

Patient-Reported Toxicities During Chemotherapy Regimens in Current Clinical Practice for Early Breast Cancer

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Key Words. Breast cancer • Chemotherapy • Patient-reported symptoms

ABSTRACT

Background. This study explores the incidence of patient-reported major toxicity—symptoms rated “moderate,” “severe,” or “very severe”—for chemotherapy regimens commonly used in early breast cancer.

Patients and Methods. Female patients aged 21 years or older completed a validated Patient-Reported Symptom Monitoring instrument and rated 17 symptoms throughout adjuvant or neoadjuvant chemotherapy. Fisher’s exact tests compared differences in percentages in symptom ratings, and general linear regression was used to model the incidence of patient-reported major toxicity.

Results. In 152 patients, the mean age was 54 years (range, 24–77), and 112 (74%) were white; 51% received an anthracycline-based regimen. The proportion of patients rating fatigue, constipation, myalgia, diarrhea, nausea, peripheral neuropathy, and swelling of arms or legs as a major toxicity at any time during chemotherapy varied significantly among four chemotherapy regimens ($p < .05$).

The mean (SD) number of symptoms rated major toxicities was 6.3 (3.6) for anthracycline-based and 4.4 (3.5) for non-anthracycline-based regimens ($p = .001$; possible range, 0–17 symptoms). Baseline higher body mass index ($p = .03$), patient-reported Karnofsky performance status ≤ 80 ($p = .0003$), and anthracycline-based regimens ($p = .0003$) were associated with greater total number of symptoms rated major toxicities (alternative model: chemotherapy duration, $p < .0001$). Twenty-six percent of dose reductions (26 of 40), 75% of hospitalizations (15 of 20), and 94% of treatment discontinuations (15 of 16) were in anthracycline-based regimens.

Conclusion. Capturing multiple toxicity outcomes throughout chemotherapy enables oncologists and patients to understand the range of side effects as they discuss treatment efficacies. Continuous symptom monitoring may aid in the timely development of interventions that minimize toxicity and improve outcomes. *The Oncologist* 2019;24:762–771

Implications for Practice: This study investigated patient-reported toxicities for 17 symptoms recorded prospectively during adjuvant and neoadjuvant chemotherapy regimens for early breast cancer. An analysis of four commonly used chemotherapy regimens identified significant differences among regimens in both individual symptoms and total number of symptoms rated moderate, severe, or very severe. Longer chemotherapy regimens, such as anthracycline-based regimens followed by paclitaxel, had higher proportions of symptoms rated major toxicities. The inclusion of patient perspectives on multiple toxicity outcomes at the same time at multiple time points during chemotherapy has the potential for improving patient-provider communication regarding symptom management, patient satisfaction, and long-term clinical outcomes.

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INTRODUCTION

Survival rates for women with breast cancer have steadily improved over the past several decades, in large part because of improvements in early detection and advances in treatment [1, 2]. Early breast cancers that are localized (stage I–II, 62% of new breast cancer cases) or regional (stage III, 31% of new cases) now have 5-year survival rates of 98.9% and 85.2%, respectively [1]. Systemic therapy including endocrine therapy and chemotherapy are important components of treatment advances [3, 4]. Delivering protocol-defined dosage and completing therapy are associated with improved outcomes [5] and depend on the patient's ability to tolerate treatment-related toxicities. Metrics of treatment tolerability include hospitalization, treatment discontinuation, and clinician-assessed toxicity monitored through treatment using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [6, 7].

Over the past decade, there has been growing support for patient-centered assessments of treatment tolerability as an important complement to CTCAE [8, 9]. Standardized reporting is now available through the National Cancer Institute's Patient-Reported Outcomes-CTCAE (PRO-CTCAE) scales [10–13]. Efforts are underway to integrate PRO-CTCAE measurement into clinical trials [14–19], and interest is growing in the implementation and utilization of patient-reported symptom monitoring in patient-centered clinical practice [20–29]. Like CTCAE, the focus of PRO-CTCAE is continuous symptom monitoring throughout chemotherapy, not just at the beginning and end of chemotherapy.

To date, early breast cancer is relatively understudied in the PRO-CTCAE literature. Some PRO-CTCAE studies have included women with breast cancer within larger samples of diverse patient populations [9, 13, 15, 23]. We have identified only one study pertaining exclusively to breast cancer [30]. Our interest is in patient perspectives on the tolerability of specific chemotherapy regimens commonly used in current clinical practice for early breast cancer. As an ancillary investigation to two intervention studies conducted in this patient population, we investigate patient-reported symptom severity for individual regimens using data collected prospectively throughout conventional adjuvant or neoadjuvant chemotherapy. Patient-reported tolerability profiles are then combined with hospitalization, dose reduction, and treatment discontinuation rates to provide a more complete picture of regimen tolerability.

PATIENTS AND METHODS

Study Participants

The sample was recruited between March 2014 and October 2017 from multiple institutions. The study sites included university-affiliated hospitals (University of North Carolina [UNC] Cancer Hospital, Duke University Medical Center, MD Anderson Cancer Center, Ohio State University Comprehensive Cancer Center) and community-based clinics (UNC Rex Healthcare). Women aged 21 years or older with histologically confirmed stage I–III breast cancer who were scheduled for adjuvant or neoadjuvant

chemotherapy were offered participation in one of two identical studies that differed only in age criteria for inclusion (NCT02167932 for women under age 65 and NCT02328313 for women age 65 or older; see supplemental online Appendices 5 and 6 for protocols for these two studies). Both studies entailed interventions to encourage moderate walking during chemotherapy treatment. The analysis presented in this manuscript is a secondary analysis of prospective data collected through these intervention studies. The studies were approved by the UNC-Chapel Hill Lineberger Comprehensive Cancer Center Protocol Review Committee and the institutional review boards of each study site. Written informed consent meeting university and federal guidelines was obtained from each participant.

Chemotherapy Regimens

The study protocols did not specify chemotherapy regimens; regimens were determined by treating oncologists in consultation with their patients depending on tumor stage [4] and phenotypes. The most common regimens for women in our studies were (a) doxorubicin/cyclophosphamide plus paclitaxel (AC-T), (b) docetaxel/ cyclophosphamide (TC), (c) docetaxel/carboplatin with anti-HER2 therapy (TCH), and (d) doxorubicin/ cyclophosphamide plus paclitaxel/carboplatin (AC-TC). These four regimens accounted for 83% of women enrolled in the studies, and our analysis is limited to these four regimens. Growth factors (pegfilgrastim) were used for docetaxel/cyclophosphamide and docetaxel/carboplatin regimens and for doxorubicin/cyclophosphamide when administered every 2 weeks (dose dense). Supplemental online Appendix 1 provides further details regarding chemotherapy regimens by phenotype, and supplemental online Appendix 2 provides details regarding the timing and order of chemotherapy drugs.

Measures

Patient-Reported Chemotherapy Toxicities

A patient-tested outcomes instrument called Patient-Reported Symptom Monitoring (PRSM) [31] was used to inquire about symptoms “in the past 7 days” for 17 chemotherapy-related toxicities: trouble having a bowel movement (constipation); loose or watery stools (diarrhea); pain in the abdomen; pain in general; aching joints such as elbows, knees, shoulders (arthralgia); aching muscles (myalgia); numbness or tingling in the hands or feet (peripheral neuropathy); mouth or throat sores; nausea, vomiting; arm or leg swelling; tiredness, lack of energy, fatigue; sad or unhappy feelings (depression); anxiety (worrying); insomnia (difficulty falling asleep, staying asleep, waking up early); shortness of breath (dyspnea); and hot flashes. These 17 symptoms were selected a priori because they reflect what is recognized in clinical practice as the most common side effects of chemotherapy in early breast cancer. The PRSM [31] (supplemental online Appendix 3) is very similar to the PRO-CTCAE [10, 13], which was not available to the general community when we launched the walking intervention trials. For each symptom, three questions inquired about (a) frequency of the symptom, (b) severity of the

symptom, and (c) whether the symptom kept the patient from doing things she usually did (interference). For the current study, we have analyzed only the severity of symptoms, because it is the measure that is the most comparable to CTCAE. At scheduled infusion visits throughout their chemotherapy, patients rated their symptom severity as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe, or 4 = very severe.

Our specific interest was the incidence of symptoms rated by patients as a major toxicity—"moderate," "severe," or "very severe"—at any time during chemotherapy [32]. A maximum rating of moderate, severe, or very severe was recorded only once per symptom per patient, although the patient may have scored that symptom as a major toxicity at several time points during chemotherapy. This approach to toxicity assessment is analogous to CTCAE reporting in clinical trials, in which the percent of grade 2, 3, or 4 toxicities is the incidence of the highest toxicity score at any time during chemotherapy. For each of the 17 symptoms, we calculated the percent of patients whose maximum score at any time during chemotherapy was moderate, severe, or very severe. An individual patient could rate more than one symptom as a major toxicity, as reflected in the mean total number of major toxicity symptoms per regimen.

Study participants were asked by research staff to complete a PRSM form (printed or tablet) during infusion visits throughout their chemotherapy treatment, either shortly before or during each infusion visit, and generally after they had seen their treating oncologist. For regimens that entailed weekly infusions, symptom forms were completed every other week; otherwise, they were collected every other week (dose-dense regimens) or every 3 weeks (tri-weekly regimens). By limiting all data analysis to every other week or every 3 weeks, we aimed to avoid over-representing maximum toxicity reports for regimens that were administered weekly. In the event a patient had both neoadjuvant and adjuvant chemotherapy, symptom forms were collected only during neoadjuvant chemotherapy, to ensure all patients were chemotherapy naïve at baseline when they started symptom reporting. For patients whose anti-HER2 treatment continued beyond their chemotherapy, PRSM reports were collected only for the chemotherapy portion. Symptom reports were not provided to the oncology provider or nurse. Standard clinical practice was used to manage side effects; the study protocols did not specify symptom management recommendations. Data were not collected on interventions used to manage toxicity other than dose delay or treatment discontinuation.

Physical Function

At baseline, prior to chemotherapy treatment initiation, patients self-assessed their Karnofsky performance status (Patient-KPS) [33], with scores of 80 to 100 signifying ability to carry out normal activities of daily living.

Patient Characteristics, Breast Cancer Diagnosis and Treatment, and Adverse Events

Research staff reviewed the electronic health record for data pertaining to study participant age, race, height, weight, body mass index (BMI), breast cancer stage (American Joint

Committee on Cancer, version 7) [34] and phenotype, and treatment. Staff also extracted data regarding chemotherapy-related adverse events, including hospitalizations, dose reductions, and treatment discontinuations.

Statistical Analysis

Fisher's exact tests for differences in symptom severity percentages and Wilcoxon rank sum and Kruskal-Wallis tests were used to assess differences in number of moderate, severe, or very severe symptoms by regimen. General linear regression was used to test association of patient and clinical characteristics with the incidence of major toxicities. Multivariable models were fit based on significant unadjusted results. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC), and 2-sided $p < .05$ was considered statistically significant.

RESULTS

Participant Characteristics

In our sample of 152 patients (Table 1), average age at breast cancer diagnosis was 54 years (range, 24–77), 74% were white, and 9% had a high school education or less. High proportions were overweight (34%, BMI 25–29.9) or obese (38%, BMI ≥ 30). Twenty-eight patients (18%) had HER2-positive tumors, all of whom received anti-HER2 therapy. Timing of chemotherapy was 43% neoadjuvant and 57% adjuvant. Planned duration of chemotherapy treatment was greater than 3 months for 67% of the sample. Half (51%) of the participants received an anthracycline-based regimen. Among patients whose tumor was HR positive/HER2 negative, 55% received anthracycline-based regimens and 45% nonanthracycline; among triple-negative patients, 75% received anthracycline-based regimens and 25% nonanthracycline (supplemental online Appendix 1). Taxane regimens included paclitaxel/nab-paclitaxel (51%) and docetaxel (49%). Supplemental online Appendix 2 provides further details regarding order of administration of sequential anthracycline-paclitaxel regimens, proportion of patients receiving neoadjuvant chemotherapy, and timing of infusions.

Moderate, Severe, or Very Severe Toxicities Overall and by Chemotherapy Regimen

For the four most common chemotherapy regimens, the proportion of symptom reports collected as planned was 86% for AC-TC, 81% for AC-T, 100% for TCH, and 90% for TC. The most common reason for missing reports was staffing shortage. Table 2 presents patient-reported toxicities rated "moderate," "severe," or "very severe" as the highest score at any time during the entire course of chemotherapy. For the four chemotherapy regimens combined, severity scores were highest for fatigue (68%), insomnia (58%), arthralgia (43%), anxiety (42%), constipation (41%), and myalgia (40%). Both individual symptoms ($p \leq .05$) and total number of symptoms rated as major toxicities ($p = .01$) varied significantly among the four chemotherapy regimens. Mean (SD) total number of symptoms rated as major toxicities (possible range, 0–17 symptoms) was 6.3 (3.6) for anthracycline-based regimens compared with 4.4

Table 1. Study participant ($n = 152$) characteristics at breast cancer diagnosis

Variable	<i>n</i> (%)
Age, mean (SD) [range], y	54 (12.4) [24–77]
Race, white	112 (74)
Education, high school or less	14 (9)
BMI, mean (SD) [range], kg/m ²	29 (6.6) [17–65]
BMI categories	
Underweight (BMI >18.5)	3 (2)
Normal weight (BMI 18.5–24.9)	40 (26)
Overweight (BMI 25–29.9)	52 (34)
Obese I (BMI 30–34.9)	31 (20)
Obese II (BMI 35–39.9)	19 (13)
Obese III (BMI ≥40)	7 (5)
Suboptimal patient-reported Karnofsky performance status (<80)	16 (11)
Breast cancer stage, phenotype, treatment	
Breast cancer stage, AJCC 7th edition	
I	33 (22)
II	78 (52)
III	38 (26)
HER2+	28 (18)
HR+	92 (61)
Breast cancer phenotype ^a	
HR+/HER2–	76 (50)
HR–/HER2–	48 (32)
HR+/HER2+	16 (11)
HR–/HER2+	12 (8)
Breast cancer surgery	
None	4 (3)
Lumpectomy	67 (44)
Mastectomy	81 (53)
Chemotherapy timing	
Neoadjuvant	65 (43)
Adjuvant	87 (57)
Duration of chemotherapy	
≤ 3 mo	50 (33)
> 3 mo	102 (67)
Chemotherapy regimen: anthracycline-based	78 (51)
Chemotherapy regimen: taxane	
Paclitaxel	78 (51)
Docetaxel	74 (49)
Chemotherapy regimen: drug combinations ^b	
Doxorubicin/cyclophosphamide plus paclitaxel	60 (39)
Docetaxel/cyclophosphamide ($n = 4$ had anti-HER-2)	50 (33)

(continued)

Table 1. (continued)

Variable	<i>n</i> (%)
Docetaxel/carboplatin/anti-HER-2	24 (16)
Doxorubicin/cyclophosphamide plus paclitaxel/carboplatin	18 (12)
Chemotherapy adverse events ^c	
Hospitalized (first hospitalization)	20 (13)
Treatment discontinued	16 (11)
Dose reduced (first dose reduction)	37 (24)

^aSee supplemental online Appendix 1 for chemotherapy regimens by breast cancer phenotype.

^bSee supplemental online Appendix 2 for further details regarding chemotherapy drug combinations.

^cSee supplemental online Appendix 4 for clinician notes regarding reasons associated with chemotherapy adverse events.

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; HER2+, HER2-positive; HER2–, HER2-negative; HR+, hormone receptor positive; HR–, hormone receptor negative.

(3.5) for regimens that were not anthracycline based ($p = .001$).

To account for varying durations of chemotherapy regimens, major toxicity percentages presented in the bottom half of Table 2 are limited to the first 12 weeks of chemotherapy for each regimen. In this sensitivity analysis, major toxicity incidences for myalgia and peripheral neuropathy no longer differed significantly among the four regimens, as these symptoms were most frequently due to the largely post-12 weeks initiation of weekly paclitaxel. The total number of moderate, severe, or very severe symptoms did not differ significantly among the four regimens during the first 12 weeks of treatment ($p = .203$).

Association of Patient and Clinical Characteristics with Total Number of Items Rated Moderate, Severe, or Very Severe

In Table 3, associations of patient characteristics, breast cancer stage and phenotype, and treatment with number of major toxicities are presented. In unadjusted analysis, higher BMI ($p = .008$), Patient-KPS <80 ($p = .001$), longer duration of chemotherapy ($p \leq .001$), and anthracycline-based chemotherapy ($p = .0009$) were associated with higher number of major toxicities. In multivariable analysis, higher BMI (estimate 0.09; 95% confidence interval [CI], 0.01–0.18; $p = .028$), Patient-KPS <80 (estimate 3.23; 95% CI, 1.49–4.96; $p = .0003$), and anthracycline-based regimen (estimate 2.01; 95% CI, 0.91–3.10; $p = .0003$) remained independently associated with higher number of major toxicities. We did not include duration of chemotherapy in the multivariable model because of high correlation with anthracycline-based chemotherapy. In multivariable analysis that substituted duration of chemotherapy for anthracycline-based chemotherapy, Patient-KPS ($p = .0001$) and BMI ($p = .018$) remained independently significant, as well as chemotherapy duration ($p < .0001$).

Hospitalization, Dose Reductions, and Treatment Discontinuations

First incidences of hospitalization and dose reduction were investigated, as well as early treatment discontinuation

Table 2. Incidence of patient-reported symptoms rated MSVS by chemotherapy regimen (percent) during entire course of treatment and first 12 weeks of treatment

Toxicities	All regimens (n = 152), %	AC-T (n = 60; 39% of total), %	TC (n = 50; 33% of total), %	TCH (n = 24; 16% of total), %	AC-TC (n = 18; 12% of total), %	p value ^a
Entire course of treatment						
Fatigue	68	83	48	67	78	.001
Insomnia	58	65	52	46	67	.268
Arthralgia	43	50	38	25	56	.111
Anxiety	42	40	46	29	56	.343
Constipation	41	47	30	25	72	.005
Myalgia	40	48	32	21	61	.018
Pain	39	40	40	29	44	.751
Diarrhea	38	35	34	71	17	.002
Nausea	38	45	18	38	67	.001
Hot flashes	36	43	30	21	50	.110
Peripheral neuropathy	32	48	10	25	50	<.0001
Depression	27	28	22	25	39	.545
Mouth/throat sores	26	32	14	29	33	.120
Swelling in arms/legs	21	23	30	4	11	.043
Dyspnea	19	25	16	13	17	.564
Abdominal pain	18	18	12	33	17	.192
Vomiting	9	10	4	17	11	.286
Total number (SD) of MSVS symptoms	5.4 (3.7)	6.2 (SD 3.6)	4.3 (SD 3.6)	4.6 (SD 3.4)	6.8 (SD 3.7)	.01
	Range 0–14	Range 0–14	Range 0–14	Range 0–13	Range 0–14	
First 12 weeks of treatment						
Fatigue	63	75	46	58	78	.008
Insomnia	56	63	52	42	61	.285
Arthralgia	38	42	38	25	39	.573
Anxiety	40	38	44	25	56	.222
Constipation	40	45	30	21	72	.003
Myalgia	30	30	30	17	44	.286
Pain	36	35	38	29	39	.885
Diarrhea	36	33	34	63	17	.017
Nausea	33	40	18	29	56	.012
Hot flashes	30	35	28	13	44	.099
Peripheral neuropathy	20	27	10	21	28	.122
Depression	24	27	22	21	28	.901
Mouth/throat sores	24	30	14	29	22	.213
Swelling in arms/legs	17	13	30	4	11	.026
Dyspnea	16	22	16	8	11	.494
Abdominal pain	16	17	12	29	11	.305
Vomiting	9	8	4	17	11	.258
Total number (SD) of MSVS symptoms	4.8 (3.6)	5.3 (3.5)	4.26 (3.60)	4.1 (3.3)	5.7 (4.0)	.203
	Range 0–14	Range 0–14	Range 0–14	Range 0–13	Range 0–14	

^aBolded p values were included in the multivariable analysis unless noted otherwise in the text.

Abbreviations: AC-T, doxorubicin/cyclophosphamide plus paclitaxel; AC-TC, doxorubicin/cyclophosphamide plus paclitaxel/carboplatin; MSVS, moderate/severe/very severe; TC, docetaxel/cyclophosphamide (anti-HER2); TCH, docetaxel/carboplatin (anti-HER2).

(supplemental online Appendix 4). Twenty patients (13%) were hospitalized, primarily because of neutropenic or other fever (45%). Supplemental online Appendix 2 provides information on timing of the first hospitalization, such as during

doxorubicin/cyclophosphamide therapy in patients receiving AC-T chemotherapy (ten patients). Sixteen patients (11%) had chemotherapy discontinued before completion of planned treatment, 25% due to peripheral neuropathy. In

Table 3. Association of patient and clinical characteristics with total number of patient-reported moderate/severe/very severe symptoms ($n = 152$)

Variable	Univariate estimate (95% CI)	<i>p</i> value ^a	Multivariable estimate (95% CI)	<i>p</i> value ^a
Age	−0.01 (−0.06, 0.04)	.6735		
Race, white	0.12 (−1.20, 1.45)	.8529		
Education, high school or less (ref: some college or higher)	1.52 (−0.48, 3.52)	.1365		
BMI	0.12 (0.03–0.20)	.0083	0.09 (0.01–0.18)	.0276
Patient-reported Karnofsky performance status <80	3.06 (1.22–4.90)	.0011	3.23 (1.49–4.96)	.0003
Breast cancer stage				
I	Referent			
II	0.75 (−0.73, 2.24)	.3190		
III	0.65 (−1.05, 2.35)	.4524		
Breast cancer surgery prior to chemotherapy				
None	Referent			
Lumpectomy	−1.29 (−2.66, 0.09)	.0668		
Mastectomy	−0.60 (−2.00, 0.81)	.4051		
Timing of chemotherapy				
Neoadjuvant	Referent			
Adjuvant	−0.95 (−2.12, 0.21)	.1090		
HER2+	−1.07 (−2.56, 0.42)	.1600		
HR+	−0.70 (−1.89, 0.48)	.2451		
Breast cancer phenotype				
HR+/HER2−	Referent			
HR−/HER2−	0.47 (−0.83, 1.78)	.4756		
HR+/Her2+	−1.67 (−3.62, 0.28)	.0924		
HR−/HER2+	0.16 (−2.04, 2.36)	.8849		
Duration of chemotherapy (days) ^b	0.04 (0.02–0.05)	<.0001		
Chemotherapy regimen				
Anthracycline-based	1.90 (0.78–3.03)	.0009	2.01 (0.91–3.10)	.0003
Not anthracycline-based	Referent		Referent	

^aBolded *p* values were included in the multivariable analysis unless noted otherwise in the text.

^bDuration of chemotherapy was not included in the multivariable analysis because of multicollinearity with chemotherapy regimen.

Abbreviations: BMI, body mass index; CI, confidence interval; HER2+, HER2-positive; HER2−, HER2-negative; HR+, hormone receptor positive; HR−, hormone receptor negative.

ten patients, discontinuation was during paclitaxel therapy in patients receiving AC-T chemotherapy. Thirty-five patients (23%) had at least one dose reduction, including 24% due to peripheral neuropathy, seven during paclitaxel therapy in patients receiving AC-T chemotherapy, and nine during TC therapy in patients receiving AC-TC chemotherapy.

Figure 1A and B presents dose reduction and treatment discontinuation in patients reporting moderate, severe, or very severe toxicity. Significantly more patients reporting major depression had dose reduction (39%) compared with no dose reduction (22%; $p = .041$), and similarly for patients reporting vomiting (19% reduction compared with 5% no reduction; $p = .008$). Significantly fewer patients reporting major arthralgia had dose reduction (25%) compared with no reduction (45%; $p = .032$). All other dose reduction/no reduction and treatment discontinuation/no discontinuation pairings were not significantly different.

CONCLUSION

This study investigated patient-reported toxicities recorded prospectively during neo(adjuvant) chemotherapy regimens for early breast cancer in current clinical practice. Our specific focus was on toxicities that patients rated moderate, severe, or very severe. An analysis of four commonly used chemotherapy regimens identified significant differences among the regimens in both individual symptoms and total number of symptoms rated as major toxicities. Not surprisingly, longer chemotherapy regimens, such as anthracycline-based regimens followed by paclitaxel, had higher proportions of symptoms rated major toxicities. However, comparing the first 12 weeks of chemotherapy of the four regimens (duration of the shortest chemotherapy regimen), the total number of symptoms rated major toxicity nevertheless ranged from 4.1 to 5.7 for various regimens. Some symptoms, such as anxiety, may resolve as patients

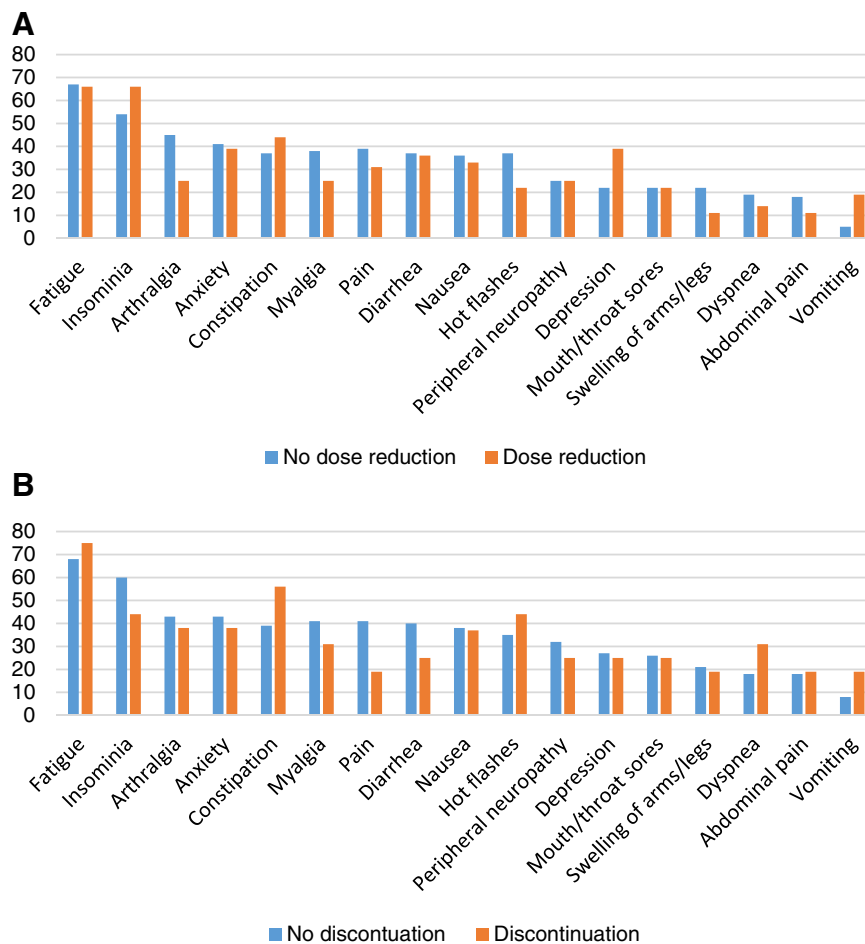


Figure 1. Adverse events among patients reporting moderate/severe/very severe (MSVS) symptoms. **(A):** Percent of patients reporting MSVS symptoms by dose reduction and no dose reduction. **(B):** Percent of patients reporting MSVS symptoms by discontinuation and no discontinuation.

become accustomed to their chemotherapy treatment. Others—such as depression, insomnia, constipation, diarrhea, and nausea—that are amenable to proven interventions, are important to monitor and address in a timely manner to improve patient satisfaction and quality of life during chemotherapy.

Regardless of regimen, ongoing patient-reported symptom monitoring brings to light the extent to which patients perceive a variety of chemotherapy-related symptoms as major toxicities. Patients with higher BMI, lower Patient-KPS scores, and lengthy regimens reported a significantly greater number of severe toxicities. The finding pertaining to BMI may reflect the association between obesity and higher symptom severity for chemotherapy-induced peripheral neuropathy that has been observed in prior studies [35–39].

We reviewed the breast cancer literature to identify studies that were comparable to our own, searching for prospective studies that included patient-reported symptom toxicities collected during chemotherapy administration, instead of surveys after treatment asking patients to recall their experience. In the studies we identified, a variety of validated patient-reported outcome measures (PROs) commonly used in symptom prevalence and severity research [40, 41] were used, such as the EORTC-QLQ-C30 (30 items) quality of life measure [42–44] or single-symptom measures such as the Fatigue

Scale from the Profile of Mood States [45]. The comparability of research-oriented PRO scales to the single-item PRO-CTCAE [10–13] or the Patient Reported Symptom Monitoring [31] form used in our study for tracking multiple toxicity outcomes at the same time remains to be determined and warrants further research. With regard to clinical practice implications, an important consideration is that research-oriented PRO measures require knowledge of scale scoring and interpretation, whereas PRO-CTCAEs are just one item per symptom and are as easy to use and understand as CTCAEs.

We identified only one study using a multi-symptom survey that was comparable to our study. This was a ten-item CTCAE-derived Italian questionnaire that was administered after the first and third cycle of adjuvant chemotherapy [30]. Symptom incidence after the third cycle was highest for fatigue (78%), nausea (73%), dysgeusia (51%), anorexia (53%), and constipation (49%). Toxicity results were presented for all chemotherapy regimens combined, not separately for the chemotherapy regimens in the sample—5-fluorouracil/epirubicin/cyclophosphamide (64%), doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide (22%), or docetaxel/cyclophosphamide (14%). In general, few studies report toxicities for individual chemotherapy regimens [43], and these were mostly for single-symptom studies such as fatigue [46, 47]. A final observation

regarding our search for comparable studies is that most studies limit the number of cycles at which patient-reported symptoms are collected [30, 42, 43, 46–48] instead of aiming to collect patient reports throughout chemotherapy.

In the growing literature pertaining to patient-reported symptom monitoring during active treatment, our study has important strengths. First, we have prospectively documented the spectrum of patient-reported symptoms in early breast cancer throughout four commonly used chemotherapy regimens. Reflecting current clinical practice, our sample includes both anthracycline-based and non-anthracycline-based regimens, and neoadjuvant as well as adjuvant chemotherapy. Our comparison of chemotherapy toxicities associated with different treatment regimens covers the entire course of treatment; however, we also conducted a sensitivity analysis limited to the first 12 weeks of chemotherapy to account for potential differences in symptom reporting that may be due to the duration of chemotherapy. Within both time frames, moderate, severe and very severe toxicities were reported by upwards of 40% of patients for multiple symptoms.

Second, our focus on 17 symptoms encouraged patients to report “no/mild” as well as more severe symptoms. The symptom reporting form used in our study has the advantage of validation in patients with cancer [31], using formatting that is familiar to clinicians (analogous to the CTCAE) and no scoring procedures that require specific knowledge of the measure (such as reverse scoring individual items or averaging a number of items to achieve an overall score). Our multisymptom report form is similar to the now readily available PRO-CTCAE [10, 12], which was not available to us when we started our study, and which we suggest be used for patient-reported symptom evaluation in future studies. Study participants were able to easily complete the symptom report form in a few minutes before or as they started their infusion. All of these features facilitate ease of use for patient-reported symptom reporting in clinical practice.

A limitation of our study is that toxicity reports were collected from patients only during regularly scheduled chemotherapy visits, either biweekly or every 3 weeks. When patients were asked to report symptom severity “in the past 7 days,” the absence of weekly data collection could have resulted in under-reporting of symptoms whose severity had declined from their peak toxicity outside the 7-day time frame. Weekly symptom reports throughout chemotherapy would have increased the accuracy of major toxicity estimates. However, if symptom reporting were to be incorporated into clinical practice, our schedule of patient reports every other week or every third week during chemotherapy infusion would be feasible unless symptom reports were captured electronically during nontreatment weeks [21, 49, 50].

Another potential limitation is that patients receiving shorter regimens (e.g., TC) had less time to report symptom severity compared with patients with longer regimens. To address this concern, we presented data on both full treatment duration and the first 12 weeks of treatment (Table 2). During full treatment, severity differed significantly among regimens for seven symptoms (fatigue, constipation, myalgia, diarrhea, nausea, peripheral neuropathy,

and swelling of arms/legs); within the 12-week time frame, all toxicity levels remained significantly different by regimen, except myalgia and peripheral neuropathy.

Prior studies have reported how PRO-CTCAE coupled with clinician alerts throughout treatment can trigger early interventions that, in turn, reduce adverse events such as hospitalizations, visits to the emergency room, and early discontinuation [28] and even improve overall survival in patients with metastatic disease [51]. Our study did not include alerts to oncology providers or nurses. However, we note that primary reasons for hospitalizations in our sample were neutropenic/other fever and infections—conditions that are not likely to be apparent from the 17 symptoms monitored in our study. The symptom of numbness/tingling in hands/feet is directly related to 25% of the treatment discontinuations and 24% of the dose reductions due to peripheral neuropathy. However, other prevalent reasons for these two adverse events pertain to neutropenic fever and blood counts—again, not apparent in the other 16 symptoms.

In general, we found that treatment discontinuation/continuation rates and dose reduction/no reduction rates were not significantly different even when patients rated their symptoms moderate to very severe. Patients appear to cope with multiple treatment toxicities, perhaps to ensure treatment efficacy through full completion of the treatment plan.

Patient-reported symptom severity reflects overall quality of life during treatment and a patient’s treatment experience but may also reveal the need for physician-guided palliative intervention. The inclusion of patient perspectives on how treatment affects their quality of life [8] has the potential for improving symptom management, patient satisfaction, and long-term clinical outcomes, including overall survival [28, 51, 52]. Capturing multiple toxicity outcomes in one report at multiple time points during chemotherapy enables oncologists and their patients to understand the range of side effects as they discuss treatment efficacies [40].

The chemotherapy regimens used in early breast cancer have major differences in toxicities [53–55]. For clinicians and patients these differences are of major importance as they may influence treatment decisions [56]. Future research should focus on how best to integrate an understanding of patient-reported toxicity experiences with different chemotherapy regimens into patient-centered decision-making and care during chemotherapy, in ways that are feasible and meaningful to both patients and providers.

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