Cancer survivors treated with platinum-based chemotherapy affected by ototoxicity and the impact on quality of life: a narrative synthesis systematic review

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ABSTRACT

Objective: To identify any change in quality of life (QoL) caused by chemotherapy-induced toxicities, such as hearing loss and tinnitus, to provide information in order to improve services and aid clinicians in their decision-making.

Design: This systematic review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist. The search terms were cancer, platinum-based chemotherapy, ototoxicity and “quality of life”. Titles and abstracts, followed by full texts, were screened by two independent researchers. The relevant data were extracted and quality analysis was performed using the NIH Quality Assessment Tool.

Study sample: About 308 titles and abstracts were screened, and 27 full-text articles were screened. Ten articles representing 11 studies were included in the review. Study design included cross-sectional studies, randomised control trials and longitudinal studies.

Results: Diagnostic criteria consisted of audiograms, questionnaires and patient complaints. The study quality ranged from 21.43% to 85.71%. Overall results found that those treated with cisplatin had more hearing loss and tinnitus than those treated with other therapies. Furthermore, those with hearing loss and tinnitus were more likely to have a lower QoL.

Conclusions: There is an urgent need to standardise diagnostics when investigating ototoxicity and its effect on QoL, particularly for research into risk factors, prevention and management.

Introduction

Cancer continues to be a life-altering diagnosis, however, due to medical advances, there has been an overall decline of 26% in cancer deaths within the past two decades (Siegel, Miller, and Jemal 2018). Treatment effects, though, can often cause long-term physical and psychological challenges for survivors (Skalleberg et al. 2017; Alfano and Rowland 2006). For this reason, there is a requirement to look into how these long-term effects impact (QoL) for those who are adapting to a life with and beyond cancer.

Platinum-based chemotherapy is typically used to treat most solid tumours, including breast, testicular and ovarian cancers (Oun, Moussa, and Wheate 2018; Theile 2017; Kelland 2007). Due to its cost-effective systematic and cytotoxic effects, it has been one of the most efficient and widely available chemotherapies (Paken et al. 2016). However, it is widely known that platinum-based chemotherapy can cause ototoxicity (Campbell and Le Prell 2018; Saladin et al. 2015). Ototoxicity refers to any hearing deficit or tinnitus resulting from a temporary or permanent inner ear dysfunction, following treatment with an ototoxic drug (Paken et al. 2016). Ototoxic drugs include aminoglycoside antibiotics such as gentamicin, loop diuretics such as torasemide and neurologic drugs, such as sodium valproate (Bisht and Bist 2011). Ototoxic effects commonly manifest as tinnitus and/or high-frequency hearing loss that can later progress to lower frequencies (Waissbluth, Peleva, and Daniel 2017). Both tinnitus and hearing loss are associated with a higher risk of depression, social isolation, anxiety (Nordvik et al. 2018) and dementia (Gurgel et al. 2014; Deal et al. 2016).

It may not be possible to identify the specific time point during treatment at which an effect first appears, making it challenging to determine the causality and risk of each therapy received (Stein, Syrjala, and Andrykowski 2008). For this reason, literature reporting adverse health effects associated with chemotherapy can be imprecise and lacking in detail.

Furthermore, collating systematic evidence on adverse effects can be difficult. Specific toxicities are rarely included in keywords, titles or abstracts. To overcome this challenge, a compromise between sensitivity and precision must be made when performing a systematic search (Golder and Loke 2009).
To date, there have been no systematic reviews carried out exploring the impact on quality of life (QoL) from platinum-based chemotherapy-induced ototoxicity.

Materials and methods

Eligibility criteria

The four themes that had to be present in an article were: any mention of cancer, platinum-based chemotherapy, ototoxicity and QoL. Known key articles were checked in the searches to ensure all relevant articles were included in the search. There was no limitation on the date range of this search.

The inclusion criteria consisted of: any combination of treatments which included platinum-based chemotherapy for curative intent, any type of formal QoL assessment, any type of formal hearing loss and/or tinnitus assessment, written in the English language, any study design providing the relevant results were obtained after treatment and any cancer type other than head and neck. Any paediatric study was excluded, in addition to review articles, grey literature and both in vitro and in vivo studies.

Information sources

This systematic review was conducted following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist. Due to the nature of this systematic review and the difficulties in searching for adverse effects of chemotherapy, specificity and precision were optimised in order to capture the most relevant articles and reduce unrelated articles. The terms used were edited accordingly to meet the standards of each search engine.

Search engines used were OVIDSP, NCBI, Web of Science and Cochrane. Databases searched, therefore, consisted of Medline, PsycINFO and PsycARTICLES, Embase, PubMed, Web of Science Core Collection and the Cochrane Database.

Study selection

Titles and abstracts were imported to Endnote, duplicates were removed and the remainder were screened by two independent authors (SP and JT) against the eligibility criteria. Any disagreement was resolved by consensus. Full-text articles of potentially relevant papers were also assessed for eligibility, resolving any discrepancies by consensus.

Data extraction process

Determinants such as paper characteristics, type of study design, sample size, patient demographics and the measurements used and analysed, in addition to the results of the specific study, were all extracted. The information that could be compared across studies was then analysed accordingly, with the remaining information displayed as a description in order to capture the full results.

Risk of bias in individual studies

A quality assessment was carried out on each of the studies included in this review using a 14-item study quality assessment tool involving pre-defined principles, the NIH’s Quality Assessment Tools (NHLBI 2018). An item was scored 1 for matching the criteria, and scored 0 if it was not clear or did not match the criteria. Aggregate percentages were used to classify poor-quality (≤50%), and high-quality (>50%) studies. This tool was chosen based on a systematic review carried out by Mols et al. (2005). The tool was chosen as it assessed relevant aspects for each study type involved in this review. The high-quality and low-quality studies were grouped, and their results were compared to evaluate consistencies and anomalies.

Synthesis of results

Due to the heterogeneity of the results reported in this review, it was not possible to statistically combine the results. Therefore, a narrative analysis was carried out, and these descriptive results of each study were compared with one another.

Outcome measures from the studies were extracted and compared, including the diagnostic criteria and grading systems used.

Risk of bias across studies

The majority of the adverse effects within the studies were not clearly defined, therefore, the risk of bias between studies was relatively high. Moreover, not all diagnostic criteria were specified, meaning some studies reported presence of ototoxicity but did not clarify its severity or symptom characteristics, i.e. whether it was hearing loss or tinnitus. The non-randomised studies were also considered to carry a high risk of bias, as trials without blinding are prone to bias (Loke, Price, and Herxheimer 2007).

Results

Study selection

A total of 645 articles were identified through the database searches performed. From this, 337 articles were excluded due to duplications, grey literature and there being no abstracts available. The resulting 308 titles and abstracts were screened. The screening procedure can be seen in Figure 1.

Study characteristics

The following study characteristics were extracted, as shown in Table 1: location of study, type of study design, population characteristics, number of participants, number of participants treated with platinum-based chemotherapy, diagnostic measurements for ototoxicity, hearing loss, tinnitus and QoL, type of platinum-based chemotherapy, follow-up period, main objective of study and a descriptive summary of the study.

There were six cross-sectional studies included in this systematic review, each with variable timeframes since diagnosis (Bentzen et al. 2013; Bokemeyer et al. 1996; Calhoun et al. 1998; Miaskowski et al. 2018a, 2018b, 2018c). In total, 856 participants were included; 565 of these received platinum-based chemotherapy. Two randomised control trials compared cisplatin-based regimens with other types of treatments and included 553 patients, with 313 of these having a platinum-based treatment (Bezjak et al. 2008; Saad, Ghali, and Shawki 2017). Only one longitudinal study was included in this systematic review, following 666 patients with metastatic testicular cancer on two different
cisplatin regimens, with 286 (52%) being followed up at 2 years (Fosså et al. 2003). Finally, one paper involved two separate pilot studies on low-stage testicular cancer survivors from Norway and the UK (Fossa and Foss 1996). This study involved comparing opinions on toxicities of those treated with infradiaphragmatic radiotherapy, cisplatin or surveillance and the opinions of a variety of healthcare professionals. From the 309 participants involved, 71 of this received cisplatin.

Most did not report the demographics within each comparison group, but as a whole. For example, the Bentzen et al. paper describes patient characteristics as 79% women and 21% men, with a median age of 61, and a range of 40–89 years old for survivors who responded to the survey (Bentzen et al. 2013). Although the information contains those treated with cisplatin ($n = 56$), it is not possible to isolate the gender split and age range of this exact subgroup.

Eight of the studies included cisplatin as the platinum-based chemotherapy, and three of the studies carried out by Miaskowskind colleagues do not specify which platinum-based chemotherapy was used (Miaskowski et al. 2018a, 2018b, 2018c). Only one study investigated the difference between carboplatin and cisplatin (Saad, Ghali, and Shawki 2017). Moreover, only one study compared the toxicities with those treated with cisplatin to the normal population (Bentzen et al. 2013).

**Risk of bias**

The NIH Quality Assessment Tool (NHLBI 2018) was used to assess each of the individual studies. The appraisal criteria involved answering 14 binary questions on the quality of the article. Table 2 displays the quality score for each assessment and the quality percentage calculated, with green being a good-quality study and red being a poor-quality study. Those with a score of $>50\%$ ($n = 7$) were classed as a high-quality study, and those $\leq 50\%$ ($n = 4$) were classed as a poor-quality study. The studies
| Author (year) | Cancer type | Platinum-based chemotherapy | Number of patients total (number of patients receiving platinum-based chemotherapy) | Time of evaluation following treatment | Patient characteristics | Control | Location |
|---------------|-------------|-----------------------------|---------------------------------------------------------------------------------|--------------------------------------|------------------------|---------|----------|
| Cross-sectional studies | Bentzen et al. (2013) | Squamous cell carcinoma of anal region | Cisplatin v non-cisplatin 128 (56) | ≥2 years | Patients diagnosed between 2000 and 2007 with curative intent. Those treated with cisplatin had >200 mg/m². The median time since diagnosis was 66 months (range 25–112). | Age/sex matched the participants to the normal population (n = 269). | Norway |
| Bokemeyer et al. (1996) | Testicular cancer | A mixture of different chemotherapy cocktails containing cisplatin (P): PVB, PEB, PEBVc, P(high dose)EB, PVB/PE 90 (90) | Median of 58 months (range 12–159 months) | Cancer survivors in remission for 12 months. The median age of diagnosis was 28 (range 19–53). The median follow up was 53 months (range 15–159). | Participants grouped in terms of treatment (PVB, PEB, PEBVc, P(high dose)EB, PVB/PE) and compared. | Germany |
| Calhoun et al. (1998) | Advanced-stage ovarian cancer | A minimum of 6 cisplatin cycles 15 (15) | Mean 6.6 years (range 2.5–12 years) | Cancer patients with a mean age of 61.3 years (range 44–87) who had been living with cancer for a mean of 6.6 years (range 2.5–12 years). | Gynaecologic oncologists (n = 10). | USA |
| Miaskowski et al. (2018a, 2018b, 2018c) | Various | Platinum-based chemotherapy (PBC) 623 (404) | ≥3 months | Cancer survivors treated with PBC 3+ months from their last cycle and had scale 3 or above on CIPN score. N = 623 (68.4% had CIPN). | Cancer survivors treated with PBC, 3+ months since last cycle and no reports in CIN, hearing loss or tinnitus. | San Francisco, USA |
| Various | Platinum-based chemotherapy (PBC) | 623 (371) | ≥3 months | Cancer survivors treated with PBC 3+ months following their last cycle who reported hearing loss, Tinnitus and/or CIN (n = 371). | A comparison of cancer survivors reporting tinnitus, hearing loss, hearing loss and CIN, hearing loss and tinnitus and CIN. | San Francisco, USA |
| Various | Platinum-based chemotherapy (PBC) | 623 (85) | ≥3 months | Cancer survivors treated with PBC 3+ months following their last cycle who reported hearing loss, Tinnitus and CIN (n = 85). | Cancer survivors without any signs of CIN. | San Francisco, USA |
| RCT | Bezjak et al. (2008) | Early stage NSCLC | Adjuvant chemotherapy (4 cycles of cisplatin and vinorelbine) vs. observation Month 0: 482 (2422), month 36: 89 (50) | Intervals at 5, 9 and 12 weeks and at 6, 9, 12, 18, 24, 30 and 36 months | Cancer patients, 65% male, median 61 years, followed up at 0 and 36 months following treatment. | Cancer patients treated with observation (n = 240 at month 0, n = 39 at month 36). | Canada |
| Author (year) | Cancer type | Platinum-based chemotherapy | Number of patients total (number of patients receiving platinum-based chemotherapy) | Time of evaluation following treatment | Patient characteristics | Control | Location |
|--------------|-------------|-----------------------------|--------------------------------------------------------------------------------|----------------------------------------|------------------------|---------|----------|
| Saad, Ghali, and Shawki (2017) | Stage IV NSCLC | Gemcitabine and carboplatin vs. gemcitabine and cisplatin | 71 (36 cisplatin, 35 carboplatin) | At cycle 3 and 6 of treatment | Patients with stage IV NSCLC excluding grade 3+ neuropathy, 55% <55 years and 77.9% male. 44 patients had multiple sites. | Cancer patients treated with cisplatin compared to carboplatin. | Egypt |
| Longitudinal | Fosså et al. (2003) | Metastatic testicular cancer | Cisplatin day 1 through 5 at 20 mg/m² vs. cisplatin days one through 3 at 50 mg/m² on days 1 and 2. | 666 (666) | Intervals at 3, 6, 12 and 24 months | Cancer patients, mean age 31, range 16–63, 286 (52%) followed up after 2 years. | Comparison between cisplatin regimes. | Norway, The Netherlands, Rotterdam, UK and Belgium |
| Pilot study | Fossa and Fossg (1996) | Low-stage testicular cancer | Surveillance vs. infradiaphragmatic radiotherapy vs. 2–6 cycles of cisplatin | 103 (45) | ≥3 months | Disease-free patient who had undergone treatment, stage 1 seminoma. | European urologists (n = 20), oncologists and radiotherapists (n = 13). | Norway/UK |
| Low-stage testicular cancer | Surveillance vs. infradiaphragmatic radiotherapy vs. 2 cycles of 100 mg/m² cisplatin. | 206 (26) | ≥3 months | 107 cancer survivors from Norway and 99 relapse-free patients from the UK. | Opinions from cancer survivors compared to opinions from doctors (n = 10). | Norway/UK |

Table 2. Displays the study and the critical appraisal score for each study, using the NIH Quality Assessment Tool.

| Author (year) | Bentzen et al. (2013) | Bokemeyer et al. (1996) | Calhoun et al. (1998) | Miaskowski et al. (2018a, 2018b, 2018c) | Bezjak et al. (2008) | Saad, Ghali, and Shawki (2017) | Fosså et al. (2003) | Fossa and Fossg (1996) |
|--------------|-----------------|-----------------|-----------------|-----------------|----------------|-----------------|----------------|----------------|
| Quality analysis | 7/14 | 9/14 | 7/14 | 10/14 | 10/14 | 9/14 | 11/14 | 9/14 |
| | 50.00% | 64.29% | 50.00% | 71.43% | 71.43% | 64.29% | 78.57% | 64.29% |
| | | | | | | | | 85.71% |
| | | | | | | | | 21.43% |
| | | | | | | | | 21.43% |

Using a traffic light system, green results represent a high score (good quality), amber a medium score and red results are poor quality scores.
were grouped according to quality to compare any differences in results and identify any contradicting information.

The papers with a quality score of \( \leq 50\% (n = 4) \) all compared opinions of patients and healthcare professionals. The papers concluded that most patients perceived the effects of ototoxicity as tolerable, whereas those in health professions perceived the toxicity to affect QoL. However, these studies were all based on hypothetical scenarios and not real-life experiences, therefore it could be hypothesised that patients may not realise the extent to which QoL can change when experiencing ototoxicity, compared to professionals. All but one study scoring \( >50\% \) concluded that QoL is indeed affected by tinnitus and/or hearing loss, adding that severity correlated with the dosage and number of cycles. However, one high-quality study carried out by Bezjack et al. (2008) found no difference in the QoL assessed across different treatments, regardless of experiencing ototoxicity. Yet, this study found that ototoxicity did indeed persist beyond treatment (Bezjak et al. 2008). There were no significant differences in results from the high-quality studies compared to the lower-quality studies.

**Results of the individual studies**

The data extracted in Table 3 demonstrates that there is no standardised outcome measurement used to assess ototoxicity. For example, many of the measurements used in the study analysed ototoxicity, yet did not specify or define ototoxicity. These studies could have measured either hearing loss or tinnitus. Furthermore, many studies did not consider the severity or grading of ototoxicity. One study did, however, perform pure tone audiometry with bone conduction thresholds on patients to assess the extent of their hearing loss (Bokemeyer et al. 1998).

The studies carried out by Miaskowski assessed eight aspects of QoL in addition to a questionnaire identifying the severity of hearing loss and the severity of tinnitus as separate items. Tinnitus was defined as “ringing or buzzing in the ears” (Miaskowski et al. 2018a, 2018b, 2018c). The studies compared those with hearing loss, tinnitus and neuropathy to those with just one of the toxicities and those with no toxicities. However, these studies do not report which platinum-based chemotherapy was used, the regimen used, the dosage or how many cycles each patient received.

**Discussion**

Overall, the results found that those treated with platinum-based chemotherapy, specific cisplatin, had significantly more hearing loss and tinnitus than the comparison population, with higher doses correlating to persisting symptoms. These results are corroborated by the wider literature, as it is reported that on average, 60–70% of adult patients experienced ototoxicity when treated with cisplatin (Chirtes and Albu 2016; Campbell and Le Prull 2018; Frisina et al. 2016; Travis et al. 2014). Tinnitus has also been reported in previous studies, particularly those with high doses of cisplatin (Campbell and Le Prull 2018). This review found that those with tinnitus and hearing loss were more likely to have a lower QoL.

It is common for there to be a reduction in QoL following the first three cycles of platinum-based chemotherapy in adults (Kalyanam et al. 2018). Furthermore, it is well documented that hearing loss negatively impacts mental wellbeing and QoL, although the use of hearing aids appear to improve general QoL within the first year, emphasising the importance of early and proper diagnosis (Hogan et al. 2015; Fellinger et al. 2007). Tinnitus has also been shown to be a significant burden on QoL and has a strong association with depression in the general population (Zeman et al. 2014; Nondahl et al. 2007). From this, it can be inferred that ototoxicity in cancer survivors can directly cause a reduction in QoL. However, due to the heterogeneity of the study designs and the lack of research carried out in this field, it cannot be categorically stated that this is true.

The studies included in this review were highly variable in both their methodology and results. The results clearly highlight the lack of standardisation in reporting QoL and ototoxicity diagnostics. Furthermore, the lack of grading means that individuals could be suffering from ototoxic effects and it not be reported adequately in study settings, or the opposite, where the reporting overestimates the ototoxic effect. Therefore, it is difficult to assess the strength of the results as a whole, as the nature of this field is heterogeneous. The lack of standardised diagnostic and grading systems is the most significant weakness in the reviewed studies. By pooling together similar data and carrying out a meta-analysis, powerful information could be identified and published, which in turn will help inform and develop better care and management for those experiencing ototoxicity. This research has typically consisted of a multitude of small-scale studies looking into different factors, making it difficult to compare information statistically. However, the information and data regarding genetic susceptibilities of ototoxicity have been statistically systematically analysed. Studies of high-quality and large population sizes have found that between 29% and 40% of testicular cancer patients have an ototoxic phenotype (Wheeler et al. 2015). Furthermore, a meta-analysis of phenotypes have found a multitude of genes, including those that play a role in calcium homeostasis and are associated with an increased risk of ototoxicity (Tserga et al. 2019).

Audiometry is a standardised and widely available method for quantifying hearing status. There are also a variety of validated tinnitus questionnaires that are used clinically for diagnosing and quantifying tinnitus severity readily available. Ideally, it should be clinical practise that in the event a patient presents with ototoxicity that these assessments be carried out. However, because chemotherapy is associated with many acute and life-threatening side effects, it is unrealistic and time-consuming to have measurement tools for each individual and specific side effect. However, it is of high clinical importance for the dose-limiting or permanent side effects to be identified and managed. For this reason, questionnaires such as the scale for chemotherapy-induced long-term neurotoxicity (SCIN) which group together the neurotoxic side effects are well-used outcome measures (Oldenburg et al. 2006). These type of assessments, although more time-efficient, lack collecting valid information. For example, the questions are vague and do not allow clinicians to differentiate one toxicity from another, meaning the management and support offered is not useful. Another example of this is the holistic needs assessment (HNA), which asks if “you have had any change in sight or hearing” (Wells, Semple, and Lane 2015; Biddle et al. 2016). This, although helpful in developing a tailored care plan, does not identify specific side effects, the severity of them or if it affects QoL. Furthermore, by identifying a change in hearing and/or sight, it is unclear which specialist the patient should be referred to, an optician or an audiologist? Therefore, the balance between not overwhelming a patient, yet also collecting reliable and detailed information about their side effects appears a seemingly impossible challenge. This has been highlighted regularly in literature, with many new proposals on
Table 3. Displays the results extracted from the individual studies in the systematic review.

| Author                  | Aim of study                                                                 | Outcome measures                                      | Quality of life | Other Results                                                                 |
|-------------------------|------------------------------------------------------------------------------|-------------------------------------------------------|-----------------|--------------------------------------------------------------------------------|
| Bentzen et al. (2013)   | To compare the long-term QoL of cancer patients compared to the QoL of the normal population. | SCIN questionnaire: Have you suffered from ringing in your ears? Scored from 0 to 3 | SCIN            | Telephone interviews with predefined, structured questions                     |
|                         |                                                                               | SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0 to 3 | EORTC QOL-C30 and EORTC QOL-C29 questionnaire: How would you rate your overall quality of life during the past week? |
|                         |                                                                               |                                                       |                 |                                                                                  |
| Bokemeyer et al. (1996) | To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors. | Patient complaint | Pure-tone audiometry and bone conduction thresholds | None | Blood samples, medical histories, physical examination and patient complaints |
|                         |                                                                               |                                                       | Wellbeing was scored from 0 to 10 | 18 (21%) patients had persisting ototoxicity, 8 (95%) patients had transient ototoxicity and 60 (70%) patients had no ototoxicity. There were 86 audiograms performed showing 31 (36%) patients with chemotherapy-induced hearing loss. However, it was only possible to exclusively evaluate 45 of the 86 audiograms due to others having confounding hearing issues. Every patient which a cumulative dose of 650 mg/m² complained of persisting ototoxicity. There was a threefold increased risk for ototoxicity in patients with a history of noise exposure. Those with high dose of cisplatin had significantly worse QoL than those with low dose, and those with persisting toxicities reported a worse QoL. The PEB and High CDP + cisplatin regimens results in significantly increased late toxicities. |
| Calhoun et al. (1998)   | To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists answers on a survey. | None | None | Utility score comparing symptoms to 1 (good health) and 0 (death) | None | A total of 8 women had experienced at least mild ototoxicity. Patients scored ototoxicity as 0.92 and oncologists as 0.69 in the utility questionnaire. Patients who had experienced toxicities assigned a higher utility score for toxicities, especially those they had personally experienced. It was concluded that patients tolerated toxicities in the face of maintaining stable disease. Physicians were less favourable. |
| Miaskowski et al. (2018a, 2018b, 2016c) | To compare a variety of QoL toxicities in women and compare it to oncologists answers on a survey. | FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0 to 4 | FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0 to 4 | None | QoL-PV, SF-12, CES-D scale, LS fatigue scale, sleep disturbance GDS, Attentional Function Index AI, stress PSS and IES-R questionnaires i.e.: during the past |
|                         |                                                                               |                                                       | QoL-PV          | None | CIPN survivors statistically had a higher BMI, a higher SCQ score, a lower KPS score and were born prematurely. Only 613 survivors completed the hearing loss item and from these, 34.5% reported hearing loss (score 1±). These survivors were significantly older, had a higher SCQ score, a lower KPS score, more likely to be male and |

(continued)
| Author | Aim of study | Tinnitus | Hearing loss | Ototoxicity | Quality of life | Other | Results |
|--------|--------------|-----------|--------------|-------------|-----------------|-------|---------|
| Bezjak et al. (2008) | To identify the QoL outcome in an analysis of an RCT. | None | 15 items from NCIC CTG questionnaire: loss of hearing scored from 0 to 4 | None | EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week? | None | Those treated with chemotherapy had significantly worse fatigue, lower appetite, hair loss and vomiting which all subsided. There was no difference in QoL overall, but statistically significant worse hearing loss in... |
| To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy. | FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0 to 4 | FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0 to 4 | None | QoL-PV, SF-12, CES-D scale | LFS fatigue scale, sleep disturbance GSDS, Attentional Function Index AI, stress PSS and IES-R questionnaires i.e.: during the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting friends, relatives, etc.? | None | Those who had CIN/HL/TIN were statistically more likely to be male from a lower economic background with no childcare responsibilities. They also experienced a more severe hearing loss than those in the other subgroups, had a lower KPS score, more likely to have clinical depression, a higher BMI, a higher number of comorbidities, had a significant increase in anxiety, experienced lower morning energy, lower attention function scores and lower QoL. Those with only CIN/HL were more likely to be older, have a higher anxiety score, but no difference in stress (IES-R or PSS score) and no difference in spiritual wellbeing. |
| To identify the impact of CIN on symptom burden and QoL. | FACT/GOG-Ntx questionnaire: I get ringing or buzzing in my ears scored from 0 to 4 | FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0 to 4 | None | QoL-PV, SF-12, CES-D scale | LFS fatigue scale, sleep disturbance GSDS, Attentional Function Index AI, stress PSS and IES-R questionnaires: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting friends, relatives, etc.? | None | From the 609 survivors, 68.9% had CIN and 31.4% did not have CIN. Those with all HL/TIN/CIN were significantly older, more likely to be unemployed, had a lower annual household income with no childcare responsibilities, a higher BMI, a higher number of comorbidities, a lower KPS score, had received fewer cancer treatments, had more back pain, were more likely to have clinical depression and kidney disease and didn’t exercise. This population also had a significantly lower QoL with every specific item addressed on the questionnaire other than spiritual wellbeing. |

Table 3. Continued.
| Author | Aim of study | Tinnitus | Hearing loss | Ototoxicity | Quality of life | Other | Results |
|--------|--------------|----------|--------------|-------------|----------------|-------|---------|
| Saad, Ghali, and Shawki (2017) | To compare the two treatment regimens in terms of toxicities and QoL. | None | None | NCI-CTCAE grading system, however, is not clear | FACT-L and TOI questionnaires: I am content with the quality of my life right now scored from 0 to 4 | None | Rates of ototoxicity were significantly higher in Gem/Cis group. Ototoxicity was reported in 9 patients (25%) in the cisplatin group at Grade 1, and no ototoxicity was reported in the carboplatin group. |
| Fosså et al. (2003) | To describe QoL in metastatic testicular cancer patients treated with cisplatin. | None | None | TC Module EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week? | None | A total of 42 (6%) patients stopped chemotherapy due to ototoxicity. Tinnitus was higher in those treated with the 4 cycles and 3-day regimen at all time points and overall. A mean of 4.9 had tinnitus at baseline, with 9% improving, 69% who had no change and 26% worsened. A mean of 3.1 had hearing loss at baseline, with 3% improving, 76% experienced no change and 21% had worsening of symptoms. At 6 months the group receiving the 4 cycles and 3-day regimen had worse hearing loss. Long term ototoxicity was reported by 20–25% of patients. Tinnitus occurs in 50% of patients and hearing loss for speech frequencies in 10% and for high frequency in 60% of patients. |
which diagnostic criteria should be used to identify the presence and severity of ototoxicity, yet no standardised measures are implemented clinically at the present time (Theunissen et al. 2014; Chang 2011; Waisbluth, Peleva, and Daniel 2017; Crundwell, Gomersall, and Baguley 2016; Degeest et al. 2016).

There are many potential confounding factors when assessing ototoxicity and how it impacts QoL, including age at treatment, number of follow-ups and the timing of these follow-ups, type of treatment, dosage of treatment, type of QoL assessment and the setting these were carried out in. Furthermore, the language used in the assessment tools can also lead to patients providing unreliable and confusing information, which does not always reflect their true experience. The readability of the questionnaires, therefore, is also an important confounding factor that should be considered when analysing this type of information (Atcherson et al. 2013; Gray, Zraick, and Atcherson 2019; Douglas and Kelly-Campbell 2018).

The term “ototoxicity” must be defined when publishing trials and research studies. There needs to be a clear definition of what the authors mean, and differentiation between hearing loss and tinnitus information (Waisbluth, Peleva, and Daniel 2017). Without this, a detailed analysis of the severity and effect on QoL remains a challenge.

Finally, although survival rates remain the priority in cancer treatment, there needs to be more emphasis on the importance of permanent toxicities. As people survive longer and it becomes clear that there will be a life beyond cancer, QoL becomes increasingly important. More awareness of how long-term toxicities, such as hearing loss and tinnitus, can affect QoL needs to be integrated into clinical practice. By raising awareness, the risk of these issues being neglected will decrease. Patients guided through the survivorship journey can be given relevant and tailored support, be it hearing aids, tinnitus sound therapy or cognitive behavioural therapy (CBT). Ototoxicity is currently neither preventable nor curable, therefore, it is essential that a deeper understanding and increased awareness of how hearing loss and tinnitus affects the QoL of cancer survivors be established in order to improve long-term symptom management.

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Declaration of interest

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