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Hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy

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ABSTRACT

Purpose: The purpose of this study was to evaluate for differences in demographic, clinical, and pain characteristics, as well as measures of sensation, balance, perceived stress, symptom burden, and quality of life (QOL) among survivors who received neurotoxic chemotherapy (CTX) and who reported only chemotherapy-induced neuropathy (CIN, n = 217), CIN and hearing loss (CIN/HL, n = 69), or CIN, hearing loss, and tinnitus (CIN/HL/TIN, n = 85). We hypothesized that as the number of neurotoxicities increased, survivors would have worse outcomes.

Methods: Survivors were recruited from throughout the San Francisco Bay area. Survivors completed self-report questionnaires for pain and other symptoms, stress and QOL. Objective measures were assessed at an in person visit.

Results: Compared to survivors with only CIN, survivors with all three neurotoxicities were less likely to be female and less likely to report child care responsibilities. In addition, survivors with all three neurtoxicities had higher worst pain scores, greater loss of protective sensation, and worse timed get up and go scores. These survivors reported higher state anxiety and depression and poorer QOL. For some outcomes (e.g., longer duration of CIN, self-reported balance problems), significantly worse outcomes were found for the survivors with CIN/HL and CIN/HL/TIN compared to those with only CIN.

Conclusions: Our findings suggest that compared to survivors with only CIN, survivors with CIN/HL/TIN are at increased risk for the most severe symptom burden, significant problems associated with sensory loss and changes in balance, as well as significant decrements in all aspects of QOL.

1. Introduction

Research on the neurotoxic effects of chemotherapy (CTX) in cancer survivors has focused primarily on an evaluation of somatosensory changes in the upper and lower extremities (i.e., chemotherapy-induced neuropathy (CIN)). While the exact prevalence of CIN in cancer survivors is unknown, estimates range from 38% to 90% (Kerckhove et al., 2017). In addition, limited evidence suggests that CIN results in significant decrements in physical function (Miaskowski et al., 2017), significant psychological distress (Leach et al., 2016; Miaskowski et al., 2017), sleep disorders (Hong et al., 2014; Miaskowski et al., 2017), and increased risk for falls (Bao et al., 2016; Gewandter et al., 2013; Kolb et al., 2016; Tofthagen et al., 2012).

Recently, the prevalence and impact of two additional neurotoxic effects of CTX, namely hearing loss and tinnitus, have begun to be evaluated in cancer survivors. Most of this research, albeit limited, focused on an evaluation of hearing loss and tinnitus in survivors who received platinum for testicular (Frisina et al., 2016; Oldenburg et al., 2007) or head and neck cancer (Huang et al., 2016; Malgonde et al., 2015; Theunissen et al., 2015). Findings from these studies suggest that these problems contribute to significant decreases in quality of life (QOL). Only a few small studies have evaluated for audiovestibular toxicities in patients with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer (Bacon et al., 2003; Jenkins et al., 2009; Ozguroglu et al., 2006; Salvinelli et al., 2003; Skalleberg et al., 2017). In addition, while taxanes are known to produce CIN (Kerckhove et al.,

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2017), only one clinical study was identified that evaluated the effects of taxanes on the auditory system (Sarafraz and Ahmadi, 2008). While the findings from this study were negative, results of preclinical studies suggest that the administration of taxanes results in hearing loss (Atas et al., 2006; Dong et al., 2014).

Given the paucity of research on the neurotoxic effects of CTX in cancer survivors, we recently evaluated for CIN, hearing loss, and tinnitus in a sample of cancer survivors who received a platinum and/or a taxane (Miaskowski et al., In press). Of these 609 survivors, 18% did not have any of these neurotoxicities and 14.1% had all three neurotoxicities. Compared to the no neurotoxicity group, survivors with all three neurotoxicities (i.e., CIN, hearing loss, and tinnitus) were older, less likely to be employed, had a higher body mass index (BMI), had a higher number of comorbid conditions, and reported a poorer functional status, In addition, these survivors reported higher levels of depressive symptoms, anxiety, fatigue, and sleep disturbance; higher levels of perceived stress; and poorer QOL outcomes. In terms of objective measures of sensation and function, the survivors with all three neurotoxicities had significant decrements in light touch, cold, pain, and vibratory sensations, as well as significant decreases in balance and physical function. Of note, no between group differences were found in the types of CTX regimens received, the total dose of CTX administered, the length of time since the cancer diagnosis, and the number of metastatic sites.

No studies were found that attempted to determine if the number of neurotoxicities associated with CTX had differential effects on important survivor outcomes. Therefore, the purpose of this study was to evaluate for differences in demographic, clinical, and pain characteristics, as well as measures of sensation, balance, perceived stress, symptom burden, and QOL among adult cancer survivors who received neurotoxic CTX and who reported only CIN, CIN and hearing loss (CIN/HL), or CIN, hearing loss, and tinnitus (CIN/HL/TIN). We hypothesized that as the number of neurotoxicities increased, survivors would have worse outcomes.

2. Methods

2.1. Survivors and settings

The methods for this larger study are described in detail elsewhere (Miaskowski et al., 2017). In brief, survivors were recruited from throughout the San Francisco Bay area. Survivors with CIN met the following inclusion criteria: were ≥18 years of age; had received a platinum and/or a taxane compound; had completed their course of CTX ≥3 months prior to enrollment; had changes in sensation and/or pain in their feet and/or hands of ≥3 months duration following the completion of CTX; had a rating of ≥3 on a 0 to 10 numeric rating scale (NRS) for any one of the following sensations from the Pain Qualities Assessment Scale (i.e., numb, tender, shooting, sensitive, electrical, tingling radiating, throbbing, cramping, itchy, unpleasant) (Galer and Jensen, 1997); if they had pain associated with the CIN, had an average pain intensity score in their feet and/or hands of ≥3 on a 0 to 10 NRS; had a Karnofsky Performance Status (KPS) score of ≥50; and were able to read, write, and understand English (Watson and Evans, 1992).

Survivors with CIN were excluded if they had: peripheral vascular disease, vitamin B12 deficiency, thyroid dysfunction, HIV neuropathy, another painful condition that was difficult for them to distinguish from their CIN, a hereditary sensory or autonomic neuropathy (Rotthier et al., 2009), and/or a hereditary mitochondrial disorder (McFarland and Turnbull, 2009). A detailed patient history was obtained to evaluate for the presence of these conditions. Of the 1450 survivors who were screened, 754 were enrolled, and 609 completed the self-report questionnaires and the study visit. To answer the aims of this study, data from 371 survivors (i.e., 58.5% (n = 217) with only CIN, 18.6% (n = 69) with CIN/HL, 22.9% (n = 85) with CIN/HL/TIN) were evaluated.

2.2. Study procedures

Research nurses screened and consented the survivors over the phone; sent and asked them to complete the self-report questionnaires prior to their study visit; and scheduled the in person assessment. At this assessment, written informed consent was obtained, questionnaires were reviewed for completeness, and objective measurements were done.

2.3. Study measures

2.3.1. Demographic and clinical characteristics

Survivors provided information on demographic characteristics and completed the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977; Karnofsky et al., 1948; Schnadig et al., 2008) and the Self-Administered Comorbidity Questionnaire (SCQ) (Brunner et al., 2008; Cieza et al., 2006).

2.3.2. Hearing loss and tinnitus

Two items from the Functional Assessment of Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) subscale were used to evaluate hearing loss (i.e., I have trouble hearing) and tinnitus (i.e., I get ringing or buzzing in my ears) (Huang et al., 2007). Each item was rated on a 0 (not at all) to 4 (very much) scale. Survivors with CIN who reported a score of 0 were classified in the only CIN group. Survivors with CIN who reported a score of > 0 on these questions were classified into either the CIN/HL group or the CIN/HL/TIN group.

2.3.3. Pain characteristics

Survivors completed the Brief Pain Inventory (Daut et al., 1983) and the Pain Qualities Assessment Scale (Victor et al., 2008).

2.3.4. Sensation

Light touch was evaluated using Semmes Weinstein monofilaments (Bell-Krotoski, 2002). Cold sensation was evaluated using the Tiptherm Rod (Papanas and Ziegler, 2011; Viswanathan et al., 2002). Pain sensation was evaluated using the Neurotip (Papanas and Ziegler, 2011). Vibration threshold was assessed using a vibrometer (Duke et al., 2007). For all of the measures of sensation, the upper and lower extremities on the dominant side were tested.

2.3.5. Balance

Self-report questions from the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) were used to assess balance (Tofthagen et al., 2011). The objective measures of balance were the timed get up and go test (TUG) (Mathias et al., 1986) and the Fullerton Advanced Balance (FAB) test (Hernandez and Rose, 2008; Rose et al., 2006).

2.3.6. Symptom burden

Survivors completed self-report questionnaires that evaluated trait and state anxiety (Spielberger et al., 1983), depressive symptoms (Radloff, 1977), diurnal variations in fatigue and energy (Lee et al., 1991), sleep disturbance (Lee, 1992), and changes in attentional function (Cimprich et al., 2011).

2.3.7. Perceived stress

Stress associated with the cancer and its treatment was evaluated using the Impact of Event Scale – Revised (IES-R) (Weiss and Marmar, 1997). A global evaluation of perceived stress due to life circumstances was evaluated using the Perceived Stress Scale (PSS) (Cohen et al., 1983).

2.3.8. QOL

A generic evaluation of QOL was done using the Medical Outcomes Study-Short Form (SF12) (Ware et al., 1996). The disease specific