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Natural history of postural instability in breast cancer patients treated with taxane-based chemotherapy: A pilot study

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ABSTRACT

Over 230,000 new cases of breast cancer are expected to be diagnosed in the United States in 2015. Taxane-based chemotherapy is often an effective treatment, but can also cause adverse symptoms in patients due to neurotoxicity. These side effects can impair postural control in patients; however, this instability has scarcely been quantified. The purpose of this pilot study was to gain insight into the natural history of postural instability in breast cancer patients being treated with taxane-based chemotherapy. Thirty-two breast cancer patients (31 female/1 male; 47.6 ± 11.2 year; 16 stage II/16 stage III) completed eyes open and eyes closed quiet standing trials in the oncology clinic where they were being treated. These trials were collected at five timepoints throughout their chemotherapy treatment: (1) before initiating chemotherapy to provide a baseline, (2–4) before starting subsequent chemotherapy cycles, and (5) 1–3 months after receiving their last taxane infusion. After the first chemotherapy cycle, patients demonstrated increases in 95% confidence ellipse area of center of pressure (CoP) [45.2%, $p = 0.01$] and root mean squared CoP excursion [18%, $p = 0.006$] compared to baseline values for the eyes closed condition. These balance deficiencies progressed with cumulative taxane exposure. Postural instability persisted 1–3 months after completing chemotherapy with increases in 95% CoP ellipse area [86.8%, $p = 0.002$], root mean squared CoP excursion [32.6%, $p = 0.001$], and mean CoP velocity [30.4%, $p = 0.024$]. The balance impairments demonstrated by patients in this study appear to be clinically relevant when compared to balance impairments previously reported in other patient populations.

1. Introduction

Over 230,000 new cases of breast cancer are expected to be diagnosed in the United States alone in 2015 [1]. Fortunately, diagnostic and treatment advances including chemotherapy have yielded a current all-time high in survival rates for all stages of breast cancer [1]. As breast cancer survivors are living longer, there has been greater focus on understanding the side effects of treatment and taking steps to mitigate them during and after chemotherapy [2,3]. In addition to improving the experiences of survivors during and after treatment, evidence is mounting that quality of life interventions can increase the amount of therapy received and may also improve survival [4].

While chemotherapy agents such as taxanes and platinum compounds have contributed to improved clinical outcomes, they can also cause many adverse symptoms including fatigue, pain, and numbness along with central and peripheral nervous system impairments [2,3,5–8]. Previous investigations have reported the detrimental effects that these toxicities can have on human postural control in other populations [9–14], but balance deficits in patients exposed to neurotoxic chemotherapy agents have scarcely been quantified. Similar to diabetic [15] and elderly populations [16,17], patients treated with neurotoxic chemotherapy can be at an increased risk of falling [18,19]. Additionally, a retrospective

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study identified balance deficits in breast cancer patients after completing taxane-based chemotherapy, which provides evidence for the presence of postural instability in patients undergoing neurotoxic chemotherapy [20]. However, the natural history of these balance deficits during repeat exposures to chemotherapy has yet to be elucidated. Reports on time-dependent changes in symptoms during taxane-based chemotherapy have, to-date, focused on patient-reported outcomes [21]. While patient reported symptoms are currently used to assess chemotherapy toxicities in the oncology clinic, they can be subjective and have coarse rating scales, making it difficult to discern early changes that may identify patients who are at risk for developing severe symptoms [2,22].

We propose that objective, high-resolution, and clinically-oriented measures may improve clinicians' ability to detect detrimental effects earlier during the course of treatment. Posturography offers these measure attributes by utilizing center of pressure (CoP) movement to gain insight into human postural control. This approach has been used to identify balance deficits in other balance impaired populations such as the elderly [23–25] and diabetic patients [9,10]. The purpose of this pilot study was to establish the natural history of postural instability in breast cancer patients being treated with taxane-based chemotherapy. We hypothesized that patients would demonstrate balance deficits that would increase with cumulative chemotherapy exposure.

Table 1
Patient demographics and treatment summary.

General Characteristics	
Enrolled (n)	32 (100%)
Completed Study	27 (84%)
Dropped Out	4 (13%)
Death	1 (3%)
Sex (f/m)	31/1
Age (year)	47.6 ± 11.2
Mass (kg)	74.6 ± 20.1
Height (m)	1.64 ± 0.08
BMI (kg/m^2)	27.9 ± 7.8
Diabetes (n)	0
Cancer Stage at Diagnosis (n)	
I	0 (0%)
II	16 (50%)
III	16 (50%)
IV	0 (0%)

Chemotherapy Regimen	n (%)
Doxorubicin/Cyclophosphamide prior to taxane therapy	26 (81%)
Taxane Therapy	
Paclitaxel weekly	18 (56%)
Paclitaxel every 2 weeks	6 (19%)
Docetaxel every 3 weeks	7 (22%)
Weekly Paclitaxel → Docetaxel every 3 weeks (switched after cycle 1)	1 (3%)

Age, Mass, Height, and BMI are presented as mean ± SD.

2. Methods

2.1. Participants

Breast cancer patients (stages I–III) who were initiating taxane-based chemotherapy were recruited for this study. Patients unable to stand or walk without assistance, having a pre-existing diagnosis of neuropathy of any kind, or having previous exposure to taxane at any time were excluded from the study. Patients who had previous exposure to other chemotherapy or targeted therapy known to be associated with neuropathy (e.g., platinum therapy, bortezomib, vinblastine) within one year of starting in the study were also excluded. Prior exposure to other types of chemotherapy, such as doxorubicin and cyclophosphamide, were allowed. Patients that satisfied the inclusion criteria were enrolled in the study after providing institutional review board-approved informed consent (Table 1).

2.2. Protocol

Patient balance was assessed at 5 timepoints: (1) prior to starting chemotherapy to provide a baseline, (2–4) before starting subsequent chemotherapy cycles, and (5) 1–3 months after receiving their last taxane infusion. As shown in Table 1, patients received different taxane-based treatments which caused the number of days between timepoints to vary on an individual basis. All balance measurements were collected by trained clinical research coordinators in the oncology clinic where the patients were being seen for regularly scheduled appointments. Balance tasks consisted of quiet standing while looking straight ahead with the eyes open as well as eyes closed. One trial was performed for each condition. The quiet standing trials were performed in a narrow stance (medial foot surfaces separated by 5 cm) with arms resting at the patients' sides for 30 seconds. Patients were also asked to complete functional reaching tasks and a limits-of-stability task; however, due to inconsistencies in how these tasks were administered and performed, the data could not be analyzed.

A custom LabVIEW program (Version 2011; National Instruments; Austin, TX) was developed to collect CoP data. The program also provided clinical personnel with step-by-step instructions on the administration of the balance tasks to ensure consistency in how the tests were administered between visits and operators. CoP data were calculated and recorded by the LabVIEW program using force and moment measurements from a BP5046 balance plate (Bertec Corporation; Worthington, OH). Over the course of the study, two versions of the LabVIEW program were utilized. The first version collected CoP data at 50 Hz while the second was increased to 1000 Hz. All CoP data were then 4th order low-pass Butterworth filtered at 20 Hz before being analyzed. While the use of two versions of the LabVIEW data collection program introduces a discontinuity in the methods, the balance parameters calculated from the two versions were checked to ensure consistency. Balance parameters calculated from trials collected at 1000 Hz were found to agree within 2% with those calculated from the same trials downsampled to 50 Hz before processing. Custom MATLAB (Version 2014b; MathWorks; Natick, MA) scripts were used to process all CoP data.

2.3. Quantifying postural control

Summary measures of CoP trajectory, consisting of 95% confidence ellipse area (EA), root mean squared CoP excursion (RMS), and mean CoP velocity (MVEL), were selected to characterize patients' postural stability. Detailed descriptions of the calculations for these balance parameters are provided elsewhere [23]. Briefly, EA provides a measure of spatial control of the CoP where it defines the area of an ellipse that contains approximately 95% of the data. A larger EA indicates greater dispersion of the CoP and a less tightly controlled CoP position. RMS characterizes the root mean squared displacement of the CoP from its mean position. A higher RMS suggests that, on average, the CoP is an increased distance away from the mean position and towards a boundary of the base of support [23,26], which is indicative of a decrease in postural stability. MVEL is the total distance traveled of the CoP divided by the duration of the trial. MVEL provides insight into the extent of corrective CoP actions taken during a balance task, where an increased MVEL indicates less appropriate CoP adjustments (i.e., overcorrecting) were made to maintain stability. EA, RMS, and MVEL have previously been