Incidence of taxane-induced pain and distress in patients receiving chemotherapy for early-stage breast cancer: a retrospective, outcomes-based survey

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ABSTRACT

Introduction

With the widespread use of sequential anthracycline/taxane–based chemotherapy for early-stage breast cancer, clinicians are becoming rapidly aware of toxicities associated with those regimens. Despite the low incidence reported in the literature of significant arthralgia and myalgia with those regimens, it is clinically evident that a substantial proportion of patients develop such toxicities. We performed a pilot study to investigate the extent of this problem.

Patients and Methods

Patients who had received prior adjuvant or neoadjuvant chemotherapy [doxorubicin–cyclophosphamide followed by paclitaxel (AC-T), doxorubicin–cyclophosphamide followed by docetaxel (AC-D), or 5-fluourouracil–epirubicin–cyclophosphamide followed by docetaxel (FEC-D)] completed a retrospective outcomes-based survey. The survey utilized the Functional Assessment of Cancer Therapy–Taxane Scale, the Memorial Symptom Assessment Scale, and a modified Brief Pain Inventory.

Results

Interviews were conducted with 82 patients. Interviewees had received AC-T (43%), FEC-D (43%), and AC-D (14%). Pain as a side effect of either the anthracycline or the taxane chemotherapy was reported by 87% of patients. Most of the patients (79%) indicated that their worst pain occurred during the taxane component of treatment. Compared with paclitaxel, docetaxel was reported to cause more pain. Narcotics for pain management were required by 35 of 82 patients (43%).

Conclusions

A significant number of patients receiving sequential anthracycline/taxane–based chemotherapy for early-stage breast cancer experience pain, particularly during the taxane component. Prospective patient-reported outcome assessments are needed to help individualize treatment interventions and to improve symptom management in this population.

KEY WORDS

Breast cancer, taxanes, anthracyclines, toxicities

1. INTRODUCTION

Sequential anthracycline/taxane combination chemotherapy regimens have increasingly become a standard of care in the adjuvant and neoadjuvant treatment of breast cancer. In Canada, the most commonly used regimens include doxorubicin–cyclophosphamide for 4 cycles followed by docetaxel for 4 cycles (AC-D) [1,2]; doxorubicin–cyclophosphamide for 4 cycles followed by paclitaxel for 4 cycles (AC-T); and 5-fluorouracil–epirubicin–cyclophosphamide for 3 cycles followed by docetaxel for 3 cycles (FEC-D) [3,4]. Unfortunately, despite the antitumour activity of these regimens, anthracyclines and taxanes are both associated with significant toxicities.

The literature on the AC-T, AC-D, and FEC-D regimens cites myelosuppression as the main dose-limiting side effect. In clinical practice, however, we have found that debilitating taxane-induced arthralgias and myalgias are the greater clinical challenge. These symptoms typically begin 24–48 hours after the taxane infusion and last for 3–5 days [5]. Considerable variability exists in the reported incidences of these symptoms (Table I),

TABLE I Reported incidences of taxane-induced arthralgias and myalgias

Taxane	*Treatment type and study population*	*Incidence of arthralgias and myalgias (%)*	*Reference*
Paclitaxel	Adjuvant chemotherapy for node-positive breast cancer	12	Mamounas *et al.,* 2005 [6]
	Adjuvant treatment for early HER2+ breast cancer	38.6–55.5[a]	Slamon *et al.,* 2006 [7]
Docetaxel	Treatment for locally advanced and metastatic breast cancer	2.3	Smith *et al.,* 2002 [8]
	Adjuvant treatment for operable breast cancer	33	Jones *et al.,* 2006 [9]

[a] Incidences reported on different arms of the trial.
HER2+ = positive for the human epidermal growth factor receptor 2.

but a significant number of patients require opioid analgesia for their symptoms, and some patients discontinue their chemotherapy because of the pain. Potential reasons for the discrepancies between the reported incidence of these side effects and clinical experience include the use of different assessment tools by the different studies, varying demographics in the study populations, and a lack of standardized reporting of concurrent pain-management medications in trials.

Given the importance of managing patient toxicities, further investigation is required to fully elucidate the true incidence of these side effects and its impact on the subsequent medical management of the patient. Our pilot study was designed to retrospectively examine the incidence and impact of pain during sequential anthracycline/taxane–based chemotherapeutic regimes in breast cancer patients, focusing especially on arthralgias and myalgias.

2. PATIENTS AND METHODS

Eligibility criteria for the study were

- a diagnosis of early-stage breast cancer;
- adjuvant or neoadjuvant AC-T, AC-D, or FEC-D treatment administered between January 2006 and July 2007;
- ability to speak and understand English; and
- ability to give informed consent.

Patients were included if they had received at least 1 cycle of anthracycline and 1 cycle of taxane treatment. Patients were identified through pharmacy and hospital records. Demographic information about study participants—including age, ethnicity, menopausal status, clinical stage, tumour characteristics, type of breast surgery, and chemotherapy regimen received—was extracted from hospital records. The study design received ethics approval from the local research ethics board.

Chemotherapy side effects were assessed both qualitatively and quantitatively. Qualitative assessments were made by asking patients to identify the cycle of chemotherapy during which they experienced the most pain. Patients were asked to identify the cycle of anthracycline treatment and the cycle of taxane treatment that they found the most distressing and to choose which of the two was worse. Questions regarding the need for pain medications while on treatment and for admission to hospital during treatment were also included. To assess the location of taxane-induced pain, patients were provided with a visual body grid adapted from the Brief Pain Inventory (BPI) [10]. They were asked to point out the areas in which they experienced pain during taxane treatment. Two of the authors assessed the body diagrams independently and recorded the areas circled by the patients to calculate the major body areas of taxane-induced pain.

To quantitatively assess pain and side effects from the anthracycline part of the chemotherapy regimen, we used the Memorial Symptom Assessment Scale (MSAS) [11]; for the side effects from taxane treatment, we used both the MSAS and the Functional Assessment of Cancer Therapy–Taxane Scale (FACT-Taxane) [12]. The MSAS and the FACT-Taxane are validated self-report instruments that both quantitatively assess treatment-induced distress. As well, the MSAS and FACT-Taxane tools both have various subscales that can be calculated. Table II gives a synopsis of the scoring systems and the subscales of each assessment tool used in the study. With the MSAS tool, we used both the Total MSAS score (TMSAS) and the Global Distress Index score (MSAS-GDI) as indicators of the total burden of side effects during treatment with either anthracyclines or taxanes. Symptom scores for pain were used as the quantitative measure for pain during chemotherapy. For the FACT-Taxane tool, we used the FACT-Taxane Trial Outcome Index (TOI) score to compare the burden of toxicity between treatment with docetaxel and treatment with paclitaxel.

2.1 Analysis

The MSAS symptom scores, TMSAS scores, and MSAS-GDI scores were calculated as previously described [11].

TABLE II Synopsis of the pain-assessment tools used

Tool and scale or subscale	*Measures*	*Scoring*	*Reference*
Memorial Symptom Assessment Scale (MSAS)			
Symptom score	Individual symptom rated in three dimensions: frequency, severity, and distress-induced	Average of three symptom dimensions rated on a scale of 0–4	Portenoy *et al.*, 1994 [11]
Total MSAS Score	All 32 symptoms on the MSAS tool	Sum of all 32 symptom scores	
Global Distress Index	Psychological and physical distress	Average frequency score of 4 psychological symptoms and the average of the distress associated with 6 physical symptoms	
Functional Assessment of Cancer Therapy–Taxane (FACT-Taxane)			
FACT-Taxane Trial Outcome Index	Assesses quality of life in the physical, social/family, emotional, and functional domains along with taxane-specific side effects	Each symptom question rated on a scale of 0–4; the algorithm for calculating the final score is outlined in the cited reference.	Cella *et al.*, 2003 [12]

The Student *t*-test was used to check for statistical significance in the differences in the means of the MSAS symptom scores for pain, the TMSAS scores, and the MSAS-GDI scores for patients during anthracycline treatment and during treatment with the taxane. Only patients that had entered values for all three dimensions of a MSAS pain symptom score (pain frequency, severity, and associated distress) were included in the analysis of mean MSAS scores; however, the responses of patients that left one dimension of the MSAS pain symptom score unrated were still included in the analyses of the individual dimensions. For the FACT-Taxane TOI data, the Student *t*-test was also used to find any statistically significant differences between the average FACT-Taxane TOI scores of patients that received paclitaxel and those that received docetaxel.

3. RESULTS

Table III outlines the demographics of the 82 women [median age: 50 years (range: 27–70 years)] that met the inclusion criteria. Participants had received AC-T (43.2%), FEC-D (43.2%), and AC-D (14.6%). Of the 82 women, 11 (13%) reported experiencing no pain during their entire course of treatment with chemotherapy. The remaining 71 women (87%) experienced pain during at least 1 cycle of treatment, and of those 71 women, nearly all (65 of 71) subjectively felt that they experienced worse pain during taxane treatment than during anthracycline treatment.

The findings suggested by the qualitative assessment were reflected in the analysis of the MSAS data. The average MSAS symptom scores for pain were significantly higher during treatment with taxanes than during treatment with anthracyclines regardless of regimen (FEC-D, AC-D, AC-T: Figure 1). Furthermore, when the ratings in each individual dimension of the MSAS pain symptom score (frequency, severity, distress) were compared for anthracycline and for taxane treatment, significantly more patients rated each dimension "severe" during taxane treatment (Figure 2). Collectively, these data clearly indicate that patients were experiencing more significant

TABLE III Demographic characteristics of the patients

Characteristic	*Patients* (n)	*(%)*
Age		
≤40	16	20
41–50	28	34
51–60	24	29
≥61	14	17
Ethnicity		
Black	3	4
Asian	9	11
Hispanic	3	4
Caucasian	67	82
Menopausal status		
Premenopausal	31	38
Perimenopausal	8	10
Postmenopausal	43	52
Surgery		
Lumpectomy	46	56
Mastectomy	30	37
None	6	7
Chemotherapy regimen		
FEC-D	35	43.2
AC-T	35	43.2
AC-D	12	14.6

FEC-D = 5-fluorouracil–epirubicin–cyclophosphamide/docetaxel; AC-T = doxorubicin–cyclophosphamide/paclitaxel; AC-D = doxorubicin–cyclophosphamide/docetaxel.

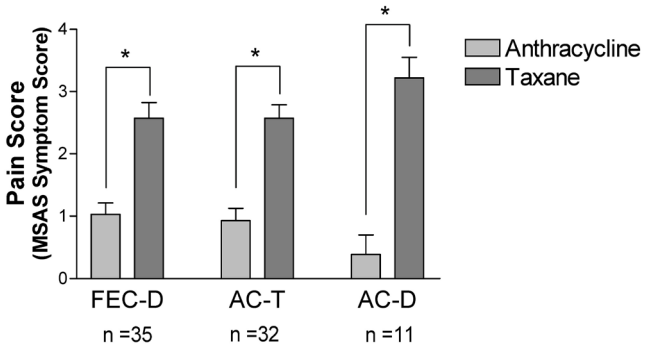

*FIGURE 1 Increased Memorial Symptom Assessment Scale (MSAS) scores for pain during taxane treatment. The average MSAS pain score reported by patients is shown for the anthracycline and taxane portions of treatment in the three chemotherapy regimens studied. * $p < 0.001$ by Student* t*-test. Error bars indicate the standard deviation. FEC-D = 5-fluourouracil–epirubicin–cyclophosphamide followed by docetaxel; AC-T = doxorubicin–cyclophosphamide followed by paclitaxel; AC-D = doxorubicin–cyclophosphamide followed by docetaxel.*

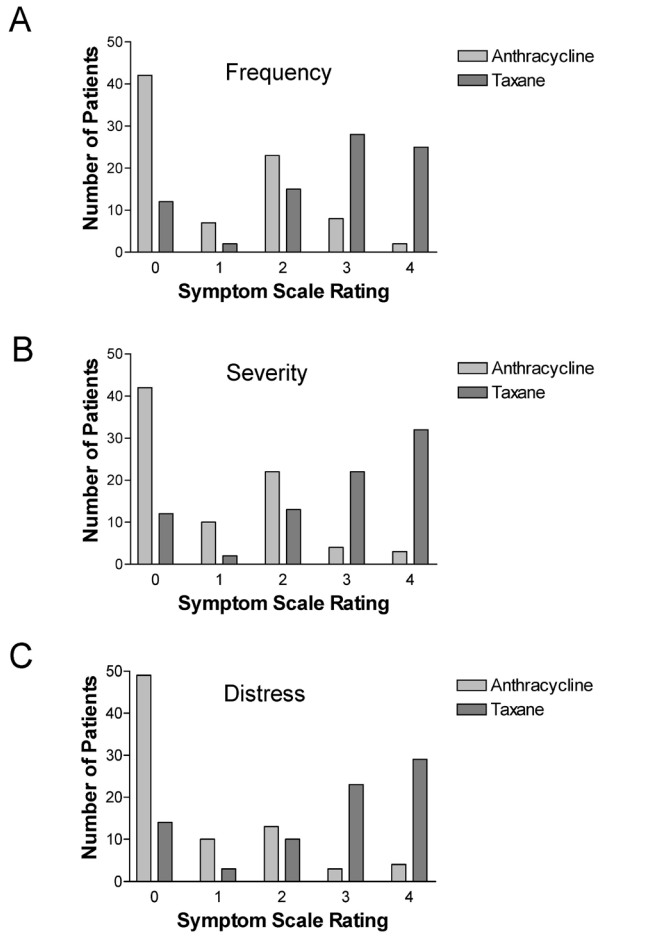

*FIGURE 2 Compared with anthracyclines, taxanes induced more intense pain in all dimensions studied. The graphs show the distribution of patient responses on the Memorial Symptom Assessment Scale (MSAS) for(A) frequency of pain (*n *= 82), (B) severity of pain (*n *= 81), and (C) distress induced by pain (*n *= 80) during treatment with anthracyclines and with taxanes.*

pain during treatment with taxanes. Analysis of the FACT-Taxane survey results did not demonstrate any significant differences in quality-of-life scores for patients receiving docetaxel as compared with patients receiving paclitaxel.

Despite worse pain symptom scores during the taxane component of treatment, the TMSAS scores and the subscale scores of the MSAS-GDI during treatment with taxanes were not significantly higher than those seen during the anthracycline component of therapy (Table IV). Scores were significantly higher in the MSAS-GDI and TMSAS only during docetaxel (D) treatment in the AC-D regimen, signifying that symptom burden and distress may have become significantly worse during D than during AC. Conversely, overall assessment during the paclitaxel (T) part of AC-T regimen improved with T. No significant changes were noted with taxane administration after FEC. That finding suggests that pain is only one factor of symptom burden and distress: Pain is clearly more prevalent during the taxane part of treatment, but the overall symptom burden and distress is not significantly different between the anthracycline and taxane components for most patients.

Further characterization of the pain experienced during taxane treatment was performed using the modified BPI tool. Of the 71 patients that described their pain using the modified BPI tool, almost half (35 patients) were affected by arthralgias localized to a specific joint. As well, 22 patients experienced myalgias, indicating pain within a specific muscle or group of muscles. Another 30 patients indicated pain consistent with a peripheral neuropathy, because they experienced burning discomfort along a nerve distribution. Whole-body pain was reported by 8 patients. Sites commonly reported for the arthralgias and myalgias included fingertips and

TABLE IV Memorial Symptom Assessment Scale (MSAS) scores, anthracyclines versus taxanes

Scale and treatment	*Anthracycline scores [mean (SD)]*	*Taxane scores [mean (SD)]*	p *Value*
Global Distress Index			
AC-T (*n*=35)	1.55 (0.93)	1.48 (1.07)	0.66
FEC-D (*n*=35)	1.21 (0.89)	1.39 (0.84)	0.12
AC-D (*n*=12)	1.30 (0.74)	1.90 (0.92)	0.039
Total MSAS score			
AC-T	1.39 (0.72)	1.23 (0.66)	0.023
FEC-D	1.17 (0.59)	1.26 (0.56)	0.22
AC-D	1.21 (0.55)	1.50 (0.68)	0.042

SD = standard deviation; AC-T = doxorubicin–cyclophosphamide/paclitaxel; FEC-D = 5-fluorouracil–epirubicin–cyclophosphamide/docetaxel; AC-D = doxorubicin–cyclophosphamide/docetaxel.

toes (39%), lower back (30%), legs (29%), upper back (26%), arms (20%), chest (14%), abdomen (8%), and head (8%). Thus, we found that taxanes induced pain all over the body and not in a predictable pattern.

Pain was significant enough to require narcotics for pain management in 35 patients. None of the surveyed patients stopped treatment because of pain. Age, menopausal status, and stage of cancer did not correlate with presence or severity of pain.

4. DISCUSSION

We found that most patients (71/82) reported experiencing some pain during treatment with anthracycline/taxane regimes. Moreover, despite the low incidence of arthralgia and myalgia reported in the literature, we found that a significant number of patients reported arthralgia (35/82) and myalgia (22/82) in addition to pain consistent with a peripheral neuropathy (30/82) during treatment with a taxane. Additionally, overall pain scores were significantly worse during the taxane component of treatment. Overall symptom burden and distress scores, however, were worse only in the taxane component of AC-D; this finding was not seen with either AC-T or FEC-D. It is possible that this observation resulted from the use of higher individual doses of anthracycline with FEC than with AC, indicating that both types of chemotherapy induced considerable distress. Such a scenario may have led to a lesser apparent worsening of symptoms when the taxane was introduced. Collectively, our data indicate that pain, and specifically myalgias and arthralgias, was a large component of the distress induced by taxanes.

Our study has a number of limitations. It was a small, single-centre, retrospective pilot study. As such, recall bias and selection bias may have significantly affected the study findings. Our results do, however, confirm anecdotal findings that taxane-induced pain affects a significant number of patients. This pilot project demonstrates a need to explore these common and clinically significant side effects in a prospective fashion.

5. FUTURE DIRECTIONS

To develop specific intervention strategies in this patient population, a prospective longitudinal study is being planned to determine the true incidence of these toxicities and any associated patient characteristics. Specifically, we are interested in determining the severity, location, and duration of the most distressing symptoms of sequential anthracycline/taxane combination chemotherapy regimens. As well, we want to assess the effect of these symptoms on the ability of patients to continue treatment as planned. We will follow up with intervention strategies that will help to individualize treatment, evaluate the potential effectiveness of those strategies, and improve symptom management in this population.

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