Title

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Journal

BMJ Supportive & Palliative Care, 13(3)

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Publication Date

2023-09-01

DOI

10.1136/spcare-2022-003684

Peer reviewed

HHS Public Access

Author manuscript

BMJ Support Palliat Care. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

BMJ Support Palliat Care. 2023 September ; 13(3): 345–353. doi:10.1136/spcare-2022-003684.

"Cancer Survivors and Neurotoxic Chemotherapy: Hearing loss and tinnitus"

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Abstract

Objectives ––Little is known about hearing loss and tinnitus associated with neurotoxic chemotherapy. Study evaluated for differences in occurrence rates and effects of hearing loss and tinnitus in survivors who received a platinum alone, a taxane alone, or a platinum and taxane containing regimen.

Methods ––Total of 273 survivors with breast, gastrointestinal, gynecologic, or lung cancer completed self-report measures of hearing loss and tinnitus and had an audiometric assessment that obtained pure tone air conduction thresholds bilaterally at frequencies of between 0.25 kHz to 16.0 kHz. To adjust for age- and gender-related changes in hearing, each survivor's audiogram was evaluated using the National Health and Nutrition Examination Survey (NHANES)-modified Occupational Safety and Health Administration (OSHA) standards. Survivor was classified as having hearing loss if at any frequency they scored poorer than the 50th percentile for their age and gender. Survivors were categorized as having tinnitus if they reported that for ≥10% of their time awake, they were consciously aware of their tinnitus. Differences among the chemotherapy groups were evaluated using parametric and non-parametric tests.

Results ––For most of the demographic and clinical characteristics, no differences were found among the three chemotherapy groups. Occurrence rates for audiogram-confirmed hearing loss ranged from 52.3% to 71.4%. Occurrence rates for tinnitus ranged from 37.1% to 40.0%. No differences were found among the three chemotherapy groups in the occurrence rates or effects of hearing loss and tinnitus.

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Author contributions: All authors substantially contributed to the conception and design of the study, data analysis, data interpretation and the drafting of the manuscript. All authors approved the final version of the manuscript.

Competing interests: The authors have no conflicts of interest to declare.

Conclusion ––—These findings suggest that regardless of the chemotherapy regimen common mechanistic pathway(s) may underlie these two neurotoxicities.

Summary of study implications –

Findings from this study provide the first evidence that regardless of whether survivors received platinum- and/or taxane-containing chemotherapy regimens, over 50% had audiogram confirmed hearing loss and over 35% reported clinically meaningful levels of tinnitus. Survivors warrant referrals to audiology for testing and an evaluation of the need for a hearing aid.

Keywords

cancer; chemotherapy; hearing loss; neurotoxicity; platinum; taxane; tinnitus

INTRODUCTION

Research on hearing loss associated with neurotoxic chemotherapy has focused primarily on pediatric patients who received platinum.[1] In adults, the limited amount of research has reported on hearing loss associated with the administration of platinum compounds in patients undergoing active treatment for testicular[2–7] or head and neck[8–10] cancer. While exact prevalence rates are unknown, platinum-induced ototoxicity is reported to be a bilateral and symmetrical sensorineural hearing loss. Risk factors for cisplatin-induced ototoxicity include: higher cumulative dose, younger age at exposure, receipt of concomitant radiation, being male, and co-administration of potential ototoxic compounds (e.g., antibiotics).[11] Additional factors that may contribute to hearing loss in patients receiving cisplatin include a genetic predisposition[12 13] and pre-exposure hearing ability.[11]

Taxanes, administered as single agents or in combination with platinum compounds, induce neurotoxic effects in the peripheral nervous system.[14] However, extremely limited information is available on taxane-induced ototoxicity. In one preclinical study that used rat cochlear organotypic cultures,[15] paclitaxel damaged cochlear hair cells in a dose-dependent manner. In addition, the drug damaged auditory nerve fibers and spiral ganglion nerves near the base of the cochlea. In terms of clinical studies, only a few case reports and small studies have evaluated for hearing loss associated with platinum and/or taxane compounds in patients with breast, gastrointestinal, gynecological, or lung cancer and findings from these studies are inconclusive.[16–21]

An equally devastating neurotoxic effect of platinum compounds is tinnitus that occurs in 19% to 42% of patients who receive the drug.[13] Tinnitus describes the conscious perception of an auditory sensation in the absence of a corresponding external stimulus. In general, the types of sensations are of an elementary nature and include descriptions of hissing, sizzling, and ringing.[22] The main risk factor for tinnitus is hearing loss. However, this association is not simple or straightforward. Some people with troublesome tinnitus have audiometrically normal hearing. In contrast, many people with hearing loss do not have tinnitus.[23] No studies have provided a detailed characterization of tinnitus in patients with breast, gastrointestinal, gynecologic or lung cancer who received a platinum and/or a taxane compound.

Given that these four cancers represent the most common cancer diagnoses in the United States; that platinum and/or taxane regimens are among the most common treatments for these patients; and that no data are available on ototoxicity and tinnitus in survivors with these cancer diagnoses, the purposes of this study were to evaluate for differences in the occurrence rates and effects of hearing loss and tinnitus in survivors (n=273) who received a platinum containing chemotherapy regimen (i.e., platinum alone), a taxane containing chemotherapy regimen (i.e., taxane alone), or a platinum and taxane containing regimen (i.e., both platinum and taxane). We hypothesized that survivors who received a combination regimen would have higher occurrence rates of and more severe effects from hearing loss and tinnitus.

PATIENTS AND METHODS

Survivors and settings

This study is part of a larger study that evaluated for chemotherapy-induced peripheral neuropathy (CIPN) and hearing loss and tinnitus in cancer survivors who received neurotoxic chemotherapy. Survivors were recruited from throughout the San Francisco Bay area using a variety of recruitment strategies (e.g., investigator registry, clinician referral, medical record review, emails to participants in the Dr. Susan Love Foundation's Love Research Army® Program). Survivors with and without CIPN were ≥18 years of age, had received a platinum and/or a taxane compound, had a Karnofsky Performance Status (KPS) score of ≥50,[24] were able to read, write, and understand English; and were willing to complete questionnaires that took 90 to 150 minutes over 2 weeks and travel to UCSF for a 3 hour study visit. For the hearing and tinnitus evaluation, survivors were excluded if they had tinnitus of >8 on a 0 to 10 numeric rating scale prior to chemotherapy; had hearing loss prior to chemotherapy that prevented understanding a one-to-one conversation; had a history of vestibular schwannoma, had radiation to head or neck, or had diagnosis of cancer to the brain. A detailed history was obtained to evaluate for the presence of these conditions. Of the 1012 survivors who were screened (primary reason for ineligibility was not meeting the inclusion criteria for the chemotherapy-induced peripheral neuropathy portion of the study), 365 were enrolled and 273 completed the self-report questionnaires and the study visit. Visit completions were interrupted by the COVID-19 pandemic.

Study procedures

Survivors communicated their willingness to participate in the study by phone or email. Research staff phoned survivors and determined their eligibility to participate. For survivors who met our inclusion criteria, the research nurse or audiologist obtained consent over the phone; asked the survivors to complete the self-report questionnaires prior to their study visit either electronically or by hard copy; and scheduled the study visit. During the study visit, the research staff obtained written informed consent, reviewed the study questionnaires for completeness, and performed the audiometric testing. The study visit was conducted by research nurses and audiologists in a large, dedicated research space that contained all the necessary equipment to conduct the study procedures including a double-walled sound-treated unit for hearing testing.

Measures

Demographic and clinical characteristics—Survivors completed a demographic questionnaire, the KPS scale,[24] and the Self-Administered Comorbidity Questionnaire (SCQ).[25] Survivors were interviewed to obtain information on their cancer diagnosis, previous and current cancer treatments, and chemotherapy regimens. Medical records were reviewed for detailed information on cancer diagnosis, previous cancer treatments, and chemotherapy regimens.

Subjective evaluation of hearing loss—Survivors completed the Audiology Case History Form that obtained information on survivors' hearing history and current perceptions of hearing loss. If the survivor endorsed the statement that they had hearing loss, they provided information on the use of hearing aids. Survivors who indicated at enrollment that they had hearing loss completed the Hearing Handicap Inventory for Adults (HHIA).[26]

The 25-item HHIA was developed to determine the effects of hearing loss on an individual's life. Each item was rated as either "no" (0 points), "sometimes" (2 points) or "yes" (4 points). Two subscale scores and a total score were calculated. The emotional subscale estimates the behavioral and emotional responses of an individual in relationship to his/her hearing loss. The social subscale measures the effects of hearing loss in different social situations. The total score ranges from 0 (no handicap) to 100 (total handicap), the emotional subscale ranges from 0 to 52, and the social subscale ranges from 0 to 48. Scores are grouped into the following categories: 0 to 16 = no handicap; 18 to 42 = mild to moderate handicap; and ≥44 = significant handicap).[26]

Audiometric testing—Prior to audiometric assessment, survivors underwent video otoscopy (Teslong, Irvine, CA) and tympanometry (Titan, Interacoustics, Eden Prairie, MN). Pure tone air conduction thresholds were obtained bilaterally at frequencies of between 0.25 KHz to 16.0 KHz covering the speech frequency range. An audiometer (Pello Interacoustics, Eden Prairie, MN), with insert earphones, that utilized the GSI-AMTAS automated threshold assessment (Grayson-Sadler, Eden Prairie, MN) was used to perform the audiometric assessment.[27] A bone oscillator, insert earphones, and circumaural high frequency earphones were used to assess air and bone conduction hearing thresholds.

Subjective evaluation of tinnitus—Survivors completed the Tinnitus Case History Form that was designed to obtain detailed information on tinnitus. If the survivor indicated that s/he had tinnitus (i.e., "ringing or sounds in your ears or head"), they completed the Tinnitus Functional Index (TFI).[28]

The 25-item TFI provides a comprehensive coverage of a broad range of symptoms associated with tinnitus perception and an overall measure of tinnitus severity.[28] The 25 items on the TFI are scored into eight functional subscales (i.e., intrusiveness, sense of control, cognition, sleep, auditory, relaxation, QOL, emotional distress). Items were rated on a 0 to 10 scale. The total TFI score was calculated by summing all of the valid responses, dividing by the number of valid responses, and multiplying by 10. TFI scores can range from 0 to 100 with a higher score indicating a greater impact of tinnitus on daily functioning. Scores are grouped into the following categories: 0–17 is classified as not a problem, 18–31

as a small problem, 32–53 as a moderate problem, 54–72 as a big problem and 73–100 as a very big problem. A score of >25 indicates the need for referral and intervention.[28]

Analysis

Determination of pre- and post-categorizations of hearing loss and tinnitus

—Survivors who responded yes to the self-report questions regarding hearing loss and tinnitus were categorized as having these symptoms prior to the study visit. Following the study visit (i.e., post-categorization), to adjust for age- and gender-related changes in hearing, each survivor's audiogram was evaluated using the National Health and Nutrition Examination Survey (NHANES)-modified Occupational Safety and Health Administration (OSHA) age adjustment standards.[29 30] A survivor was classified as having hearing loss if at any frequency they scored poorer than the 50th percentile for their age and gender.

Because tinnitus can only be evaluated using subjective measures, survivors were categorized as having tinnitus if they reported that they were consciously aware of their tinnitus for ≥10% of their time awake. This categorization of tinnitus is conservative given that the Tinnitus Research Initiative defines the occurrence of tinnitus as being present at least 5 minutes per day for 4 days per week.[31]

Data analysis—Study data were collected and managed using the Research Electronic Data Capture (REDCap) system hosted at UCSF.[32] REDCap is a secure, web-based software platform designed to support data capture for research studies. Data were analyzed using SPSS Version 28 (IBM Corporation, Armonk, NY). Differences among the three chemotherapy groups (i.e., only platinum, only taxane, or both platinum and taxane) in demographic and clinical characteristics and occurrence and impact of hearing loss and tinnitus were evaluated using parametric and non-parametric tests. A p-value of <.05 was considered statistically significant. Post hoc contrasts were done using a Bonferroni corrected p-value of <0.017 (i.e., .05/3 possible pairwise contrasts).

RESULTS

In this study that evaluated 273 survivors, 12.8% had received only a platinum-containing regimen, 56.8% a taxane-containing regimen, and 30.4% a platinum- and taxane-containing regimen.

Demographic and clinical characteristics

As shown in Table 1, no differences were found among the three chemotherapy groups for the majority of the demographic and clinical characteristics. Compared to the only platinum group, survivors in the other two groups were more likely to be female, less likely to have gastrointestinal or lung cancer, and had a higher number of prior cancer treatments. Compared to the only taxane group, survivors in the both platinum and taxane group had fewer years since their cancer diagnosis and had a higher number of metastatic sites.

Ototoxicity

As shown in Figure 1A, no differences were found among the three chemotherapy groups in the occurrence rates for self-reported hearing loss prior to the study visit (p=0.861). Across the three chemotherapy groups, the occurrence of self-reported hearing loss ranged from 30.5% (both platinum and taxane) to 34.3% (only platinum).

As shown in Figure 1B, no differences were found among the three chemotherapy groups in the occurrence of audiogram confirmed hearing loss (p=0.104). Across the three chemotherapy groups, post-categorization occurrence rates for audiogram confirmed hearing loss ranged from 52.3% (only taxane) to 71.4% (only platinum).

As shown in Table 2, no differences were found among the three chemotherapy groups in the HHIA subscale and total scores, categorization of degree handicap associated with hearing loss, or the use of hearing aids. Of the total sample, 25.4% self-reported hearing loss that was confirmed on audiogram; 31.0% self-reported that they did not have hearing loss that was found on audiogram; 7.4% self-reported hearing loss that was not confirmed on audiogram, and 36.2% self-reported that they did not have hearing loss and no hearing loss was found on audiogram.

Tinnitus

As shown in Figure 2A, no differences were found among the three chemotherapy groups in the occurrence rates for tinnitus prior to the study visit (p=0.707). Across the three chemotherapy groups, the occurrence of tinnitus ranged from 40.3% (only taxane) to 45.7% (only platinum).

As shown in Figure 2B, no differences were found among the three chemotherapy groups in the post-categorization occurrence rates for tinnitus (p=0.951). Across the three chemotherapy groups, post-categorization occurrence rates for tinnitus ranged from 37.1% (only platinum) to 40.0% (only taxane).

As shown in Table 2, except for the subscale sense of control, no differences were found among the three chemotherapy groups in the TFI subscale and total scores or the categorization of the problems associated with tinnitus.

DISCUSSION

This study is the first to evaluate for differences in the occurrence and effects of hearing loss and tinnitus in a large sample of cancer survivors with primarily breast, gastrointestinal, gynecologic, and lung cancers who received only a platinum, only a taxane, or a combination chemotherapy regimen. Contrary to our a priori hypothesis, the occurrence rates for and impact of these two neurotoxicities were similar across all three chemotherapy regimens. Equally important, except for cancer diagnosis and gender, for the majority of the demographic and clinical characteristics, no differences were found among the three chemotherapy groups. As expected, a higher percentage of survivors with gastrointestinal cancer received a platinum containing regimen; survivors with breast cancer received either platinum alone or a combination regimen; and survivors with gynecologic cancers received

a combination regimen. The higher percentages of women in the only taxol and combination regimen groups align with the differences in cancer diagnoses. Given that no differences were found among the three chemotherapy groups for the occurrence and impact of both hearing loss and tinnitus, it is reasonable to suggest that common mechanistic pathway(s) may underlie the development of both neurotoxicities.

Hearing loss

According to the US Preventive Services Task Force,[33] 16% of adults 18 years of age or older in the United States report difficulty hearing. However, as noted in one study,[34] the prevalence of perceived hearing loss increases with age with 43% of adults ≥70 years of age reporting hearing loss compared to 19% of adults aged 40 to 69 years and 5.5% of individuals aged 18 to 39 years. While the overall prevalence of chemotherapy-induced ototoxicity is unknown, not unexpectedly, the self-reported prevalence rate for hearing loss in our sample with an average age of 61.1 (±11.9) years ranged from 30.5% to 34.3%. Equally important and consistent with previous work that demonstrate that self-reported hearing loss has very poor concordance with hearing loss determined by pure tone audiometry,[35] the occurrence rates for hearing loss increased to between 52.3% and 71.4% when it was confirmed using age- and gender-adjusted audiographic norms.[29] Given that our study is the first to report these high rates of hearing loss in cancer survivors with the most common solid tumors and chemotherapy regimens; that a significant percentage of survivors are underestimating the occurrence of hearing loss; that these auditory deficits are not reversible; and that only 17.2% of our sample was using a hearing aid, oncology clinicians need to assess for hearing loss prior to and during chemotherapy and make appropriate referrals for an audiogram and follow-up.

In addition to the audiometric assessment, the impact of hearing loss, which does not always correlate with audiometric assessments,[36] was evaluated using the HIAA for the first time on oncology patients. Our mean total HIAA scores are comparable to scores (i.e., 23.9 to 26.8) reported by a sample of adults with hearing loss (mean age 65.1 years) who were living in urban and rural parts of Alabama.[37] In contrast, our scores are higher than scores (i.e., 5.6 to 7.7) reported by a sample of German adults between 55 and 81 years of age with different degrees of hearing loss.[38] Of note, 47.1% of our sample who self-reported hearing loss had HHIA scores that indicated a moderate to severe handicap from this neurotoxicity. While the mechanisms for hearing loss associated with chemotherapy, particularly for the taxanes[20] and combination regimens, are not completely understood, given that no differences were found among out three chemotherapy groups in any of the objective and subjective measures, these findings suggest that common mechanistic pathway(s) may underlie this neurotoxicity.

Compared to the general population rate for tinnitus of between 10% and 15%,[39] in oncology, the rates of 19% to 42% were reported specifically for patients with testicular cancer who received platinum.[13] Using a conservative estimate, our study is the first to report prevalence rates for clinically meaningful levels of tinnitus that ranged from 37.1% (only platinum) to 40.0% (only taxane) across three chemotherapy regimens in patients with breast, gastrointestinal, gynecologic, and lung cancers. Similar to the HHIA, this study is

the first to report findings on the TFI in oncology patients. The total TFI score for our entire sample (i.e., 18.7 (±17.7)) is slightly higher than TFI total scores (i.e., 16.6 (±21.8)) reported by individuals with tinnitus who were drawn from the general population in the Netherlands.[40] Equally important, similar to this Dutch study,[40] 20.2% of our survivors had a small problem with tinnitus and 19.3% had moderate to very big problems with tinnitus. While the mechanisms that underlie tinnitus are not well understood, similar to hearing loss, given that no differences were found among out three chemotherapy groups in the occurrence rates for and impact of tinnitus, these findings suggest that common mechanistic pathway(s) may underlie this neurotoxicity.

Some limitations warrant consideration. While age and gender were controlled for in our evaluation of the audiograms, given that the sample was primarily female, White, and well-educated, our findings may not generalize to all cancer survivors. In addition, given the cross-sectional design, future studies need to evaluate for hearing loss and tinnitus across the continuum of cancer care.

Given that the primary focus of previous studies was on the ototoxic effects of platinum-containing regimens, the findings from this study demonstrate that similar occurrence rates and impact exist for hearing loss and tinnitus across regimens that use only platinum, only taxanes, or combinations of the two drugs for some of the most common solid tumors. Given the paucity of research on the mechanisms that underlie chemotherapy-induced ototoxicity, our findings suggest that common underlying mechanisms for both hearing loss and tinnitus warrant evaluation in preclinical and clinical studies.

Acknowledgements:

Recruitment was facilitated by Dr. Susan Love Foundation’s Love Research Army® Program.

Funding:

This study was funded by the National Cancer Institute (NCI, CA151692) and the American Cancer Society (ACS). Dr. Miaskowski is an American Cancer Society Clinical Research Professor. This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Key Message Box

What is already known on this topic

Hearing loss occurs with platinum.

Ocurrence of tinnitus is unknown.

What this study adds

>50% of survivors of the most common cancers have hearing loss.

>35% of survivors of the most common cancers have tinnitus.

No differences in symptom occurrence rates with single or combination regimens.

How this study might affect research, practice, or policy

Survivors receiving neurotoxic chemotherapy should be screened for hearing loss and tinnitus on a routine basis

Survivors with hearing loss should have an audiogram to evaluate the need for a hearing aid

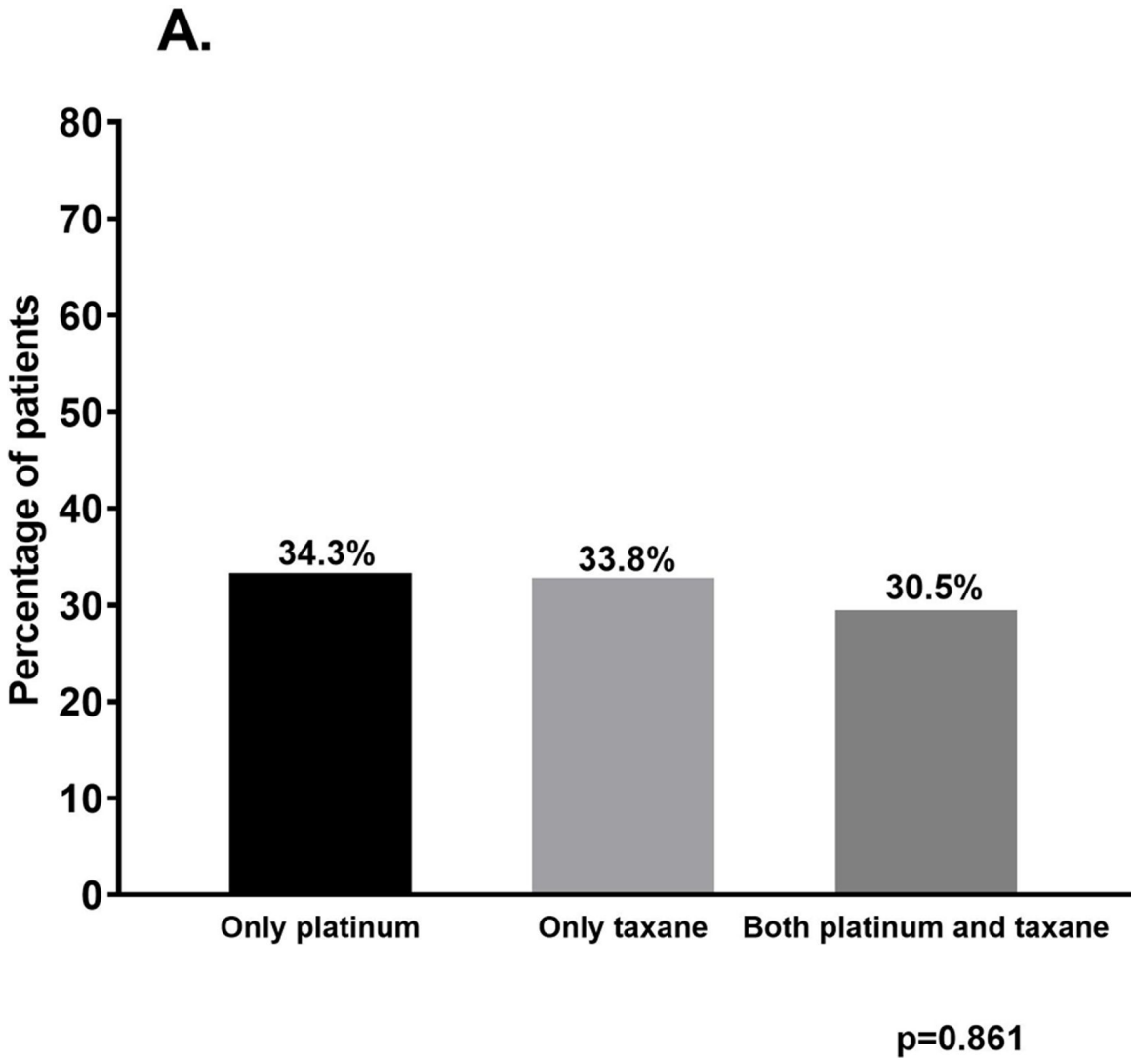

Figure 1A –.
Differences in the percentage of survivors who self-reported hearing loss across the three chemotherapy regimens (p=0.861).

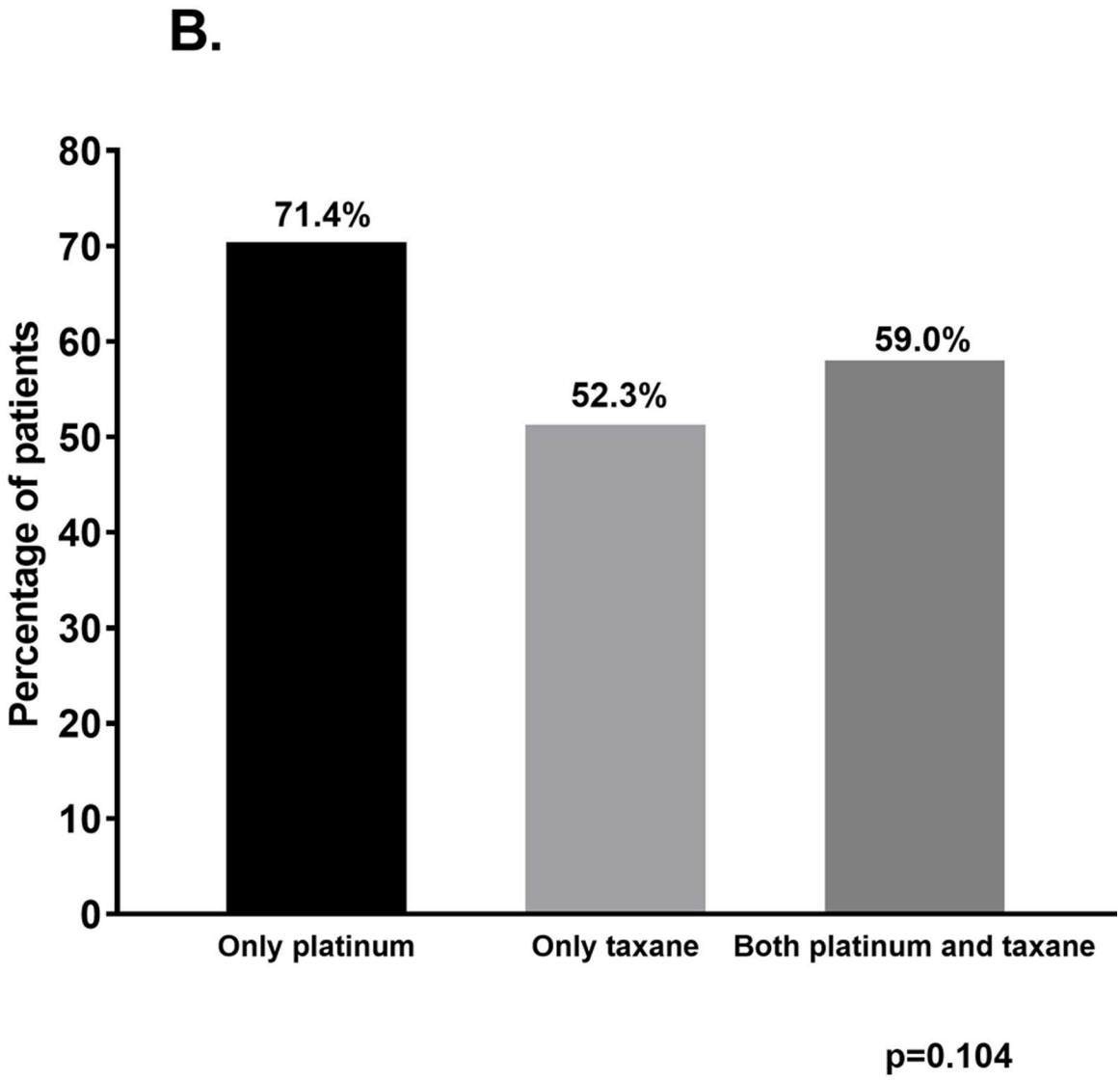

Figure 1B –.

Differences in the percentage of survivors with audiogram-confirmed hearing loss across the three chemotherapy regimens (p=0.104).

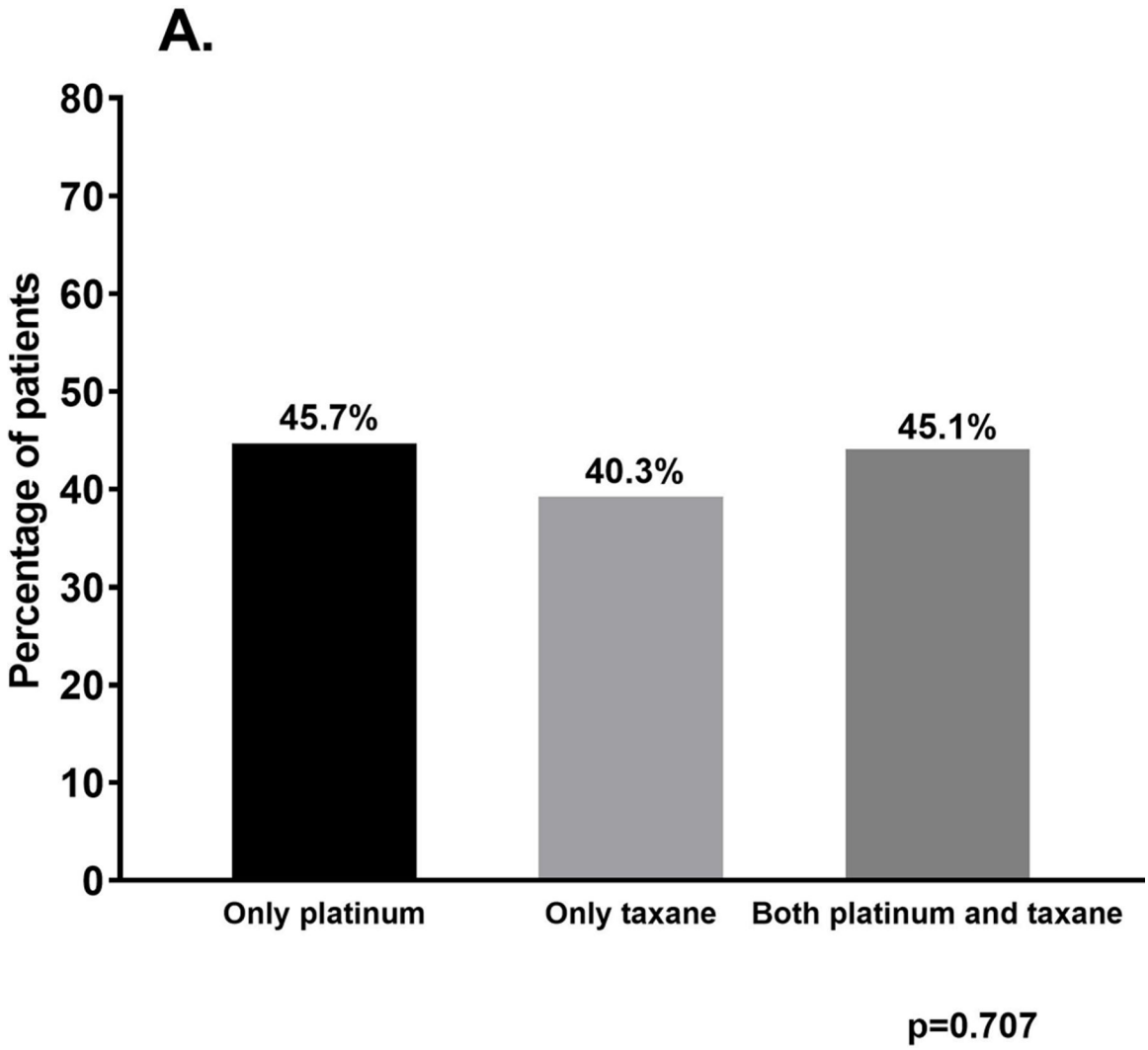

Figure 2A –.

Differences in the percentage of survivors who self-reported tinnitus across the three chemotherapy regimens (p=0.707).

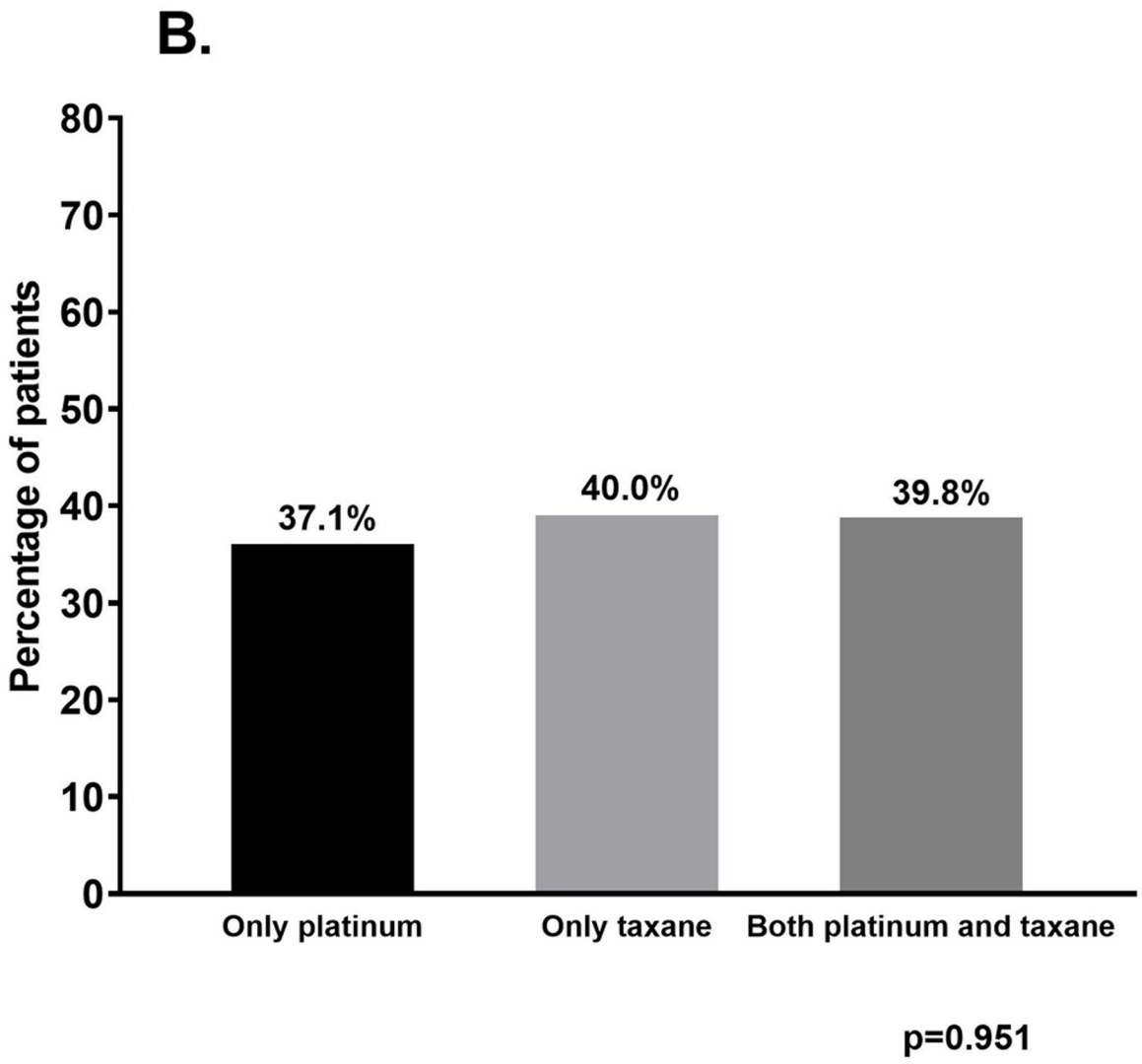

Figure 2B –.

Differences in the percentage of survivors with tinnitus defined as the occurrence of tinnitus being present at least 5 minutes per day for 4 days per week across the three chemotherapy regimens (p=0.951).

Table 1 –

Differences in Demographic and Clinical Characteristics Among the Chemotherapy Regimen Groups

Characteristic	Only Platinum (1) 12.8% (n=35)	Only Taxane (2) 56.8% (n=155)	Both Platinum and Taxane (3) 30.4% (n= 83)	Statistic, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	63.5 (15.0)	60.3 (11.2)	61.6 (11.7)	F=1.16, p=.315
Education (years)	15.8 (2.1)	16.3 (2.5)	16.4 (2.2)	F=0.83, p=.437
Body mass index (kilograms/meter squared)	25.7 (4.9)	27.8 (6.4)	27.8 (7.9)	F=1.56, p=.212
Karnofsky Performance Status score	85.2 (13.3)	87.7 (9.8)	86.8 (10.8)	F=0.81, p=.446
Number of comorbidities	2.0 (1.4)	1.7 (1.5)	1.9 (1.4)	F=0.96, p=.385
Self-Administered Comorbidity Questionnaire score	4.3 (3.2)	3.6 (3.7)	3.9 (3.1)	F=0.60, p=.552
Years since cancer diagnosis (mean)	6.0 (5.9)	9.0 (7.3)	6.2 (5.6)	F=6.15, p=.002 2 > 3
Years since cancer diagnosis (median)	3.9	6.7	4.8	KW=15.13, p<.001 2 > 1 and 3
Number of prior cancer treatments	2.4 (0.7)	3.2 (0.7)	3.2 (0.9)	F=16.64, p<.001 1 < 2 and 3
Number of current cancer treatments	0.1 (0.3)	0.6 (0.6)	0.4 (0.5)	F=9.56, p<.001 1 < 2
Number of metastatic sites (out of 7)	0.9 (0.8)	0.7 (0.8)	1.0 (1.0)	F=3.47, p=.033 2 < 3
Number of metastatic sites without lymph node involvement (out of 6)	0.3 (0.6)	0.2 (0.5)	0.5 (0.8)	F=7.18, p<.001 2 < 3
Dose of platinum compounds for patients who received only a platinum (mg/m^2)	754.9 (503.0)	n/a	n/a	n/a
Dose of taxane compounds for patients who received only a taxane (mg/m^2)	n/a	717.8 (766.1)	n/a	n/a
Dose of drugs for patients who received both a platinum and a taxane compound				
Platinum dose (mg/m^2)	n/a	n/a	1929.9 (688.0)	n/a
Taxanedose (mg/m^2)			874.2 (759.5)	

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Characteristic	Only Platinum (1) 12.8% (n=35)	Only Taxane (2) 56.8% (n=155)	Both Platinum and Taxane (3) 30.4% (n= 83)	Statistic, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
	% (n)	% (n)	% (n)	
Female (% yes)	57.1 (20)	95.5 (147)	96.4 (80)	X^2=54.60, p<.001 1 < 2 and 3
Married/partnered (% yes)	65.7 (23)	66.5 (103)	65.4 (53)	X^2=0.03, p=.987
Lives alone (% yes)	26.5 (9)	24.0 (37)	29.3 (24)	X^2=0.77, p=.680
Employed	37.1 (13)	56.2 (86)	41.5 (34)	X^2=7.01, p=.030 no significant pairwise contrasts
Ethnicity				
White	82.9 (29)	65.8 (102)	76.8 (63)	X^2=12.35, p=.136
Black	2.9 (1)	3.9 (6)	2.4 (2)	
Asian or Pacific Islander	5.7 (2)	12.3 (19)	14.6 (12)	
Hispanic	5.7 (2)	7.1 (11)	4.9 (4)	
Mixed or Other	2.9 (1)	11.0 (17)	1.2 (1)	
Annual household income				
<$20,000	5.7 (2)	6.7 (10)	3.9 (3)	KW=2.81, p=.246
$20,000 - $59,999	28.6 (10)	20.1 (30)	28.6 (22)	
$60,000 - $99,999	28.6 (10)	18.1 (27)	20.8 (16)	
>$100,000	37.1 (13)	55.0 (82)	46.8 (36)	
Child care responsibilities (% yes)	2.9 (1)	22.9 (33)	12.5 (10)	X^2=9.46, p=.009 1 < 2
Adult care responsibilities (% yes)	2.9 (1)	9.1 (13)	8.8 (7)	X^2=1.44, p=.488
Smoker (ever)	45.2 (14)	37.7 (57)	27.8 (22)	X^2=3.61, p=.165
Comorbid conditions (% yes)				
Osteoarthritis	29.4 (10)	33.1 (51)	35.4 (28)	X^2=0.40, p=.820
Back pain	38.2 (13)	31.1 (47)	29.1 (23)	X^2=0.93, p=.627

Characteristic	Only Platinum (1) 12.8% (n=35)	Only Taxane (2) 56.8% (n=155)	Both Platinum and Taxane (3) 30.4% (n= 83)	Statistic, p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Depression	14.7 (5)	17.0 (26)	18.2 (14)	X^2=0.20, p=.904
High blood pressure	17.6 (6)	28.9 (44)	25.6 (21)	X^2=1.87, p=.393
Heart disease	14.7 (5)	2.6 (4)	3.8 (3)	X^2=9.75, p=.008 1 > 2
Diabetes	9.1 (3)	4.6 (7)	5.1 (4)	X^2=1.11, p=.574
Lung disease	11.8 (4)	2.6 (4)	6.2 (5)	X^2=5.60, p=.061
Anemia or blood disease	0.0 (0)	5.2 (8)	6.1 (5)	X^2=2.1, p=.357
Ulcer or stomach disease	3.0 (1)	3.9 (6)	2.5 (2)	X^2=0.32, p=.853
Kidney disease	0.0 (0)	0.6 (1)	0.0 (0)	X^2=0.75, p=.687
Liver disease	3.1 (1)	1.3 (2)	0.0 (0)	X^2=2.11, p=.348
Rheumatoid arthritis	9.4 (3)	3.4 (5)	5.0 (4)	X^2=2.19, p=.335
Type of cancer				X^2=267.41, p<.001
Breast	0.0 (0)	95.5 (148)	51.8 (43)	1 < 3 < 2
Gastrointestinal	68.6 (24)	0.6 (1)	4.8 (4)	1 > 2 and 3
Gynecological	5.7 (2)	0.0 (0)	38.6 (32)	2 < 1 < 3
Lung	14.3 (5)	0.0 (0)	1.2 (1)	1 > 2 and 3
Other	11.4 (4)	3.9 (6)	3.6 (3)	NS
Any metastatic disease (% yes)	68.6 (24)	52.8 (89)	64.2 (52)	X^2=1.70, p=.428
Patients who had a dose reduction or delay due to neuropathy (% yes)	35.3 (6)	21.5 (17)	23.2 (13)	X^2=1.48, p=.477

Abbreviations: KW=Kruskal-Wallis test, mg = milligrams, m^2 = meters squared, SD = standard deviation

Table 2 –

Differences in Hearing and Tinnitus Characteristics Among the Chemotherapy Regimen Groups

Characteristic*	Only Platinum (1)	Only Taxane (2)	Both Platinum and Taxane (3)	Statistic, p-value
Hearing Handicap Inventory Adult Scores	Mean (SD)	Mean (SD)	Mean (SD)	
Social-situational (0 – 48)	14.1 (6.1)	9.9 (8.9)	10.4 (8.5)	F=1.10, p=.339
Emotional (0 – 52)	12.5 (7.8)	10.0 (10.0)	9.4 (8.2)	F=0.45, p=.640
Total score (0 – 100)	26.6 (12.4)	19.9 (18.2)	19.6 (15.1)	F=0.78, p=.460
	% (n)	% (n)	% (n)	
Hearing Handicap Inventory Adult Categorization				
No handicap (0 – 16)	18.2 (2)	56.9 (29)	60.0 (15)	X^2=6.31, p=.177
Moderate handicap (18 – 42)	54.5 (6)	31.4 (16)	28.0 (7)	
Significant handicap (>44)	27.3 (3)	11.8 (6)	12.0 (3)	
Wear a hearing aid (% yes)	16.7 (2)	21.6 (11)	8.3 (2)	X^2=2.01, p=.367
Tinnitus Functional Index Scores (all 0 to 100)	Mean (SD)	Mean (SD)	Mean (SD)	
Intrusive	25.4 (20.4)	33.0 (22.5)	29.7 (23.6)	F=0.78, p=.460
Sense of control	24.4 (20.2)	42.8 (26.4)	27.0 (24.6)	F=6.25, p=.003 2 > 1 and 3
Cognitive	10.8 (10.1)	16.9 (22.6)	12.8 (16.2)	F=0.90, p=.408
Sleep	9.2 (10.4)	18.0 (27.2)	15.4 (22.5)	F=0.87, p=.422
Auditory	17.9 (22.3)	16.9 (23.4)	12.0 (15.6)	F=0.73, p=.485
Relaxation	12.1 (16.8)	22.7 (28.8)	18.4 (23.8)	F=1.16, p=.317
Quality of life	7.2 (8.3)	9.6 (17.8)	7.6 (12.7)	F=0.27, p=.763
Emotional	6.3 (7.7)	13.9 (20.0)	11.8 (16.5)	F=0.78, p=.460
Total score	13.9 (11.7)	21.2 (19.8)	16.6 (15.7)	F=1.49, p=.231

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Characteristic*	Only Platinum (1)	Only Taxane (2)	Both Platinum and Taxane (3)	Statistic, p-value
	% (n)	% (n)	% (n)	
Tinnitus Functional Index Categorization				
No problem (0 – 17)	56.3 (9)	58.1 (36)	66.7 (24)	
Small problem (18 – 31)	37.5 (6)	19.4 (12)	13.9 (5)	
Moderate problem (32 – 53)	6.3 (1)	12.9 (8)	13.9 (5)	X^2=7.37, p=.497
Big problem (54 – 72)	0.0 (0)	4.8 (3)	5.6 (2)	
Very big problem (73 – 100)	0.0 (0)	4.8 (3)	0.0 (0)	

Abbreviations: SD = standard deviation

* Hearing Handicap Inventory Adult and Tinnitus Functional Index were completed only by survivors who reported hearing loss and/or tinnitus at enrollment.