Platinum-Induced Ototoxicity

Introduction

A number of drugs including platinum-based anticancer agents, aminoglycosides and loop diuretics are associated with damage to the inner ear and/or vestibular system leading to toxicity presenting as hearing loss and tinnitus. Ototoxicity is permanent once established and risk factors include patient’s age, dose, duration and frequency of exposure to the ototoxic agent and renal function.

Platinum based drugs remain important therapies in childhood and adult cancers. These drugs can induce a number of severe toxicities including nephrotoxicity and neuropathies. It has been estimated that between 4%-91% of patients receiving cisplatin develop a significant hearing loss and this ototoxicity currently defies any preventative strategy or prophylactic therapeutic.

Platinum-induced hearing loss in children can be particularly disabling, compromising language and cognitive development, learning ability and quality of life. In adults too, hearing loss can lead to communication difficulties and reduced physical and psychological wellbeing, isolation and depression.

The risk of permanent hearing damage from platinum chemotherapy is stimulating the development of otoprotectants for co-administration with platinum to reduce hearing damage without impacting the anti-tumor activity of the platinum agent.

The Pathophysiology of Platinum-Induced Ototoxicity

Histopathologic studies of platinum-based ototoxicity have shown that these agents cause progressive destruction of outer hair cells, inner hair cells, and supporting cells within the organ of Corti in the basal region of the cochlea. Cisplatin appears to block transduction channels within the outer hair cells of the cochlea, and to be associated with the generation of reactive oxygen species, depletion of intracellular glutathione and interference with antioxidant enzymes within the cochlea. Hair cell loss in the vestibular labyrinth and damage to the stria vascularis, a layer of highly vascular pigmented granular cells on the outer wall of the cochlear duct, have also been described.

Frequency of Ototoxicity Associated with Cisplatin Chemotherapy

Chemotherapeutic agents that contain the heavy metal platinum were first introduced in the early 1970s and have demonstrated efficacy in the treatment of a variety of malignant neoplasms in adult and children. The first of these agents, cisplatin (cis-diamminedichloroplatinum II), is an effective agent in the treatment of lung, advanced testicular, bladder, ovarian, head and neck cancers and many childhood malignancies.
Side effects associated with its use include high-frequency sensorineural hearing impairment (i.e., ototoxicity), peripheral neuropathy, and renal impairment with tubular necrosis and interstitial nephritis\(^1\). Ototoxicity remains an irreversible, dose-limiting side effect\(^1\).

A number of studies have documented that children treated with cisplatin are at high risk for incurring significant hearing loss. Allen et al\(^1\) examined 12 pediatric patients (mean age of 7.8 years) who were treated with cisplatin at mean cumulative doses of 442.5 mg/m\(^2\) over an average of 7.1 doses. Significant sensorineural hearing loss was seen in the high frequencies: 43.5% at 4 kHz; 81.0% at 6 kHz; and 90.5% at 8 kHz.

Montaguti\(^1\) monitored platinum ototoxicity in 26 children who were treated for various malignancies. The doses and treatment schedule of cisplatin varied by diagnosis. The authors reported that 86% of patients treated with cisplatin experienced a decrease in hearing secondary to ototoxicity.

Park\(^1\) studied cisplatin ototoxicity in 21 children who were between the ages of 3 to 19 years. All of the children in this study showed significant changes in at least one portion of their hearing test battery when cumulative doses exceeded 401 mg/m\(^2\).

Li\(^1\) evaluated off-treatment audiograms from 153 children aged 6 months to 18 years. Children were treated with cisplatin for germ cell tumors, hepatoblastoma, neuroblastoma, or osteosarcoma. Cisplatin doses ranged from 40 to 200 mg/m\(^2\)/cycle with cumulative doses of 120 to 1213 mg/m\(^2\) (median 397 mg/m\(^2\)). Twenty six patients (17%), developed mild hearing loss, and in 54 patients (35%), the hearing loss was moderate to severe. The authors reported that an age of <5 years at treatment and a cumulative cisplatin dose of >400 mg/m\(^2\) substantially increased a child’s risk for significant hearing loss. After adjusting for cumulative dose, larger individual doses of cisplatin were not found to be statistically significantly associated with the development of hearing loss. Patients under 5-years old were 21 times more likely to acquire moderately severe high frequency hearing loss compared with patients who were between 15 and 20-years old. The authors noted, however, that there appeared to be a large individual variability in susceptibility to cisplatin ototoxicity.

Ilveskoski\(^1\) obtained repeated audiograms from 30 children treated with cisplatin and concluded that, for young patients treated with high cumulative doses of cisplatin, the risk of acquiring severe hearing loss was over 50%.

The reported true incidence of cisplatin ototoxicity in pediatric patients is variable, ranging from 26% to over 90% due to many treatment- and patient-related factors. Data from clinical trials can be difficult to compare due to differences in the dose of the drug administered, both within a cycle and the total amount administered over multiple cycles, the time interval between courses, method of administration, treatment duration, and differences in patient populations.
Ototoxicity and Carboplatin Chemotherapy

Carboplatin (cis-diammine 1, 1-cyclobutane dicarboxylato-platinum II) is a second-generation platinum analogue that has been demonstrated to be efficacious in the treatment of ovarian, small-cell lung, germ cell, and head and neck cancers. Although, generally regarded as less toxic than cisplatin, evidence of carboplatin-induced ototoxicity has been reported by several investigators. For example, Montaguti reported ototoxicity in 33% of children treated with carboplatin for various malignancies.

When carboplatin is administered with or immediately following other ototoxic agents, e.g., cisplatin, enhanced ototoxicity can be seen. Parsons reported on 11 children with advanced neuroblastoma who received high dose carboplatin conditioning for bone marrow transplant. All patients had prior platinum treatment as well as exposure to other ototoxic medications, such as aminoglycoside antibiotics and diuretics. All 11 children demonstrated a decrease in hearing sensitivity following administration of carboplatin, and nine of these children (82%) required hearing aids.

Hearing loss following administration of carboplatin was found in four children (33%). The authors concluded that hearing loss following carboplatin conditioning was more likely to occur in children who were pre-treated with cisplatin, and a history of cisplatin treatment appeared to be a greater risk factor for hearing loss than the dose of carboplatin administered.

Dose of Platinum Agent and Relationship to Ototoxicity

A number of studies have reported a relationship between single or cumulative doses of cisplatin and carboplatin and the incidence of ototoxicity. Therefore, patients who receive lower doses of cisplatin and/or carboplatin are less likely to experience ototoxicity. Laurell and Jungnelius reported that there was no specific dose threshold below which the incidence of ototoxicity was reduced, however, they noted that mild ototoxicity was reported with moderate doses of cisplatin (430 mg/m² cumulative dose). In 1990, Kennedy reported that high-tone hearing loss occurred after the administration of carboplatin at doses of 300 to 400 mg/m² for five to six cycles (1500 to 2400 mg/m² cumulative dose) in approximately 20% of patients, but clinically significant ototoxicity did not occur. MacDonald reported that no ototoxicity was detected with doses of carboplatin ranging from 70 to 500 mg/m² and only 2.5% rate of ototoxicity was found in patients with brain tumors treated with doses of 560 mg/m². Park reported that for cumulative doses exceeding 401 mg/m² cisplatin, 100% of patients exhibited a significant decrease in hearing sensitivity, however, clinically significant changes were not observed until cumulative doses greater than this were reached. Freilich stated that carboplatin cumulative doses of 1500 mg/m² were
not associated with increased ototoxicity in children and that carboplatin ototoxicity is greater in children than adults. In 1998, Bokemeyer\textsuperscript{27} observed that the cumulative dose is significant as no ototoxicity was reported with cumulative doses of 297 mg/m\textsuperscript{2} of cisplatin, whereas a cumulative dose of 337 mg/m\textsuperscript{2} induced transient ototoxicity, and doses of 678 mg/m\textsuperscript{2} were associated with persistent ototoxicity in adults.

**Clinical Signs and Symptoms of Platinum Induced-Ototoxicity**

Platinum-based ototoxicity occurs in a progressive and dose-dependent manner\textsuperscript{29,30}. Auditory sequelae include high-frequency sensorineural hearing loss and tinnitus. The tinnitus commonly subsides but hearing loss is almost always permanent. It is most commonly bilateral, although cases of unilateral hearing impairment are occasionally reported. High frequency hearing sensitivity is usually affected initially, as high frequency regions within the cochlea appear to be more susceptible to cisplatin\textsuperscript{5}. With continued exposure to cisplatin, the hearing loss tends to increase in severity and progressively spreads to affect hearing at the lower frequencies associated with speech\textsuperscript{8}.

Hearing loss profoundly affects the quality of life. Loss of pure-tone sensitivity in the 2 to 4 kHz frequency range results in difficulty discriminating consonant sounds especially when attempting to identify words in the presence of background noise and hearing loss exceeding the 20 dB hearing level (HL) in the speech frequencies impacts family and social interaction as well as work status\textsuperscript{1}.

In young children who have received platinum-based therapy, clinical, behavioral and psychological studies have demonstrated impairment of language acquisition with learning disability and cognitive dysfunction. In older children, both educational and behavioral effects have been reported, and in the elderly population, studies have documented impairment in functional status, cognitive status, depressive symptomatology and disability\textsuperscript{1}.

**Diagnosis and Measurement of Ototoxicity**

Ototoxicity is subjectively experienced as hearing loss and tinnitus resulting from sensorinueral damage. Irreversible hearing loss, typically in the high frequency range (4 to 8 kHz) and very high frequency range (9 to 20 kHz), has been documented as early as the first cisplatin dose and typically worsens, progressively affecting lower frequencies, in a cumulative dose-dependent fashion. Symptoms of tinnitus, although not always associated with loss of hearing, tend to precede measurable decreases in hearing thresholds\textsuperscript{31}; the hearing loss is considered irreversible.

One set of criteria used to define ototoxicity is based on the WHO grading system and a numeric grading system developed by the US National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0 (2003). However, the appropriateness of this classification system has been questioned because it does not specifically consider high frequency hearing loss. Other studies have identified ototoxicity as the presence of a clinically significant hearing loss exceeding a defined auditory threshold level and two methods of diagnosing and monitoring hearing loss have been developed: the
ASHA (American Speech-Language-Hearing Association) criteria and the Brock grading system.

Audiological monitoring is an essential part of the management of adults and children receiving platinum-based therapy. Pure tone audiometry, including high-frequency detection, is the first choice due to the sensitivity of the technique and its potential for early detection of ototoxic damage. High-frequency monitoring, from baseline, informs physicians of early ototoxic effects, allowing them an opportunity to change a patient’s course of treatment.

Audiologic evaluation in young children with limited attention and ability to cooperate during testing is more complex and the numeric system developed by Brock, is considered the most appropriate approach. The Brock grading system was designed to account for the typical slope and configuration of ototoxic hearing loss and it can be used to indicate the expected disability or handicap that would be expected, given the frequencies affected and the amount of hearing impairment.

Children with Grade 1 hearing loss will not be expected to have difficulty understanding speech in most listening conditions; however, they will require preferential classroom seating and educational monitoring. Children with high frequency hearing loss including 4 kHz (Grade 2) will likely have difficulty hearing and discriminating the high frequency consonant speech sounds and have difficulty understanding speech in noise or over distance. They may benefit from amplification or assistive listening devices, such as a classroom sound field or personal FM system, particularly during the early language-learning years. Children with hearing loss extending into the frequencies 2 kHz and lower (Grades 3 and 4) will require hearing aids for speech and language development and for communication.

Products in Development

There are several potential agents that have shown activity in preclinical or clinical settings. Some are based upon free radical scavenging and include sodium thiosulfate, D-methionine, and acetylcysteine; other approaches include neural growth factors and agents that induce inner ear hair cell proliferation.
References


