuchi A, et al. Feasibility and validity of the Patient Neurotoxicity Questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02. *Support Care Cancer*. 2009;17:1483–1491.
33. Cavaletti G, Jann S, Pace A, et al. Multi-center assessment of the Total Neuropathy Score for chemotherapy-induced peripheral neurotoxicity. *J Periph Nerv Syst*. 2006;11:135–141.
34. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;106(9):dju244.
35. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32(18):1941–1967.
36. Eckhoff L, Feddersen S, Knoop AS, et al. Docetaxel-induced neuropathy: A pharmacogenetic case-control study of 150 women with early-stage breast cancer. *Acta Oncologica*. 2015;54:535–542.
37. Schneider B, Li L, Radovich M, et al. Gnome-wide association studies for taxane-induced peripheral neuropathy in ECOG-5103 and ECOG-1199. *Clin Can Res*. 2015;21(22):5082–5091.
38. Kroetz DL, Baldwin RM, Owzar K, et al. Inherited genetic variation in EPHA5, FGD4, and NRDG1 and paclitaxel (P)-induced peripheral neuropathy (PN): Results from a genome-wide association study (GWAS) in CALGB 40101. *J Clin Oncol*. 2010;28:238s (suppl; abstr 3021).
39. Sucheston LE, Zhao H, Yao S, et al. Genetic predictors of taxane-induced neurotoxicity in a SWOG phase III intergroup adjuvant breast cancer treatment trial (S0221). *Breast Cancer Res Treat*. 2011;130:993–1002.