The Sound of Silence: A Proxy for Platinum Toxicity

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In the article that accompanies this editorial, Frisina et al¹ report on ototoxicity after cisplatin-based chemotherapy in the Platinum Study. This study comprehensively assesses hearing impairment, both as audiometric and as patient-reported outcome, as well as tinnitus in 488 cisplatin-treated testicular cancer (TC) survivors. One out of five survivors was found to have such severe hearing loss that a hearing aid was recommended. However, only 1.2% of the participants reported actually using such a device.

Cisplatin-based chemotherapy was introduced in the late 1970s by Larry Einhorn and cures most patients with metastatic TC.² However, long-term complications and late effects after cancer treatment are increasingly recognized as a major contributor to morbidity of survivors, influencing quality of life (QoL) and representing a burden for the growing community of cancer survivors. Similar to the unique position of TC as a model for a curable neoplasm,³ TC survivors represent a prime cohort for long-term survivorship studies because of their good life expectancy as a result of high cure rates and young age at diagnosis.^{4,5}

Although the report by Frisina et al¹ is a valuable contribution to the literature, it would have benefitted from inclusion of additional information, such as pretreatment assessments, the impact of ototoxicity on health-related QoL, details about and adjustment for other ototoxic agents (eg, aminoglycosides), and occupational hearing loss after completion of cisplatin-based chemotherapy. The cohort represents TC survivors receiving standard cisplatin-based chemotherapy for metastatic disease for which we do have some long-term ototoxicity outcomes,⁶ whereas high-quality data on ototoxicity after adjuvant chemotherapy with either one or two cycles of bleomycin, etoposide, and cisplatin (BEP) or carboplatin as well as after high-dose chemotherapy are still lacking.

In general, long observation periods—a prerequisite for survivorship research—make translation of the impact of former to contemporary treatment challenging. Testicular cancer is an exception. For the last four decades, no alternative regimen was superior to BEP.⁷ In accordance with current guidelines, roughly nine out of 10 participants received three or four cycles of BEP or four cycles of etoposide and cisplatin (EP).⁸ Normative data from healthy individuals comprising median quartile threshold values for different age groups were applied to categorize decibel thresholds of individual TC survivors in an ordinal fashion up to 8 kHz as adjustment for physiologic age-related hearing decline—an approach similar to the percentiles of pediatric growth curves. Retesting this survivor cohort in some years would yield

longitudinal data allowing testing of whether this group is vulnerable to subsequent age-related declines. A hypothesized reduced functional reserve leading to accelerated hormonal ageing could recently be demonstrated in TC survivors with a similar percentile categorization.⁹ Except for patients with TC who depend strongly on unimpaired hearing capability (eg, musicians, composers, or ornithologists), the risk of high-frequency hearing impairment should generally play no role in treatment planning of advanced testicular cancer in view of the high curative potential of platinum-based chemotherapy in this setting.

In this study, hearing loss according to the American Speech-Language-Hearing Association criteria was found in 80% of TC survivors, including 18% with a severe (71 to 90 dB) or profound (> 90 dB) hearing loss. On the other hand, one cycle of cisplatin increased the hearing threshold only by 2.5 dB. Thus, cisplatin-based chemotherapy for metastases should not cause more than 10 dB of hearing loss. Age-related hearing decline probably represented much of the observed hearing loss as defined by the American Speech-Language-Hearing Association, which might not be optimal for cross-sectional studies without preceding measurements.¹⁰ Calculation of hearing decline over various frequencies is complex: “For each patient i , the geometric mean Y_i was calculated using standard methods by taking the arithmetic mean of the natural log-transformed hearing threshold, d_i , from n frequencies and then using exponentiation to return the computation to the original decibel scale (ie, log-average).”¹ Understanding this end point, which scores high on specificity and poor on patient relevance (Fig 1),¹¹ is difficult for most readers who are not familiar with this field.

High specificity is needed for disentangling the impact of a single component on a given end point. Chemotherapy-related development of cardiovascular disease (CVD), for example, is complex to assess both due to interaction of different chemotherapy components and further dilution of the cause-effect relationship by multiple genetic and environmental risk factors. Chemotherapy-induced ototoxicity, on the other hand, is almost exclusively linked to cisplatin. Hypertension and hearing loss might be associated independent of cisplatin treatment.¹² However, both symptoms might represent different cisplatin-related long-term toxicities despite adjustment for the cumulative cisplatin dose.¹³

Residual serum platinum increases the risk of paresthesia and Raynaud phenomenon more strongly than the applied cumulative cisplatin dose.¹⁴ Residual platinum, however, was not associated with tinnitus or hearing impairment assessed by the Scale for

Fig 1. Specificity versus patient relevance. Illustration of the cause-effect chain and the tradeoff between relevance and specificity of different measures of side effects. Reproduced with permission from Jensen et al.¹¹

Chemotherapy-Induced Neurotoxicity, the same questionnaire that the Platinum group used as patient-reported outcome for the current study.¹⁵ Intriguingly, residual platinum, measured a median of 11 years after its application, was significantly associated with paresthesia in the fingers and toes 10 years later (ie, 20 years after treatment). At that time point, the applied cumulative cisplatin dose was no longer associated with any of the Scale for Chemotherapy-Induced Neurotoxicity items in multiparametric analyses. Hypothesized ongoing damage of nerve fibers and/or blood vessels was supported by a comprehensive Dutch study on residual platinum, applied cumulative dose, and renal function combined with careful phenotyping of long-term outcomes like paresthesia, hypogonadism, high LDL cholesterol, and hypertension.¹⁶ Hypertension was, among several other toxicities, significantly associated with higher exposure to residual platinum levels. We thereby assume the described association between hearing impairment and hypertension reflects two separate outcomes of the initial treatment, with hearing impairment being more stable after the initial damage caused by the peak cisplatin concentration, whereas hypertension probably was aggravated by ongoing endothelial damage by long-term circulating residual platinum.¹³

Ototoxicity might serve as a proxy for cisplatin-induced neurotoxicity, and CVD and could be used as an easily assessable surrogate for cisplatin susceptibility of normal tissue, opening paths for early interventions and assisting in clinical decision making. It might also prove decisive in two currently controversial areas of TC management where similar excellent survival causes a stalemate. The first is how to manage clinical stage I TC.^{17,18} Both the proponents of active surveillance for all and those propagating adjuvant chemotherapy on the basis of risk factors agree that overall survival is essentially the same for both approaches. Both parties claim advantages of their approach with regard to expected long-term toxicity, which we unfortunately still do not know enough about concerning adjuvant chemotherapy.

The second controversial area is whether International Germ Cell Consensus Classification good-risk patients with TC should receive three cycles of BEP or four cycles of EP.¹⁹⁻²¹ The authors refrained from addressing this issue despite their finding of significantly increased long-term hearing impairment after four as compared with three cycles of cisplatin-based chemotherapy. Importantly, long-term toxicities associated with the cumulative doses of cisplatin/etoposide include leukemia, second malignant neoplasm, CVD, and pulmonary problems, with the latter not being associated with bleomycin.^{22,23} Pooling long-term toxicity data after three cycles of BEP and four cycles of EP for a meta-analysis of these outcomes might be worthwhile, especially because we have learned that extrapolation of acute toxicities is not always correct in the long term: less long-term neuropathy after chemotherapy with vinblastine as opposed to etoposide in combination with cisplatin and bleomycin was surprising, because vinblastine causes substantially more short-term paresthesia than etoposide.^{6,24} Thereby, phase IV studies could help decision making in the absence of level I evidence.

QoL is, besides survival, the most important aspect for patients. Thus, the article by Frisina et al¹ would have benefitted strongly from its inclusion, ideally with pretreatment assessments as well. Although QoL differences are only modest between TC survivors and healthy controls,^{25,26} chemotherapy-treated TC survivors may have reduced physical and general health as well as social functioning.²⁷ Both hearing impairment and tinnitus could well impair social functioning. The clinical evidence for the Platinum group's recommendation of regular audiometric testing would gain immensely by demonstration of this association and, ideally, its reversal by possibly underused hearing aids.

The priority of weighing ototoxicity against cisplatin's superior effectiveness in metastatic TC is succinctly captured by Thomas Bernhard's (Austrian novelist, playwright, and poet, 1931-1989) "everything is ridiculous if one thinks of death."

In conclusion, cisplatin-induced ototoxicity, with its large interindividual variation, might represent a valid surrogate marker for susceptibility to platinum-induced healthy tissue damage. Because the validity of genetic studies is not better than their phenotype, ototoxicity as end point could facilitate identifying genetic causes for platinum toxicity.^{28,29} Clinicians are reminded to think of and inform about ototoxicity before cisplatin treatment and to avoid additional ototoxic agents such as aminoglycosides in this patient population.³⁰

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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