Chapter

Cisplatin Ototoxicity in Children

Penelope Brock, Kaukab Rajput, Lindsey Edwards, Annelot Meijer, Philippa Simpkin, Alex Hoetink, Mariana Kruger, Michael Sullivan and Marry van den Heuvel-Eibrink

Abstract

Cisplatin is a highly effective chemotherapy medicine used in the treatment of many childhood cancers. Like all medications, cisplatin has many side effects and as always the treatment of cancer in children is a balance between the risks of the medications used and their potential benefits. While many side effects of cisplatin chemotherapy are reversible, one major side effect is permanent and irreversible hearing loss (ototoxicity) in both ears which may worsen with time. The severity of cisplatin-related ototoxicity is associated with age and the cumulative dose received: the younger the child and the higher the total dose, the more severe the hearing loss may be. The spectrum of hearing loss varies from mild to moderate high tone hearing loss, to profound loss across the hearing range and permanent deafness. In addition to hearing loss, some children, especially adolescents, also experience tinnitus and vertigo. Cisplatin ototoxicity is one of most important of the many long-term effects experienced by children who are cured of their cancer. The burden of this toxicity may be compounded by other long-term health issues that emerge with time. This chapter will focus on cisplatin-induced hearing loss, its mechanisms, its health impact on the young person and ways to mitigate or reduce the severity of ototoxicity. This chapter has been written by a multi-disciplinary team including paediatric oncologists, audiologists, a psychologist, a health scientist and a parent of a child growing up with high frequency hearing loss.

Keywords: cisplatin, chemotherapy, cancer, children, ototoxicity, hearing loss, tinnitus, vertigo, prevention

1. Introduction

Cisplatin is a chemotherapy medicine which can cause hearing loss, tinnitus and vertigo. The most common and well documented toxicity affecting the ear is hearing loss and will be the main focus of this chapter [1, 2].

1.1 Cisplatin

Cisplatin was first successfully used in the late 1970s as chemotherapy, in addition to surgery, for the treatment of men with testicular cancer and published in a landmark study in 1980 [3]. At that time Dr. Jon Pritchard at the Great Ormond Street Hospital for Children (GOSH) in London was researching new treatments for

childhood cancer and had a particular patient with widespread ovarian cancer who would previously have been moved to palliative care. However, seeing the effect of cisplatin on testicular cancer in young men, he thought it might work on ovarian cancer in young women and got urgent permission to treat his patient with this new medication. The child's tumour had a spectacular response and shrank enough for the surgeon, at the time Professor Spitz, to successfully remove the tumour without having to perform a hysterectomy. She was cured and when she had children of her own, Jon became Godfather to her first child. The History of cisplatin and its introduction to medicine was captured by The Wellcome Trust in 2006 [4].

However, the challenge of introducing this powerful new chemotherapy to treat children with cancer was its toxicity, it was extremely emetogenic provoking severe nausea and vomiting, and was toxic to the kidneys (renal toxicity), ears (ototoxicity) and peripheral nervous system (neurotoxicity). Research into the side effects of this medicine on children at GOSH began in 1985 when Dimitrios Kouliouskas started studying the renal toxicity [5, 6].

In 1987, both in Brussels and London, a combination treatment of cisPLAtin and DOxorubicin was showing promise in the treatment of children with large liver tumours (hepatoblastoma). These tumours need expert surgery to remove the whole tumour intact; this combination was able to shrink hepatoblastomas to make surgery safer and in some cases make it possible to remove previously unresectable tumours. It was Jon Pritchard who coined the phrase "PLADO" for this combination treatment when passing a Play-Doh store on the way back to the airport in Brussels. Later that same year at the annual meeting of the International Society of Paediatric Oncology (SIOP) in Jerusalem Jon, along with Dr. Jacques Plaschkes (Paediatric Surgeon, Berne), Dr. Giorgio Perilongo (Padua) and others formed the International Society of Paediatric Oncology Epithelial Liver group SIOPEL to improve the treatment of children with liver cancer.

With increased use of cisplatin an alarming incidence of hearing loss was observed and at GOSH, Consultant Audiologist Sue Bellman noted a striking pattern seen on hearing tests (audiograms). Audiograms are a measure of the intensity of sound in decibels (dB) required for a person to hear a particular frequency measured in Hertz (Hz). The patterns seen in children with cisplatin-related hearing loss were very consistent and led to the development of an ototoxicity grading scale (the Brock Grading Scale) which could be used to evaluate the hearing loss acquired by one child and compare it to that of other children treated with cisplatin [7]. In this way different treatment regimens of cisplatin could be compared for ototoxicity. The grading scale showed that some children were more susceptible to cisplatin ototoxicity compared to others when given the same cumulative dose. This idiosyncratic and varied severity suggests possible biological or genetic susceptibility to hearing loss and has led to years of study of the genetic predisposition of patients towards cisplatin ototoxicity.

Cisplatin remains one of the most effective chemotherapy drugs for childhood cancer and is a key component in the treatment of solid tumours, specifically, malignant germ cell tumours, liver tumours, neuroblastoma, osteosarcoma and retinoblastoma, but also brain tumours, particularly medulloblastoma and ependymoma. However, the occurrence of irreversible hearing loss that occurs in approximately 50% of cisplatin-treated children, is a serious clinical challenge [8–10].

The impact of the hearing loss, tinnitus and potentially vertigo caused by cisplatin has serious consequences for the child, their family and the society in which they live [11]. Very young children with even mild forms of hearing loss have difficulty developing the skills of language leading to communication problems and reduced school performance [1]. Acquired hearing loss in adolescents with previously normal hearing, causes serious social and emotional difficulties [12].

In children with brain tumours, cisplatin-related ototoxicity is made more debilitating by damage to the hearing from surgery and radiotherapy, and ototoxicity may compound the learning difficulties caused by radiation to the whole brain.

Other platinum based medications have been developed, (carboplatin and oxaliplatin), with the aim of reducing toxicity but they do not have the efficacy in many cancers to replace cisplatin except in certain circumstances. Carboplatin, which is now widely used in childhood cancer, is less ototoxic (its main toxicity is to bone marrow), but it cannot be substituted for cisplatin without careful clinical trial evidence that it is as effective. When used in combination with cisplatin, the combined ototoxicity is greater than the sum of the two individual drugs [13]. When carboplatin is used at high dose, such as for bone marrow ablation prior to autologous bone marrow transplantation, it is ototoxic.

As it is unlikely cisplatin will be replaced by other agents to treat childhood cancer any time soon, monitoring its impact on a child's development and education, increasing awareness of its effects and support for families, and finding ways to prevent ototoxicity are the key medical needs for the foreseeable future. The results of recent oto-protection clinical trials testing agents to mitigate cisplatin hearing loss have recently been assessed and a clinical guideline published [14, 15].

1.2 Hearing and balance

Hearing and balance are the two senses that are perceived by means of the inner ear that consists of the cochlea (the organ of hearing) and the vestibular system (the organ of balance), see **Figure 1**.

Hearing is the perception of sound and the vestibular system detects motion of the head and body. Together with vision and propriosepsis, which is the internal sense of positioning within the body, these senses are elementary for orientation and sense of safety in the world. For the developing child, normal hearing is essential to learn to detect, discriminate and identify sounds, culminating in the ability to use and understand spoken language, enjoy music and identify potential harm. A normal function of the vestibular system is essential for learning to move freely and efficiently. The importance of hearing for the development of speech

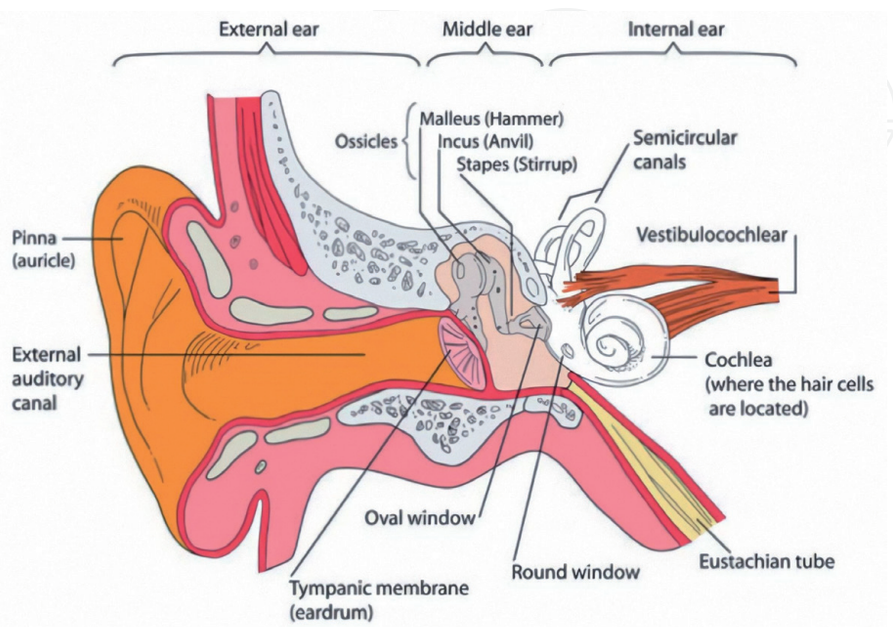

Figure 1.
The ear.

and spoken language is well recognised and in several countries national newborn hearing screening programs have been implemented to detect congenital hearing loss as early as possible, and enable timely intervention. Hearing loss has many impacts on daily auditory functioning, communication, psychosocial wellbeing, and general health, so high quality hearing care for children is best delivered by multidisciplinary teams consisting of medical specialists, audiologists, speech language therapists and (developmental) psychologists. Acquired hearing loss may have multiple causes, but one of the common causes in childhood follows treatment for childhood cancer with cisplatin.

For a sound to be perceived, it has to travel through the external ear, the middle ear, the cochlea and the auditory nervous system to the auditory cortex in the brain. Sound waves are collected by the pinna and channelled by the external auditory canal to the tympanic membrane, causing it to vibrate. The middle ear is an air-filled cavity containing the ossicles (malleus, incus and stapes). The footplate of the malleus rests on the eardrum (tympanic membrane). When the membrane vibrates in response to sound it causes movement of the malleus. This movement is, in turn, transmitted via the incus and the stapes to the fluid filled cochlea.

The normal cochlea is a coiled structure with two and a half turns. It is divided lengthways into three fluid-filled compartments by two membranes (the basilar and Reissner's membrane). These create three fluid filled spaces, the scala tympani is the lower compartment, the cochlear duct (scala media) the middle one and the scala vestibuli the upper compartment, as shown in **Figure 2**. The inner ear hearing apparatus (the organ of Corti) consists of two types of sensory hair cells, the inner hair cells and the outer hair cells, resting on the basilar membrane, also shown in **Figure 2**.

When the middle ear stapes footplate moves, pressure waves in the cochlear fluid produce movement of the basilar membrane and the inner and outer hair cells in the organ of Corti. Excitation on the surface of the inner hair cells creates a neurotransmitter impulse which is transmitted along the cochlear nerve (VIIIth

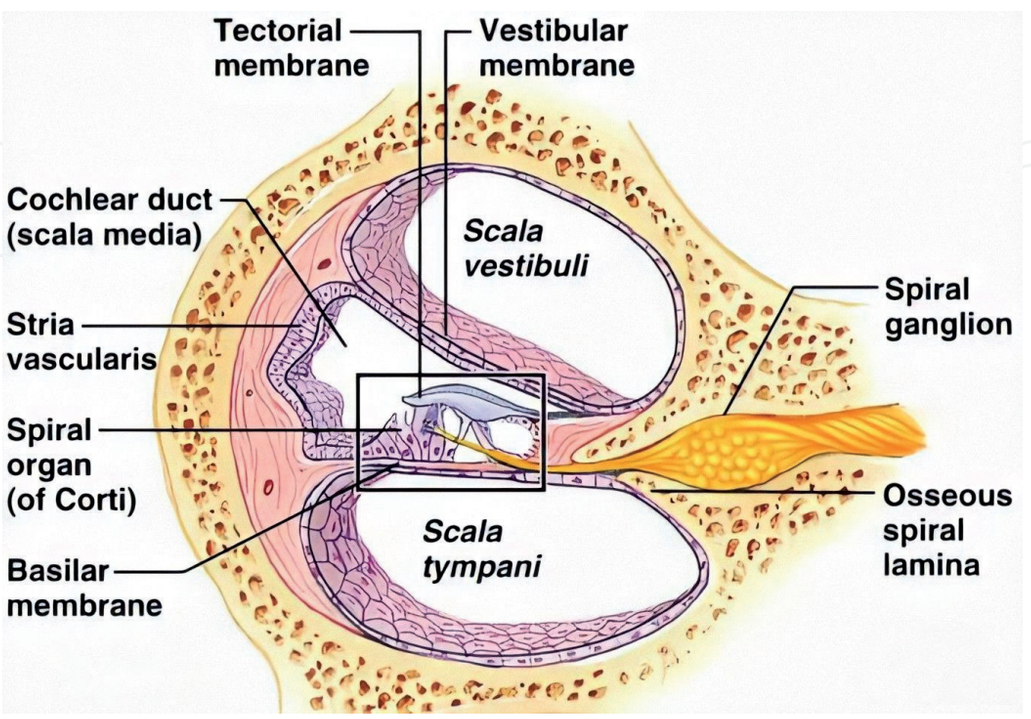

Figure 2.
Cross section of the cochlear scalae in the basal turn.

cranial nerve) to the brain stem and auditory region of the brain. Damage to both the inner and outer hair cells from cisplatin, causes loss of this signal transmission, with the highest sound frequencies lost first.

2. Cisplatin and cisplatin-related toxicity

Childhood cancer is divided into haematological cancer and solid tumours. Haematological cancers occur in the bone marrow and lymph glands (leukaemia and lymphoma) and solid tumours occur in organs such as the liver, kidneys and nerves; solid tissues such as bone and muscle; and the brain (brain and spinal tumours). Cisplatin is currently used alone or in combination with other chemotherapy to treat solid tumours and brain tumours, and only rarely for leukaemia or lymphoma.

When given to children intravenously cisplatin causes acute nausea and vomiting, and may cause renal impairment (nephrotoxicity), neurotoxicity and ototoxicity. When given to adult patients, the dose limiting toxicity is neurological (peripheral neuropathy, tinnitus and vertigo) whereas in children its major long-term effect is ototoxicity with permanent irreversible hearing loss. The severity of ototoxicity varies with age being more severe in younger children, the dose of cisplatin administered at each treatment and cumulative dose of cisplatin given during the course of treatment. However, susceptibility to these effects and their severity vary from individual to individual. Some children will develop very little toxicity despite large cumulative doses and others will develop relatively severe toxicity with only one or a few doses. The significant heterogeneity in the occurrence of ototoxicity among similarly treated patients, suggests that genetic susceptibility contributes to the occurrence of cisplatin-related hearing loss in individual children [16–19] (section 2.5.3).

2.1 Cisplatin mechanism of action

Cisplatin is a simple chemical compound made up of an atom of the platinum metal bound with two atoms of chlorine on one side (cis) and two molecules of ammonia on the other side. When in solution in the blood surrounded by a high concentration of chloride ions cisplatin remains in its neutral form. However, when cisplatin enters a normal cell or a cancer cell which has lower concentrations of chloride ions, cisplatin undergoes spontaneous hydrolysis with water. In this activated state it can enter the nucleus of a cell and become irreversibly bound into the double strands of nuclear DNA forming a cisplatin-DNA adduct (**Figure 3**).

Both normal and cancer cells have complex molecular mechanisms that have evolved to repair the damage to DNA caused by toxins such as cisplatin and other chemotherapy agents. If a cell can activate its molecular repair mechanism and successfully repair the damaged DNA, it will survive and continue to thrive, but if the damage is irreparable, both normal and cancer cells can switch on a molecular process called programmed cell death (apoptosis) and the affected cell will die. Cells can also resist the effect of cisplatin by producing free radicle oxygen molecules within the cell cytoplasm that neutralise the cisplatin molecule. The use of cisplatin in the treatment of children with cancer relies on the fact that solid tumour cancer cells are less able to repair DNA damage than normal cells, and are less resistant to cisplatin, making them more susceptible to apoptosis than the child's normal tissues. However, within the cells of some normal tissues such as within the hearing apparatus, the kidney and peripheral nerves are directly damaged by the effects of cisplatin.

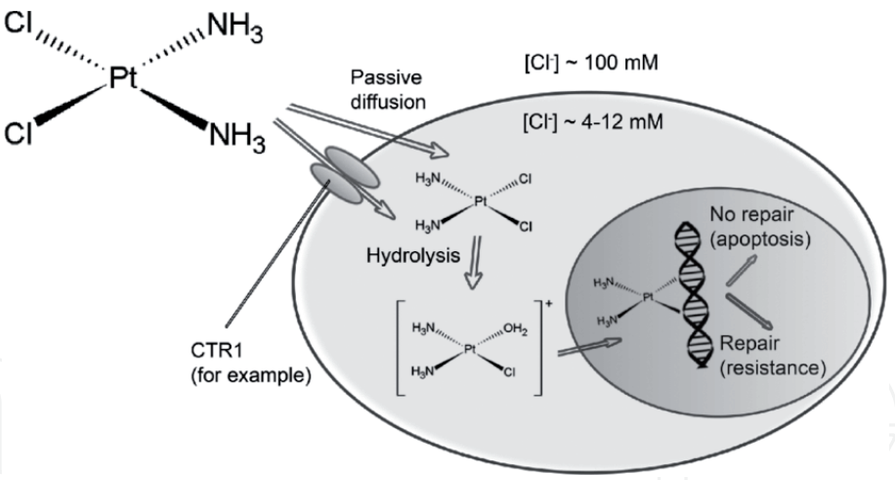

Figure 3.
Cisplatin structure and mechanism of action [20].

2.2 Cisplatin administration

Cisplatin is administered intravenously. It is infused via a central venous catheter over various times but usually between 1 and 6 hours, and given with a large amount of hydration fluid with a high chloride concentration to reduce its toxicity. The hydration is usually administered over 24 hours so the child must stay in hospital during its administration. If the child is not hospitalised throughout this time, adequate hydration needs to be managed by other means.

In the early years, cisplatin was administered for an hour following a period of hydration of about 6 hours, with another 24 hours hydration afterwards.

Times of administration of cisplatin began to lengthen in the late 1980's when it was found that lengthening the infusion time reduced the severity of the nausea and vomiting the child experienced. Cisplatin infusion times in Europe reached up to 96 hours continuous infusion. However, with the introduction of new classes of antiemetic drugs in the 1990's, specifically the HT3 inhibitors (ondansetron and others) the cisplatin infusion times were able to be reduced [20].

In some settings and for some cancers, the dose of cisplatin was split over 5 days reducing the need for 24-hour hydration and hospitalisation. So, in place of a standard dose, and very emetogenic dose of 100 mg/m^2 on one day, 20 mg/m^2 would be given on day 1 through 5.

2.3 Cisplatin and emesis

Cisplatin is highly emetogenic. The nausea and vomiting which ensues appears to be universal. Fortunately, the introduction of the HT3 inhibitors in the 1990s and additional classes of antiemetics more recently, the severity of emesis can be greatly modified in most children [20]. However, effective antiemesis requires a cocktail of antiemetics to be given at least 30 minutes prior to administering cisplatin and that the best antiemetic control is achieved from the very first cisplatin dose. Inadequate antiemetic treatment at the start of cisplatin therapy can lead to the development of anticipatory vomiting which is a particular problem in adolescents. This is when a patient starts to vomit when the idea of receiving chemotherapy is triggered for example on sight of the hospital or if they meet a

ward staff member in a shop. Once anticipatory vomiting has become established it is very difficult to control.

2.4 Cisplatin nephrotoxicity

Cisplatin is almost entirely excreted through the kidney. When in its ionised form, cisplatin is very toxic to kidneys, so to ensure cisplatin is excreted in non-ionised form it needs a high concentration of chloride ions in the posthydration fluid. Nephrotoxicity in young children is partially reversible although this may be due to further maturation of the kidney in very young children rather than actual improvement [5, 6].

2.5 Cisplatin ototoxicity

The hearing loss caused by cisplatin is permanent and bilateral and it may worsen with time. It is worse in very young children, the ear at this age appears to be more susceptible to damage compared to that in older children and adults. Cisplatin causes high frequency hearing loss which may happen following the first cycle of treatment and once acquired it tends to worsen with increasing cumulative doses of cisplatin and eventually may spread towards the lower frequencies important for speech [7].

2.5.1 How cisplatin enters the ear

Cisplatin enters the inner ear or cochlea through a number of molecular transport pathways as shown in **Figure 4** [21]. The cochlea (and vestibulum) are surrounded by several distinct barriers separating the inner ear vasculature and the inner ear fluid compartments that are filled with perilymph, endolymph or intrastrial fluid. Their anatomical sites are not yet clearly identified, but Neiberg et al. [22] summarise them as follows: "tightly coupled vascular endothelial cells form the blood-perilymph or blood-labyrinth barrier (BLB)". The same authors consider the separation between blood, endolymph and intrastrial fluid as being more complex: "tightly coupled strial endothelial cells form the barrier between blood and intrastrial fluid". This latter is separated from endolymph by epithelial marginal cells in conjunction with endothelial basal cells from the intrastrial compartment. These are also referred to as the blood-strial barrier or intrastrial fluid-blood barrier. The more general use of the term BLB covers all of these barriers.

The BLB plays an important role in cochlear homeostasis to maintain its functional integrity. As a highly specialised capillary network it selectively allows the passage of nutrients and ions in and out of the cochlea, and functions as a shield to protect the inner ear from toxic agents. However, cisplatin seems to affect the stria vascularis and might cause breakdown of the BLB [23]. The permeability of the BLB is also influenced by inflammation, diuretics, noise and a number of other factors [22]. Several organs including the liver, spleen and kidneys are able to rapidly clear cisplatin and its derivatives. Due to its unique structure, however, this ability is considered to be low for the cochlea [24]. Thus, the BLB may serve as a port of entry for cisplatin, from which it is hard to escape. Cisplatin may be retained in the cochlea for several months to years after treatment [24]. Another drawback of the BLB that is mentioned in [22] is the difficulty it poses to deliver otoprotective agents to the cochlea, as systemic delivery is highly inefficient, while local delivery is inherently invasive with limited permeability of the round window membrane.

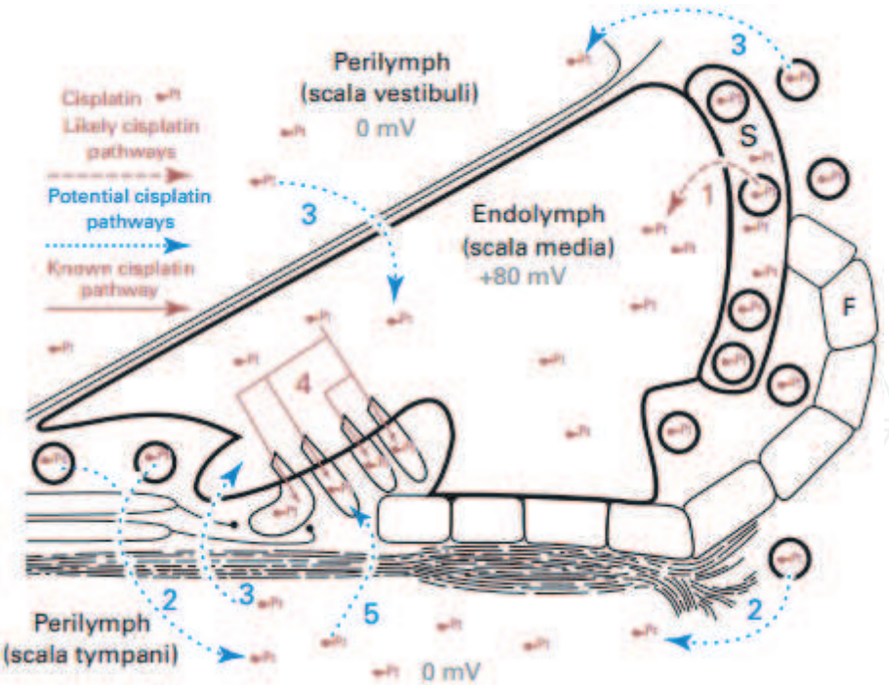

Figure 4.
Model of the cochlea and cisplatin (Pt) trafficking routes. Potential pathways for systemic Pt to cross the blood-labyrinth barrier and enter hair cells include (1) a transstrial trafficking route from strial capillaries to marginal cells, followed by clearance into endolymph; (2,3) traversing the blood lymph barrier into perilymph and subsequently into endolymph via transcytosis across the epithelial perilymph/endolymph barrier. (4) once in endolymph, Pt enters haircells across their apical membranes. (5) Pt in the scala tympani could also pass through the basilar membrane into extra cellular fluids within the organ of Corti and enter haircells across their basolateral membranes. S stria vascularis; F spirocytes in spiral ligament [22].

2.5.2 Destruction of the hair cells of the cochlea

Cisplatin causes irreversible damage to the hair cells of the cochlear apparatus located in the inner ear. Once within the perilymph cisplatin may remain permanently trapped in the inner ear and may continue to cause delayed hearing loss [24]. The molecular mechanism of cisplatin related ototoxicity and destruction of the hair cells is currently unknown. It is thought to involve the production and activation of Reactive Oxygen Species, (ROS), within the cell cytoplasm which the cell attempts to neutralise by a specific molecular mechanism. However, the capacity of the hair cells to neutralise ROS may become exhausted with time or exceeded by the cisplatin dose, leading to hair cell death. Hair cells in the cochlea are fixed in number and do not regrow, so once destroyed hearing begins to be lost. This would explain why higher doses of cisplatin given per day cause more toxicity. **Figure 5** shows how the hydrated complex is neutralised by the cell [25].

2.5.3 Genetic susceptibility to hearing impairment

Over the years, several studies have focused on genetic susceptibility to cisplatin-induced hearing loss using candidate single nucleotide polymorphism (SNP) approaches and more recently genome wide association studies (GWAS). Results to date are conflicting, as studies were often underpowered and did not included multiple testing or replication efforts. Differences in patient populations (e.g., ancestry), sample size, methods of audiometric testing and end point definitions with regards to audiological testing or classification attributable factors that may explain these discrepancies in results and have shown, that certain cohort and

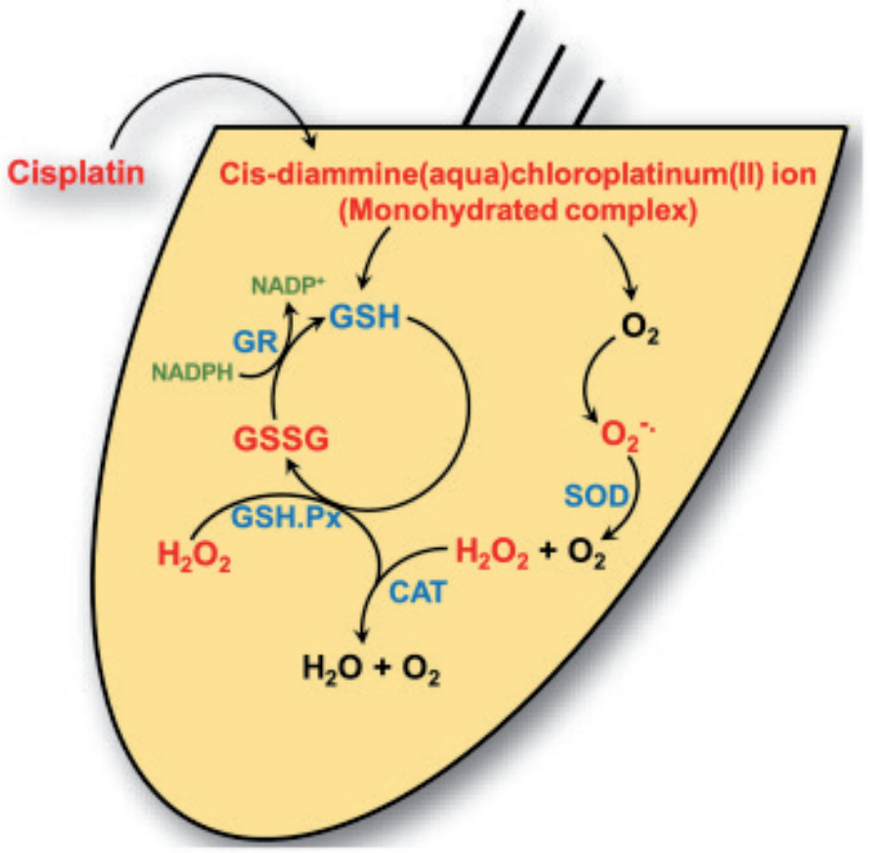

Figure 5.
Cisplatin's interaction with the cochlear antioxidant defence system. Cisplatin is converted to a cis-diammine(aqua)chloroplatinum(II) (a monohydrate cisplatin complex) upon entering the cell cytoplasm. These reactive platinum species can react with molecular oxygen (O_2) to generate superoxide (O_2^{--}) which is detoxified by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2) and oxygen. Hydrogen peroxide is further detoxified by catalase to water (H_2O) and oxygen. Cisplatin reactive intermediates readily bind to and oxidise the antioxidant reduced glutathione (GSH) to oxidised glutathione (GSSH). Glutathione peroxidase (GSH.Px) consumes GSH to produce glutathione disulfide (GSSG) in the process of converting H_2O_2 to H_2O. Glutathione reductase (GR) reduces GSSR to GSH by using the reduced form of nicotinamide adenine dinucleotide phosphate (NADP+) NADPH, as cofactor [24].

treatment factors (e.g. cranial irradiation, type of platinum agent, total cumulative doses and use of co-medication) may be even more important than genetic susceptibility. In addition, comparison of genetic studies to date have been hampered by heterogeneity in phenotype definitions **Table 1** [26–28].

Currently, efforts are being made to identify and meta-analyse relevant genetic variants, to enable the selection of children with a high risk of platinum related hearing loss to facilitate clinical decision making and where possible to intervene to prevent ototoxic damage. Alongside intensifying hearing screening any other intervention would require careful clinical risk assessment aided by thoughtful discussions with parents, carers and older children themselves. This could then lead to agreeing on an alternative cancer treatment plan for the child [29].

2.5.4 Hearing assessment in children

Functional hearing is represented by 'air conduction' thresholds measured using headphones, and 'bone conduction' thresholds measured using a vibrator placed on the mastoid bone. The air conduction thresholds indicate the status of the external ear, middle ear, cochlea and central auditory nervous system. The bone conduction thresholds indicate the status of only the cochlea and central auditory nervous system.

Candidate gene studies			
SNP	**Described variants**	**Reference**	**Statistically significant**
ACYP2	rs1872328	1#,2, 16#	Yes see also below in GWAS studies
TPMT	rs12201199 rs1142345 rs1800460	1#,3,4,6,12,15# 1#,3,4,6,12,15# 1#,3,4,6,12,15#	CR CR CR
COMT	rs9332377 rs4646316	1,3,4, 6,12 1,3,4,6,12	CR CR
SOD2	rs1880	13#,15#	CR
ABCC3	rs1051640	6, 15#	CR
LRP2	rs22288171 rs2075252	7#,15# 7#,8, 12, 15#	CR CR
GSTM1	null	7#,12	No
GSTM3	*B	10	Yes but no replication
GJB2	rs80338939	9	Yes but no replication
GSTP1	rs1695	5,12,15#	CR
SLC22A2	rRs316019	15#	Yes but no replication
GWAS studies			
ACYP2	rs1872328	13#	Yes GWAS n = 238 replication in historical subjects n = 68 paediatric brain tumours
		1#	Yes CGA n = 156 brain tumours
		2	Yes CGA n = 149 various CNS and solid tumours
		15#	No CGA in 900 various ped cancers
WFS1	rs62283056	14#	Yes GWAS n = 511 replication in 18.620 subjects testicular cancers
		15#	No CGA in 900 ped cancer patients

**SNPS that were tested once, but not found to be associated with ototoxicity were not included. CR = conflicting result CDA = candidate gene approach. #: studies that adjusted for multiple testing.*
(1) Thiesen, Pharmacogenetics and genomics, 2017; (2) Vos,Ppharmacogenetics and genomics, 2016; (3) Hagleitner, PloSone, 2014; (4) Yang, Clinical Pharmacology and Therapeutics, 2013; (5) Rednam, 2013; (6) Pusegoda, Clinical Pharmacology and Therapeutics 2013; (7) Choeypasert,2013;, (8) Riedeman, 2008; (9) Knoll, Laryngoscope, 2006; (10) Peters, AntiCancer drugs, 2000; (11) Brown,Cancer Med, 2015; (12) Ross, Nat Gen, 2009; (13) Xu, Nat Gen, 2015; (14) Wheeler, Clin Cancer Research, 2017; (15) Langer, EJC, 2020).

Table 1.
Relevant SNP studies on cisplatin related hearing loss in childhood cancer by candidate gene studies.*

2.5.4.1 Testing of the status of the external and middle ear

A check-up of external - and middle ear status is required to exclude any conditions causing obstruction for the sound to reach the cochlea. When sound is

obstructed from reaching the cochlea, this is called a conductive hearing loss. Causes for conductive hearing loss include accumulation of cerumen, infections or tympanic membrane perforation [30]. Otoscopy allows for visual inspection of the auditory canal, the tympanic membrane and part of the middle ear. Tympanometry may be used to indicate the presence of middle ear pathology, by measuring the mechano-acoustic properties of the middle ear system [31]. A probe is placed in the ear canal for a few seconds, which delivers a tone and changes the air pressure. The way in which the pressure changes affect the sound level developed in the ear canal can provide useful information about the status of the middle ear.

2.5.4.2 Behavioural testing of inner ear status

Several behavioural tests are available to estimate hearing thresholds in children. The reliability of these tests depends on the child's age, neurological status, development and motivation.

The usual way to assess hearing function in older children and adults is to measure the air and bone conduction thresholds, i.e. the quietest sounds which can be detected, as most hearing problems are associated with raised (poorer) thresholds. Audiometry is the process of measuring hearing thresholds at a range of frequencies (pitches). Thresholds may be measured in various ways and are usually displayed on an audiogram, which shows the thresholds at each audiometric frequency. Different types of hearing loss and their classifications can be found in a previous IntechOpen book [32]. **Figure 6** shows a typical Pure Tone Audiogram of normal hearing on the left and moderate cisplatin induced high frequency sensorineural hearing loss on the right.

The horizontal axis shows the test frequencies. Octave intervals are tested from 125 or 250 to 8000 Hz (8 kHz). The vertical axis is the level of sound in decibels - termed dB HL (Hearing Level) where the quietest levels are at the top. Thus, the "normal range" is anything down to 20 dB HL (vertical axis) and thresholds higher than 20 dB HL (lower on the audiogram) represent a clinically significant hearing loss. Where there is no conductive hearing loss the air - and bone conduction

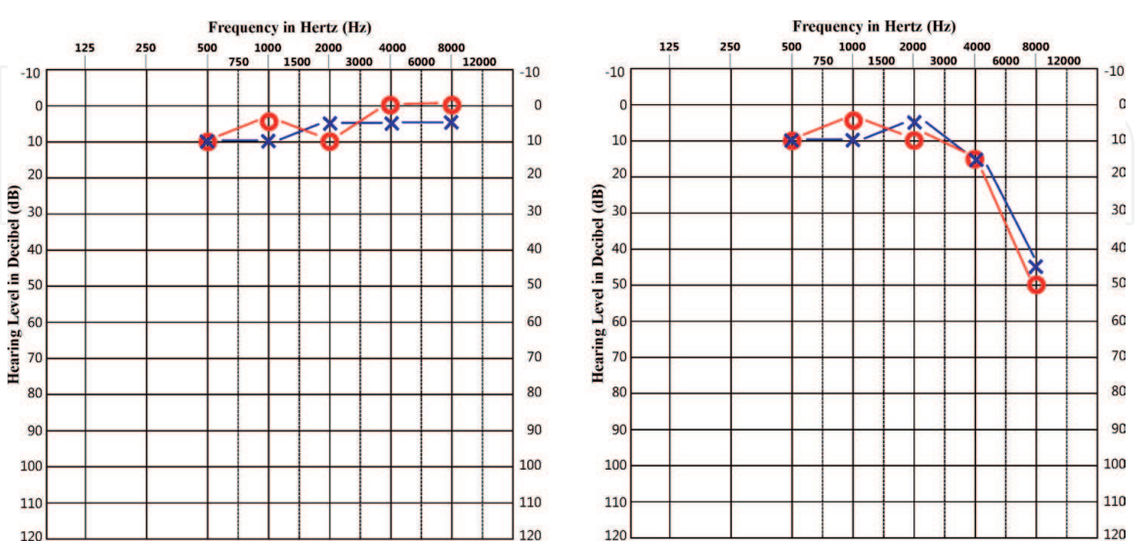

Figure 6.
An audiogram showing normal hearing on the left, and an audiogram depicting a typically symmetrical high frequency hearing loss on the right. The red line represents the results for the right ear, and the blue line the results for the left ear. The x-axis portrays the frequency of sound in hertz, and the y-axis the hearing level in decibel with acoustic reference zero for calibration given in ISO-381-1 for frequencies up to 8 kHz and in ISO-381-5 for the extended high frequencies (Meijer A.J.M. Childhood cancer related hearing loss and tinnitus. Utrecht University; 2021).

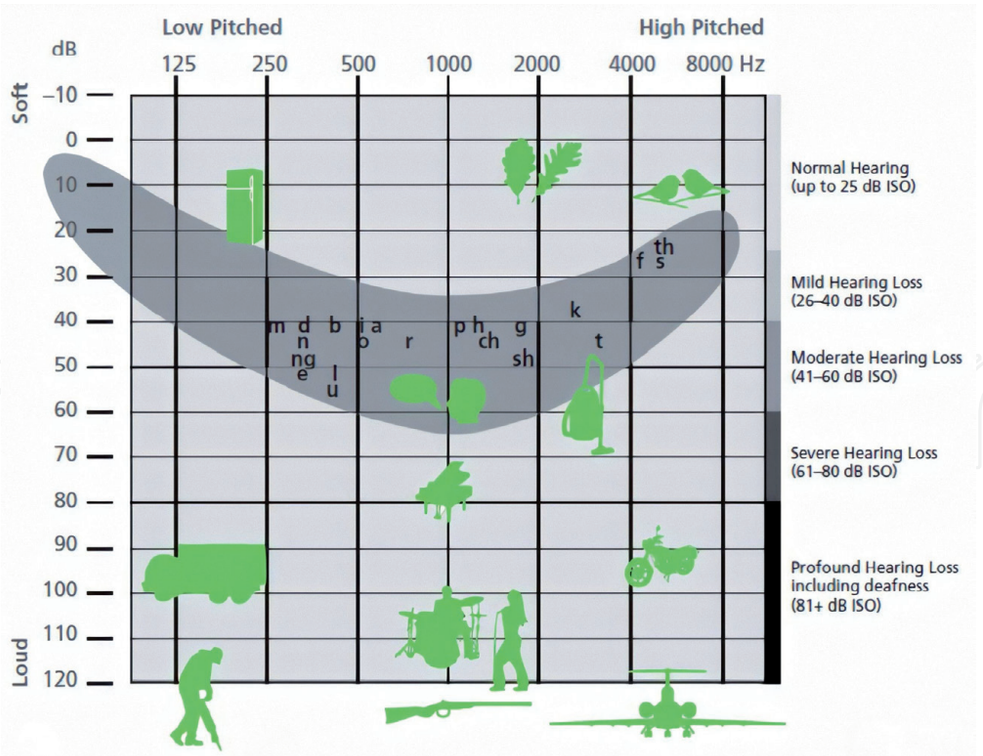

Figure 7.
The speech banana.

thresholds are more or less the same, but when there is a hearing loss the air conduction thresholds are depressed further.

Figure 7 shows the levels and conductive frequencies of a variety of environmental sounds and components of speech (the so-called "speech banana") in an audiogram format. Overlaying any audiogram onto this can indicate which sounds are audible and those which would be inaudible, which can illustrate the functional implications of various configurations of hearing loss.

For the results of audiometry to be reliable, the child has to understand the instructions and has to be motivated to comply. For children younger than 5 years of age, audiometry is generally too challenging. Therefore, several other behavioural tests are available to estimate hearing thresholds in children. The reliability of these tests depends on the child's age, neurological status, development and motivation.

Visual reinforcement audiometry is applied to estimate hearing thresholds in young children (6 months to 3 years of age). A visual reinforcer, such as an animated toy or picture is used to generate and maintain a head turn response to the sound stimulus presented through a speaker or ear phones.

To measure hearing thresholds in children aged 3 to 5 years, conditioned play audiometry may be applied. The child is conditioned to respond to a sound by performing an action (putting blocks in a box or stacking rings on a stick) [30].

Conventional audiometry has been considered the gold standard for obtaining hearing thresholds between 0.125 to 8 kHz in children of 5 years and older. The child presses a button in response to the sound stimulus. Additionally, the extended high frequencies (EHF) up to 16 kHz may be tested for identification of early ototoxic damage. EHF testing is less widely applied as special calibration of the equipment is required (A.J.M. Meier et al. in press).

2.5.4.3 Objective testing of inner ear status

For infants up to 6 months of age, behavioural tests are too inaccurate for hearing threshold estimation. To asses hearing of children of this age, objective tests are

available and widely used in programs for new born hearing screening. These tests can also be used to confirm the outcome of behavioural testing in older children, and may be applied in children/adolescents who are not able to cooperate.

A simple and fast way to objectively assess hearing is a test of otoacoustic emissions (OAE), in which a soft probe is placed into the ear canal and the OAE or "cochlear echo" is recorded in response to moderate level clicks or a combination of pure tones delivered via the same probe. OAEs reflect the function of outer hair cells and are only produced in ears with normal hearing or a mild loss of 20–30 dB HL. Presence of an OAE response confirms normal or near-normal hearing. Absence of a response indicates the possibility of a hearing loss and the need for follow-up testing, though it is often due to temporary factors such as excessive head movement or middle ear fluid.

The main follow-up test in this age group is auditory brainstem response (ABR) testing. Disposable electrodes are attached to the baby's head and rapid clicks or tone pips are delivered to the ear by an insert probe. The electrodes detect field potentials generated by the lower auditory pathways (cochlea and brainstem), producing a characteristic waveform response. The intensity of the stimuli is reduced until the waves are no longer visible, providing a close approximation to behavioural hearing thresholds. When the equipment is well calibrated and click stimuli are used, hearing thresholds around 3 kHz can be estimated, type of hearing loss can be determined (conductive or sensorineural) and integrity of the VIIIth cranial nerve and lower brainstem can be assessed. ABR is preferably measured during sleep, but in some situations sedation must be applied ([30], A.J.M. Meier et al. in press).

2.5.5 Monitoring of ototoxicity in children

As cisplatin-induced ototoxicity in children may have a negative impact on speech-language development and quality of life, early detection of hearing loss by audiological assessments is important. Monitoring during and after cancer therapy facilitates audiological management including counselling of patients and family, and support of hearing function if necessary (hearing aids, assistive listening devices, speech and language therapy) [33]. During therapy, monitoring may also provide the opportunity to modify cisplatin dose, depending highly on the availability of an evidence-based alternative, and whether or not cisplatin is the backbone of treatment. For example, dose adjustment may not be applicable in patients with liver tumours, for whom cisplatin is the key component of survival [34].

2.5.5.1 Timing and frequency of testing

A baseline assessment before start of cisplatin treatment, where possible, is important to identify pre-existing hearing loss, and is accompanied by questions on medical history including previous ear and hearing problems, family history, a check for dysmorphic features and presence of tinnitus. The timing of monitoring and the testing schedule during cancer therapy highly depends on the protocol and patient-specific circumstances. Serial assessments can be considered for patients who receive cisplatin, including a check of middle ear and inner ear function, and presence of tinnitus. A post-treatment assessment is used to identify hearing loss or to record progressive changes in hearing status, often performed within three months after cessation of treatment (A.J.M. Meier et al. in press). It may be necessary to continue monitoring up to several years after treatment to detect a delayed onset of hearing loss. Surveillance is advised annually for young survivors, every other year for older children, and every five years for adolescents and young adult survivors [35].

2.5.6 Grading of hearing loss in children

When cisplatin was first used in young children at GOSH there were no appropriate grading scales with which to compare ototoxicity measurements taken from children receiving the same or different treatments including cisplatin. There were the common toxicity criteria of adverse events (CTCAE) and the American Speech-Language Hearing Association (ASHA) criteria, but both compared hearing measured after treatment to baseline hearing. These approaches can be used in older children where baseline hearing can be established. In very young sick children it is difficult to get a reliable baseline and the tests used at a very young age are not the same as the tests used later on. Sue Bellman, the audiologist at the time at GOSH studied the particular pattern of hearing loss which the children were developing. She designed a scale which was published by Brock in 1991 and became known as the Brock grading [7]. Brock grading was later thought not to be sensitive enough and was developed further and a new scale published by Kay Chang in 2010 [36]. There followed a consensus meeting at the annual general meeting of SIOP in Boston and the SIOP scale was introduced and published in 2012 [21]. Grading can be done from the audiogram locally but when comparison of grading is required for the purposes of studying the toxicity of one treatment regimen with another in a clinical trial then central review of audiograms is necessary to assure consistency and quality. This is particularly the case in international clinical trials where the audiogram needs to be uploaded to the trial database for review.

2.5.7 The developmental and psychological impacts of hearing loss

The developmental and psychological impacts of deafness on children are diverse and substantial. In addition to the primary influence of hearing loss on the acquisition of language and literacy skills, children with any degree of hearing loss are at increased risk of experiencing social, emotional and behavioural difficulties as well as potential influences on quality of life, identity and self-esteem. All these consequences are well documented for children with congenital hearing loss, with research typically focusing on children with severe or profound deafness, and recently, those who have received cochlear implants. Research findings reveal a highly complex picture, with a large number of factors interacting to result in the difficulties presented by any individual child, including for example their language and communication skills, the cause of their deafness, their educational provision, and parental socio-economic status. The picture is somewhat less clear for children who have a mild or moderate hearing loss (often referred to as minimal hearing loss, and the largest group of children affected by ototoxicity), or those who acquired a loss during childhood due to illness directly (for example meningitis), or as in the case of ototoxicity, due to the treatment of illness. However, there is increasingly empirical evidence that is relevant in relation to the developmental and psychological impacts of ototoxicity-induced hearing loss.

The most significant impact of hearing loss is during infancy and early childhood, when language skills are developing at their fastest but delays may go unrecognised or untreated until the child enters school [37]. Thus age of exposure to ototoxic drugs is of particular importance, since even if the hearing loss is confined to the high frequencies, it can have subtle but significant impacts on speech perception and therefore speech production and intelligibility [38, 39]. Audibility and recognition of high-frequency speech sounds (s, f, th, sh, h, k, and t) and perception of fricative phonemes (e. g./s/) supports phonological and morphological development in young children with normal hearing and children with hearing loss [39]. Delays in language development acquired at this time may be hard to reverse, even with appropriate amplification and speech therapy [40].

A review of the literature on minimal hearing loss (comprising 69 articles, 6 of which included children with high-frequency hearing loss) concluded that although some individuals appeared to have no observable speech-language or academic difficulties, others experience considerable problems [37]. Those children that perform in the normal, average range on tests of language skills and academic attainments may in fact be under-performing in relation to their cognitive potential (IQ). In addition, children who appear not to have been negatively affected in terms of language and academic development, may still present with significant psychosocial problems. As a group, children with any degree of hearing loss, as well as those specifically with minimal hearing loss, exhibit higher rates of behaviour problems such as noncompliance, aggression, hyperactivity, impulsivity, and inattention than their hearing peers. They also have more emotional problems such as lower energy levels, higher stress and poorer self-esteem.

The psychosocial impact of hearing loss is also seen in terms of the effect on quality of life. A systematic review of 41 articles [41], showed that children with hearing loss generally report a lower quality of life than their normally-hearing peers. Their meta-analysis on four studies employing the Paediatric Quality of Life Inventory (PedsQL), revealed statistically and clinically significant differences in PedsQL scores between children with normal hearing and those with hearing loss, in the Social and School domains. Recently, a study reported detrimental effects of hearing loss on quality of life in children and adolescents who suffered hearing loss following ototoxic treatment compared with those whose hearing was unaffected [11]. All the areas assessed were impacted, including the ability to communicate with family and peers, level of independence, interactions with peers and emotional well-being. Long-term follow-up of childhood cancer survivors indicates significant hearing loss as predictive of poorer outcomes for school, employment and independent living [42].

As a result of these developmental and psychosocial consequences of ototoxicity-induced hearing loss it is essential that children are not only closely monitored in terms of their hearing thresholds, but also the wider language, learning, social, emotional and behavioural impacts. A range of interventions may be needed, including speech and language therapy, classroom and teaching accommodations and strategies to maximise access to speech and peer interactions, as well as therapeutic interventions to address emotional and behavioural problems.

2.5.8 Resource challenged nations and cisplatin hearing loss

The Global Initiative for Childhood Cancer (GICC) which was launched in 2018 by the WHO in partnership the International Society of Paediatric Oncology has the goal of improving the Global survival of children with cancer to 60% by 2030. As child cancer services develop and more gain children access cancer care, it will be necessary to develop policy and services to address the long term effects of chance treatment [43]. Cisplatin, is included in the WHO Essential Medicines List for Children (2017), but severe acquired hearing loss in child cancer survivors may have very significant impact on learning and future education opportunities of survivors and increase the health burden in families [44, 45]. Studies from low-and middle-income countries report the prevalence of hearing loss in community screened children as about 10%, while it is 23% for children with co-morbidities, such as HIV, tuberculosis, chronic suppurative otitis media and impacted cerumen% [46, 47]. Adding cisplatin as childhood cancer treatment may therefore increase the prevalence of hearing loss, which increases the need for early identification in the context of limited resources. Community health care workers have been successfully trained to assist and implement screening for hearing loss in communities, which should be used to assist in continuous assessment of hearing in children, surviving childhood cancer after cisplatin treatment and return

to their communities [45]. These identified children should be referred back to the major urban treatment centres for further more sophisticated hearing assessment and management. However, it should be noted that in Sub-Saharan Africa, and in the most populous parts of South East Asia there is a general lack of audiologists and limited access to testing and hearing support, which may hamper rehabilitation. These resource-constricted countries should therefore establish partnerships with developed countries and non-governmental organisations to assist them in the management of childhood cancer survivors with hearing loss due to cisplatin [48].

2.5.9 The parent's perspective

A parent with a child going through treatment is always trying to find the balance between a desperate longing for their child to be cancer free whilst enduring the least possible short and long-term side effects. At the start of treatment, when doctors explain the risks of potential hearing loss when using cisplatin, it can be hard to fully appreciate and understand the long-term impact for your child. At this stage of treatment many different outcomes are as yet unknown. This is especially true if the child receiving treatment is very young and unable to communicate verbally. The impact of having to wear hearing aids and other assistive listening devices is unknown and therefore almost impossible to comprehend. Whilst going through treatment the support given by doctors and nurses is invaluable. Once treatment ends access to that level of specialised support ends too. Parents are delighted to have a child free from cancer but all too often they are left to deal with the consequences of long-term side effects on their own. This can mean that young children learning to speak, read and write are not given adequate learning support since parents do not always know how best to help them or even what kinds of basic learning support to ask for. At a young age the child will not know in what circumstances they find it difficult to hear and parents need to be aware of every situation in order to be able to help the child develop coping strategies. This is especially true in nursery and primary school settings where a child could quickly feel overwhelmed. It would be easy for that child to be incorrectly labelled as reclusive, of low ability or naughty in class. As the child gets older, they will be able to deal with situations more easily themselves but will easily get tired and quickly zone out. Parents might need to advocate for their child and make the school aware of their needs. Interventions could include sitting at the front of exam halls, increasing teacher awareness in situations like sports pitches, playgrounds, swimming pools and in noisy classrooms. It is easy for a child with hearing loss to retreat from interactions or to become frustrated and then behave poorly. Parents need assistance and information to know how best to help and support their child. Children need to be encouraged to ask for help rather than be singled out or stigmatised.

2.5.10 The search for otoprotectants

As soon as it was known that cisplatin caused irreversible hearing loss researchers began to look for drugs to protect against this side effect. Different medications have an impact at different points in the metabolism of the cell **Figure 8** [49].

2.5.10.1 Preclinical studies of ototprotectants

The most promising pre-clinical studies have come from Edward Neuwelt's team in Portland Oregon [50–52]. They have been working on Sodium Thiosulfate (STS) and N-Acetyl Cysteine (NAC). As can be seen in **Figure 8** these 2 drugs can act at different points both inside and outside the cell.

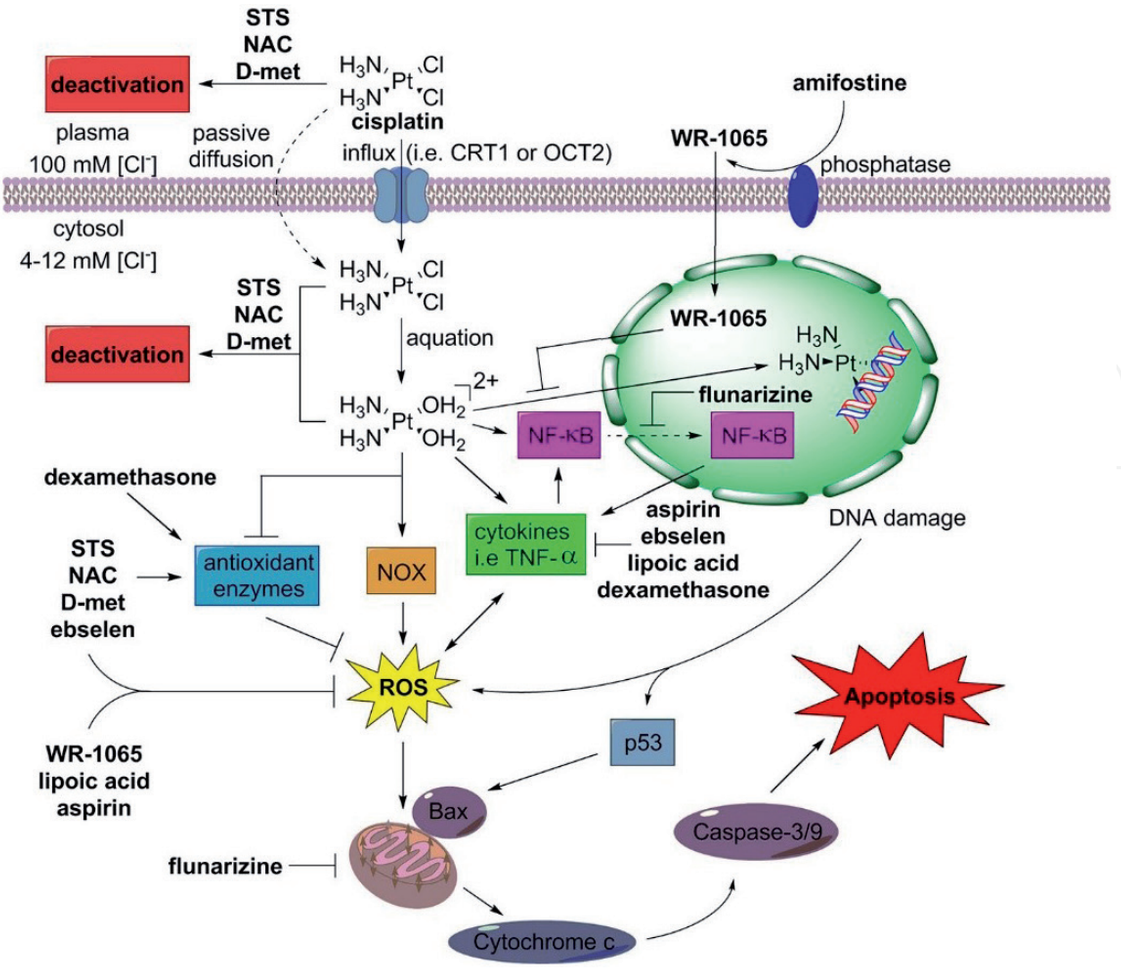

Figure 8.
General mechanistic pathways of cisplatin-induced cytotoxicity in auditory cells and the mechanistic pathways by which the otoprotective clinical candidates combat cisplatin toxicity [47]. https://doi.org/10.1021/acs.jmedchem.7b01653.

2.5.10.2 Clinical trials of otoprotectants in children

In 2019 a clinical guideline paper was written by a multidisciplinary team led by Lillian Sung and David Freyer [15]. The conclusion of this paper was that to date the most promising otoprotectant is STS, see **Table 2** taken from this paper. STS is close to being licenced both in North America and Europe. The evidence for the use of STS in children comes from two phase III trials [53, 54] which both showed that the incidence of hearing loss can be reduced by 50% in children receiving STS as a 15 minute infusion given 6 hours after the cisplatin infusion ends.

2.6 Cisplatin neurotoxicity

In adults, peripheral sensitive neurotoxicity which ranges from paresthesias to ataxic gait is the dose limiting toxicity of cisplatin [55]. This means that when patients develop severe neurotoxicity the dose of cisplatin needs to be adapted or stopped. In young children neurotoxicity is rarely observed.

2.7 Hearing conservation from the public health perspective

Cisplatin hearing loss is considered to worsen with time. It is not clear whether this is due to ongoing toxicity from platinum retained in the cochlea or the addition of further assaults on the ear or both. Hearing educational programs for the young

	Studies (n)	Patients (n)	Effect size *	95% CI	I^2 (%)	Value
Amifostine vs no treatment						
Any ototoxicity	5	465	RR 0.96	0.71 to 1.29	49%	0.78
Severe ototoxicity	4	223	RR 0.85	0.34 to 2.12	0%	0.72
Sodium diethyldithiocarbamate vs no treatment						
Severe ototoxicity	2	255	RR 0.73	0.08 to 6.44	56%	0.77
Sodium thiosulfate vs no treatment						
Any ototoxicity	2	205	RR 0.51	0.37 to 0.71	0%	<0.0001
Intratympanic acetylcysteine vs no treatment						
Threshold at 4 kHz	2	62	MD-2.7	−14.9 to 9.5	0%	0.66
Threshold of 8 kHz	2	62	MD-1.6	−14.8 to 11.6	0%	0.81
Intratympanic dexamethasone vs no treatment						
Threshold at 4 kHz	2	92	MD-0.7	−5.8 to 4.5	0%	0.80
Threshold at 8 kHz	2	92	MD-8.7	−18.1 to 0.7	34%	0.07
Continuous cisplatin infusion vs bolus cisplatin infusion						
Any ototoxicity	2	78	RR 1.60	0.62–4.13	0%	0.33

*RR = risk ratio MD = mean difference *RR less than 1 and MD less than 0 favour intervention.*

Table 2.
Data synthesis of trials for cisplatin-induced ototoxicity prevention.

are few and far between [56]. It is clear that children who have received cisplatin as part of their therapy for cancer need to be supported but also educated as they go through follow up to conserve their hearing. It is possible that at the end of treatment ototoxicity damage is not yet apparent to the young person as it may only affect the higher frequencies out of their speech range. With time however as hearing worsens as a result of the toxicity, possibly in interaction with noise induced hearing loss [57], it may reach the speech frequencies and become apparent. Hearing conservation strategies should be introduced to the parents and child at an early stage and should encourage exclusion/reduction of factors which can lead to damage to residual hearing. Not all of these factors can be excluded however it is only fair that parents and patients are made aware of the additional risk to hearing that they bring. These include: loud sounds and noises; other ototoxic medication e.g., aminoglycosides; unhealthy diets; intracranial pressure changes for example as can occur with certain sports such as scuba diving; barotrauma; head injury and exposure to radiation and proton beam therapy. Where possible children and adolescents should be discouraged from listening to loud music through headphones over long periods of time, encouraged to wear protective ear plugs if exposed to loud noise, wear protective head gear when cycling; use a head rest/child safety car seat adjusted to height.

To raise awareness of policy makers to address the problems of preventable hearing loss worldwide, the WHO World Health Assembly adopted a resolution in 2017

(WHA70.13) to provide guidance for member states for the integration of ear and hearing care into national health plans. In response The World Report on Hearing has been developed (https://www.who.int/activities/highlighting-priorities-for-ear-and-hearing-care), proposing a set of interventions for prevention, screening, rehabilitation and communication.

2.8 Future challenges

A better understanding of the predisposing genetic factors and how to influence them as well as the introduction of licenced otoprotectants will hopefully reduce the incidence of acquired ototoxicity. In the meantime children who have already developed hearing loss or other ototoxicity need expert support, audiological intervention as well as encouragement, acceptance, patience and tolerance to support them fully socially integrating.

3. Conclusion

Cisplatin ototoxicity is a serious medical problem in children with cancer whos' cure depends on the use of this drug. Progress has been made on understanding the mechanisms causing the toxicity and some of the predisposing factors. Expert counselling and management of the hearing loss, tinnitus and or vertigo is very important for all children. Understanding and adaptation at home, school and in the work place can facilitate better integration and outcomes for people suffering from acquired toxicity. Otoprotective drugs are being researched to reduce the severity of hearing loss and some will hopefully soon be licenced for use. However further research is needed in all areas to improve the quality of life for children who acquire this challenging side effect of treatment.

Acknowledgements

We would like to acknowledge Edward Neuwelt and his dedicated team of collaborators for all of the pre-clinical work on both STS. Also to David Freyer, Kristy Knight and Kay Chang for their dedication to the monitoring of late effects and particularly hearing loss in children receiving cisplatin and their efforts to research and prevent it.

Conflict of interest

Penelope Brock has been a consultant with Fennec Pharmaceuticals since 2017. All other authors have no conflict of interest.

Author details

Penelope Brock[1*], Kaukab Rajput[1], Lindsey Edwards[1], Annelot Meijer[2], Philippa Simpkin[3], Alex Hoetink[4], Mariana Kruger[5], Michael Sullivan[6] and Marry van den Heuvel-Eibrink[2]

1 Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

2 Princess Máxima Centre for Pediatric Oncology, Utrecht, The Netherlands

3 Independent Researcher, London, UK

4 University Medical Centre, Utrecht, The Netherlands

5 Stellenbosch University, South Africa

6 Royal Children's Hospital, Melbourne, Australia

*Address all correspondence to: peppybrock@gmail.com

References

[1] Knight KR, Kraemer DP, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: Use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol. 2007;

[2] Knight KR, Chen L, Freyer D, Aplenc R, Bancroft M, Bliss B, et al. Group-Wide, Prospective Study of Ototoxicity Assessment in Children Receiving Cisplatin Chemotherapy (ACCL05C1): A Report From the Children's Oncology Group. J Clin Oncol. 2017;

[3] Einhorn LH. Chemotherapy of disseminated testicular cancer. Cancer. 1980;20(3):625-629.

[4] The Discovery, Use and Impact of Platinum Salts as Chemotherapy Agents for Cancer The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 4 April 2006 [Internet]. Available from: https://discovery.ucl.ac.uk/id/eprint/14884/1/14884.pdf

[5] Brock PR, Koliouskas DE, Barratt TM, Yeomans E, Pritchard J. Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr. 1991;

[6] Skinner R. Nephrotoxicity of cancer treatment in children. Pediatric Health. 2010.

[7] Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: A practical grading system. Med Pediatr Oncol. 1991;

[8] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. N Engl J Med. 2006;

[9] Clemens E, de Vries ACH, am Zehnhoff-Dinnesen A, Tissing WJE, Loonen JJ, Pluijm SFM, et al. Hearing loss after platinum treatment is irreversible in noncranial irradiated childhood cancer survivors. Pediatr Hematol Oncol. 2017;

[10] Clemens E, Broer L, Langer T, Uitterlinden AG, de Vries ACH, van Grotel M, et al. Genetic variation of cisplatin-induced ototoxicity in non-cranial-irradiated pediatric patients using a candidate gene approach: The International PanCareLIFE Study. Pharmacogenomics J. 2020;

[11] Rajput K, Edwards L, Brock P, Abiodun A, Simpkin P, Al-Malky G. Ototoxicity-induced hearing loss and quality of life in survivors of paediatric cancer. Vol. 138, International Journal of Pediatric Otorhinolaryngology. 2020.

[12] Childhood Cancer PFDD [Internet]. Childhood Cancer Hearing Loss. An externally-led public-focused drug development workshop: Chemotherapy-induced hearing loss in pediatric oncology. Available from: www.childhoodcancerpfdd.org

[13] Kushner BH, Budnick A, Kramer K, Modak S, Cheung NK V. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer. 2006;

[14] Freyer DR, Brock P, Knight K, Reaman G, Cabral S, Robinson PD, et al. Interventions for cisplatin-induced hearing loss in children and adolescents with cancer. The Lancet Child and Adolescent Health. 2019.

[15] Freyer DR, Brock PR, Chang KW, Dupuis LL, Epelman S, Knight K, et al. Prevention of cisplatin-induced

ototoxicity in children and adolescents with cancer: a clinical practice guideline. Lancet Child Adolesc Heal [Internet]. 2020;4(2):141-150. Available from: http://dx.doi.org/10.1016/S2352-4642(19)30336-0

[16] Clemens E, van der Kooi ALF, Broer L, van Dulmen-den Broeder E, Visscher H, Kremer L, et al. The influence of genetic variation on late toxicities in childhood cancer survivors: A review. Critical Reviews in Oncology/Hematology. 2018.

[17] Langer T, Clemens E, Broer L, Maier L, Uitterlinden AG, de Vries ACH, et al. Usefulness of current candidate genetic markers to identify childhood cancer patients at risk for platinum-induced ototoxicity: Results of the European PanCareLIFE cohort study. Eur J Cancer. 2020;138.

[18] Mukherjea D, Rybak LP. Pharmacogenomics of cisplatin-induced ototoxicity. Pharmacogenomics. 2011.

[19] Dolan ME, Newbold KG, Nagasubramanian R, Wu X, Ratain MJ, Cook EH, et al. Heritability and linkage analysis of sensitivity to cisplatin-induced cytotoxicity. Cancer Res. 2004;

[20] Brock P, Brichard B, Rechnitzer C, Langeveld NE, Lanning M, Söderhäll S, et al. An increased loading dose of ondansetron: A north European, double-blind randomised study in children, comparing 5 mg/m2 with 18 mg/m2. Eur J Cancer Part A. 1996;

[21] Brock PR, Knight KR, Freyer DR, Campbell KCM, Steyger PS, Blakley BW, et al. Platinum-induced ototoxicity in children: A consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol. 2012;30(19):2408-2417.

[22] Nyberg S, Abbott NJ, Shi X, Steyger PS, Dabdoub A. Delivery of therapeutics to the inner ear : The challenge of the blood-labyrinth barrier. 2019;0935(March):1-12.

[23] Shi X. Pathophysiology of the cochlear intrastrial fluid-blood barrier. Hear Res. 2016;338:52-63.

[24] Breglio AM, Rusheen AE, Shide ED, Fernandez KA, Spielbauer KK, McLachlin KM, et al. Cisplatin is retained in the cochlea indefinitely following chemotherapy. Nat Commun [Internet]. 2017;8(1). Available from: http://dx.doi.org/10.1038/s41467-017-01837-1

[25] Sheth S, Mukherjea D, Rybak LP, Ramkumar V. Mechanisms of Cisplatin-Induced Ototoxicity and Otoprotection. Front Cell Neurosci. 2017;11(October):1-12.

[26] Ratain MJ, Cox NJ, Henderson TO. Challenges in interpreting the evidence for genetic predictors of ototoxicity. Clinical Pharmacology and Therapeutics. 2013.

[27] Boddy AV. Genetics of cisplatin ototoxicity: confirming the unexplained? Clin Pharmacol Ther. 2013;94(2):198-200.

[28] Clemens E, Brooks B, De Vries ACH, van Grotel M, van den Heuvel-Eibrink MM, Carleton B. A comparison of the Muenster, SIOP Boston, Brock, Chang and CTCAEv4.03 ototoxicity grading scales applied to 3,799 audiograms of childhood cancer patients treated with platinum-based chemotherapy. PLoS One. 2019;14(2):1-15.

[29] Drögemöller BI, Wright GEB, Lo C, Le T, Brooks B, Bhavsar AP, et al. Pharmacogenomics of Cisplatin-Induced Ototoxicity: Successes, Shortcomings, and Future Avenues of Research. Clinical Pharmacology and Therapeutics. 2019.

[30] Sabo DL. The audiologic assessment of the young pediatric patient: The clinic. Trends in Amplification. 1999.

[31] Ting CS, Huang KW, Tzeng YC. Correlation between video-otoscopic images and tympanograms of patients with acute middle ear infection. Indian J Otol. 2016;

[32] IntechOpen Book Update on Hearing Loss Chapter Classification of Hearing Loss [Internet]. Available from: https://www.intechopen.com/books/update-on-hearing-loss/classification-of-hearing-loss

[33] Maru D, Malky G Al. Current practice of ototoxicity management across the United Kingdom (UK). Int J Audiol. 2018;

[34] Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: Its evolution and the current status as per the SIOPEL trials. Journal of Indian Association of Pediatric Surgeons. 2014.

[35] Clemens E, van den Heuvel-Eibrink MM, Mulder RL, Kremer LCM, Hudson MM, Skinner R, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. The Lancet Oncology. 2019.

[36] Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. Journal of Clinical Oncology. 2010.

[37] Winiger AM, Alexander JM DA. Minimal hearing loss: From a failure-based approach to evidence-based practice. Am J Audiol. 2016;25(3):232-245.

[38] Knight KRG, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: Underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005;

[39] Spratford M, McLean HH MR. Relationship of grammatical context on children's recognition of s/z-inflected words. J Am Acad Audiol. 2017;28(799-809).

[40] Tomblin JB, Harrison M, Ambrose SE, Walker EA, Oleson JJ, Moeller MP. Language outcomes in young children with mild to severe hearing loss. Ear Hear. 2015;

[41] Roland L, Fischer C, Tran K, Rachakonda T, Kallogjeri D, Lieu JEC. Quality of Life in Children with Hearing Impairment: Systematic Review and Meta-analysis. In: Otolaryngology - Head and Neck Surgery (United States). 2016.

[42] Brinkman TM, Bass JK, Li Z, Ness KK, Gajjar A, Pappo AS, et al. Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. Cancer. 2015;121(22):4053-4061.

[43] WHO. WHO Global Initiative for Childhood cancer. [Internet]. Available from: https://siop-online.org/who-global-initiative-for-childhood-cancer/

[44] WHO. WHO model list of essential medicines - 21st list, 2019: page 28. [Internet]. Available from: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06.

[45] O'Donovan J, Verkerk M, Winters N, Chadha S, Bhutta MF. The role of community health workers in addressing the global burden of ear disease and hearing loss: A systematic scoping review of the literature. BMJ Glob Heal. 2019;

[46] Mulwafu W, Kuper H, Ensink RJH. Prevalence and causes of hearing impairment in Africa. Tropical Medicine and International Health. 2016.

[47] Leach AJ, Homøe P, Chidziva C, Gunasekera H, Kong K, Bhutta MF, et al. Panel 6: Otitis media and associated hearing loss among disadvantaged populations and low to middle-income countries. Int J Pediatr Otorhinolaryngol. 2020;

[48] Mulwafu W, Ensink R, Kuper H, Fagan J. Survey of ENT services in sub-Saharan Africa: Little progress between 2009 and 2015. Glob Health Action. 2017;

[49] Hazlitt RA, Min J, Zuo J. Progress in the Development of Preventative Drugs for Cisplatin-Induced Hearing Loss. J Med Chem. 2018;61(13):5512-5524.

[50] Neuwelt EA, Brummett RE, Doolittle ND, Muldoon LL, Kroll RA, Pagel MA, et al. First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. J Pharmacol Exp Ther. 1998;

[51] Doolittle ND, Muldoon LL, Brummett RE, Tyson RM, Lacy C, Bubalo JS, et al. Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. Clin Cancer Res. 2001;

[52] Doolittle ND, Peereboom DM, Christoforidis GA, Hall WA, Palmieri D, Brock PR, et al. Delivery of chemotherapy and antibodies across the blood-brain barrier and the role of chemoprotection, in primary and metastatic brain tumors: Report of the eleventh annual blood-brain barrier consortium meeting. J Neurooncol. 2007;

[53] Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017;

[54] Brock PR, Maibach R, Childs M, Rajput K, Roebuck D, Sullivan MJ, et al. Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. N Engl J Med. 2018;

[55] Avan A, Postma TJ, Ceresa C, Avan A, Cavaletti G, Giovannetti E, et al. Platinum-Induced Neurotoxicity and Preventive Strategies: Past, Present, and Future. Oncologist. 2015;

[56] Khan KM, Bielko SL, Mccullagh MC. Efficacy of hearing conservation education programs for youth and young adults : a systematic review. BMC Public Health. 2018;18.

[57] Yang C, Schrepfer T, Schacht J. Age-related hearing impairment and the triad of acquired hearing loss. 2015;9(July):1-12.