CISPLATIN-INDUCED OTOTOXICITY: THE CURRENT STATE OF OTOTOXICITY MONITORING IN NEW ZEALAND

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Abstract

Background: Many well-known pharmacologic agents have been shown to have toxic effects to the cochleo-vestibular system. Examples of such ototoxic agents include cisplatin and aminoglycoside antibiotics. Ototoxicity monitoring consists of a comprehensive pattern of audiological assessments designed to detect the onset of any hearing loss. Three main methods have emerged over the past decade, and include the basic audiological assessment, extended high frequency (EHF) audiometry, and otoacoustic emission (OAE) measurement. These measures can be used separately or in combination, depending on clinical purpose and patient considerations. It is suggested by the American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring, that baseline testing be done in a fairly comprehensive manner, including pure-tone thresholds in both the conventional- and extended high frequency ranges, tympanometry, speech audiometry, and the testing of OAEs (AAA, 2009). Anecdotal evidence suggests that New Zealand Audiologists do not currently follow a national ototoxicity monitoring protocol. Therefore the main aim of this study was to explore the current status of ototoxicity monitoring within New Zealand.

Hypothesis: It was hypothesized that hospital based Audiology departments across New Zealand each followed their own internal ototoxicity monitoring protocol based, to a large extent, on the guidelines proposed by the American Academy of Audiology and by the American Speech-Language-Hearing Association.

Method: Through the use of a Telephone Interview Questionnaire, 16 charge Audiologists were interviewed to establish their current state of knowledge regarding ototoxicity monitoring at 16 out of 20 district health boards in New Zealand. Enquiries about the current systems and procedures in place at their departments together with any suggestions and recommendations to improve on these systems were made.

Results: This study found that only 9 of the 16 DHBs interviewed currently follow an ototoxicity monitoring protocol. Furthermore, other than initially hypothesized the origin of the protocols followed by the remaining 7 departments were reported to have ranged from independently developed protocols to historically adopted protocols. One department implemented an adapted version of a protocol by Fausti et al. (Ear and Hearing 1999; 20(6):497-505). This diversity in origin however, does confirm our initial suspicion that no universal and standardized monitoring protocol is currently being followed by Audiologists working in the public health sector of New Zealand.

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Abbreviations

Cisplatin – Cis-diamminedichloroplatinum

Bcl-2 – B-cell lymphoma 2

Bax – Bcl-2-Associated X protein

OAEs – Oto-acoustic emissions

TEOAEs – Transient evoked oto-acoustic emissions

DPOAEs – Distortion product oto-acoustic emissions

EHF – Extended high frequencies

OHCs – Outer hair cells

ROS – Reactive oxygen species

TNFα – Tumour necrosis factor-alpha

ABR – Auditory brainstem response

TOMI – Tinnitus ototoxicity monitoring interview

JNK – c-Jun N-terminal kinase

AAA – American Academy of Audiology

ASHA – American Speech-Language-Hearing Association

NZSA – New Zealand Audiological Society

dB HL – Decibel hearing level

PTA – Pure-tone average

dB SPL – Decibel sound pressure level

DHBs – District health boards

1 Introduction

1.1 Ototoxicity and its causes

Ototoxicity is defined as the tendency of certain therapeutic agents to cause functional impairment and cellular degeneration of the inner ear and the eighth cranial nerve **(Figure 1)** (Govaerts, et al., 1990).

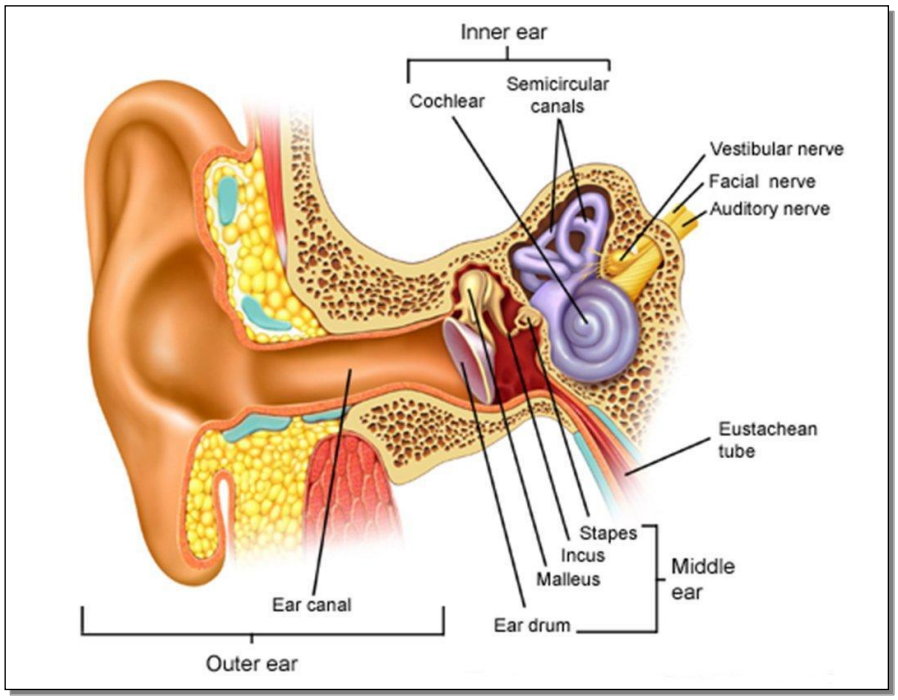

Figure 1. Anatomy of the human ear.

The propensity of specific classes of drugs to cause ototoxicity has been well established, and over 130 drugs have so far been associated with ototoxicity (Canalis & Lambert, 2000). The best documented of these include aminoglycoside antibiotics such as streptomycin and kanamycin, loop diuretics such as furosemide, and the antineoplastic agent cisplatin (Schacht & Hawkins, 2005).

That some medicines can affect hearing has been known for centuries (Stephens, 1982). In the first half of the 20th century, the arsenical compound Salvarsan (arsphenamine) was used to treat syphilis, with ototoxic side-effects. However, it was not until the 1944 discovery of streptomycin - an antibiotic that promised to eradicate infectious diseases - that the problem of ototoxicity achieved wide public awareness. At the time streptomycin was used successfully in the treatment of tuberculosis. Only one year after the discovery of streptomycin, the side effects against the inner ear and

the kidney were apparent (Schacht & Hawkins, 2005). A substantial number of treated patients were also found to have developed irreversible cochlear and vestibular dysfunction (Kahlmeter & Dahlager, 1984). These findings, coupled with ototoxicity associated with later development of other aminoglycosides (such as the highly ototoxic kanamycin and amikacin), led to a great deal of clinical and basic scientific research into the aetiology and mechanisms of ototoxicity (Fowler, 1948; Schacht & Hawkins, 2006).

Ototoxicity has typically been shown to be associated with bilateral high-frequency sensorineural hearing loss and tinnitus (Crepaldi, Umeoka, Viera, & de Moraes, 2008). Hearing loss can be temporary but is usually irreversible with most agents (Roland, 2004). Additionally, hearing loss may not manifest until several weeks or months after completion of antibiotic or antineoplastic therapy (Li, Womer, & Silber, 2004).

Table 1. Degrees of hearing loss (Jerger & Jerger, 1980).

Range of dB HL	Classification
-10 to 20 dB HL	Normal hearing
21 to 40 dB HL	Mild hearing loss
41 to 55 dB HL	Moderate hearing loss
56 to 70 dB HL	Moderately-severe hearing loss
71 to 90 dB HL	Severe hearing loss
91+ dB HL	Profound hearing loss

Permanent hearing loss or balance disorders caused by ototoxic drugs may have serious communication, educational, and social consequences (Knight, Kraemer, & Neuwelt, 2005). Therefore, the benefits of ototoxic drugs must be weighed against the potential risks, and alternative medications should be considered when appropriate. The emphasis is on prevention, as most hearing loss is irreversible. Although there are currently no therapies available to reverse ototoxic damage, scientists and clinicians continually seek new methods to minimize ototoxic injury while preserving the therapeutic efficacy of these drugs.

Ototoxicity for pure-tone thresholds between 500 Hz and 16 kHz is defined by the American Speech- Language- Hearing Association as a 20 dB or greater decrease in pure-tone threshold at a single test frequency, a 10 dB or greater decrease in threshold at two adjacent frequencies, or loss of response at three consecutive frequencies where responses were previously obtained (ASHA, 1994).

Clinical studies have demonstrated an irreversible ototoxicity incidence ranging from 9% to 91% depending on the criteria used and the cumulative dose (Blakley & Myers, 1993; Montaguti, et al., 2002). Symptoms are frequently present at the onset of measurable hearing loss. Risk factors for ototoxicity include renal insufficiency, intravenous bolus delivery, co-administration with aminoglycosides, and increased cumulative doses. Today, many well-known pharmacologic agents have been shown to have toxic effects to the cochleo-vestibular system **(Table 2)**. One such agent is cisplatin - a platinum-based antineoplastic.

Table 2. Common substances known to be associated with ototoxicity.

Type/group	Name of ototoxic substance
Aminoglycoside antibiotics	Gentamicin, streptomycin, tobramycin, neomycin, netilimicin, kanamycin, amkicacin, dihydrostreptomycin, ribostamycin
Non-aminoglycoside antibiotics	Vancomycin, erythromycin
Loop diuretics	Furosemide, ethacrynic acid, bumetanide, torsemide
Chemotherapeutic agents	Cisplatin, carboplatin, nitrogen mustard
Salicylates	Aspirin
Anti-malarial drugs	Quinine, chloroquine
Environmental chemicals and other substances	Lead, mercury, carbon monoxide, arsenic, carbon disulfide, tin, hexane, toluene, alcohol

1.2 Cisplatin

Cisplatin is a platinum based compound **(Figure 2)** and is one of the most potent cytotoxic drugs currently available to treat different types of cancer including medulloblastoma, neuroblastoma, osteosarcoma, and cancers of the testes, ovaries, cervix, bladder, lung, and head and neck (Rybak & Whitworth, 2005).

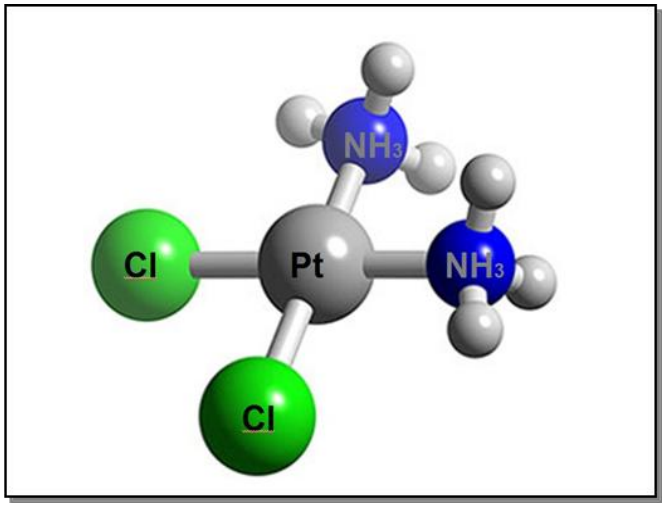

Figure 2. A 3D model of the cisplatin structure (Harrison, 2005).

Cisplatin's antitumor properties can be attributed to its chloride ligand displacement reactions which ultimately lead to DNA cross linking, and can be seen in **(Figure 3)**.

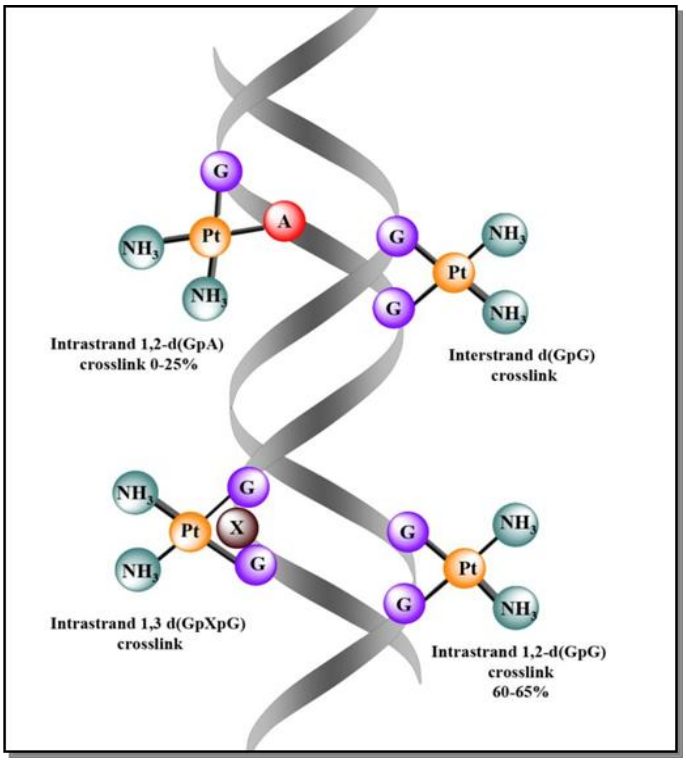

Figure 3. DNA adduct formation with cisplatin leaving two amino groups coordinated on the platinum atom (Boulikas, 2007).

Cisplatin-induced ototoxicity has been shown to occur in between 3% (Forastiere, Takasugi, Baker, Wolf, & Kudla-Hatch, 1987) and 100% of patients (Kopelman, Budnick, Sessions, Kramer, & Wong, 1988). In another study, however, elevated hearing thresholds were demonstrated in 75-100% of patients treated with cisplatin (McKeage, 1995). Ototoxicity is one of a number of severe side effects which limit

the clinical efficacy of cisplatin. Others include nephro-, neuro-, and gastro-toxicity (Rademaker-Lakhai, et al., 2006). Of these side effects, peripheral neurotoxicity and ototoxicity are potentially the major dose-limiting factors, in that they are cumulative and in general only partially reversible with discontinuation of therapy (Hill, Morest, & Parham, 2008).

Cisplatin-induced ototoxicity generally manifests as tinnitus and sensorineural hearing loss (Van der Hulst, Dreschler, & Urbanus, 1988). This hearing loss is dose related, cumulative, bilateral, and usually permanent and has been reported to occur at high frequencies (Roland, 2004). Other than higher dosage and longer duration of cisplatin therapy, the risk factors useful for predicting the risk of ototoxicity remain undetermined (Rademaker-Lakhai, et al., 2006).

Previous studies have shown that cisplatin results in the loss of outer hair cells (OHCs) specifically **(Figure 4** and **Figure 5)**, and that the loss of hair cells starts at the base of the cochlea (Nakai, et al., 1982).

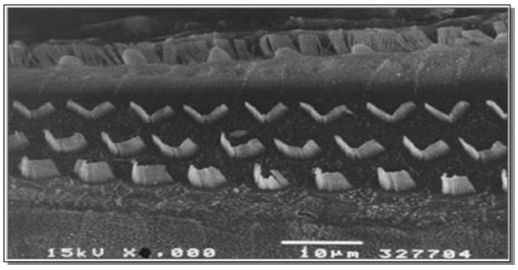

Figure 4. Normal OHCs in the basal portion of the cochlea, with their orderly arrangement of stereocilia (Kasse, et al., 2008).

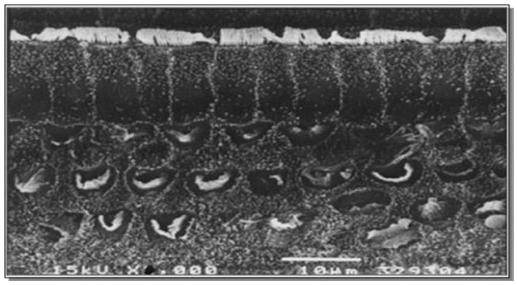

Figure 5. Extensive OHC injury in the basal portion of the cochlea due to cisplatin treatment (Kasse, et al., 2008).

In addition to the OHCs, it is suggested that the marginal cells of the stria vascularis and fibrocytes of the spiral ligament are also injured (Van Ruijven, De Groot, Klis, & Smoorenburg, 2005).

1.3 Aminoglycosides

As mentioned before, the discovery of the aminoglycoside antibiotics in the 1940s were the long-sought remedy for tuberculosis and other serious bacterial infections in developing countries (Wu, Sha, & Schacht, 2000). Commonly used aminoglycosides include amikacin, gentamicin, and tobramycin (Li, et al., 2004). They exhibit antimicrobial activity against a wide spectrum of different micro-organisms, including Gram-negative and Gram-positive bacteria, mycobacterium and protozoa (Durante-Mangoni, Grammatikos, Utili, & Falagas, 2009). The most frequently prescribed molecules are gentamicin, tobramycin an amikacin. Aminoglycosides exert their activity by binding to the aminoacyl site of 16S ribosomal RNA within the 30S ribosomal subunit (Fourmy, Recht, Blanchard, & Puglisi, 1996). The mechanism of action thus involves penetration within the target cell and direct interference with bacterial protein synthesis.

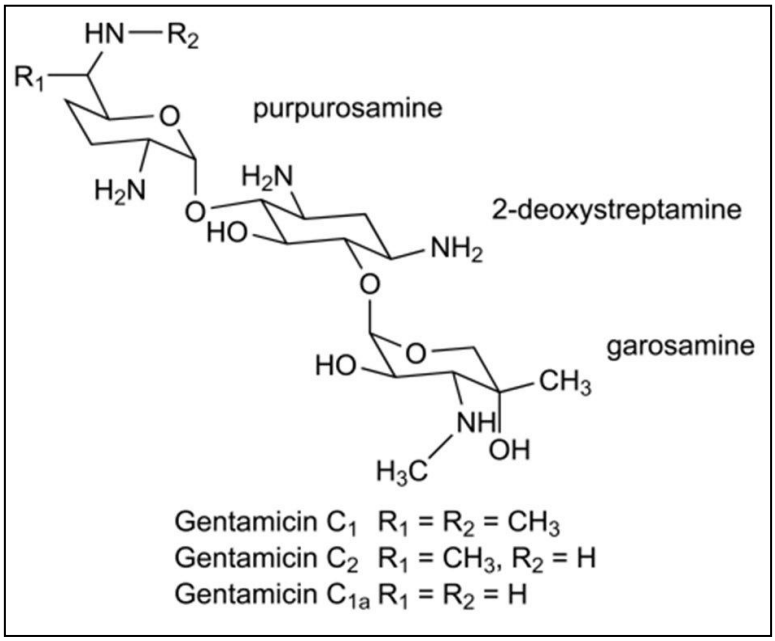

Figure 6. Molecular structure of Gentamicin ("Pharmaceutical Press," 2006).

These drugs are usually administered intravenously in two to four doses a day in patients with normal renal function (Barza, Ioannidis, Cappelleri, & Lau, 1996). The major adverse effects of these drugs are dose-dependent nephro- and ototoxicity, with impairment of both hearing and vestibular functions (Durante-Mangoni, et al., 2009). Approximately 15-20% of patients receiving aminoglycosides experience significant hearing loss and/or balance disorders (Taleb, et al., 2009). Hypersensitivity reactions, nausea, vomiting, headache, tremor, arthralgia (joint pain) and hypotension have also

been reported (Wu, et al., 2000). Experimental evidence accumulated over the last decade has left little doubt that reactive oxygen species (ROS) participate in the mechanism of aminoglycoside ototoxicity. This process is similar to that seen in cisplatin ototoxicity and is described in full below.

1.4 Mode of Ototoxicity

Apoptosis (programmed cell death) is a normal physiological event. The correct cell density is achieved and maintained by carefully controlled levels of generation and degeneration of cells. Whether a specific cell lives or dies therefore depends on this delicate balance between the pro- and anti-apoptotic factors (Cheng, Cunningham, & Rubel, 2005). A toxic insult from cisplatin can activate a cascading effect on cell death genes ultimately resulting in cell death. It can cause the lateral wall fibrocytes in the cochlea to produce TNFα, which is capable of initiating apoptosis in a variety of cells. This process can involve the anti- and pro- apoptosis members of the Bcl-2 and Bax family of proteins (Dinh, et al., 2008). These proteins constitute a critical check-point within a common cell death pathway which determines a cell's susceptibility to apoptosis (Alam, et al., 2000). Bax and Bcl-2 possess the ability to bind to and to inhibit each other (Wiren, Toombs, Semirale, & Zhang, 2006), and this preferential expression of one factor over the other may dictate the outcome of an affected cell after an insult: that is, cell survival (Bcl-2) versus apoptosis (Bax). It is thus clear that antioxidant defences in cochlear tissues can be depleted by cisplatin and that this depletion can result in an increase in reactive oxygen species. Excessive ROS overwhelms the antioxidant defence mechanisms and results in a calcium influx within the cochlear outer hair cells, which in turn activates the apoptotic pathway causing outer hair cell death. A similar mechanism of cisplatin ototoxicity is well defined by Rybak, Whitworth, Mukherjea and Ramkumar (2007) and is shown in **(Figure 7)**.

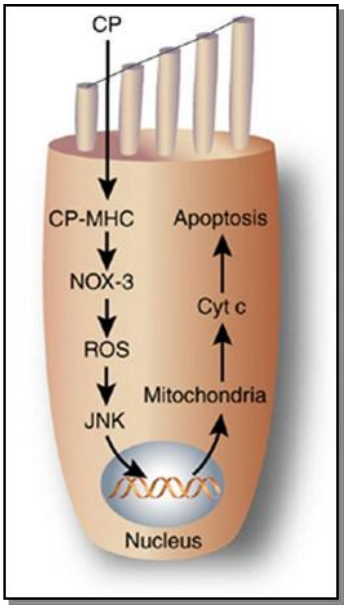

Figure 7. Mechanisms of cisplatin-induced outer hair cell death: Cisplatin (CP) enters the OHCs through mechano-electrical transduction channels; CP is aquated and forms monohydrate complex (MHC) which is more highly reactive; CP and/or MHC activates NOX-3, which results in the production of reactive oxygen species (ROS); ROS, in turn, activate JNK; these molecules then trans-locate to the cell nucleus to activate genes involved in the cell death pathway; these subsequent genes trans-locate to the mitochondria, causing the release of cyt-c, which trigger apoptosis (Rybak, Whitworth, Mukherjea, & Ramkumar, 2007).

The generation of ROS is a normal part of homeostasis and much of the data on the role of ROS in tissue damage comes from cell or organ culture experiments. Henderson, Hu, McFadden & Zheng (1999) warn that it could be risky to simply extrapolate the results from *in vitro* experiments to the ear because the state of equilibrium between ROS and the set of antioxidant molecules is complex. The enhancement of antioxidant levels through drug application or genetic manipulation has also been shown to promote hair cell survival while preserving function (Kawamoto, et al., 2004).

In current cancer treatment protocols, cisplatin treatment is often re-evaluated at the detection of ototoxicity by switching to another less antineoplastic (and less ototoxic) agent such as carboplatin. However, for this ototoxicity to be detected there must be a comprehensive hearing monitoring programme in place.

1.5 Ototoxicity Monitoring

Ototoxicity monitoring consists of a comprehensive pattern of audiological assessments designed to detect the onset of any hearing loss resulting from the administration of an ototoxic agent, whether it be an industrial chemical or a

pharmacological treatment. According to Fausti et al. (1993), the interactions between ototoxicity and drug administration parameters such as dosage, duration of treatment and serum concentration is highly variable. A physician cannot solely rely on dosage or serum concentrations to predict the risk of ototoxicity. Therefore, all baseline testing should ideally be performed prior to any ototoxic drug administration as this will allow the physician the opportunity to balance the merits of a stronger dose or alternative treatments before hearing loss progresses into the speech range. However, the lack of evidence of ototoxicity can justify prolonged and more aggressive treatment, which could ultimately lead to a better outcome for patients treated with ototoxic drugs. Through close monitoring, changes in hearing thresholds can forewarn the Audiologist and patient to the potential need for early amplification assistance.

Until very recently, ototoxicity could only be monitored by conventional pure tone audiometry (PTA). Although ototoxicity can be monitored through a high frequency tone-burst auditory brain stem response (ABR), this test is lengthy, could lack frequency specificity and response interpretation at ultra high frequencies is variable and subjective (Campbell, 2007). Although a study done by Stavroulaki et al. (1999) proved that conventional audiometry normally detects hearing loss at a late, irreversible stage, a study done in the same year by Fausti et al. (1999) in the same year showed that identifying and testing a small range of frequencies, provides sensitive early detection to Audiologists. Adding to this argument, a study by Vaughan et al. (2002) demonstrated that an uppermost target frequency for a limited frequency range can be determined for each individual patient with a rapid and efficient protocol. These authors also propose that the use of smaller frequency increments could provide increased sensitivity for early detection of hearing loss within the speech range that are not usually included in routine clinical threshold testing.

Two large American bodies for Audiologists are the American Speech-Language-Hearing Association (ASHA) and the American Academy of Audiology (AAA). In 1994 ASHA formed an Ad Hoc Committee on Audiologic Management of Individuals Receiving Ototoxic and/or Vestibulo-toxic Drug Therapy. Consequently, the “Guidelines for the audiologic management of individuals receiving cochleo-toxic drug therapy” was developed (ASHA, 1994). The AAA compiled a task force

consisting of seven well respected professionals who developed the AAA's Position Statement and Clinical Practice Guidelines on Ototoxicity Monitoring (AAA, 2009). Both of these guidelines and principles are outlined and discussed below.

1.5.1 ASHA

The American Speech-Language-Hearing Association outlines six basic principles of a cochleo-toxic monitoring program: 1) Specific criteria for identification of toxicity, 2) Timely identification of at-risk patients, 3) Pre-treatment counselling regarding potential cochleo-toxic effects, 4) Valid baseline measures (pre-treatment/early in treatment), 5) Monitoring evaluations at sufficient intervals to document progression of hearing loss or fluctuation insensitivity, and 6) Follow-up evaluations to determine post-treatment effects.

1) *Specific criteria for identification of toxicity*

   Subsequent changes in hearing thresholds are always compared relative to baseline results. ASHA criteria indicating ototoxicity induced hearing loss is set as: a) $\geq$ 20 dB decrease at any one test frequency, b) $\geq$ 10 dB decrease at any two adjacent test frequencies, or a c) loss of response at three consecutive test frequencies where responses were previously obtained. These changes must be confirmed at a follow-up appointment.

2) *Timely identification of at-risk patients*

   Any patients, who are treated with a therapeutic drug known or suspected to have a cochleo-toxic side effect, require monitoring. Risk factors for hearing loss are summarized in **Table 3** (Li, et al., 2004; Mehl & Thomson, 1998). A monitoring program should be implemented as soon as such a patient has been identified. Accurate and timely identification requires access to a registry of all patients receiving potentially ototoxic medication, and open communication between all medical personnel involved in treated and caring for these patients.

Table 3. Risk factors for hearing loss.

Risk factors for congenital hearing loss	Risk factors for hearing loss in adults receiving ototoxic treatment
Asphyxia	Age
Meningitis	Young children
Congenital or peri-natal infections	Older adults
Anatomic defects or Stigmata	Renal insufficiency
Hyperbilirubinemia	Intravenous bolus delivery
Family history of hearing loss	Co-administration with aminoglycosides
Low birth weight	Increased cumulative doses
Neonatal illnesses requiring mechanical ventilation	Cranial irradiation
	Noise exposure
Ototoxic medications	Diet

3) *Pre-treatment counselling regarding potential cochleo-toxic effe*cts

It is proposed that the physician should counsel patients regarding the potential effects of the ototoxic drugs, the risks and the benefits the drug therapy may have. The Audiologist should counsel the patient on signs and symptoms of hearing loss and the potential effects it may have on communication. Furthermore, patients should be aware of symptoms such as tinnitus, fullness, loss of balance or any changes in hearing sensitivity and they should be encouraged to inform their medical team and Audiologist if and when they occur. The possible synergistic effects of noise and ototoxicity should be stressed to those patients who work or live in an environment with excessive noise levels.

4) Valid baseline measures

As baseline audiometry is crucial for the successful implementation of an ototoxicity monitoring program, it is suggested that all patients receiving ototoxic medication undergo accurate evaluations. Should this initial evaluation, for whatever reason, not be able prior to the first dose of ototoxic medication, it is suggested that it be carried out no later than 24 hours after. A comprehensive assessment should include, but is not limited to, a comprehensive case history, a tinnitus questionnaire such as the Tinnitus Ototoxicity Monitoring Interview (TOMI), otoscopy, tympanometry, acoustic reflexes, speech discrimination measurements,

pure-tone audiometry, extended high frequency audiometry, bone conduction testing, and an objective measure such as oto-acoustic emissions.

5) *Monitoring evaluations at sufficient intervals*

Monitoring evaluations should be scheduled parallel with each subsequent medical appointment in order to effectively and accurately detect ototoxic effects. These appointments are patient specific and will vary according to each individual's type of cancer, dose of medication and frequency of administration.

6) *Follow-up*

Follow-up testing should be done at intervals appropriate to detect post-treatment ototoxicity, or to document (unlikely) recovery.

1.5.2 AAA

It is suggested by the American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring, that baseline testing be done in a fairly comprehensive manner, including pure-tone thresholds in both the conventional- and extended high frequency ranges, tympanometry, speech audiometry, and the testing of OAEs (AAA, 2009). The basic audiological assessment, extended high frequency (EHF) audiometry and otoacoustic emission (OAE) measurements have formed the basis for ototoxicity monitoring over the past ten years. Depending on clinical purpose and patient considerations, these measures can either be used individually or jointly.

1.5.3 Extended High-frequency Audiometry

Extended high-frequency audiometry and evoked otoacoustic emissions have been shown to be more sensitive to initial ototoxic damage due to greater vulnerability of the basal region of the cochlea (Campbell, 2003). EHF audiometry measures pure-tone thresholds at frequencies higher than 8 kHz and can extend up to 20 kHz, depending on the equipment used. Cisplatin-induced ototoxicity initially affects the OHCs within the basal region of the cochlea where high-frequency sounds are

processed **(Figure 8)**. It is therefore imperative that pure-tone audiological evaluation include the upper regions of hearing not usually tested in conventional audiometric evaluation.

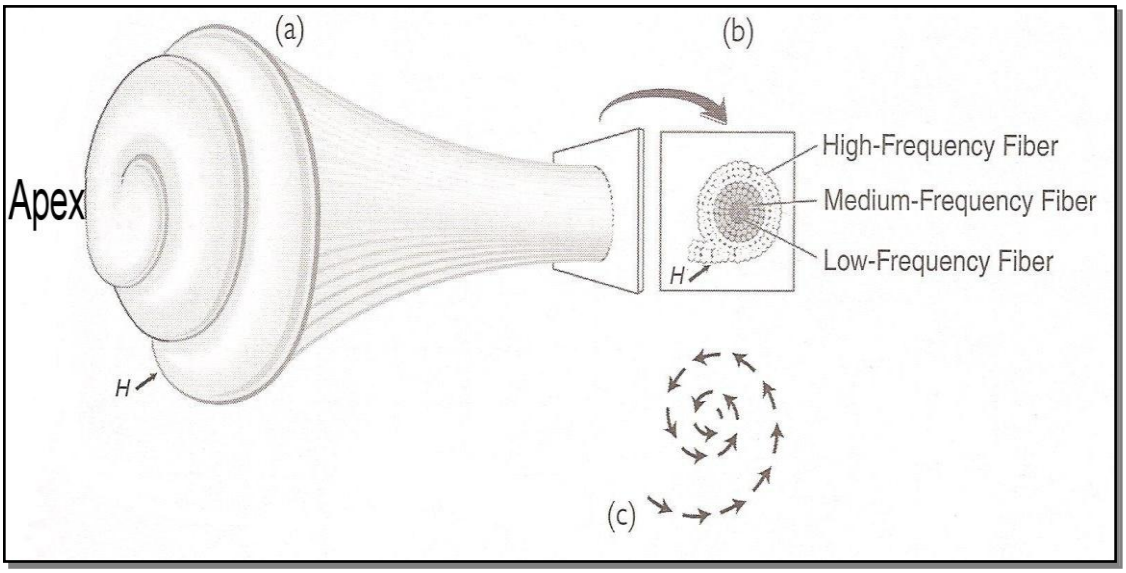

Figure 8. a) The auditory nerve fibres and their tonotopic array. b) Cross-section of auditory nerve fibres, with the "H' indicating the hook area or extreme basal aspect of the cochlea.
c) The arrows indicate the approximate tonotopic course of auditory nerve fibres from high to low frequencies in this cross-section of the auditory nerve (Musiek & Baran, 2007).

1.5.4 Otoacoustic Emissions

Patient fatigue caused by illness and treatment regimes can often interfere with behavioural testing; potentially reduce accuracy of the data obtained. An objective evaluation of the cochlear outer hair cells can be measured with OAEs. Early changes in OAE measurements may suggest cochlear damage that could progress to hearing loss (Leigh-Paffenroth, Reavis, & Gordon, 2005). Transient-evoked OAEs (TEOAEs) and distortion product OAEs (DPOAEs) are most commonly used in the clinic.

1.5.4.1 High frequency DPOAEs

DPOAEs are objective, non-invasive and do not require active participation, and are therefore generally well tolerated by ailing patients. When stimulated by two tones f_1 and f_2 ($f_2 > f_1$) of neighbouring frequencies, the outer hair cells evoke intermodulation vibrations due to their non-linear transmission characteristics and corresponding intermodulation distortion. In humans, the $2f_1$-f_2 DPOAE has the highest amplitude and is therefore primarily used for diagnosing cochlear dysfunction **(Figure 9)**. DPOAEs are generated within the region of overlap of the travelling waves of the two primary tones close to the f_2 place. The level L_{dp} of the $2f_1$-f_2 DPOAE and the related

noise floor (average of 6 spectral lines around $2f_1$-f_2) are measures for determining DPOAE amplitude and signal-to-noise ratio.

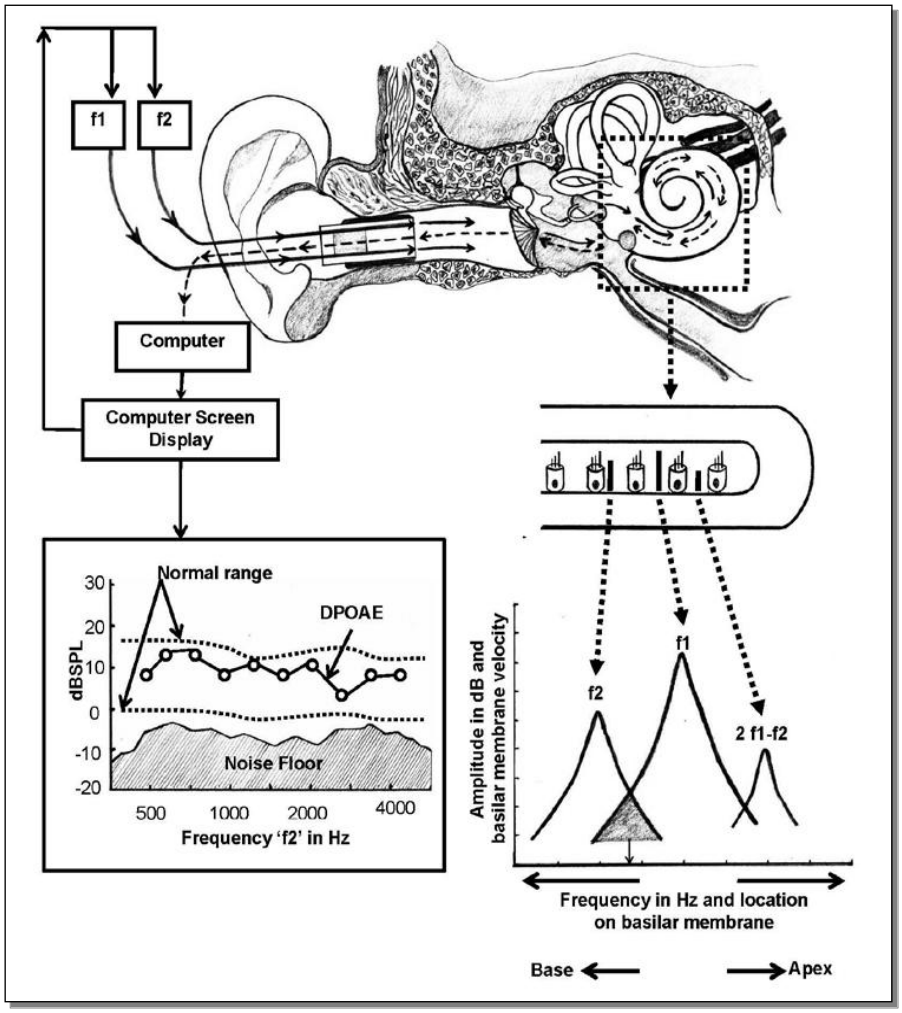

Figure 9. Illustration of the measurement of distortion product otoacoustic emissions (DPOAEs) showing a probe assembly that fits into the external ear canal, the delivery of the signals to the ear via the middle ear, the generation of OAEs by outer hair cells in the cochlea and, finally, propagation of OAE energy as sound into the external ear canal (Anuradha Bantwal) (MAICO).

In a study by Knight et al. (2007) it was found that EHF audiometry usually detected ototoxicity prior to its detection through DPOAEs, although both EHF audiometry and DPOAE thresholds changed prior to thresholds measured in conventional audiometry. However, DPOAEs are still considered a useful tool as it is time efficient and does not require a behavioural response from the patient.

According to Gorga et al. (1995) changes in outer hair cell function are seen as decreases in DPOAE amplitudes, decreases in the signal-to-noise ratio of the response, and/or a loss of DPOAEs, specific to regions of outer hair cell damage.

There are several advantages for using DPOAEs over TEOAEs. Firstly it is suggested that DPOAEs may detect ototoxicity earlier than TEOAEs (Lonsbury-Martin & Martin, 2001), possibly because the former can more reliably be measured at higher frequencies where ototoxicity is first noticed. Secondly DPOAEs can be used to indicate the degree and configuration of the hearing loss if that data cannot be obtained from behavioural testing. Thirdly it has been found that a reduction in EHF audiometry coincides with a DPOAE reduction at around 8 kHz and below. Lastly DPOAEs can often be recorded more reliably in the presence of more severe SNHL than TEOAEs.

There is currently no universally accepted criterion for ototoxic change in DPOAEs. Finding an objective method for early detection and follow-up of hearing loss has been a priority of researchers for a long time (Biro, et al., 2006). Such a method would enable clinicians to make rational decisions regarding the modification of treatment protocols with cisplatin.

1.5.5 Tinnitus Monitoring

According to Seligman (1996), tinnitus is a common side effect of many ototoxic drugs, particularly cisplatin. When monitoring for ototoxicity, it has been suggested by the American Academy of Audiology's Position Statement and Clinical Practice Guidelines for Ototoxicity Monitoring (1999) that systematic questioning about tinnitus symptoms be done at each appointment. Tinnitus assessment methods are not often reported, and are mostly analyzed by patient self-report. The Tinnitus Ototoxicity Monitoring Interview (TOMI) **(Table 4)** is a useful tool in establishing the onset and any perceptual changes that occur during ototoxicity monitoring. Given the population of patients treated for cancer it can be expected that the life-threatening illness may overbear tinnitus self-report as these patients may be overwhelmed and consumed with other issues.

Table 4. The Ototoxicity Monitoring Interview (Campbell, 2007).

1. [Clinician at the first visit] Did you have persistent tinnitus before the start of treatment?	☐ No	☐ Yes		
1a. If yes, how long have you had tinnitus?	☐ Less than 1 year	☐ 1-2 years	☐ 3-5 years	
	☐ 6-10 years	☐ 11-20 years	☐ More than 20 years	
	☐ Not sure			
2. Have you noticed any persistent tinnitus since you started the treatment?	☐ No	☐ Yes		
	If no, the interview is complete. No further questions are required. If Yes, continue to question 3.			
3. What does your tinnitus sound like? (Mark all that apply)	☐ Ringing	☐ Hissing	☐ Buzzing	☐ Sizzling
	☐ Crickets	☐ Whistle	☐ Hum	
	☐ Other:			
4. Does your tinnitus have a pulsing quality to it?	☐ No	☐ Yes		
5. Where is your tinnitus located?	☐ Left ear only	☐ Right ear only		
	☐ Both ears	☐ Inside head		
	☐ Other:			
6. Is your tinnitus louder on one side of your head than the other?	☐ Right is louder than left			
	☐ Left is louder than right	☐ Equal		
7. How loud is your tinnitus on average?	☐ Not loud at all	☐ Slightly loud	☐ Moderately loud	
	☐ Very loud	☐ Extremely loud		
8. How much of the time do you think your tinnitus is present?	☐ Occasionally	☐ Some of the time		
	☐ Most of the time	☐ Always		
9. On average, how much of a problem is your tinnitus?	☐ Not a problem	☐ Slight problem	☐ Moderate problem	
	☐ Big problem	☐ Very big problem		

[Clinician: Ask the following questions only if the patient (1) had tinnitus before the start of treatment, or (2) reported tinnitus previously with this TOMI. The objective is to determine if the patient's tinnitus is being affected by the drug treatment. If the patient has previously responded to this interview, each response should reflect the period of time since the last interview. Otherwise, each response reflects the period of time since before the start of treatment.

10. Has the sound of your tinnitus changed?	☐ No ☐ Yes ☐ Not sure If yes, how is it different?
11. Has the location of your tinnitus changed?	☐ No ☐ Yes ☐ Not sure If yes, how is it different?
12. Has the loudness of your tinnitus changed?	☐ No ☐ Yes, louder now ☐ Yes, quieter now ☐ Not sure
13. Has the amount of time your tinnitus is present changed?	☐ No ☐ Yes, more often ☐ Yes, less often ☐ Not sure

1.6 The New Zealand health system

The New Zealand health system is divided into twenty semi-autonomous district health boards (DHBs), with Southern DHB divided into two constituencies namely Otago and Southland **(Table 5)**. These DHBs have existed since 1 January 2001 when the New Zealand Public Health and Disability Act 2000 came into force, and are responsible for providing, or funding the provision of health and disability services in their district. The statutory objectives of DHBs include: improving, promoting and protecting the health of communities, promoting the integration of health services, especially primary and secondary care services, and promoting effective care or support of those in need of personal health services or disability support.

Table 5. District Health Boards in New Zealand.

District Health Boards - North-Island	**District Health Boards - South-Island**
1. Northland DHB (Whangerei) 2. Waitemata DHB (Auckland) 3. Auckland DHB 4. Counties Manukau DHB 5. Waikato DHB (Hamilton) 6. Lakes DHB (Taupo) 7. Bay of Plenty DHB (Tauranga) 8. Tairawhiti DHB (Gisborne) 9. Taranaki DHB (New Plymouth) 10. Hawke's Bay DHB (Napier) 11. Whanganui DHB 12. MidCentral DHB (Palmerston North) 13. Hutt DHB (Wellington) 14. Capital and Coast DHB (Wellington) 15. Wairarapa DHB (Masterton)	16. Nelson Marlborough DHB 17. West Coast DHB (Greymouth) 18. Canterbury DHB (Christchurch) 19. South Canterbury DHB (Timaru) 20. Southern DHB: Divided into two constituencies, Otago (Dunedin) and Southland (Invercargill)

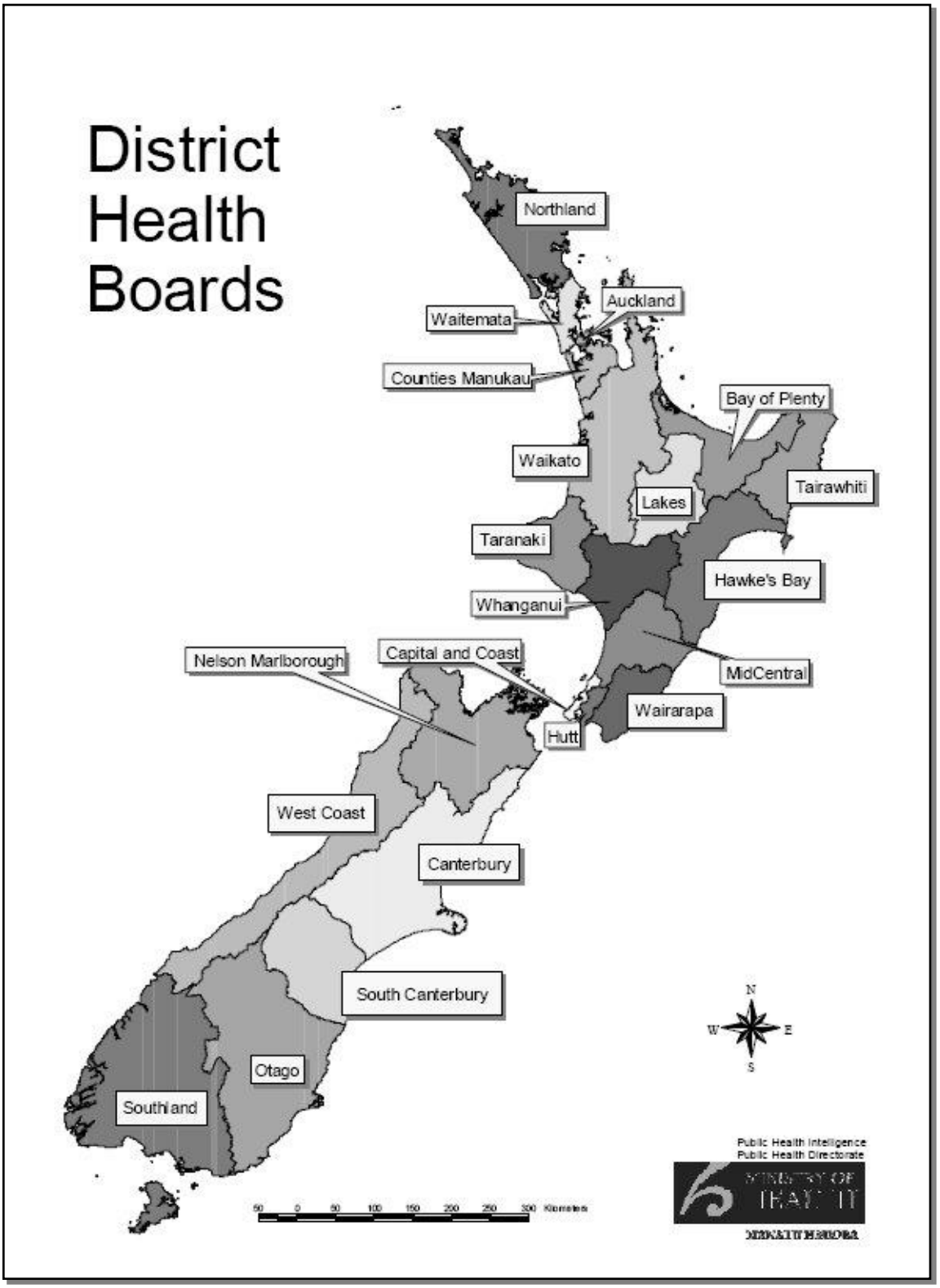

Figure 10. District Health Boards in New Zealand
(Retrieved from: http://www.moh.govt.nz/moh.nsf).

The population served by each DHB is shown in **(Figure 11)** and is based on numbers by Statistics NZ Population Projections of September 2007. Waitemata (North-Auckland) and Canterbury is shown to serve the largest populations, followed by Auckland (Central), and Counties Manukau.

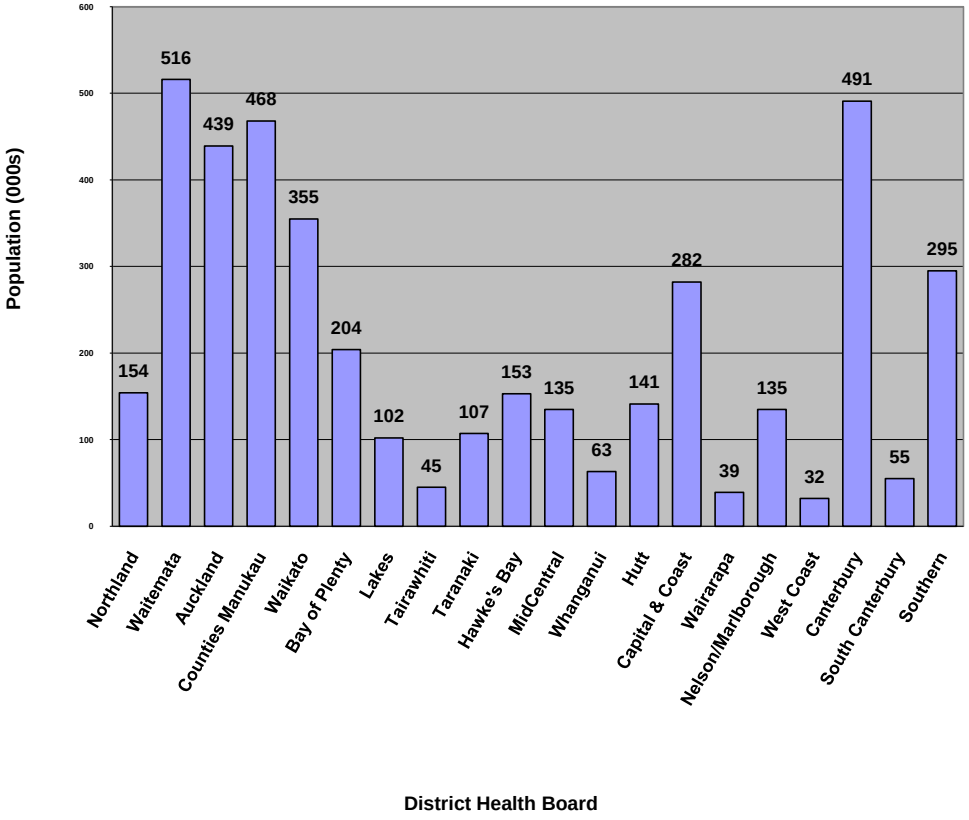

Figure 11. Populations served by each District Health Board in New Zealand.

A recent study by Alchin (2010) found that 7 of 23 individuals (30.4%) receiving ototoxic treatment in one DHB in New Zealand did not have and audiological assessment prior to beginning their treatment. Furthermore the author found that 87% (20 of participants) had extended high frequency audiometry included in the test battery, but none of the baseline assessments included OAEs, acoustic reflexes or speech audiometry. Of the number of participants who did receive a baseline audiometric evaluation, 31% did not have any other follow-up assessments during or after cisplatin therapy. The results of this study thus strongly indicate a lack of stringency in ototoxicity monitoring. The governing body for practicing Audiologists in New Zealand (NZAS) does not currently have any standards of practice for ototoxicity monitoring. The main aim of this study was to establish the current state of

ototoxicity monitoring in the twenty district health boards across New Zealand, via telephonic interview.

1.7 Telephonic Interviewing using Questionnaires

The telephone has enabled researchers to play a vital role in public health research and practice for many years (Kempf & Remington, 2007). Participation in telephone surveys is not only critical for examining cross-sectional characteristics of populations subgroups and for tracking trends and risk behaviours over time, but also to identify risk factors associated with multiple health conditions, and for the assessment of the effects of interventions. The primary purpose of telephone surveys is to make valid and reliable conclusions about populations that can be generalized on the basis of the answers of sampled respondents. However, the many challenges that can hamper data collection are listed in **Table 6**.

Table 6. Continuing and emerging challenges for telephone survey research (Kempf & Remington, 2007).

Ongoing challenges	New and emerging challenges
Selecting participants	
Sampling	Cell phone sampling
Telephone coverage	Number portability
Response rates	Answering machines
Participation rates	Caller Identification (ID)
Call scheduling	Privacy managers and call blocking
Collecting information	
Reliable and valid responses	Privacy and confidentiality
Mode effects	Respondent burden

As this study was concerned with a distinct set of known individuals, most of the participant selection challenges did not apply.

1.5 Statement of the problem

To summarize, ototoxicity is defined as the tendency of certain therapeutic agents to cause functional impairment and cellular degeneration of the inner ear and the eighth cranial nerve. Numerous pharmacologic agents have been shown to have toxic effects to the cochleo-vestibular system. One such drug is the platinum-based antineoplastic agent, cisplatin. Cisplatin is one of the most potent cytotoxic drugs currently available to treat different types of cancer. The clinical efficacy of cisplatin is however limited

by its severe ototoxicity. Ototoxicity monitoring consists of a comprehensive pattern of audiological assessments designed to detect the onset of any hearing loss. Three main methods have emerged over the past decade, and include the basic audiological assessment, extended high frequency (EHF) audiometry, and otoacoustic emission (OAE) measurement. These measures can be used separately or in combination, depending on clinical purpose and patient considerations. It is suggested by the American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring, that baseline testing be done in a fairly comprehensive manner, including pure-tone thresholds in both the conventional- and extended high frequency ranges, tympanometry, speech audiometry, and the testing of OAEs (AAA, 2009). However, New Zealand Audiologists do not currently follow a national ototoxicity monitoring protocol. It is therefore the author's hope that this current study will form the basis for the development of a national protocol which can readily be adapted by all practising Audiologists within New Zealand.

1.6 Hypothesis and Research Question

Since no formal protocols or best practise guidelines are available through the New Zealand Audiological Society, it is hypothesized that Senior/Charge Audiologists working within the public health sector within New Zealand are not conducting uniform monitoring procedures with regards to ototoxicity monitoring.

2 Method

2.1 Participants

Charge/senior Audiologists from 16 of the 20 District Health Boards in New Zealand were interviewed via telephone. The remaining four District Health Boards reported that they did not conduct ototoxicity monitoring and instead referred their patients to the bigger centers for monitoring.

The contact details for all participants were collected from the New Zealand Ministry of Health website (http://www.moh.govt.nz/moh.nsf/indexmh/contact-us-dhb).

Participants were included in this study if they were a Senior/Charge Audiologist employed by one of New Zealand's District Health Boards and conducted ototoxicity monitoring at their Audiology Department.

2.2 Materials

2.2.1 Interview Questionnaire

Participants were questioned on a range of topics, including their prior knowledge of ototoxicity and the ototoxicity monitoring procedures for first and subsequent appointments currently in place at their place of employment. They were also asked to suggest ways in which the present system could be improved. Because the questionnaire sought to obtain information regarding the perceptions of Audiologists on the ototoxic effects of cisplatin therapy, both open- and close ended questions were used. The questionnaire was developed by the author and Dr. Greg O'Beirne, senior lecturer in Audiology at the University of Canterbury with input from Dr. Rebecca Kelly, also from the University of Canterbury.

2.3 Procedures

Once ethical approval was obtained (**Appendix A**) the researcher started the data collection phase by randomly phoning participants at different times during weekdays. Data collection occurred over a two week period from 18 to 29 October 2010. If a participant agreed to be interviewed on first contact, the interview was conducted immediately. The researcher only had to re-book a more suitable interview time for three of the participants. Sixteen out of a possible 16 participants agreed to partake in this study, giving a response rate of 100%. No monetary incentive was offered.

Interviews lasted approximately 45 minutes each, and data was gathered by directly transcribing onto the questionnaire. During data collection, the answered questionnaires were kept in a lock-up file cabinet owned by the researcher. All identifiable data gathered was destroyed on completion of this study.

2.4 Statistical Methods

Due to a small sample size of 16, detailed statistical analysis of data was not appropriate. The focus of this study was to determine the *subjective views and opinions* of charge Audiologists who are currently conducting ototoxicity monitoring in New Zealand. Descriptive statistics and content analysis were utilized to analyze the information obtained from this study. The goal of descriptive statistics was to provide a summary measure of some characteristic of the sample data (Blanche,

Durrheim, & Painter, 2008). Data were subjected to thematic analysis which was used to obtain reappearing themes (Holstein & Gubrium, 2003). Common themes were highlighted and grouped to establish major themes.

2.5 Ethical Considerations

Ethical approval from the Human Ethics Committee (Ref: HEC 2010/77/LR) was granted on October 15th, 2010 (**Appendix A**). Verbal consent was obtained from each participant prior to conducting the telephonic interview, and participant confidentiality was maintained in accordance with the conditions of ethical approval from the above-mentioned ethics committee.

3 Results

The qualitative data is presented in the order that the Telephone Interview Questionnaire was conducted with the 16 participants interviewed for this study. A copy of the questionnaires is provided in **Appendix B**. Where numerical values are summarised, results are given as the mean ± standard deviation.

3.1 Demographics (Questions 1 – 10)

1. What is the name of the District Health Board (DHB) where you spend most/all of your time?

Sixteen charge Audiologists representing 16 out of the 20 DHBs in New Zealand took part in this study, and is listed in **Table 7** below.

Table 7. Sixteen District Health Boards represented in this study.

District Health Boards - North-Island	District Health Boards - South-Island
1. Northland DHB (Whangerei) 2. Waitemata DHB (Auckland) 3. Auckland DHB 4. Counties Manukau DHB 5. Waikato DHB (Hamilton) 6. Lakes DHB (Taupo) 7. Bay of Plenty DHB (Tauranga) 8. Tairawhiti DHB (Gisborne) 9. Taranaki DHB (New Plymouth) 10. Hawke's Bay DHB (Napier) 11. MidCentral DHB (Palmerston North) 12. Capital and Coast DHB (Wellington)	13. Nelson Marlborough DHB 14. Canterbury DHB (Christchurch) 15. South Canterbury DHB (Timaru) 16. Southern DHB: Divided into two constituencies, Otago (Dunedin) and Southland (Invercargill)

The four DHBs not included in this study are shown in **Table 8** below.

Table 8. Four District Health Boards not included in this study.

District Health Boards - North-Island	District Health Boards - South-Island
17. Whanganui DHB 18. Hutt DHB (Wellington) 19. Wairarapa DHB (Masterton)	20. West Coast DHB (Greymouth)

2. Do you work at other DHBs or satellite clinics?

None of the 16 participants worked at other DHBs or satellite clinics.

3. How long have you been working as an Audiologist?

Work experience for participants interviewed ranged from 1 year to 36 years (mean: 16.4 ± 10.6).

4. Where did you obtain your qualification?

Due to the small number of participants who agreed to partake in this study and privacy regulations the data for this question will not be included in the results section.

5. When did you graduate?

The participants interviewed graduated between 1977 and 2009 (mean: 1993.6 ± 10.2).

6. How long have you worked in your current position?

Work experience in their current position as Charge Audiologist at a DHB ranged from 1 year to 23 years (mean: 7.7 ± 7.6) for all participants in this study.

7. How long have you worked in the NZ hospital system?

The 16 participants had varied work experience in the NZ hospital system ranging from 1 year to 36 years (mean: 13.9 ± 10.9).

8. Have you ever worked in hospital-based audiology overseas?

Twelve out of the 16 participants had never worked in hospital-based audiology overseas.

9. If so, what country and for how long?

Four of the participants had had hospital-based work experience in audiology in the United Kingdom (2 participants), the United Arab Emirates (1 participant) and the Philippines (1 participant).

10. Where did you learn about ototoxicity monitoring?

The source of the participants' knowledge of ototoxicity monitoring is shown in **Table 9**.

Table 9. Acquisition of knowledge regarding ototoxicity monitoring.

Knowledge acquired	Number of participants out of 16
On the job	6
University Program	12
Own reading	6
Conference	2

3.2 Prior knowledge of Ototoxicity (Questions 11 – 26)

11. As far as you know, what medical treatments can permanently affect hearing?

Medical treatments that can permanently affect hearing are shown in **Table 10.**

Table 10. Medical treatments that can permanently affect hearing.

Medical Treatments	Number of participants out of 16
Cisplatin	14
Cranial radiation	2
Carboplatin	3
Aminoglycosides	16

Other medical treatments listed by 3 participants included:

Aspirin, heart and blood pressure medication, salicylates, loop diuretics, furosemide, anti-tuberculosis-, malaria- and renal medications.

12. What percentage of patients receiving cisplatin chemotherapy do you believe could develop hearing loss?

Twelve out of the 16 participants gave a value ranging from 0% to 75%. Four participants did not want to guess.

13. What percentage of patients receiving amino-glycosides do you believe could develop hearing loss?

Twelve out of 16 participants gave a value ranging from 0% to 65%. The same four participants, who did not want to guess in question 12 above, did not want to guess for this question either.

14. If they did develop a hearing loss from cisplatin chemotherapy, what configuration would the hearing loss typically take on?

All sixteen participants agreed that a high frequency hearing loss would develop from cisplatin chemotherapy.

15. How severe is this hearing loss likely to be?

The majority of participants were of the opinion that cisplatin induced ototoxicity would induce a moderate hearing loss.

Table 11. Severity of cisplatin induced hearing loss.

Severity	Number of participants out of 16
Mild	2
Moderate	10
Moderately-Severe	3
Severe	4
Profound	1
Either of the options	1

16. What impact do you think this hearing loss would have on their daily life?

Ten participants were of the opinion that a moderate hearing loss caused by cisplatin would have a moderate impact on their daily life **(Table 12)**.

Table 12. The impact of hearing loss on daily life.

Impact	Number of participants out of 16
No impact	0
Slight impact	1
Moderate impact	10
Severe	4
* Depends if the hearing loss has spread into the speech frequency ranges (0.5 - 4 kHz)	2

* This option was not part of the questionnaire, but two participants volunteered this data as their answer.

17. What is the likelihood of patients receiving cisplatin chemotherapy developing tinnitus?

The majority of participants recognized the fact that it is very likely for cisplatin chemotherapy treatment to result in Tinnitus.

Table 13. Likelihood of cisplatin to induce Tinnitus.

Likelihood	Number of participants out of 16
Not likely	0
Slight likelihood	2
Moderate likelihood	3
Very likely	9
Uncertain	2

18. In your opinion, is the tinnitus likely to be of transient or permanent nature?

Four participants were of the opinion that cisplatin induced Tinnitus would be transient in nature, while 12 participants felt it would be permanent.

19. What impact do you think the tinnitus would have on their daily life?

Participants felt that cisplatin induced Tinnitus would have a slight to moderate impact on the daily lives of cancer patients.

Table 14. The possible impact of cisplatin induced Tinnitus.

Impact	Number of participants out of 16
No impact	1
Slight impact	7
Moderate impact	7
Severe	1

20. Are patients receiving cisplatin chemotherapy likely to develop balance problems?

Nine participants agreed that cisplatin chemotherapy is not likely to cause balance disturbances in cancer patients.

Table 15. The possibility of balance problems being induced by cisplatin.

Likelihood	Number of participants out of 16
Not likely	9
Slight likelihood	5
Moderate likelihood	1
Very likely	1

21. If they do, what impact do you think the balance problems would have on their daily life?

The effect of possible balance problems in patients treated with cisplatin chemotherapy is shown in **Table 16**.

Table 16. The possible impact of balance problems on daily life.

Impact	Number of participants out of 16
No impact	4
Slight impact	3
Moderate impact	7
Severe	1
It depends on the severity	1

22. In your opinion, what is the purpose of ototoxicity monitoring for cancer patients?

The responses obtained from the participants could be grouped into four main responses:

1) Ten participants agreed that early identification of a hearing loss should be established by the Audiologist, with the hope that the Oncologist might alter the treatment protocol to prevent further hearing loss from occurring;

2) Two participants thought that nothing could be done to prevent a hearing loss from occurring due to cisplatin chemotherapy;

3) Another two participants would like to monitor hearing loss caused by chemotherapy should patients later on decide to lodge a claim with the Accident Compensation Corporation (ACC) to obtain hearing aids. These two participants would like to be able to distinguish the percentage of hearing loss caused by chemotherapy from that related to other possible causes such as a long term history of noise exposure;

4) A further two participants agreed that the main reason for ototoxicity monitoring was to plan possible intervention for patients affected by hearing loss due to cisplatin chemotherapy.

23. What benefits do you believe are there for the patient in ototoxicity monitoring?

The four main benefits in ototoxicity monitoring for the patient were:

1) rehabilitation, 2) prevention of further hearing loss, 3) support, and 4) social benefits.

Table 17. Benefits of ototoxicity monitoring to the patient.

Benefit	Number of participants out of 16
Rehabilitation	6
Prevention of further hearing loss	6
Support	3
Social benefits	1

The participants mentioned that early identification should lead to early rehabilitation. They also mentioned that support is offered to patients in a monitoring program as it gives them an understanding of their hearing loss and a point of contact for future

discussions regarding rehabilitation. Participants felt that reassurance is offered in the sense that the patient knows that the treatment they are receiving is holistic. One participant pointed out that early identification of a hearing loss and the implementation of prompt rehabilitation through amplification holds a social benefit for the patient.

24. What is your knowledge of ototoxicity monitoring protocols?

Out of the 16 participants, one participant felt that his/her knowledge of ototoxicity monitoring protocols was excellent. Five participants felt they had good knowledge of the protocols, while half (8 participants) rated their knowledge as being fair. Two said they had poor knowledge of ototoxicity monitoring protocols.

25. Can you name some ototoxicity monitoring protocols?

Out of the 16 participants 3 could name a protocol which has been developed by the American Speech-Language-Hearing Association (ASHA) while 1 participant was aware of a protocol developed by The American Academy of Audiology (AAA). One participant has mentioned the use of the Brock Scale for Ototoxicity monitoring.

26. Are you aware of any NZAS ototoxicity protocols or 'best practice guidelines' regarding monitoring?

Thirteen participants were correctly unaware of the New Zealand Audiological Society (NZAS) having ototoxicity protocols or 'best practise guidelines'. Two participants thought that such protocols and/guidelines do in fact exist, and one participant said he/she 'assumed that the NZAS would have such guidelines but couldn't say for certain.

3.3 First appointment (Questions 27 – 47)

27. Can you please describe in as much detail as you can, the referral process that leads to a patient receiving potentially ototoxic treatments being seen by Audiology?

The majority of the 16 participants interviewed described the referral process as follows with only insignificant differences amongst departments:

Oncology refers patients to Audiology via either fax or internal mail. Appointments are often needed urgently/on the day or on a very short notice period. When the referral was made on the day, the Audiologist tries to see the patient immediately. With a longer notice period, Audiology makes an appointment with the patient via telephone or an appointment letter that is sent out in the mail. The patient then arrives for their first appointment. Three participants acknowledged that patients often miss their first baseline audiometric evaluation and only arrives for testing after the first dose of treatment has been administered.

28. Are there any assurances or checks that are made to make sure the patient is seen for audiological assessment before their first ototoxic treatments?

Thirteen out of the 16 participants said that there are no assurances or checks made at their departments to make sure the patient is seen for audiological assessments before their first ototoxicity treatment. Only 3 participants mentioned that they run assurance checks. Two of the above mentioned participants said that their administration staff rings patients before the first appointment to remind them, but that they also ring patients who did not arrive for their baseline assessments to establish the reason behind their absence. The third participant mentioned that his/her hospital has a specialized department who phones all patients prior to their appointments to confirm appointment dates and times.

29. How important is it to obtain baseline audiometric results?

All sixteen participants were in agreement that it is very important to obtain baseline audiometric results.

30. When adult patients arrive at the audiology clinic, how informed do you think they are about the risk to their hearing from their treatment?

The level of information that participants feel cancer patients have regarding the risk to their hearing from their treatment is shown in **Table 18** below.

Table 18. The level of prior knowledge of risk to hearing from ototoxic treatment.

Level of prior knowledge	Number of participants out of 16
Uniformed	2
Slightly informed	5
Moderately informed	7
Well informed	1
Uncertain	1

31. Where do you think most patients get this information?

Most of the participants feel that patients get his information from Oncologists **(Table 19)**.

Table 19. Patient's sources of information regarding risk to their hearing.

Sources of information	Number of participants out of 16
ENT	1
Oncologist	15
Oncology nurse	2
Audiologist	1

32. Whose responsibility should it be to inform the patient about the potential risk to their hearing?

Out of the 16 participants interviewed the majority (14 participants) felt it should be the responsibility of Oncologist to inform the patient of the potential risk to their hearing. One participant said the responsibility should be that of the Ear-, Nose- and Throat (ENT) specialist and one assigned the responsibility to the audiologist. Three participants didn't identify a specific medical discipline and felt it should stay with the 'referrer'.

33. Does your Audiology department have ototoxicity monitoring protocols?

Seven of the 16 participants have ototoxicity monitoring protocols at their departments while the majority of participants (9 participants) do not.

34. Where did this list or practice come from?

Three participants explained that their current protocol originated from their own research on the topic of ototoxicity monitoring, while a fourth participant followed a protocol that was adopted from Auckland hospital. A fifth participant couldn't identify the exact origin of their protocol and mentioned that is was a 'historical protocol that had been there from the start'. Participant number six adopted a protocol from an article that appeared in one of the "Ear and Hearing" journals of 1999. The last participant said that they are currently following a protocol that originated as a result of a clinical trial that was running at their hospital.

35. How are these protocols circulated amongst audiologists?

Of the 7 participants who currently have a protocol, 5 have written down copies at their departments while 2 have electronic copies available on the hospital intranet. Four of these 7 participants, however, pass the protocols on from one colleague to another by 'word-of-mouth'.

36. Is it compulsory to follow it, or are they guidelines only?

Three of the 7 participants agreed that it is compulsory to follow these ototoxicity monitoring protocols, while 4 participants use the protocols as guidelines only.

37. How often are they followed?

Of the 7 participants, 1 reported to 'always' follow the protocols while another follows it only 'sometimes'. Five participants follow their protocols 'most of the time'.

38. How much time is typically allocated for a first appointment with this type of patient?

Anywhere from 15 minutes to 1 hour is allocated for first appointments.

Table 20. Amount of time allocated for first appointments.

Time allocated for first appointments	Number of participants out of 7
15 minutes	1
20 minutes	1
30 minutes	6
45 minutes	4
1 hour	4

One participant mentioned that an hour appointment for obtaining baseline audiometry results 'would be an over-kill'.

39. I will now name some audiometric evaluations. Can you please say "yes" if you use these methods as part of your test battery?

Some audiometric evaluations used by the participants in this study can be seen in **Table 21**.

Table 21. Audiometric evaluations conducted at the different DHBs.

Audiometric evaluation	Number of participants out of 16
Case history	11
Otoscopy	15
Tympanometry	15
Speech audiometry	16
Ipsi reflexes	9
Contra reflexes	5
Conventional audiometry	16
High frequency audiometry	15*
Screening TEOAEs	0
Diagnostic TEOAEs	0
Screening DPOAEs	0
Diagnostic DPOAEs	9 7 = up to 8 kHz 1 = 5-10 kHz 1 = up to 12 kHz 7 = don't use OAEs at all.
Tinnitus evaluations	0
Balance evaluations	0
Other	1 participant makes use of the "Brock Scale for Ototoxicity monitoring".

* The remaining one participant does not use high frequency audiometry because of a lack of normative data available for the ultra high frequencies.

40. I will now list some factors that might influence what you include in your current test battery. Please say "yes" if it applies to your clinic.

Five participants do ototoxicity monitoring out of 'clinical necessity', while 11 participants follow a 'best practice' approach to monitoring. Five out of the 16 participants are restricted by the equipment owned: 1 department doesn't own OAE equipment, and the other 4 participants do not have high frequency audiometers at their departments. Nine of the 16 participants feel they are restricted in what they can do because of limited time available for appointments. Two out of 16 participants are restricted because equipment isn't always available to use due to small office areas. Equipment is therefore often located in a room that is being used by another audiologist. Two audiologists felt they lacked both training and knowledge on the topic of ototoxicity monitoring.

41. After the first set of results is obtained, are reports (by Audiology) sent to anyone?

The majority of participants (9 participants) send out a report after baseline audiometric results are obtained together with a copy of the results to the referrer. Seven participants do not send out any reports. Instead they only send a copy of the audiogram to the referrer.

42. If so, who?

Oncologists were listed by the participants as being reported back to most frequently during ototoxicity monitoring.

Table 22. Professionals receiving reports on ototoxicity monitoring.

Results and/or copy of the audiogram to:	Number of participants out of 16
ENT specialist	3
Oncologist	13
Include the GP	4
Include the patient	2

43. How long would it typically take for this report to be sent?

Time frames for reports to be sent out ranged from being faxed through immediately to a report following within 4 weeks of the initial appointment.

44. How do you think this audiometric information is used by the referring clinician?

Two main points were highlighted by the participants. Firstly 7 of 16 participants didn't know *how* the information was being used, and secondly 9 of 16 participants were not sure if the information was being used *at all* by the referring clinician.

45. Do you think it influences treatment choices/options?

Four participants thought that the audiometric information was not used at all by the referring clinician while 7 participants thought that it was. Two participants were uncertain and another 3 said they were 'hopeful' that it was being used to influence treatment choices for their patients.

46. Who decides if the patient needs to be seen again by Audiology?

Fourteen of the 16 participants agreed that the Oncologist decides when the patient needs to be seen again, while 4 said that the decision lies with the audiologist. One participant mentioned that Audiology will monitor the patients once they're on their caseload, and that Oncology "*sometimes let patients slip through the cracks*" when is comes to monitoring.

47. Who decides when this appointment will take place?

Ten participants felt that the Oncologist was in charge of the decision when the next appointment would take place. Six participants felt that the decision remained with Audiology.

3.4 Subsequent appointments (Questions 48 – 51)

48. What is done differently on subsequent assessments (if anything) compared to the first? How long is this appointment typically?

Only 3 participants conduct a shorter case history on subsequent appointments. One participant won't repeat reflexes and OAEs unless a change in hearing has been noted. Four participants won't repeat bone conduction audiometry if air conduction thresholds remained stable and 2 participants won't repeat tympanometry on subsequent appointments. Six participants reported that nothing changes and that they conduct the same protocol on subsequent appointments than they did on the initial appointment.

49. Is the file updated with (or without) a new report on subsequent evaluations?

On subsequent appointments 6 participants update the file with a report while 3 departments only fax an audiogram through to the referrer, leaving 7 departments with no written updates of subsequent appointments.

50. Who decides when ototoxicity monitoring appointments stop?

Eleven participants agreed that the Oncologist decides when monitoring stops. Four participants mentioned that the Audiologist decides, and 1 participant mentioned that it is the decision of the treating physician when monitoring stops.

51. In your opinion, how long after treatment has stopped, should ototoxicity monitoring continue?

Varied responses were obtained from the participants as to how long monitoring should persist after cisplatin treatment has seized. The responses of 15 of the participants are shown below, while the remaining participant's response will be considered in the discussion section.

Table 23. Length of time that ototoxicity monitoring should continue.

Length of time that monitoring should continue:	Number of participants out of 16
1 month	2
3 months	3
6 months	2
12 months	4
2 years	1
1, 3, 6 and 12 months	1
Uncertain	2

3.5 Improvements and recommendations (Questions 52 – 63)

52. Do you think anything needs to be done at your DHB to improve ototoxicity monitoring practice or hearing and balance outcomes for patients receiving potentially ototoxic treatments?

Thirteen participants agreed that ototoxicity monitoring can be improved at their DHB. Three participants didn't think there was much they could change to improve their services.

53. What suggestions do you have?

Participants listed the following suggestions:

1. that a standardized protocol be made available to follow,
2. better communication between Oncology and Audiology,
3. more staff to be employed by the DHBs so that especially the bi-weekly follow-up appointments of these patients are possible for audiologists who are currently understaffed,
4. balance evaluations could be included in the protocols,
5. more awareness of where protocols are kept in audiology departments,

6. up-skilling of Oncologists, to stress the importance of monitoring,
7. to possibly train administration staff to use a "priority" sticker system to point out important appointments such as those needed for ototoxicity monitoring, and especially those needed for baseline audiological assessment.

54. What would you like to see happen?

Participants would like to see a national protocol, based on peer reviewed research, to be developed. They furthermore requested an NZAS protocol or 'best practise guidelines' for ototoxicity monitoring. Some participants acknowledged the need for high frequency audiometry equipment for them to conduct ototoxicity monitoring at their departments. One participant pointed out the medical staff should be better informed about drug interactions and its effect on hearing. Staff must be better informed on the importance of monitoring patients in treatment. There has to be better communication between departments and staff – both on an inter- and intra-departmental level. Another participant called for more stringent regulation to make sure that patients receiving ototoxic treatment do not fall through the cracks. Participants pointed out the need for more staff to be employed to help cope with their workload.

55. Is there a need for greater instruction / awareness among audiologists?

Fourteen out of 16 participants agreed that there should be greater instruction / awareness regarding monitoring among audiologists. Two participants did not agree.

Twelve participants would like to have more training at university while 7 would like to get more training on the job. Eight participants would like to see more workshops on the topic of ototoxicity monitoring offered at NZAS conferences.

56. Among Oncologists?

Fourteen participants thought that Oncologists need more awareness regarding ototoxicity monitoring.

57. Would you be in favour of a national ototoxicity monitoring protocol to be used by all DHBs?

All participants unanimously agreed to a national protocol to be adopted by all the DHBs.

58. If there was one, would you follow it?

All sixteen participants would follow such a protocol if there was one. Two participants mentioned the fact that it needs to be evidence-based and cost effective, i.e. not demanding too much of their time as time is so limited.

59. Would you follow it to the letter, or would you modify it to suit your clinic?

Nine participants would follow such a protocol to the letter, while 7 would modify it to suit the needs of their departments.

60. If protocol suggested an item of equipment you don't currently have, how easy would it be for you to obtain it?

Two participants thought it would be relatively easy to obtain equipment needed to conduct ototoxicity monitoring. Eight thought is would be somewhat difficult while 5 thought it would be difficult. One participant said it would be impossible to get equipment regardless.

61. Would having a national protocol make it easier for you to get that equipment?

Fifteen participants agreed that having a national protocol would help them obtain equipment needed for ototoxicity monitoring. The one remaining participant who thought it would be impossible to get equipment, also didn't think having a national protocol would help the situation.

62. Who, in your opinion should be involved in developing such a protocol?

One participant mentioned that the person who takes on the task of developing a national protocol should be 'someone who knows how to read an article and do a proper literature review'. Other stakeholders included the NZAS, Oncologists, Audiologists, ENT specialists, Paediatricians, Pharmacists, GPs, Physiotherapists, the Universities of Auckland and Canterbury, the Ministry of Health, and the Medical Council of New Zealand.

63. Thank you for your time. Do you have any questions or comments for me?

One participant requested to be informed of the outcome and results of this study.

4 Discussion

This study surveyed 16 senior/charge Audiologists employed by any of New Zealand's District Health Boards who conducted ototoxicity monitoring at their Audiology Department. Subjective evidence suggests that New Zealand Audiologists do not currently follow a nationwide ototoxicity monitoring protocol. Therefore the main aim of this study was to quantify the present standing of ototoxicity monitoring within New Zealand.

For each participant a telephone interview lasting approximately 45 minutes was conducted. Qualitative data from the telephonic interview was collected and analysed in Chapter 3. The discussion will follow the order of the telephonic interview.

4.1 Demographics (Questions 1 – 10)

Sixteen Audiologists with work experience ranging from 1 year to 36 years (mean 16.4 ± 10.6) took part in this study. The majority of participants graduated from the University of Auckland, New Zealand or from the University of Melbourne, Australia. Four participants graduated from other countries. The participants graduated between 1977 and 2009 (mean: 1993.6 ± 10.2) with work experience as a *senior* Audiologist ranging from 1 year to 23 years (mean: 7.7 ± 7.6). Four of the participants have had hospital-based work experience overseas including countries such as the United Kingdom, the United Arab Emirates and the Philippines.

There was no significant relationship between the date of graduation and self-reported knowledge of ototoxicity. The majority of participants (12) reported that they have acquired their knowledge on the topic of ototoxicity monitoring through the university program through which they graduated. No correlation however exists between the year in which the participants graduated and the source of their knowledge regarding ototoxicity monitoring.

4.2 Prior knowledge of Ototoxicity (Questions 11 – 26)

The aim of this section was to obtain information regarding the perception and prior knowledge of Audiologists with regards to the incidence, patho-physiology and impact of the ototoxic effects of cancer chemotherapy. Audiologists were also questioned on their knowledge regarding the purpose and benefits of a monitoring program and whether they were aware of the existence of such protocols.

Fourteen and 16 participants respectively, correctly identified cisplatin and aminoglycosides as the foremost medical treatments that can permanently affect hearing. Twelve out of the 16 participants believed that 0% - 75% of patients who receive *cisplatin* chemotherapy could develop a hearing loss which correlates fairly well with findings from the literature stating that 3% - 100% of patients are likely to sustain permanent damage to their hearing (McKeage, 1995). These participants also believed that 0% - 65% of patients receiving *aminoglycoside treatment* could develop a hearing loss, when in fact the estimates from research studies are far less stating that only 15% - 20% of patients will suffer damage to their hearing as a result of this group of antibiotic treatments (Taleb, et al., 2009). All of the participants agreed that a high frequency loss would develop from cisplatin chemotherapy with 10 participants stating that this hearing loss would be *moderate* in severity. Research however states that the hearing loss is *dose related*, *cumulative*, bilateral, and usually permanent (Roland, 2004). Ten participants thought that this moderate high frequency hearing loss caused by cisplatin treatment would have a moderate impact on the patients' daily life, with only 4 participants acknowledging the fact that hearing loss could potentially have a severe impact on one's life. Two participants mentioned that the severity of the hearing loss is largely dependent on whether the loss had spread into the speech frequency ranges of 0.5 kHz to 4 kHz. In a study by Fausti et al. (2005), the effect of hearing loss on activities of daily life is well described. Fausti et al. (2005) argues that when hearing is impaired to the extent that it affects speech intelligibility, it can restrict employment and recreational and social activities. Hearing loss not only compromises an individual's safety by hindering appropriate responses to warning signals and alarms, but it also contributes to psychosocial and physical health problems resulting in job and revenue loss, depression and social isolation (Mulrow, et al., 1990).

The majority of participants (9) correctly identified cisplatin to be causing permanent tinnitus which could potentially have a slight to moderate impact on activities of daily life for these patients. Nine participants also correctly identified that cisplatin is less likely to be vestibulotoxic (Sergi, Ferraresi, Troiani, Paludetti, & Fetoni, 2003).

When asked about what the purpose of ototoxicity monitoring for cancer patients was, most of the participants (10) correctly named *early identification* with the hope that the treating physician might alter the treatment protocol as a preventative measure for further hearing loss, as the main purpose of monitoring. In a study by Fausti et al. (2005) the author lists the following options the physician may consider if an ototoxic hearing change is identified: 1) changing the drug to one that has a reduced risk for ototoxicity; 2) stopping treatment; and 3) altering the drug dosage. Conversely, if no change in hearing is detected, the treating physician may decide to treat the patient more aggressively. Alarmingly, two participants believed that nothing could be done to prevent a cisplatin induced hearing loss from occurring. Interestingly, these two participants graduated within the last four to six years and listed their knowledge of ototoxicity monitoring to be "good". Equally alarming was the fact that only two more participants acknowledged the importance of monitoring hearing loss with the end goal of intervention in sight. However, when prompted about the perceived benefits of an ototoxicity monitoring program to the patient the following points were raised by participants: 1) rehabilitation (6 participants); 2) prevention of further hearing loss (6 participants); 3) support (3 participants); and 4) social benefits (1 participant).

Numerous studies have described the impact of hearing loss on individuals with a recent study by Preminger & Meeks (2010) highlighting the fact that hearing loss reduces the audibility of speech which in turn disrupts the ability to communicate with others, reducing the overall quality of life of individuals. Furthermore hearing loss has also been associated with depressive symptoms, feelings of loneliness an a small social network (Kramer, Kapteyn, Kuik, & Deeg, 2002). Therefore, as identified by the participants, the prevention of further hearing loss and the offering of appropriate support networks by Audiologists, should hopefully lead to better outcomes for patients with hearing loss. The *social benefits* listed by one participant as a benefit of ototoxicity monitoring results from early identification and implementation of prompt

rehabilitation through amplification. This participant argued that a patient previously deprived from social interaction as a direct result of hearing loss, will once again have access to the world through restored communication.

When asked about whether the participants were aware of any existing international ototoxicity monitoring protocols, only 3 participants listed the protocol developed by the American Speech-Language-Hearing Association (ASHA), while only 1 participant could name a protocol developed by the American Academy of Audiology (AAA). Thirteen participants were correct in stating that no protocol or 'best practise guidelines' on ototoxicity monitoring were available from the New Zealand Audiological Society (NZAS). The above mentioned results strongly indicate that not enough awareness amongst Audiologists and the topic of ototoxicity monitoring currently exists, and that more should be done by Audiologists themselves and/or by their professional governing body to raise the much needed awareness. This could be accomplished either through the completion of continued professional development papers and courses or through formal information sessions possibly presented by the NZAS Standards Committee at the annual audiology conference.

In summary, even though it seems as if the majority of the participants who took part in this study are relatively well informed about the incidence, patho-physiology and impact of cisplatin induced hearing loss on cancer patients, not many seem to fully recognize the importance or benefits of monitoring such patients for hearing loss. In addition not many participants seem to be familiar with the existence of available international ototoxicity monitoring protocols.

4.3 First appointment (Questions 27 – 47)

This section sought to obtain *detailed* information regarding the administrative journey a new cancer patient embarks on when undertaking chemotherapy treatment in a New Zealand public hospital. Questions regarding referral routes between Oncology and Audiology were explored with enquiries being made on whether any assurance checks are made to ensure patients are seen for audiological baseline assessment before their first ototoxic treatments. Participants were asked about their subjective opinion regarding the importance of baseline testing, how informed they

thought patients receiving ototoxic treatments are regarding the risk to their hearing, where they thought the patients source their information from, and whose responsibility they thought it is to inform the patients of such risks. Participants were also asked whether their department has an ototoxicity monitoring protocol, where it originated from, how it is being circulated amongst staff, how often this protocol is being followed by audiology staff, and whether it serves as a guideline only or whether it is compulsory to follow at all times. Questions regarding the protocol itself included the estimated time allocated for a first appointment and the methods of evaluation included for baseline testing. Furthermore factors that could possibly influence what the participants included in their test battery were explored. Lastly the topic of report writing and the concerns surrounding it was explored.

Twelve of the 16 participants interviewed described a comparable referral process with only insignificant differences amongst the different departments. Only 3 out of 16 departments currently run assurance checks to make sure patients will attend baseline audiometric evaluations. This method of checking involves a telephone call from the hospital to the patient prior to their appointment to confirm appointment dates and times. A simple change in the administrative process could be to obtain specialized "Patient Appointment Manager/Reminder" software to completely automate this labour-intensive and time-consuming task. By implementing such software, different patients can be reached through different channels. While some patients regularly check their emails, others are more likely to read a SMS message instead, while others prefer the old-style of communicating via the telephone. Therefore certain software packages offer different types of appointment reminders: via email, SMS or phone. Hospital departments can also make arbitrary combinations of these three types of appointment reminders where the patient can for instance be reminded by email 2 days before the appointment, and then be sent a SMS message one day prior to the appointment, when finally the process is completed with an automated call on the actual day of the appointment. All 16 participants agreed that baseline audiometric testing is of the utmost importance prior to starting potentially ototoxic treatments. However, a recent study by Alchin (2010) showed that this sentiment is often not implemented in practice. Alchin found that 30% of patients receiving ototoxic treatment in one DHB in New Zealand did not have an audiological assessment prior to the commencement of their treatment. This alarming statistic

could significantly be reduced by the implementation of the aforementioned computer software. This would not only reduce the seemingly large number of missed appointments but also consequently reduce the incidence of hearing loss amongst patients receiving ototoxic treatment as a direct result of their missed appointments.

Three quarters of participants interviewed (12 out of 16) felt that patients were only slightly-to moderately informed about the possible risk to their hearing from their treatment. Fifteen of the participants felt that the Oncologist was the main source of available information to the patients. Only one participant thought that the main responsibility of informing patients about what effect ototoxic treatment could potentially have on their hearing lay with the ear-, nose and throat specialist. Because the focus of this study was to determine the *subjective views and opinions* of Audiologists currently conducting ototoxicity monitoring, more research needs to be conducted to obtain objective statements from the wider medical community as to whom the responsibility currently falls upon, and whom it *should* fall upon. Only then can steps be implemented to streamline this process.

Alarmingly, 9 of the 16 departments interviewed did not presently have an ototoxicity monitoring protocol. The origin of the protocols followed by the remaining 7 departments range from 'adopted protocols that had always been there', to independently-researched and developed protocols. One department adopted a protocol from an article by Fausti et al. (1999), while another department created their own protocol only because the need for it arose as a direct result of a clinical trial currently running at the hospital. This diversity in origin confirms our initial suspicion of a lack of the existence, and use of a uniform and standardized monitoring protocol. Even though 7 departments have written copies of their protocols, 4 choose to pass the protocols on from one colleague to another via 'word-of-mouth'. We can only speculate as to why newcomers to the field of audiology in these hospitals are not encouraged to refer to the available hard copies of existing protocols. In addition, only 3 of the abovementioned 7 departments agreed that it is compulsory to follow their protocols, with the remaining 4 departments using it as a guideline only. Disappointingly, only 1 department reported 'always' following their protocol while another followed it only 'sometimes'. The remaining 5 departments follow their ototoxicity monitoring protocol 'most of the time'. As with conducting baseline evaluations, the use of a universal standardized monitoring protocol is paramount in

the establishment of a clear association between ototoxic drug and drug-induced hearing loss. In other words, for accurate associations to be made, all parties involved in conducting ototoxicity monitoring should ideally conduct the same test battery for all patients, all the time. Sadly, this does not currently seem to be the standard practise amongst hospital based Audiologists in New Zealand.

When asked about the amount of time allocated for a first appointment with a new cancer patient, half of the participants interviewed (8 out of 16) reported that 45 minutes to an hour is allocated for this type of appointment. This correlates well with the literature stating that it is not uncommon to spend 40 to 45 minutes procuring a complete baseline audiogram (Fausti, et al., 1999). One other participant was of the opinion that an hour appointment for obtaining detailed baseline audiometry results "would be an over-kill". Unfortunately, two departments only allow 15- and 20 minutes for baseline testing respectively. Even though the majority of participants reported the use of EHF audiometry, two departments offered the following as grounds for not including EHF audiometry in their department's test battery:

"*No we don't do it because there aren't any normative data available*"

and

"*No, because it gets messy having to change headphones between normal- and extended high frequency ranges. Also our department doesn't have the proper extended audiogram form to record EHF results onto*."

Even though ASHA recommends the implementation of effective programs for ototoxicity monitoring, time and cost requirements (as stated above) may be too demanding for many hospitals to support such a program. To combat this dilemma, Fausti and colleagues (1999) proposed a test protocol that is shortened, yet sensitive, using a target frequency protocol. These authors found that patients receiving treatment with cisplatin can be monitored for hearing threshold changes at only 5 targeted frequencies resulting in a 94% detection rate compared with monitoring at all 16 conventional and high frequencies. Targeting this abbreviated individualized range could provide an alternative to full frequency testing, removing the time and cost barriers that currently seem to discourage the use of monitoring programs in New

Zealand. However, the authors warn that even with validation of such a shortened procedure, it is suggested that a rapid protocol be used to identify the target-frequency range, with all testing then confined to the target frequencies. Full frequency baseline testing should still be completed and repeated if ototoxic change is noted through using the target-frequency protocol.

Lastly, when questioned about report writing and inter-departmental communication between Audiology and Oncology, 9 out of the 16 departments reported that they send out reports containing a copy of the results to the referrer. The timeframe for these reports vary from being faxed through immediately to arriving within 4 weeks of initial contact with the patient. Seven departments only forward a copy of the audiogram without an accompanying letter to the referrer, usually the Oncologist. Very rarely is the general practitioner, patient or family included in reporting back test results. Seven departments reported that they do not know *how* the test results are being used by the referring physician, while 9 departments doubt that it is being used *at all*. While one participant said

"*…they don't act on a hearing loss that's being pointed out by an Audiologist. I think they argue, "We either have a patient who is alive, with a hearing loss, or we have a dead patient"!*"

Another participant said

"*They should be comparing results, but they don't. In saying that… we don't either!*"

Such statements, although worrying, are especially insightful into the actual and current state of national ototoxicity monitoring. As pointed out by the AAA's position statement (2009), audiologic monitoring for ototoxicity is primarily performed for two purposes, firstly, the early detection of changes to hearing so that changes in the drug regimen may be considered; and secondly, so that audiological intervention can be implemented when handicapping hearing impairment has occurred as a result of ototoxic treatment. Further discussion regarding more awareness amongst both audiology and oncology, and better communication between the departments follows under section 4.5.

In summary, this section concludes that even though most departments reported that they followed a very similar referral route from oncology to audiology, many patients often miss their first baseline audiometric evaluation. As baseline testing forms the basis of interpretation of consecutive test results, it is vital that all departments endeavour to reduce the number of 'no show' appointments. Such a reduction in missed appointments could be obtained through the installation of cost effective computer software at all DHBs to manage patient appointments. Furthermore, even though these departments reported to conduct ototoxicity monitoring, their programs seemed to have originated from various sources, serving very different functions, with only 1 department reported to having 'always' followed their protocol as opposed to 'sometimes'. With only half of the participants interviewed allowing an appropriate 40 to 45 minute timeslot for baseline testing, "available time" and "proper equipment" were the two main reasons presented for not being able to incorporate more tests in their existing test batteries. By implementing a validated 5-frequency, targeted test protocol Fausti et al., (1999), Audiologist could possibly alleviate the pressures of time constraints put on them by cutting initial baseline testing times to about one-fourth of the usual time needed.

4.4 Subsequent appointments (Questions 48 – 51)

This part of the questionnaire sought to obtain a brief overview of how subsequent assessments differ from baseline testing (if at all), how long appointments typically last, *whose* decision it is to end ototoxicity monitoring and *when* monitoring should stop once treatment has stopped.

Six of 16 participants reported that they conducted the same protocol they followed for baseline testing at subsequent appointments. Three participants only carried out a shortened case history with their patients while 1 department did not repeat reflex- and OAE testing unless a change in hearing thresholds have been noted. When questioned however on what criteria constitutes 'a change in hearing', this particular participant was unable to present clear clinical guidelines and/or criteria. Furthermore it is well reported in the literature that the use of OAE testing can enable the Audiologist to detect significant changes in the status of auditory function *much earlier* than may be possible with conventional pure tone audiometry (Knight, et al.,

2007). The use of OAE testing also has the added benefit of being a more attractive alternative to both patient and clinician as it is less time consuming to the ailing patient and a more cost effective clinical tool for the clinician.

Also noteworthy is the fact that 4 participants would not repeat bone conduction testing if air conduction thresholds remained stable. Together with another 2 participants who did not repeat tympanometry on subsequent appointments, we have to be somewhat critical of the level of clinical skill and how these departments assess and monitor conductive hearing loss in these patients. Although the assessment of conductive hearing loss is not the prime concern for cancer patients receiving potentially ototoxic treatments it certainly can not be overlooked as a possible conductive component can be common among infectious disease patients and in patients who are immuno-suppressed as a direct result of chemotherapy agents (AAA, 2009).

On subsequent appointments only 6 participants update the file with a report while 3 departments only sent a copy of the latest audiogram to the referrer, leaving 7 of the 16 departments without updates after subsequent appointments. This could, to a certain extent, explain the perceived level of inter-departmental communication breakdown between the departments of oncology and audiology. A possible solution to this problem is to adopt a system across all DHBs that seem to work well for one department in particular. This particular Audiology department reported to store test results in a database which is accessible via the hospital intranet. Thereby, all updated test results for a particular patient should theoretically be at the finger tips of all the medical disciplines involved in, and responsible for, a patient's care. It is conceivable that such a system could easily be adopted by all DHBs.

When participants were asked how long after treatment had stopped they felt ototoxicity monitoring should continue, a varied response ranging from 1 month to 2 years post-treatment was obtained. Worth mentioning is the response of one participant who pointed out that

"We go on the basis of 'give us a ring if you think your hearing has changed', because the time spent on monitoring takes time away from patients who could have

been fitted with hearing aids. In other words, it takes away time from the hearing aid waiting list, which is a far more productive usage of time."

Once again the underlying themes of time constraints, cost effectiveness and efficiency come to light.

No definite criteria on how long monitoring should continue post cessation of treatment could be found from current literature. Two studies however appear to continue the monitoring process up until at least 6 months after the last dose of treatment (Campbell, 2007; Khoza, 2009). This result correlates well with the response from 7 of the 16 participants interviewed for this study. Hearing loss as a result of cisplatin ototoxicity has been reported to occur anywhere from shortly after the first dose to up to several months after treatment has stopped, with Knight et al., stating a median time to observation of ototoxicity as evaluated by ASHA criteria of 135 days (2005). As with the acquisition of thorough baseline testing, adequate follow-up with this subset of audiology patients can not be overemphasized.

In conclusion, this section highlights the following 4 points. Firstly, the lack of awareness amongst Audiologist to not only include the use of OAE testing in their test batteries but to also utilise this time- and cost-effective assessment tool in follow-up appointments with their patients. Secondly, Audiologists need to be more vigilant in their approach to assessing and monitoring the middle-ear status of these immuno-compromised patients. Thirdly, better inter-departmental communication could be obtained through implementing the storage of patient test result on hospital intra-nets which should then be easily accessible by all the independent medical disciplines involved in caring for a patient at any given time. The above mentioned system could ultimately lead to better patient outcomes. Lastly, even though 7 departments monitor their patients for late-onset hearing loss as a result of chemotherapy treatment, more awareness needs to be created amongst the remaining DHBs about the importance of continued monitoring.

4.5 Improvements and recommendations (Questions 52 – 63)

The closing section of the survey sought to obtain information regarding improvements and recommendations that Audiologists may have to improve the

current state of national ototoxicity monitoring. Participants were questioned on whether they thought anything could be done to improve monitoring at their own DHBs, what they would like to see happen on a national scale, and whether they thought more awareness amongst both Audiologists and Oncologists regarding ototoxicity monitoring was needed. Furthermore participants were asked if they would be in favour of a national protocol, and if such a protocol existed whether they would follow it or use is as a guideline only. Participants were also asked if they thought the existence of such a protocol would make it easier for them to obtain equipment that they might not currently have at their DHB. Lastly participants were asked who they thought should be involved in developing such a protocol.

From the 13 participants who believed that improvements on their current procedures of ototoxicity monitoring could be made, the following key points were listed. Participants would like to have a standardized, national protocol, based on peer reviewed research, to be made available to them. Furthermore, the participants longed for better communication between the departments of Audiology and Oncology. Audiology departments generally feel understaffed and consequently incapable of delivering quality care to this relatively high-need group of patients. A need to recruit more staff to deal with the high demand of especially bi-weekly appointments that some of these patients' care demand, currently exists. One participant would like to consider the inclusion of balance evaluations into their monitoring protocols, while another feels they could create more awareness amongst staff at their department as to where ototoxicity monitoring protocols are kept. Another participant feels Oncologists should be up-skilled on the importance of ototoxicity monitoring. Lastly, one department suggested that administrative staff be informed on and included in the use of a "priority sticker system" to visibly flag important audiology appointments such as those appointment slots needed for baseline- and follow-up ototoxicity monitoring testing.

When questioned on the need for more awareness among Audiologists and Oncologists regarding ototoxicity monitoring, 14 of the 16 participants were in agreement that both disciplines would benefit from more instruction and awareness on the topic. Participants unanimously agreed to the development and implementation of a national protocol, although interestingly only 9 departments reported that they

would follow such a protocol to the letter, with 7 DHBs admitting to most likely modifying it to suit the needs of their clinics. One commonly identified benefit of implementing such a protocol was that 15 of the 16 participants agreed it would assist them in the acquisition of the needed equipment to conduct evaluations in accordance with a set national standard.

Lastly, all participants agreed that numerous stakeholders be involved in the research and development of an ototoxicity monitoring program. Such disciplines included the NZAS, Oncologists, Audiologists, ENT specialists, Paediatricians, Pharmacists, GPs, Physiotherapists, the Universities of Auckland and Canterbury, the Ministry of Health and The New Zealand Medical Council. Participants acknowledge that all of the aforementioned disciplines and organisations would offer invaluable contributions to the undertaking of researching and developing a protocol that is not only acceptable but also current, peer reviewed, validated and standardized, as well as time- and cost effective.

4.6 Clinical Implications and future research

The main aim of this study was to investigate the current state of ototoxicity monitoring across all of the 20 DHBs which form New Zealand's primary health care system. Sixteen of the 20 DHBs took part in this study with 16 charge Audiologists who are currently responsible for conducting ototoxicity monitoring having been interviewed on this topic. We hypothesized that departments do not currently follow a uniform monitoring protocol, but are instead following independently researched and developed protocols based to a large extent on the only two guidelines currently available - namely the guidelines proposed by the American Academy of Audiology (AAA, 2009) and by the American Speech-Language-Hearing Association (ASHA, 1994). Sadly, only 7 of the 16 departments interviewed reported following a protocol with only 1 of these departments acknowledging AAA and ASHA as references to their work.

An intended consequence of this study is thus to utilize the information gathered as a tool to create awareness amongst all disciplines involved, but specifically

Audiologists and Oncologist regarding the topic of ototoxicity monitoring. It is our hope that follow-up studies will obtain supplementary information from disciplines such as Oncology in order to obtain a more balanced and quantifiable analysis. Furthermore it is anticipated that future research will lead to the development of a national, peer reviewed ototoxicity monitoring protocol that would ultimately be accepted by all Audiologists working in New Zealand. The benefit of a universally accepted protocol will hopefully be reflected by better collaboration and communication between Audiologists and other healthcare professionals such as Oncologists with the ultimate benefit of better hearing outcomes for audiology patients receiving ototoxic treatments.

4.7 Limitations of the study

The findings of this study must be considered in light of the limitations in the methodology of this study and the sample of participants that were analyzed. These limitations will be divided into Methodological and External limitations.

4.7.1 Methodological limitations:

Method of data collection: There are a number of advantages to using a questionnaire to obtain data. The data gathered through using a questionnaire could be standardized and therefore easily analysed. Also, data can be gathered relatively quickly from a large number of participants. Another advantage included being able to compare results with similar surveys used at other research institutions. Lastly, the entire process could be administered with ease by a single researcher. However, making use of a telephone questionnaire also posed the following disadvantages. Firstly, the responses of participants may be inaccurate through misinterpretation of questions. To prevent misinterpretations from occurring, participants were constantly reminded and encouraged by the researcher to ask for clarification if they at any point in time felt unsure about the aim of any particular question. Secondly, a reasonable sample size is needed before responses can be used to represent the population as a whole. As Audiologists are a very heterogeneous group, the small sample size of 16 participants is a limitation of the current study. Thirdly, although it was not the case in our study, the response rates can often be poor, with participants lacking the motivation to

complete or return questionnaires. Consequently, the researcher opted to use the questionnaire as a telephone interview, with a 100% response rate of 16 out of 16 participants being interviewed. Lastly, as this study sought to obtain subjective opinions from participants, qualitative- rather than quantitative data is presented, which may be viewed as a limitation by some.

Self-reported data: Self-reported data is often limited by the fact that it rarely can be independently verified. Participant responses had to be taken at face value. Also, according to Heppner and colleagues (2008), self-reported data contain several potential sources of bias: (1) selective memory, whereby participants may or may not remember experiences or events that occurred at some point in the past; (2) telescoping, where participants may recall events that occurred at one time as if they occurred at another time; (3) attribution, the act of attributing positive events and outcomes to one's own audiology department but attributing negative events and outcomes to external forces; and lastly (4) exaggeration, which encompasses the act of representing outcomes or embellishing events as more significant than is actually the case. To combat these potential biased responses both open- and closed questions, rating scales and fixed choice questions were used in the questionnaire.

Bias: Only the Audiologists' views on ototoxicity monitoring were obtained in this study. If time allowed, a more objective view could have been sought by including interviews with more healthcare professionals such as Oncologists and Paediatricians responsible for the care of these patients. Such data is currently being collected.

4.7.2 External limitations:

Time: Considerable delays were encountered with the initial research topic intended for this study, in a great part due to failed participant recruitment which led to a change of research topic in the middle of October 2010 – four months prior to the initial date of submission. If time allowed, a more in-depth study could have included a similar questionnaire directed towards Oncologists working alongside Audiologists in monitoring cancer patients for ototoxicity. The benefit of this would have been reflected in the acquisition of a less biased view on the current state of ototoxicity monitoring in the primary health care system of New Zealand, particularly with respect to the roles of Audiologists and Oncologists in the monitoring process. Further

disruptions to the study were caused by the Christchurch Earthquakes of September 2010 and February 2011.

5 Conclusion

Cisplatin-induced hearing loss is estimated to occur amongst 75% to 100% of patients receiving cancer treatment (McKeage, 1995). The results of a recent study by Alchin (2010), strongly indicated a lack of stringency in ototoxicity monitoring with only 7 of 23 individuals (30.4%) receiving ototoxic treatment in one DHB in New Zealand not having undergone audiological assessment *prior* to the commencement of their treatment. Of the participants who did receive a baseline audiometric evaluation, 31% did not receive any *follow-up* assessments during or after cisplatin therapy.

Results of our current study mirrored those recently found by the above mentioned author, with worrying evidence of 9 of 16 DHBs interviewed not presently following an ototoxicity monitoring protocol. Interestingly, other than initially hypothesized the origin of the protocols followed by the remaining 7 departments were reported to have ranged from historically adopted protocols to independently developed protocols. One department implemented an adapted version of the protocol of Fausti et al. (1999). This diversity in origin however, does confirm our initial suspicion of the lack of a uniform and standardized monitoring protocol.

Now that the need for a universal ototoxicity monitoring protocol has been established, it is the hope of the researcher that future studies will result in the development of this much needed protocol and guidelines.

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7 Appendices

6.1 Appendix A

Ethics Approval Letter

Human Ethics Committee
Tel: +64 3 364 2241, Fax: +64 3 364 2856, Email: human-ethics@canterbury.ac.nz

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Ref: HEC 2010/77/LR

15 October 2010

Kinau Venter
Department of Communication Disorders
UNIVERSITY OF CANTERBURY

Dear Kinau

Thank you for forwarding to the Human Ethics Committee a copy of the low risk application you have recently made for your research proposal "The current state of ototoxicity monitoring in New Zealand".

I am pleased to advise that this application has been reviewed and I confirm support of the Department's approval for this project.

With best wishes for your project.

Yours sincerely

pp MCGrimshaw

Dr Michael Grimshaw
Chair, Human Ethics Committee

6.2 Appendix B

Telephone Interview Questionnaire

The University of Canterbury

Department of Communication Disorders

Telephonic Interview with Participants in Research

The current state of ototoxicity monitoring in New Zealand

Researcher: **Kinau VENTER, Master of Audiology Student**
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Supervisor: **Dr. Greg O'BEIRNE, Senior Lecturer in Audiology**
Email: gregory.obeirne@canterbury.ac.nz
Phone: (03) 364 2987 ext. 7085

Introduction

This interview should take approximately 30 minutes to conduct.

I understand that this interview will be recorded, but only for the purpose or clarifying the information gathered, and that the recording will be deleted at the end of the study.

☐ Yes, I agree to participate ☐ No, I do not wish to participate

The purpose of this interview is twofold:

- To gather accurate information about what happens when patients who are undergoing potentially ototoxic treatment are sent for Audiological testing.
- To establish Audiologists' knowledge regarding ototoxicity monitoring.

Demographics

1. What is the name of the District Health Board (DHB) where you spend most / all of your time _____

2. Do you work at other DHBs or satellite clinics?

   ☐ Yes
   Where: _____

   ☐ No

3. How long have you been working as an audiologist? _____

   ☐ 0 - 2 years ☐ 2 - 5 years

   ☐ 5 - 10 years ☐ 10 years or more

4. Where did you obtain your qualification? _____

5. When did you graduate? _____

6. How long have you worked in your current position? _____

   ☐ 0 - 2 years ☐ 2 - 5 years

   ☐ 5 - 10 years ☐ 10 years or more

7. How long have you worked in the NZ hospital system? _____

   ☐ 0 - 2 years ☐ 2 - 5 years

   ☐ 5 - 10 years ☐ 10 years or more

8. Have you ever worked in hospital-based audiology overseas?

   ☐ Yes

   ☐ No

9. If so, what country and for how long? _____

   Country _____

   ☐ 0 - 2 years ☐ 2 - 5 years

   ☐ 5 - 10 years ☐ 10 years or more

10. Where did you learn about ototoxicity monitoring?

☐ University programme ☐ On the job

☐ Own reading – Continued Professional Development

☐ Conference

☐ Other: _____

Prior knowledge of Ototoxicity

11. As far as you know, what medical treatments can permanently affect hearing?

☐ Cisplatin ☐ Cranial radiation

☐ Carboplatin ☐ Amino-glycosides

☐ Other: _____

12. What percentage of patients receiving cisplatin chemotherapy do you believe could develop hearing loss? _____

13. What percentage of patients receiving aminoglycosides do you believe could develop hearing loss? _____

14. If they did develop a hearing loss from cisplatin chemotherapy, what configuration would the hearing loss typically take on?

☐ Flat ☐ Cookie Bite

☐ High Frequency ☐ Low Frequency

15. How severe is this hearing loss likely to be?

☐ Mild ☐ Moderate

☐ Severe ☐ Profound

16. What impact do you think this hearing loss would have on their daily life?

☐ No impact ☐ Slight impact

☐ Moderate impact ☐ Severe impact

17. What is the likelihood of patients receiving cisplatin chemotherapy developing **tinnitus**?

☐ Unlikely ☐ Slightly

☐ Moderately ☐ Very likely

18. In your opinion, is the **tinnitus** likely to be of transient or permanent

nature?

☐ Permanent ☐ Transient

19. What impact do you think the **tinnitus** would have on their daily life?

☐ No impact ☐ Slight impact

☐ Moderate impact ☐ Severe impact

20. Are patients receiving cisplatin chemotherapy likely to develop **balance problems**?

☐ Unlikely ☐ Slightly

☐ Moderately ☐ Very likely

21. If they do, what impact do you think the **balance problems** would have on their daily life?

☐ No impact ☐ Slight impact

☐ Moderate impact ☐ Severe impact

22. In your opinion, what is the purpose of ototoxicity monitoring for cancer patients?

_____
_____
_____
_____
_____

23. What benefits do you believe are there for the patient in ototoxicity monitoring?

_____
_____
_____
_____
_____

24. What is your knowledge of ototoxicity monitoring protocols?

☐ Excellent ☐ Good

☐ Fair ☐ Poor

25. Can you name some ototoxicity monitoring protocols?

☐ ASHA

☐ AAA

☐ Other: _____

26. Are you aware of any NZAS ototoxicity protocols or ‘best practice guidelines’ regarding monitoring?

☐ Yes ☐ No

First appointment

27. Can you please describe **in as much detail as you can,** the referral process that leads to a patient receiving potentially ototoxic treatments being seen by Audiology?

E.g.:

- Patient is seen by the oncologist and told to make an appointment themselves?
- Oncologist makes the audiology appointment for the patient?
- Patient is then contacted by audiology or ENT reception and appointment time is confirmed?
- Patient turns up and is seen?

28. Are there any assurances or checks that are made to make sure the patient is seen for audiological assessment before their first ototoxic treatments?

☐ Yes ☐ No

If yes:

29. How important is it to obtain baseline audiometric results?

☐ Not important ☐ Somewhat

☐ Moderately ☐ Very important

30. When **adult** patients arrive at the audiology clinic, how informed do you think they are about the risk to their hearing from their treatment?

☐ Uninformed ☐ Slightly

☐ Moderately ☐ Well informed

31. Where do you think most patients get this information?

☐ ENT ☐ ENT nurse

☐ Oncologist ☐ Oncologist nurse

☐ Audiologist ☐ Self - internet

32. Whose responsibility should it be to inform the patient about the potential risk to their hearing?

☐ ENT

☐ Oncologist

☐ Audiologist

☐ Other: _____

33. Does your Audiology department have ototoxicity monitoring protocols?

☐ Yes ☐ No

34. Where did this list or practice come from?

_____
_____
_____
_____
_____

35. How are these protocols circulated amongst audiologists?

☐ Written down copies

☐ Passed on through 'word of mouth'

☐ Other: _____

36. Is it compulsory to follow it, or are they guidelines only?

☐ Yes ☐ No

37. How often are they followed?

☐ Never ☐ Sometimes

☐ Most of the time ☐ Always

38. How much time is typically allocated for a first appointment with this type of patient? _____

☐ 0 – 15 minutes ☐ 15 – 30 minutes

☐ 30 – 45 minutes ☐ 45+ minutes

39. I will now name some audiometric evaluations. Can you please say "yes" if you use these methods as part of your test battery.

☐ Case history ☐ Otoscopy

☐ Tympanometry ☐ Speech Audiometry

☐ Ipsi-lateral acoustic reflexes ☐ Contra-lateral acoustic reflexes

☐ Conventional audiometry (specify the frequency) ☐ High frequency audiometry (specify the frequency)

☐ Screening TEOAEs ☐ Diagnostic TEOAEs (specify the frequency)

☐ Screening DPOAEs ☐ Diagnostic DPOAEs (specify the frequency)

☐ Tinnitus assessment ☐ Balance assessment

☐ Other: _____

40. I will now list some factors that might influence what you include in your

current test battery. Please say “yes” if it applies to your clinic.

☐ Clinical necessity ☐ Best practice

☐ Equipment owned by DHB ☐ Available time for appointment

☐ Equipment owned but not always available (being used)

☐ Audiologist training or knowledge

☐ Other: _____

41. After the first set of results is obtained, are reports (by Audiology) sent to anyone ?

☐ Yes ☐ No

42. If so, who?

☐ ENT ☐ Oncologist

☐ Audiologist ☐ GP

☐ Paediatrician

☐ Other: _____

43. How long would it typically take for this report to be sent? _____

☐ 1 – 2 weeks ☐ 2 – 3 weeks

☐ 3 – 4 weeks ☐ 1 month+

44. How do you think this audiometric information is used by the referring clinician?

_____
_____
_____
_____
_____

45. Do you think it influences treatment choices/options?

☐ Yes ☐ No

46. Who decides if the patient needs to be seen *again* by Audiology?

☐ ENT ☐ Oncologist

☐ Audiologist ☐ Other: _____

47. Who decides *when* this appt will take place?

☐ ENT ☐ Oncologist

☐ Audiologist ☐ Other: _____

Subsequent appointments

48. What is done differently on subsequent assessments (if anything) compared to the first? How long is this appointment typically?

_____
_____
_____
_____
_____

49. Is the file updated with (or without) a new report on subsequent evaluations?

☐ Yes, with a report ☐ No, without a report

50. Who decides when ototoxicity monitoring appointments stop?

☐ ENT ☐ Oncologist

☐ Audiologist ☐ Other: _____

51. In your opinion, how long after treatment has stopped, should ototoxicity monitoring continue?

☐ 1 month ☐ 2 months

☐ 3 month ☐ 6 months

☐ 12 months

Improvements and recommendations

52. Do you think anything needs to be done at your DHB to improve ototoxicity monitoring practice or hearing and balance outcomes for patients receiving potentially ototoxic treatments?

53. What suggestions do you have?

_____
_____
_____
_____
_____
_____

54. What would you like to see happen?

_____
_____
_____
_____
_____
_____

55. Is there a need for greater instruction / awareness among audiologists?

☐ Yes ☐ No

☐ More training at University ☐ More training on the job

☐ More workshops at NZAS conference or elsewhere

☐ Other: _____

56. Among oncologists?

☐ Yes ☐ No

57. Would you be in favour of a national ototoxicity monitoring protocol to be used by all DHBs?

☐ Yes ☐ No

58. If there was one, would you follow it?

☐ Yes ☐ No

59. Would you follow it to the letter, or would you modify it to suit your

clinic?

☐ Follow it to the letter ☐ Modify it to suit my clinic

60. If protocol suggested an item of equipment you don't currently have, how easy would it be for you to obtain it?

☐ Easy ☐ Somewhat difficult

☐ Difficult ☐ Impossible

61. Would having a national protocol make it easier for you to get that equipment?

☐ Yes ☐ No

62. Who, in your opinion should be involved in developing such a protocol?

_____
_____
_____
_____
_____
_____
_____

63. Thank you for your time. Do you have any questions or comments for me?

_____
_____
_____
_____
_____
_____
_____
_____