CISPLATIN INDUCED HEARING LOSS IN PAEDIATRIC MALIGNANCIES

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF M.S BRANCH IV OTORHINOLARYNGOLOGY EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY TO BE HELD IN APRIL 2016

DEPARTMENT OF OTORHINOLARYNGOLOGY
CHRISTIAN MEDICAL COLLEGE
VELLORE

DECLARATION

I declare that this dissertation entitled "**Cisplatin induced hearing loss in Paediatric malignancies**'' submitted towards fulfilment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University for the MS Branch IV, Otorhinolaryngology examination to be conducted in April 2016, is the bonafide work of Dr. Susana Mathew, postgraduate student in the Department of Otorhinolaryngology, Christian Medical College, Vellore

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CERTIFICATE

This is to certify that the dissertation entitled "**Cisplatin induced hearing loss in paediatric malignancies**'' is a bonafide original work of **Dr. Susana Mathew**, submitted in partial fulfilment of the rules and regulations for the M S Branch IV, Otorhinolaryngology examination of The Tamil Nadu Dr. M.G.R. Medical University to be held in April 2016.

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Introduction

The term chemotherapy was coined in the early 1900s and means- 'treating with chemicals'. The second world war saw the emergence of chemotherapy being used as anti tumour drugs. The initial discovery was that of nitrogen mustard.

Cancer chemotherapy can be divided by their mechanism of action into alkylating agents, Antimetabolites, anti-microtubule agents, inhibitors of Topoisomerase and cytotoxic compounds. One such alkylation agent is the platinum compounds which includes oxaliplatin, carboplatin and cisplatin.

The most studies and by far the most effective of the lot is Cisplatin, the mechanism of action of which was studied in depth by Rosenberg.

Cisplatin has widely been used to treat a lot of head and neck malignancies, osteosarcoma, neuroblastoma, leukemia and much more. Its role is particularly pertinent in paediatric malignancies.

Cisplatin with its widely popularised effectiveness in destroying the malignant cells, also comes with its share of side effects, a common one being ototoxicity. Especially in children, this complication can have long lasting consequences in the form of speech delay, poor scholastic performance and so on.

A good knowledge of the anatomy of the ear, especially the inner ear is needed to understand the mechanism of ototoxicity of the drug and for further research on the subject.

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The most studied and by far the most effective of the lot is Cisplatin, the mechanism of action of which was studied in depth by Rosenberg.

Cisplatin has widely been used to treat a lot of head and neck malignancies, osteosarcoma, neuroblastoma, leukemia and much more. Its role is particularly pertinent in paediatric malignancies.

Cisplatin with its widely popularized effectiveness in destroying the malignant cells, also comes with its share of side effects, a common one being ototoxicity. Especially in children, this complication can have long lasting consequences in the form of speech delay, poor scholastic performance and poor social integration.

A good knowledge of the anatomy of the ear, especially the inner ear is needed to understand the mechanism of ototoxicity of the drug and for further research on the subject.

Cisplatin is chemically ,cis-diamminedichloro-platinum, and is increasingly being used for treating paediatric malignancies. It belongs to the group of platinum based chemotherapy drugs and has in its group, oxaliplatin and carboplatin also. Cisplatin has been a blessing as it has improved survival rates of paediatric malignancies. However, it comes with its many side effects, ototoxicity being one of them. It is mainly used in haematological malignancies and as a combination therapy in non haematological malignancies.

Cisplatin ototoxicity frequently goes unnoticed.(1)

Knight et al , in their study found an incidence of hearing deterioration in 25% of their patients whom they followed up for 26 months. (1)

In another study by Anne Weissenstein et al, follow up of all children receiving chemotherapy was done for a period of 126 months. They found a 37% incidence of sensorineural hearing loss in their patients. (2)

Cisplatin produces high frequency sensorineural hearing loss mostly equal on both sides. There can also be Tinnitus and vertigo and these are one of the notorious effects of Cisplatin.

In this study , we have looked at the incidence of hearing loss with the use of Cisplatin in our hospital and also looked at its association with age and the cumulative dose.

Knight and colleagues in 2005 studied children undergoing cisplatin chemotherapy and estimated the incidence of hearing loss in them. They studied 67 children and used pure tone audiometry to measure the hearing thresholds.

They performed a baseline audiogram on these children at the start of their cisplatin chemotherapy. Audiograms were done throughout their treatment almost till 800 days . The study subjects were from the age group of 8 to 23 years.

The results showed that , of the 67 children who were treated, about 41 of them developed sensorineural hearing loss. They also calculated the median time to develop these symptoms and it was about 135 days. (1)

Children detected with hearing loss need to be carefully monitored and supportive measures like hearing aids fitted when required.

Though cisplatin is a miracle worker as far as cancer chemotherapy is concerned, its ototoxic effects can lead to deteriorating scholastic and social performance in children.

In this study we look into Cisplatin in depth and into understanding its side effect of ototoxicity. Here we look at the ototoxic profile of children undergoing chemotherapy with cisplatin with various malignancies. The ototoxicity of the drug and its relation to dosage, demography of the population and in relation to time of presentation of symptoms have been studied.

AIM

To determine the incidence of permanent hearing loss as a consequence to chemotherapy

OBJECTIVES

- To find the incidence of sensorineural hearing loss (SNHL) in patients with malignancies where ototoxic chemotherapeutic agents are used (Cisplatin)
- To find out incidence of chemotherapy induced hearing loss in different age groups.
- To find out correlation between cumulative dose of chemotherapy and hearing loss.
- To determine the time taken to develop these effects.

REVIEW OF LITERATURE

CANCER CHEMOTHERAPY

The term chemotherapy was coined in the early 1900s and means treating with chemicals. The Second World War saw the emergence of chemotherapy being used as anti tumour drugs. The initial discovery was that of nitrogen mustard. The growth of white blood cells was seen to be inhibited by nitrogen mustard. Since then, cancer chemotherapy has undergone so much of development and research and a whole lot of funding has gone into it. (3)

MECHANISM OF ACTION OF CHEMOTHERAPEUTIC DRUGS-A PREVIEW

Cancer mainly involves rapidly dividing cells. hence the main action of action cancer chemotherapy is to curb the dividing cells, in turn resulting in their death. This is known as apoptosis.(4)

The drugs do this mainly by binding to DNA or by acting as anti- metabolite.

Chemotherapeutic drugs can be classified into four main categories depending on their mode of action.

1. Alkylating agents

2. Antimetabolites

3. Anti-microtubule agents

4. Topoisomerase inhibitors

5. Cytotoxic antibiotics **(5)**

In this study , we will be looking at cisplatin in depth. Cisplatin belongs to the first group and is explained in detail below.

CISPLATIN- A HISTORICAL BACKGROUND

Cisplatin is chemically, *cis*-$[Pt(NH_3)_2(Cl)_2]$. it was in the year 1845 that it is was discovered. It was described by Michele Peyrone. Alfred Wernerin described its chemical structure in 1893.(6) It went by the name of Peyrone's salt in the historic era. (7)

The fact that cis-platin might have anti cancer properties was first showed by Rosenberg et al in 1969 (8)

In this study Escherichia coli was exposed to electric current through platinum electrodes and they observed that it not only inhibited the growth of the bacteria but also converted them into filamentous structures. (9)

This was because of the inhibition of mitosis.(10) Rosenberg was surprised to find that this was not because of the electric current per se but because of the platinum electrode which was supposed to be inert.

The next stage in its development was animal studies. it was done in mice with sarcomas and they found that cisplatin was quite potent in controlling the tumour. This led to various clinical trials.(10)

The National Cancer Institute started clinical trials with Cisplatin in the year 1972.(11)

In patients who had solid tumours which included ovarian and testicular tumours, this drug worked so well that on the 19 th of December 1978, The U.S Food and drug administration approved its use in these areas. (12)

CISPLATIN- BIOCHEMISTRY AND STRUCTURE

Cis-diamminedichloro-platinum is the chemical name of cisplatin. Cisplatin is a water soluble compound. The complex consists of two chloride atoms and two ammonia molecules around a central platinum atom.(Figure 1)

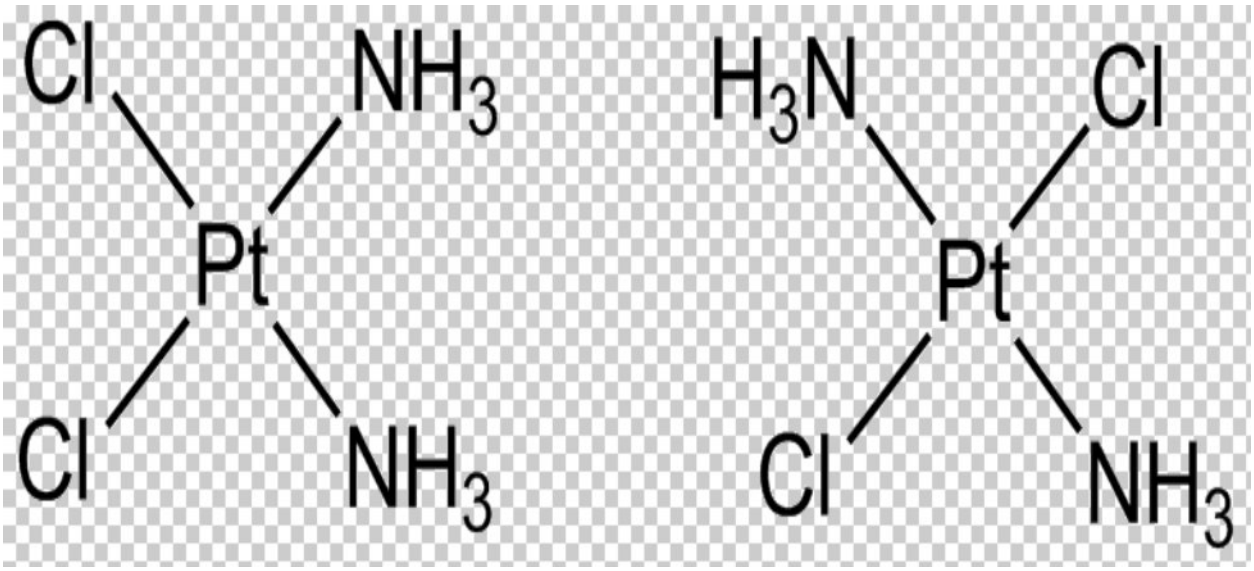


Figure 1. *Adapted from Michele Peyrone (1813–1883), Discoverer of Cisplatin - Johnson Matthey Technology Review*

The figure on the right represents the trans form and the figure on the left represents the cis form of the compound. It is the cis isoform which has been found to have anti tumour properties.

The main mechanism of action of this compound is denaturation of DNA.

The cis and trans forms form cross with guanine bases in the DNA thus leading to its denaturation. (7)

Cisplatin has 11 atoms. The centre atom is Platinum and chlorine forms bond angles with it. As such cisplatin is a square planar structure. The bond angle is almost 90 degrees while the bond between nitrogen and hydrogen is almost 109.5 degrees.

polarity

Cisplatin is considered as a polar molecule. This is because it has a negative as well as a positive charge. Chlorine atom has three unshared electrons which gives it a negative charge. the hydrogen ions on the opposite side give it a positive charge.

BONDING BETWEEN TWO CISPLATIN MOLECULES

There are mainly two types of bonds seen between cisplatin molecules.

1. London dispersion forces.

When two random molecules come in contact with each other, there is a weak bond existing between the two. This bond is very weak and temporary and is known as the London dispersion force. this bond exists between two cisplatin molecules.(13)

1. Dipole- dipole interaction

This is an electrostatic force and occurs between two polar molecules. It mainly occurs when the negative end of a molecule comes in contact with the positive end.

This is main type of bonding seen in cisplatin and accounts for its strength of bond. the negative charge is contributed by the chloride ions, while the hydrogen ions contribute to the positive charge.(14)

2. Hydrogen bonding

This type of bonding is naturally expected in the cisplatin ion as there are hydrogen and nitrogen ions. Hydrogen bonding also occurs between hydrogen and oxygen and hydrogen and fluorine ions.

But in the case of cisplatin, as these nitrogen ions are covered by hydrogen and platinum ions and hence this type of bonding cannot accurately take place. (14)

PHARMACOLOGY

The main mechanism of action of cisplatin is by denaturing the host DNA. There is a lot of unexplored area in the mechanism of action of this drug. Cisplatin brings about suppression of RNA, inhibits DNA synthesis and deregulates the cell cycle. However an in depth understanding is required to really extract the full potential of this drug.(15).

Cis platin is as such a neutral molecule. It is when it comes in contact with water, that its action occurs. This is detailed below along with an illustration. There are however certain molecules which have a rate limiting step in the mechanism of action of cisplatin. These include protein, methionine , glutathione among others. (16)

Cis platin DNA adducts

DNA consists of purines and pyrimadines. N7 base of purine is what cisplatin attaches to. These create a lot of interactions including DNA adducts, intrastrand cross links and inter strand cross links.(16) Of these intrastrand links are quite strong. There is evidence that the amount of platinum bound to DNA is directly proportional to the quantum of cytotoxicity.(17)

What ensues after the cross link interaction are as follows.

1. Formation of strong cross- links between atoms in cisplatin which leads to the tight adherence of DNA . Thus the DNA cannot undergo replication or transcription ultimately leading to cell death.(18)

2. nucleotides get misplaced leading to mutation.

3. The DNA bases get alkylated and while attempting to repair them, the DNA gets fragmented by the repair enzymes.(19)

When Cisplatin comes in contact with water, hydrolysis occurs . A hydroxyl ion is gained and a chloride ion is lost . This form a monohydrated complex(MHC). This molecule is in its protonated form and hence has a positive charge. This readily attracts the negative charge of the DNA and a series of reactions follow which ultimately leads to apoptosis thereby acting as an effective tumoricidal agent. (Fig 2)

For this effect to take place, the environment in which the molecule is should be close to physiological pH with a pKa of 6.9.

Cisplatin enters cells by diffusion and covalently binds. It is excreted in a slow phased manner. (20)

Half - life of cisplatin

The half life of cisplatin is 30 minutes. If it is covalently bound to albumin, then its half life increased to a minimum of 5 days.(21)

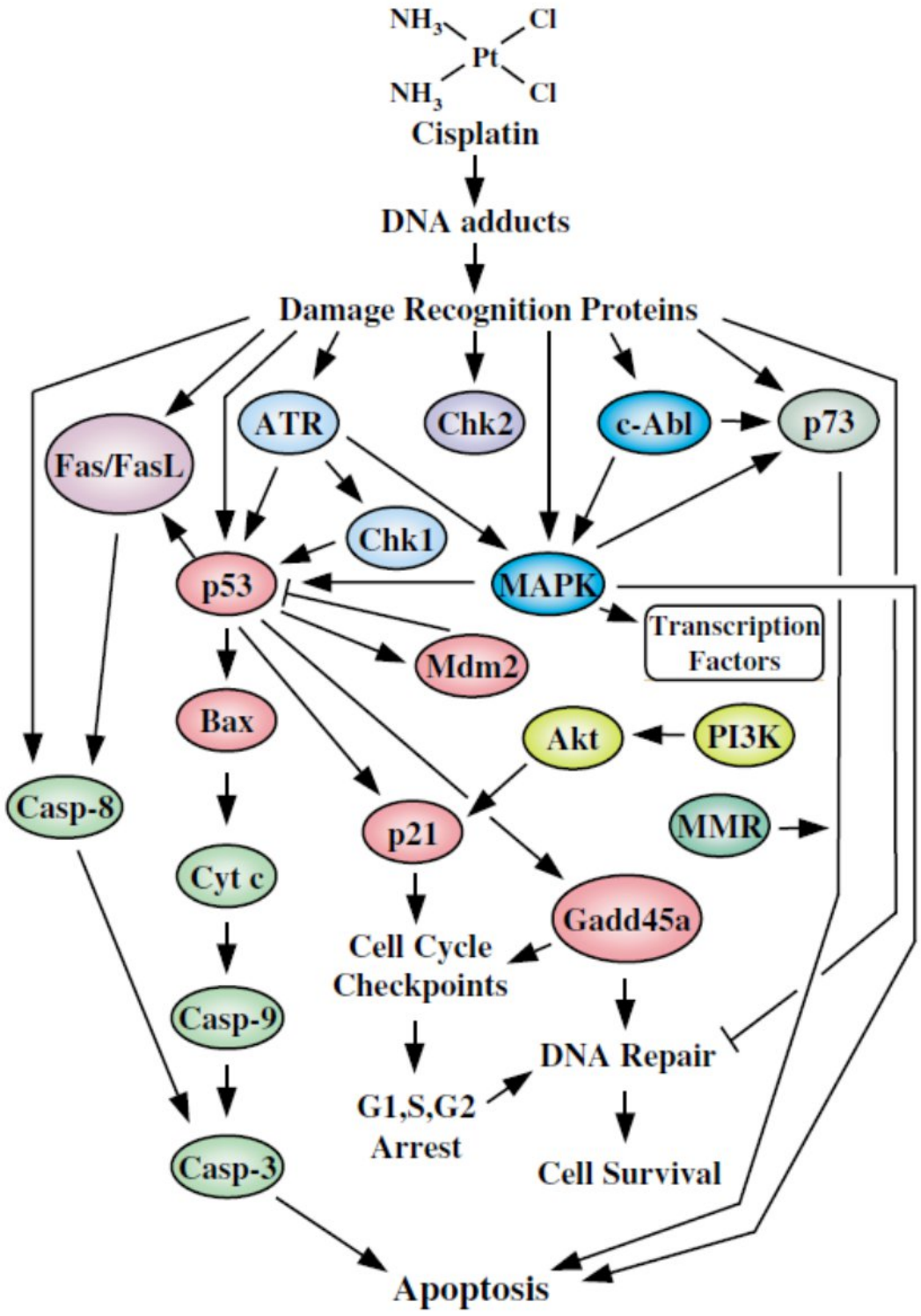


Fig. 2 *Adapted from The Discovery and Development of Cisplatin - ciszplatin.pdf*

MECHANISM OF RESISTANCE

The function of cisplatin is cell apoptosis. However, due to certain conditions, the drug cannot exert its full effect and that causes resistance. some of the causes of emergence of resistance are detailed below.

1. interaction with thiol. containing substances which can cause inactivation

2. reduced intracellular concentration of the drug.

3. Stronger DNA damage repair.

4. Action of tumour suppressor gene p53.(22)

Indications of use of cisplatin

Cisplatin is used in tumours like advanced ovarian, testicular, bladder carcinomas. It can be used in combination for osteosarcoma, medulloblastoma, malignant mesothelioma and squamous cell carcinoma of head and neck. (23)

Dosage

The maximum dose prescribed by the FDA is 100 mg/m2 /cycle once every 3 to 4 weeks . A pre hydration is mandatory. This is usually done with 5% glucose in normal

saline and this is infused over a period over 6 to 12 hours. Once the patient is adequately hydrated, Serum creatinine and BUN is normal, audiometric results are normal, cisplatin can be administered. It is usually administered over 6 to 8 hours. The solution must be protected from sunlight and care must be taken to ensure that patient is well hydrated and maintains good urine output during this period. (24)

CISPLATIN IN THE PRESENT AGE

Cisplatin is being increasingly used in solid cancers like ovarian and testicular carcinomas. It is also being used in paediatric malignancies like osteosarcoma and medulloblastoma. it is also used as a part of combination therapy.

Neurotoxicity, ototoxicity , nephrotoxicity are among the known side effects of this drug, the first two being dose limiting. In addition it also causes gastrointestinal discomfort.

Since our study is on the ototoxic profile of this drug on children we will look at this particular side effect in a bit more detail.

SIDE EFFECTS OF CISPLATIN

Like most things in the world, this magic drug too has side effects and the ototoxicity of this drug will be researched in detail here. Some of the well known side effects are -

1. Neurotoxicity

. While killing the malignant cells, the compound cis platin also affects the peripheral neurons. The neurotoxicity has been attributed to the fact that cisplatin binds to a receptor on the membranes of the peripheral nervous system. This is known as the sodium-hydrogen ion mechanoreceptor. It is a non competitive inhibition.(25)

The peripheral neurotoxicity is seen in almost half the population who have been treated with cis platin. The effects can be as mild as a tingling sensation to as severe as an encephalopathy.(26) The other symptoms include ageusia, weakness, numbness, leukoencephalopathy, loss of vibration sense etc. Tactile sensation is also lost in some cases.

This is a dose dependent side effect of cisplatin. It is therefore imperative to do nerve conduction studies before and after cisplatin administration.(27)

Various compounds have been studied and have been found to be useful to protect against neurotoxicity. These include vitamin E, Thiol containing compounds, Calcium, magnesium, certain anticonvulsants.(28)

Thus it is important to detect neurotoxicity. The symptoms may gradually improve after stoppage of cisplatin. But in some cases they persist and may even be permanent. (29)

2. Nephrotoxicity

As explained previously, reactive oxygen species are released during the mechanism of action of cisplatin . The main culprit for this nephrotoxicity is this reactive oxygen species(30)

Within a period of a 24 to 48 hours, cisplatin achieves good concentration in the kidney. it is mainly in the renal cortex that this drug accumulates. This affects the glomerular filtration rate. (31)

There have been some studies showing that iron could be a culprit for the cisplatin induced ototoxicity through a reaction known s the Haber Weiss reaction. (32)

It is dose dependent and reversible. The main tool to monitor this side effect is creatinine clearance. If this value is altered, Cisplatin must be stopped and the patient must be adequately hydrated and diuresis done if necessary.(33)

Hydration is the key to prevent or reduce the nephrotoxic effects of this drug. There are also other drugs which have shown to have beneficial effects an aid in protection against ototoxicity. These include N-acetyl cystine, glycine, Sodium thiol sulfate. etc.(34)

3. Ototoxicity

This is a dose dependent and sometimes irreversible side effect and has been explained in detail in the following pages

4. Electrolyte imbalance

Cisplatin causes decrease in Magnesium and Potassium causing hypomagnesaemia and hypokalemia. The decrease in magnesium can in turn cause decrease in calcium.(24)

Most of the electrolyte imbalance can be corrected by adequate pre hydration and concomitant administration of mannitol.

5. Nausea and vomiting

Cisplatin chemotherapy should be combined with good anti-emetics like Ondansetron because Cisplatin has known emetic properties. (31) Although 5 HT3 receptors are useful, their usefulness is still debated. One study showed that a combination of high dose dexamethasone along with an anti emetic can strongly decrease the symptoms. (35)

6. Bone marrow suppression

7. Some studies have revealed Hemolytic anaemia as its side effect. (24)

8. Cardio toxicity- Some studies have shown that cisplatin is cardio toxic and can cause some variations in the electrocardiogram especially long QT.(35)

9. Hepatotoxic.- Administration of cisplatin can increase the amount of glutathione peroxide which can induce changes responsible for ototoxicity. (36)

ANATOMY OF THE INNER EAR

Before we study the effect of cisplatin on the ear, it is useful to understand the area where it acts- the inner ear, in detail.

EMBRYOLOGY

The development of the inner ear structures start from about 21 days of gestational life.

The inner ear develops independently from the outer and the middle ear. Hence it is not uncommon to find anomalies of the external ear with a fully functional inner ear.

The ectoderm just behind the second pharyngeal pouch, in the region of the hindbrain thickens and forms what is known as the auditory or the otic placode. This otic placode slowly invaginates and forms a fluid filled structure covered with epithelium, known as the otocyst.

The otocyst gives rise to the structures of the inner ear. It initially divides into pars superior and pars inferior. The pars superior gives rise to semicircular canals and utricle and the pars inferior gives rise to saccule and cochlea.

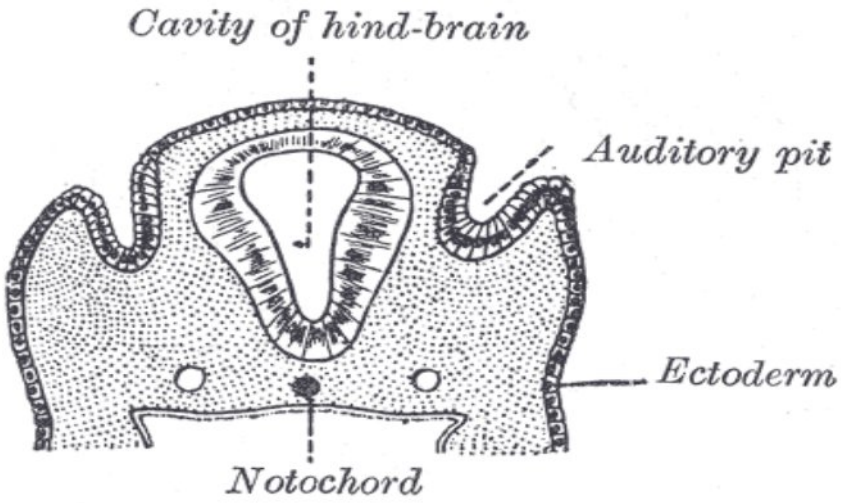


Figure showing an otic placode developing. This will eventually form an otic vesicle.

Figure 3 adapted from *Grays anatomy*.

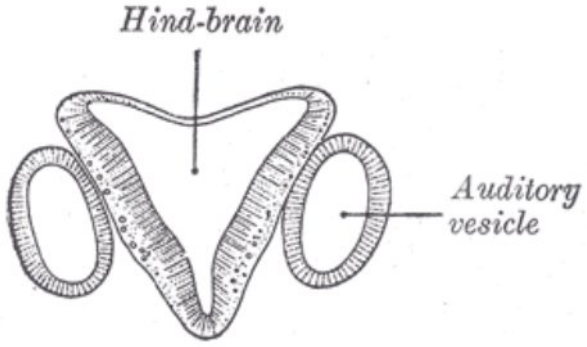


Figure 4- showing the development of the Auditory vesicle which will soon differentiated into inner ear structures. *Adapted from Gray's anatomy*.

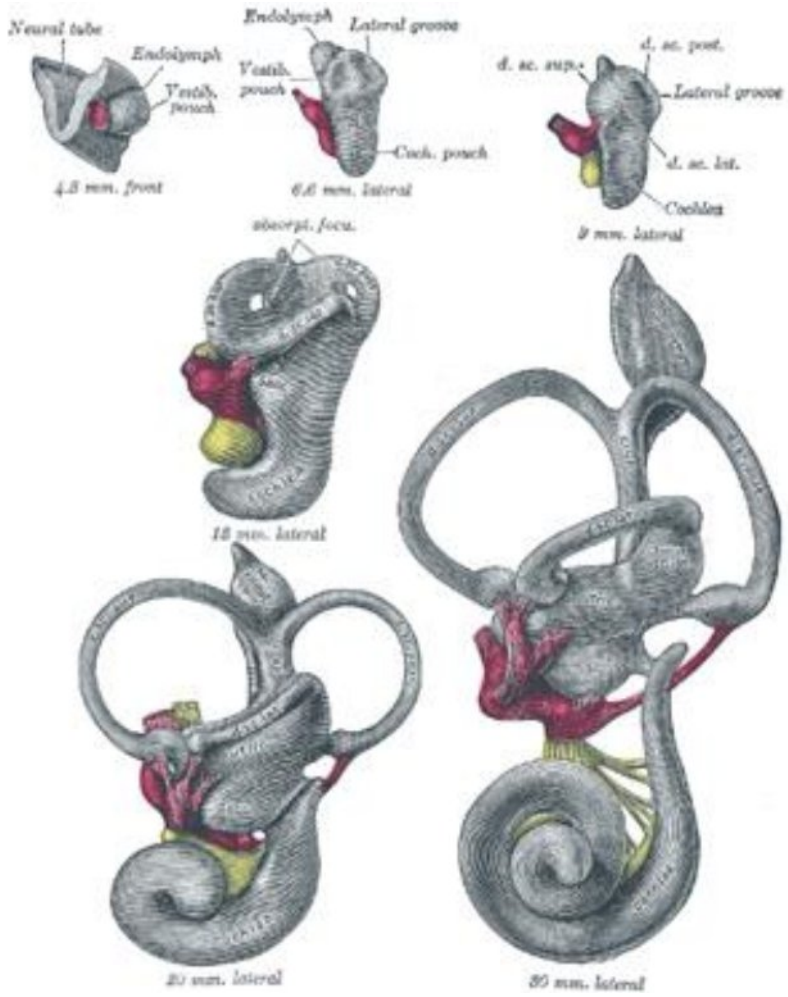


Figure 5 showing the development of the membranous and bony inner ear.

Adapted from Gray's anatomy

THE INTERNAL EAR

As we are going to study the effects of cisplatin on the hearing mechanism and of sensorineural hearing loss, it is important to understand the structures of the inner ear and also the auditory pathway of hearing.

1. Bony labyrinth

Bony labyrinth is comprised of vestibule, semicircular canals and the cochlea.

a. Vestibule

The vestibule houses the saccule in its spherical recess and utricle in its elliptical recess. It has the oval window in its lateral wall and the opening of the five semicircular canals in its postero superior wall. It also has the opening of the aqueduct of vestibule.

b. Semicircular canals

There are three semicircular canals which are the posterior, lateral and superior. The semicircular canals open into the ampulla through five openings. The posterior and superior join to form the crus commune.

c. Cochlea

the bony cochlea can be divided into three compartments. They are

- Scala vestibule

- Scala media

- Scala tympani

The footplate of stapes closes the scala vestibuli and the secondary tympanic membrane closes the tympani. The scala media is the membranous cochlea.

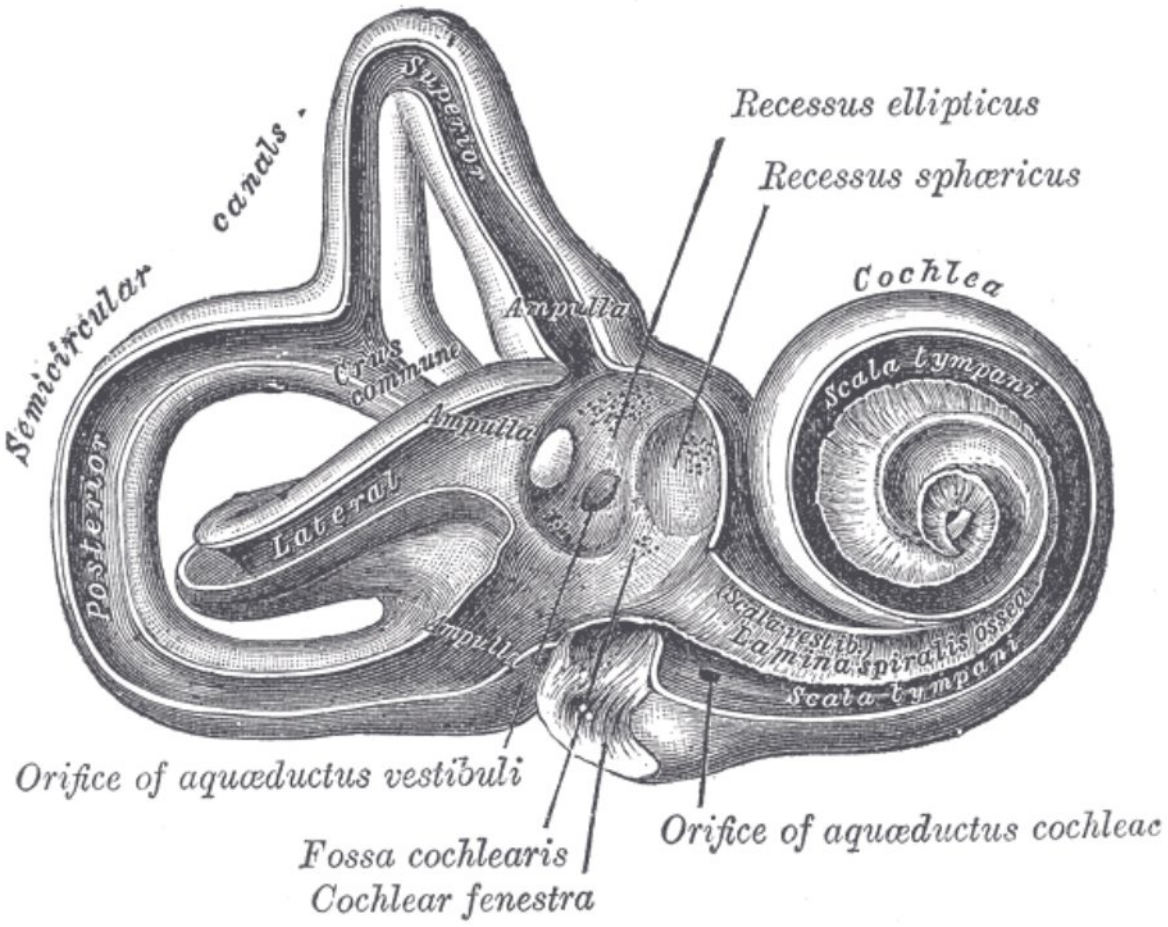


Figure 6 showing the bony labyrinth. *Adapted from Gray's anatomy*

2. Membranous labyrinth

a. Cochlear duct

The cochlear duct has three walls

- Basilar membrane which houses the organ of corti

- Reissner s membrane separates the cochlear duct from the scala vestibuli

- stria vascularis secretes endolymph and has vascularised epithelium.

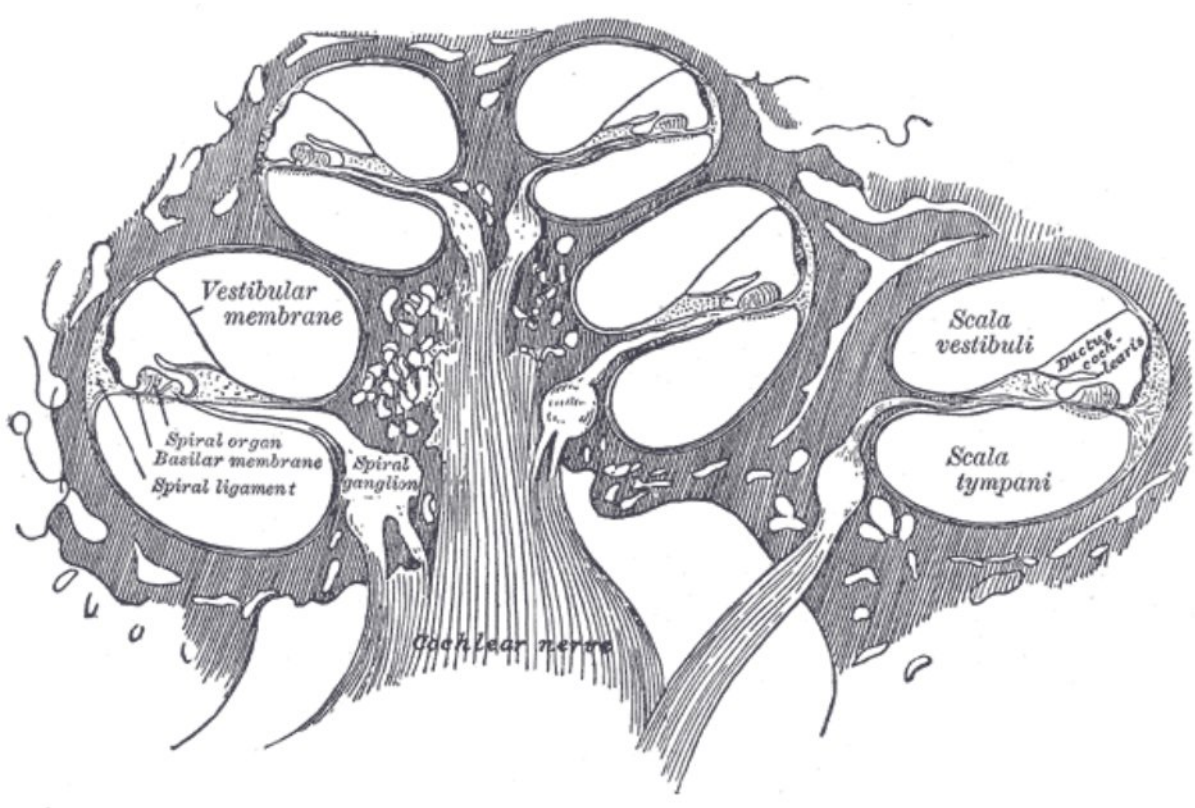


Figure 7 showing the cochlear duct. *Adapted from Gray's anatomy.*

b. Utricle and saccule

The sensory epithelium in utricle and saccule is macula and it is associated with linear acceleration and deceleration.

c. Semicircular ducts.

They are five in number. The ampulla contains crista.

d. Endolymphatic duct and sac.

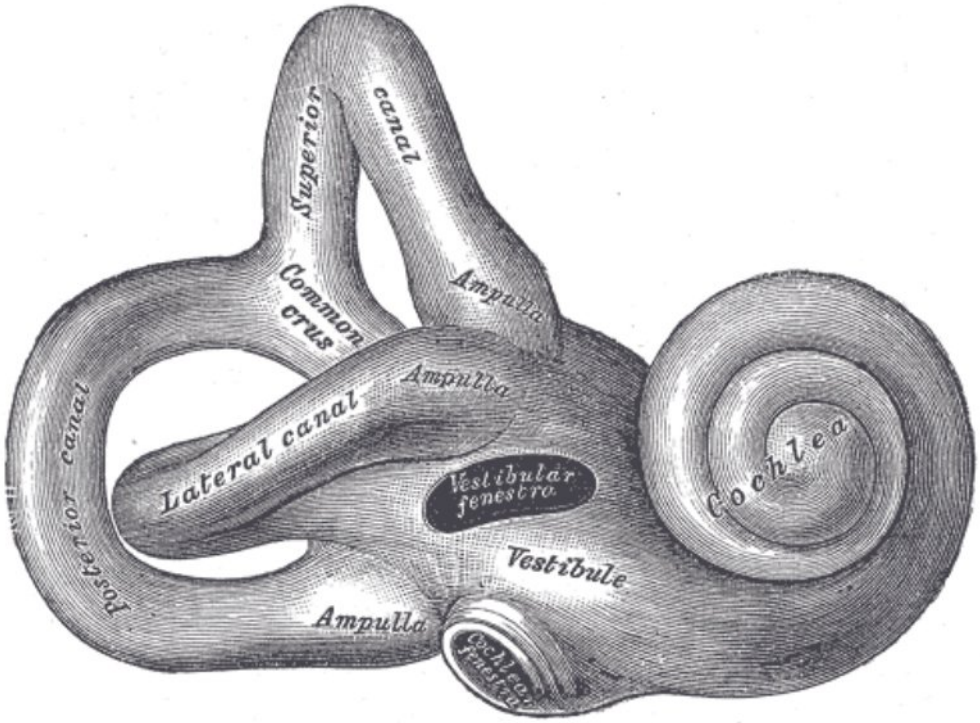


Figure 8 showing the membranous cochlea.*Adapted from Gray's Anatomy*.

Mechanism of hearing- Normal physiological associations

Before looking at the mechanism of ototoxicity , it is necessary to look at the structure of inner and outer hair cell and he auditory pathway.

The first structure to get affected in ototoxicity is outer hair cell. It is also known as type 2 hair cell.

Hair cells can be of two types.

1. Inner hair cells or the type 1 hair cells

These cells are flask shaped. They have a single nerve terminal at the base.

2. Outer hair cells.

These are also known as type 2 hair cells. They are cylindrical in shape and have multiple nerve terminals at the base.

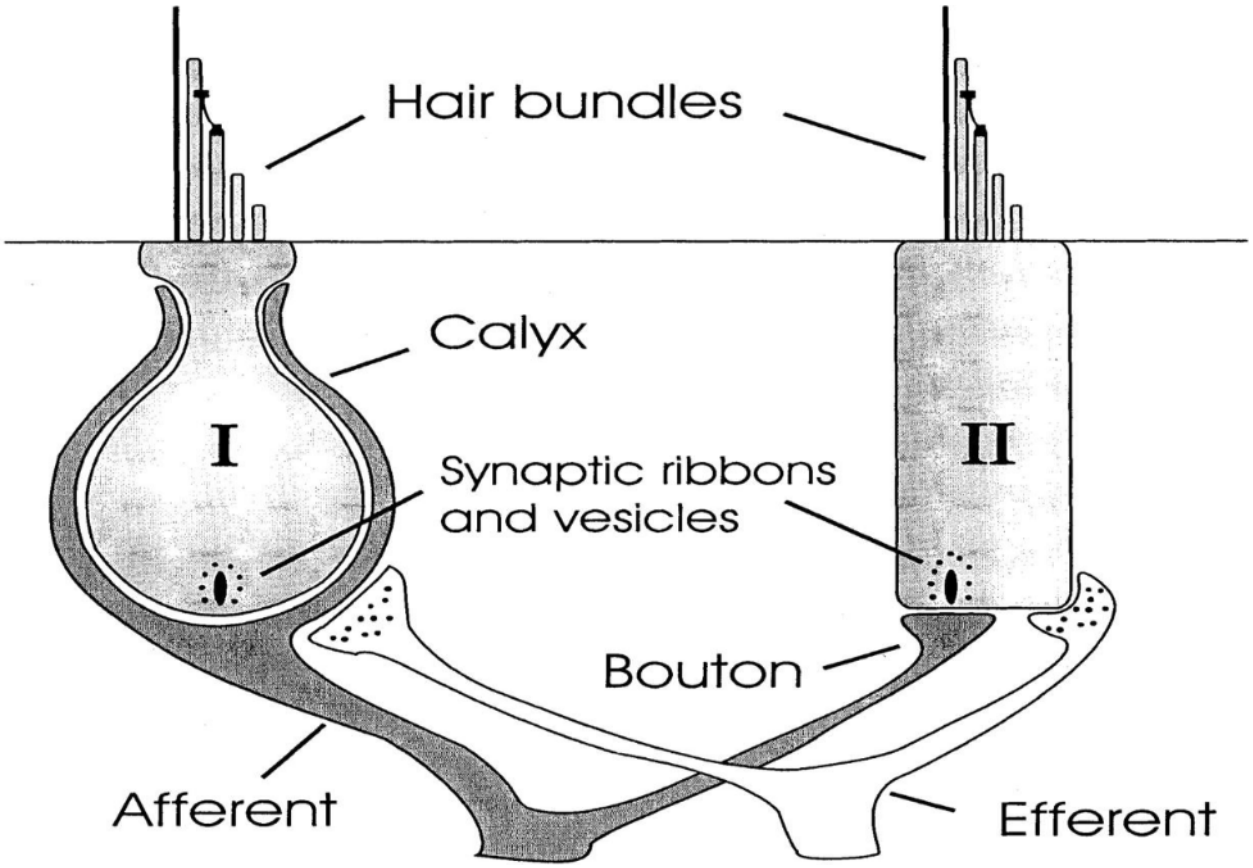
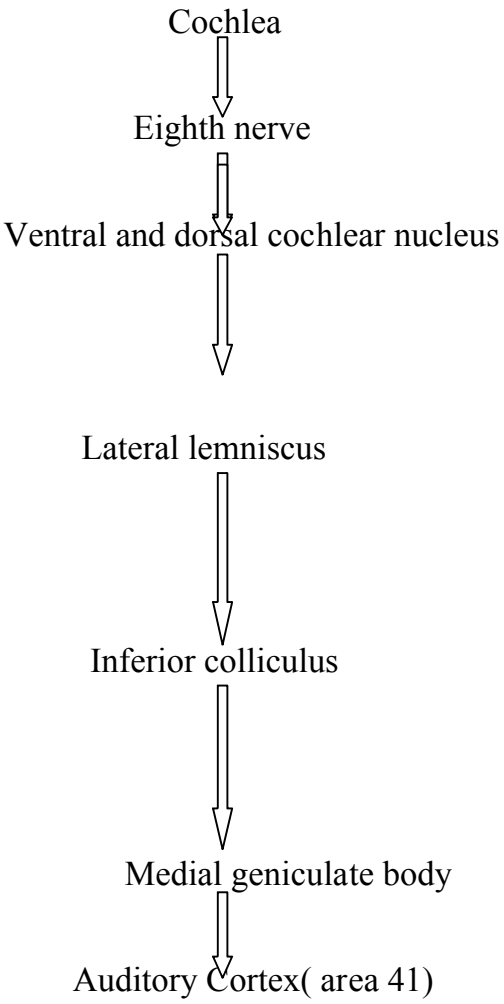


Figure 9 showing the type 1 and type 2 hair cells.

Adapted from Major *Potassium Conductance in Type I Hair Cells From Rat Semicircular Canals: Characterization and Modulation by Nitric Oxide James W. Y. Chen Journal of Neurophysiology Published 1 July 2000 Vol. 84 no. 1, 139-151*

The Auditory Pathway



Cisplatin induced ototoxicity

As explained previously, the mono aqua platin with positive charge binds to the negatively charged DNA forms cross linkages eventually leading to apoptosis. But unlike tumour cells which are rapidly proliferating, the cochlear cells rarely proliferative, if so at an undetectable pace. (37)

Cisplatin crosses the blood-labyrinthine barrier and binds to these cells which leads to release of reactive oxygen species(ROS) and pro apoptotic factors. This activates caspase and can leads to cell death. (38)

Thus cochlear hair cells undergo a dose dependent death. It has been found from animal studies that outer hair cells are most affected by cisplatin. carboplatin mainly affect the inner hair cells. The ototoxic effects are more pronounce at the base. It can also affect the apical portion if the cells are exposed to the drug for a continued period of time. (39)

Genetic studies have been going on in this area and researchers have identified two genes- the S-methyltransferase (TPMT) and catechol-O-methyltransferase which could probably play a role in the ototoxicity mechanism. further research is imperative in this area.(38)

At the molecular level NAD + has also been shown to play a major role in ototxicity effects. They cause DNA damage and help the drug penetrate the cochlear fluids. However more research is needed in its exact role. (40)

The incidence of cisplatin induced hearing loss in literature is about 60 %. The main factors contributing to this have found to be male age, cumulative dose among others.(41)

When cisplatin causes ototoxicity. it causes damage to three main areas in the cochlea.

These include-

1. The outer hair cells of the cochlea

2. neurons which are present in the spiral ganglion

3. the cells, mainly epithelial cells which are seen in the stria vascularis.(42)

Recent work on mammalian models have shown that the mean cumulative dose needed to produce ototoxicity is of the range of more than 400 mg/m2. (43)

As mentioned previously, outer hair cell are more prone to damage. The damage is seen in a sequential manner.

1. more damage is seen in the first turn of the cochlea. As the cumulative dose goes higher up, the later turns are affected.

2. it needs more concentration of cisplatin to affect the apical turns of the cochlea.

3. The outer hair cells which remain after cisplatin administration also start developing vacuolar formation and that may explain the persistent nature of this problem.

4.Stria vascularis is often the earliest one to get damaged and it shows thinning.(33)

Effect of cisplatin in the stria vascularis

Stria vascularis had a rich vascular supply. It has a lot of transporters on its surface which make it quite susceptible to damage. immunofluorescence studies have shown DNA adducts in the hexagonal cells of the stria vascularis, implicating that it is a target organ for the action of this drug.(44)

Role of transporters in the ototoxic profile of cisplatin

There is evidence that copper transporters play an important role

in the effect of cisplatin in the body. CTR 1 is the main implicated transporter and it has been seen to be expressed in outer hair cells, stria vascularis etc, accounting for the accumulation of cisplatin in these areas thereby causing ototoxicity. (45)

Anti oxidants can play an important role in protecting against ototoxicity as they can reduce the reactive oxygen species also known as ROS which are mainly implicated in hearing loss.

Amifostine was one such agent which was thought could bring about a change. But studies in animals did not bring out the desired effects. (46)

A drug named fosfomycin has been shown to have some protection against ototoxicity in animals. However, it requires further studies before this can come into practice.(47)

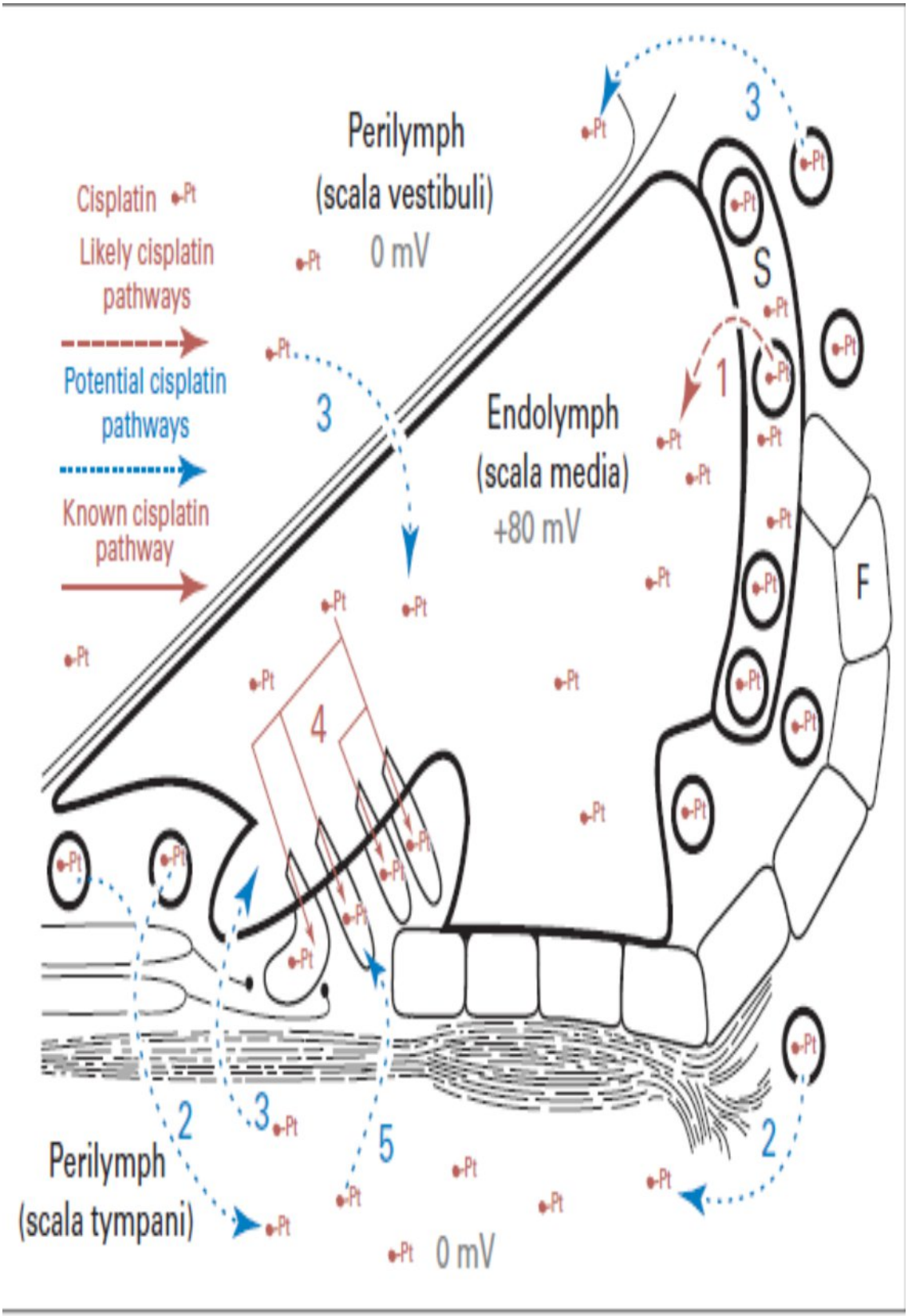

Perilymph
(scala vestibuli)
0 mV
Cisplatin
Likely cisplatin pathways
Potential cisplatin pathways
Known cisplatin pathway
Endolymph
(scala media)
+80 mV
S
F
Perilymph
(scala tympani)
0 mV
1
2
3
4
5

Figure 10. (12)

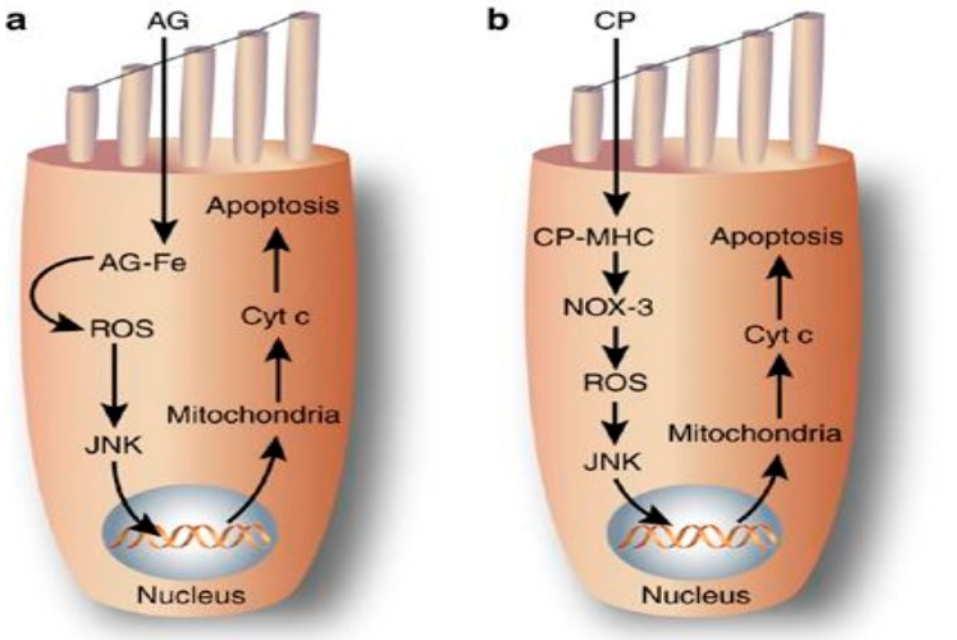


Figure 11 comparing the ototoxic action of Cisplatin versus that of aminoglycoside.

Figure a Shows aminoglycoside (AG) induced cell death which can either be caspase dependent or independent.

b shows the action of cisplatin (CP) entering into the outer hair cells. It forms a monohydrated complex(CP-MHC) which then activated reactive oxygen species and JNK. They then activate the apoptosis pathway.

Figure adapted from *Kidney International (2007) 72, 931–935 Ototoxicity L P Rybakand V Ramkumar*

Genetics of ototoxicity

There is a lot of inter individual variability among patients on exposure to cisplatin. This has led to hypothesis that there might be a genetic basis for ototoxicity. This has been further studied by pharmacogenetics.

Some of the genes implicated towards this cause are-

1. Megalin

This protein is expressed in the tubules of kidney as well as in the stria vascularis. This protein is also implicated in aminoglycoside ototoxicity.(48)

2. Glutathione S tranferase

GST s are polymorphic in nature and are mainly expressed in the cochlea.(49)

3. Thiopurine S Methyltransferase

Various studies have shown that Thiopurine S methyltransferase along with Catechol O methyl transferase is implicated in cisplatin induced ototoxicity.(50)

4. Excision Repair cross complementation group (ERCC)

This group of genes have been studied in animal models with lung cancer. It has been previously explained that cisplatin forms DNS adducts. The ERCC s help in breaking these adducts and thereby help in protection. (51)

5. Mitochondrial gene mutations.

The ribosomal RNA gene Mitochondria 12S have been implicated in aminoglycoside induced ototoxicity. There have not yet been studies showing its role in cisplatin ototoxicity.(52)

The scenario in children

The paediatric age group, unlike adults, need a greater intensity of sound to grasp the words and to comprehend the clarity of the spoken word. especially in children who are in the process of language development, this plays a major role. (53)

Hearing loss can affect language development which in turn can affect the scholastic performance. This in turn affects social interactions as well.

Studies have shown that mild hearing loss of the order of 15- 20 dB can also make students repeat a grade in school.

When high frequency sensorineural hearing loss occurs, children are unable to speak consonants like sh,t,s,p,f,z and the like. when children do not hear well, they cannot fill the gap in the sentences as they would not have attained neural maturity to do so.

Hence, this affects their vocabulary drastically. (25)

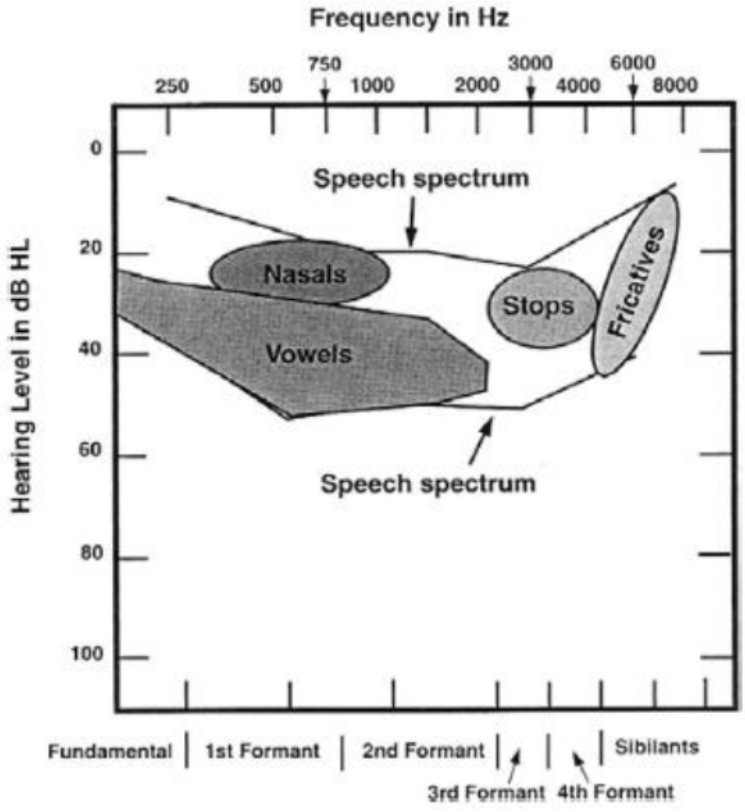


Figure 12 Graph showing hearing levels in dB and approximate intensity if varying conversational sounds.

Adapted from *Auditory Late Effects of Childhood Cancer Therapy: A Report From the Children's Oncology Group : Satkiran Grewal, MD, Thomas Merchant, DO, PhD, American Academy of Pediatrics*.

VARIOUS OTOTOXICITY GRADING IN CURRENT PRACTICE

This study uses the scoring system published by the International society of Paediatric Oncology grading system (SIOP Boston) (37)

The grading system is as follows

Grade	Parameters
Grade 0	less than or equal to 20 dB hearing loss at all frequencies
Grade 1	More than 20db hearing loss above 4000 Hz

Grade 2	More than 20 dB hearing loss at 400 Hz and above
Grade 3	More than 20 dB hearing loss at 2000 Hz or 3000 Hz and above
Grade 4	More than 40 dB hearing loss at 2000 Hz and above

The other grading systems in vogue include

1. Brock et al 1991

GRADE	PARAMETERS
0	Less than 40 dB of hearing loss at all frequencies
1	More than or equal to 40 dB hearing loss at 8000 Hz only
2	More than or equal to 40 dB hearing loss at 4000 Hz and above
3	More than or equal to 40 dB hearing loss At 2000 Hz and above

4	More than or equal to 40 dB at 1000 Hz and above

2. Children cancer group 1996

Grade	Parameters
0	No hearing loss
1	More than or equal to 40 dB at 6000 or 8000 Hz
2	More than 25 dB hearing loss at 3000 or 4000 Hz
3	More than 25 dB hearing loss at 2000 Hz
4	More than 40 dB hearing loss at 2000 Hz

3. Children's hospital Boston

Grade	Parameters
0	Less than 20 dB hearing loss at 500-8000 Hz
1	More than 20 dB hearing loss above 2000 Hz
2	More than 20 dB hearing loss at 4000 Hz and above
3	More than 20 dB at 2000 Hz and above
4	Not defined

4. National cancer institute common terminology criteria for adverse events 2010.

Grade	Parameters
0	Not defined
1	More than 20 dB shift at 8000 Hz
2	More than 20 dB threshold shift at 4000Hz
3	More than 20 dB threshold shift at 2000 Hz
4	Paediatric audiologic indication for cochlear implant and indication for additional speech language related services.

5. Grading by Chang et al.(54)

Grade	Parameters
0	Less than 20 dB hearing loss at 1. 2 and 4 kHz
1	More than 40 dB at any frequency
2	More than 40 dB AT 4000 Hz and above
3	More than 40 dB at 2000 or 3000 Hz and above
4	More than 40 dB at 1000 Hz and above

Otoprotective agents and their action

A varied number of compound have been studied for their role in otoprotection against cisplatin ototoxicity. Most of them are still in their stage of animal trials. More clinical trials are needed to assess their exact capability.

1. Amifostine

Amifostine is administered intravenously. It is metabolized into a compound known as WR 1065. This compound is known to reduce thiol. The clinical trials so far on this drug show that there is no efficacy. The American society of clinical Oncology as of now foes not approve usage of this drug.(55)

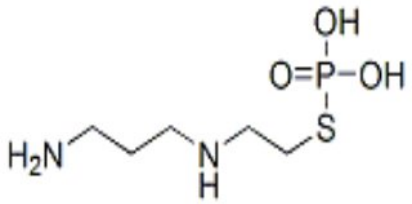


Figure 13 showing the chemical structure of amifostine.

Adapted from *chemical database*

2. Sodium Thio sulphate

This is another compound which acts as a thiol reducing agent.

Sodium thio sulphate is currently in Phase 3 trials. These studies have shown that this compound can reduce the ototoxic effects of the drug without compromising on the anti tumour efficacy of the drug, It is administered intravenously.(56)

3. N- Acetyl cysteine

This is another thiol reducing compound and is administered intravenously.

A high dose of NAC at the order of 1000mg/kg administered 30 minutes before or 4 hours after

cisplatin administration has been found to have otoprotective effects.(57)

4. D- methionine

This drug can be administered intravenously, orally or can be administered through the round window. It has maximum efficacy when administered through the round window.

It is a glutathione modulator and a free radical scavenger.

Animal studies have shown that it provides adequate otoprotection without interfering with the anti tumor properties. (58)

5. Ebselen

Ebselen is administered per orally. It is a selenium containing compound and is glutathione promoter. It has been used in animal studies. When administered , there is a drastic reduction is the number of outer hair cells that are lost usually, due o the ototoxicity if cisplatin.(59)

6. Ringer's solution or dexamethasone

This can be administered via grommets intratympanically. Studies with this are still in its initial stages. (60)

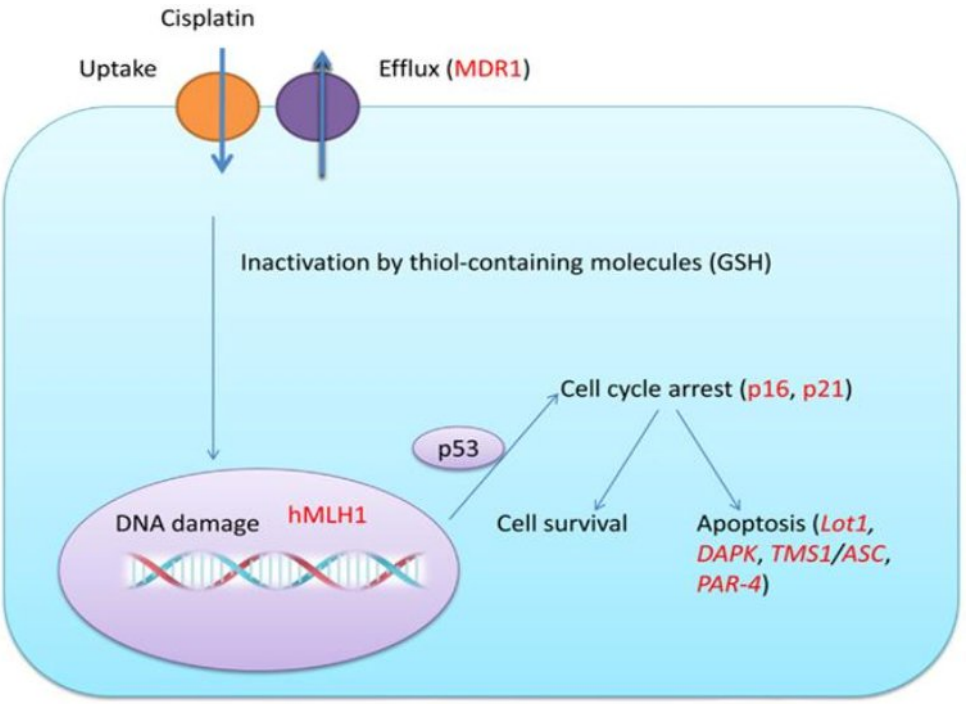


Figure 14 showing the mechanism of cis platin resistance.

Adapted from *Epigenomics of ovarian cancer and its chemoprevention Huaping Chen, Tabitha M. Hardy , Front. Genet., 04 October 2011*

A delicate balance exists between pro apoptosis and anti apoptosis. The reaction pathway which is stronger will decide the fate of the cell.

Other platinum containing compounds

Transplatin

The isomer of cisplatin is known as transplatin. Owing to its rapid dissolution before it can act at the DNA strand, it is not effective as a tumoricidal like its stereoisomer. It has a formula trans -[$PtCl_2(NH_3)_2$].

It is a toxic compound. Woollins et al developed the Kurnakov test to detect traces of transplatin in cisplatin (21)

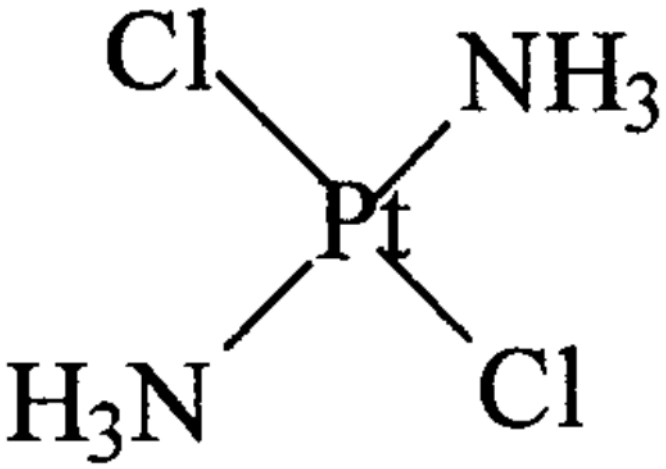


Figure 15 showing the chemical structure of transplatin. *Adapted from The Anti-tumour Agent, Cisplatin, and its Clinically Ineffective Isomer, Transplatin, Produce Unique Gene Expression Profiles in Human Cells Anne M. Galea and Vincent Murray Cancer Inform. 2008; 6: 315–355*

2. Carboplatin

The FDA approved the use of this drug in the year 1989 and was marketed under the name of Paraplatin. Most work on Carboplatin has been done at the Institute of cancer research in London.

Mechanism of action

Carboplatin mainly acts by forming DNA adducts just like cisplatin. It also works on the principle of hydration.

Dose

The dose of carboplatin needed is usually four times the dose of cisplatin

Side effects

The main side effect of carboplatin in myelosuppression. The nephrotoxic and ototoxic effects are less when compared to cisplatin.

Uses

It is highly effective in metastatic ovarian and testicular tumours.

Dicycloplatin

A new drug in study is dicycloplatin which is a combination of carboplatin and cyclobutane derivative. It is found to have a lot of potential. It is still in its phase1 form.(61)

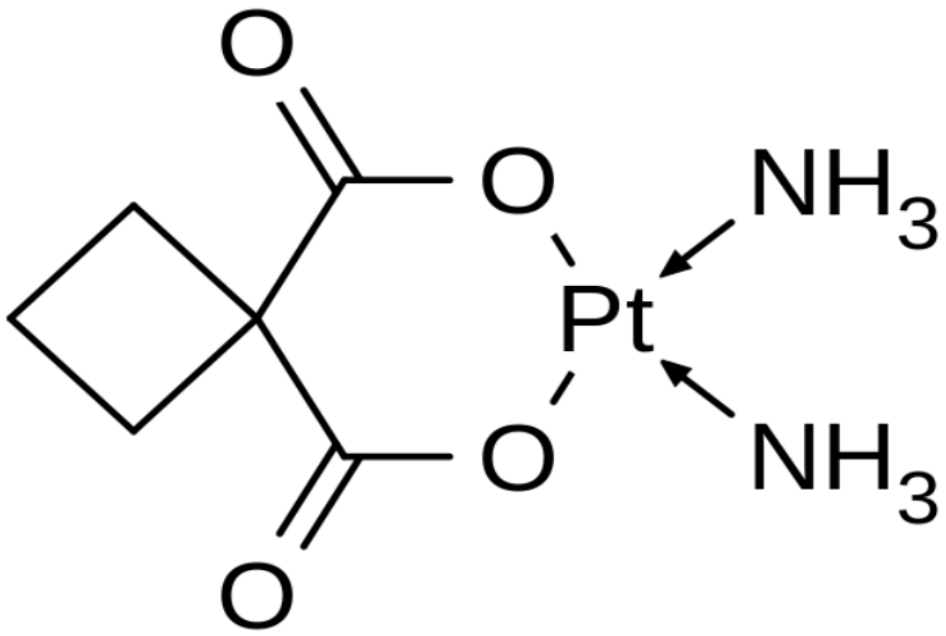


Figure 16- *Wheate NJ, Walker S, Craig GE, Oun R (September 2010). "The status of platinum anticancer drugs in the clinic and in clinical trials". Dalton Transactions 39 (35): 8113–27.*

Oxaliplatin

Oxaliplatin is another member of the platinum analogue group and is marketed under the name of Eloxatin. researchers in the Nagoya State university first invented it.

Structure

It shares its structure with cisplatin except for the fact that it had ligands which are bidentate in nature.

Mechanism of action

This drug also acts by forming DNA adducts and is activated on aquation.

Uses

Oxaliplatin is used in a regime called FOLFOX along with folinic acid. The drug has been found to be very useful in colon cancers, especially in their advanced stages.

Adverse effects

These include ototoxicity, hypokalemia, nausea, fatigue etc.

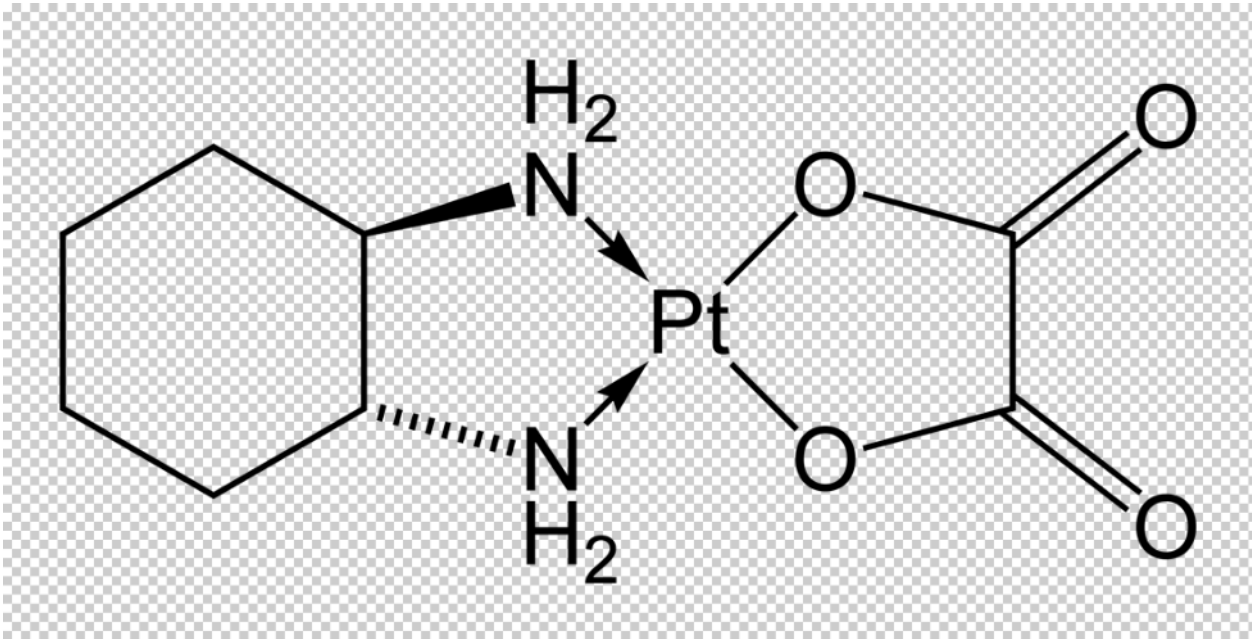


Figure 17 showing the structure of oxaliplatin. Adapted from *Ehrsson H, Wallin I, Yachnin J (2002). "Pharmacokinetics of oxaliplatin in humans". Medical Oncology 19 (4): 261–265*

3. Satraplatin

Is used mainly for prostate cancers

4.Picoplatin

This drug is still in trial phase and has been speculated to be useful in solid tumours.

5. Nedaplatin

this drug is less ototoxic than its counterparts.

6.Triplatin tetranitrate

This drug is a combination molecule.

Newer version of cisplatin- Lipoplatin

As the name suggests lipoplatin is a combination of cisplatin and a liposomal outer covering. The drug has completed phase 3 trials.

The advantage over cisplatin is that the liposomal covering acts as a protectant. the body does not see it as foreign and thus immune system does not act on it. The drug therefore acts for a longer time.

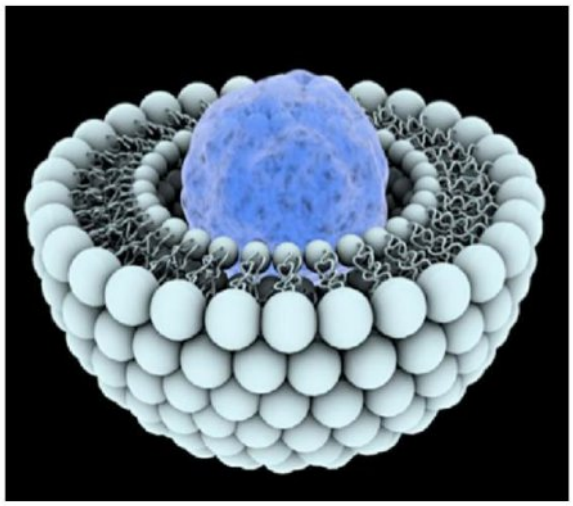


Figure 18 showing inner cisplatin molecule surrounded by liposome.

Adapted *from Journal of Drug Delivery Volume 2012 Lipoplatin Formulation Review Article G. P. Stathopoulos and T. Boulikas*

MATERIAL AND METHODS

This prospective observational study was conducted in the Department of Otorhinolaryngology, Christian Medical College, Vellore, a tertiary referral centre in Tamil Nadu.

Approval of the Institutional Review Board at Christian Medical College was obtained in December 2013 (IRB Min No.8590).

Children above five years of age, diagnosed with malignancies and planned to undergo chemotherapy with Cis-platin were briefed about the research project and requested to participate in the study.

STUDY DESIGN

Observational study

STUDY PERIOD

The prospective data were collected from December 2013 to May 2015. The retrospective data was collected from January 2012 onwards. These patients were then followed up prospectively.

SETTING

The study was done in the outpatient departments of ENT and outpatient and

inpatient departments of Paediatric oncology at the Christian Medical College, Vellore.

PARTICIPANTS

Children above 5 years with malignancies other than head and neck malignancies and planned to undergo chemotherapy with cisplatin were informed about the study, consented and recruited. They were then followed up for a period of 12 weeks.

INCLUSION CRITERIA

- Those with serviceable hearing at the start of the study. This was defined as pure tone audiogram (PTA) less than 50 dB and speech discrimination (SD) greater than 50 %.
- Those without prior chemotherapy
- Undergoing chemotherapy with cisplatin according to cisplatin chemotherapy protocol
- Age above 5 years (as Pure tone audiogram might be unreliable before that)

EXCLUSION CRITERIA

- Those who have already had chemotherapy prior to inclusion.
- below 5 years of age
- Not fit for audiology tests
- Not undergoing or has not undergone radiotherapy in the past.

SAMPLE SIZE CALCULATION

From literature, it was found that the prevalence of cisplatin induced ototoxicity was 60%

.

By applying the formula,

$n= Z^2PQ/ d^2$,

Where n=sample size

Z=95% confidence limits,

P=prevalence, Q=100-P, d=precision (10%),

The required sample size was calculated to be 80.

STATISTICAL ANALYSIS

The qualitative variables were expressed using frequencies and percentages. The incidence of hearing loss at 6 weeks of starting cisplatin and 12 weeks of staring cisplatin were studied. Chi- square test was done on age versus hearing loss and also on the cumulative dose versus the hearing loss. A graph was also made on the progression of hearing loss at 6 weeks exposure to cisplatin to 12 weeks. A chi- square test was performed with 95% confidence interval.

METHODOLOGY

Children attending the outpatient department of Paediatric oncology fulfilling the inclusion criteria were recruited after an informed consent was obtained from parent or legal guardian. A detailed history and clinical evaluation is done at the start of the study.

Before the administration of cisplatin, these patients were seen in the ENT department, a targeted history and examination was done and hearing assessment was performed. The initial hearing assessment included an Audiogram, Tympanometry and distortion product Oto acoustic emissions.

These patients were administered cisplatin according to protocol and were called back after 6 weeks for a repeat evaluation and hearing assessment. Once these details were taken, the chemotherapy was continued as per schedule.

In case radiotherapy was administered or planned to be administered, these patients were excluded.

The age of the patients were divided into three groups- 5 to 10 years, 11 to 15 years and above 15 years.

The hearing loss was graded according to the International society of Paediatric oncology, Boston grading system (SIOP Boston)

The grading system is as follows.

Grade	Parameters
Grade 0	less than or equal to 20 dB hearing loss at all frequencies
Grade 1	More than 20db hearing loss above 4000 Hz
Grade 2	More than 20 dB hearing loss at 4000 Hz and above
Grade 3	More than 20 dB hearing loss at 2000 Hz or 3000 Hz and above
Grade 4	More than 40 dB hearing loss at 2000 Hz and above

The children were then placed into these groups.

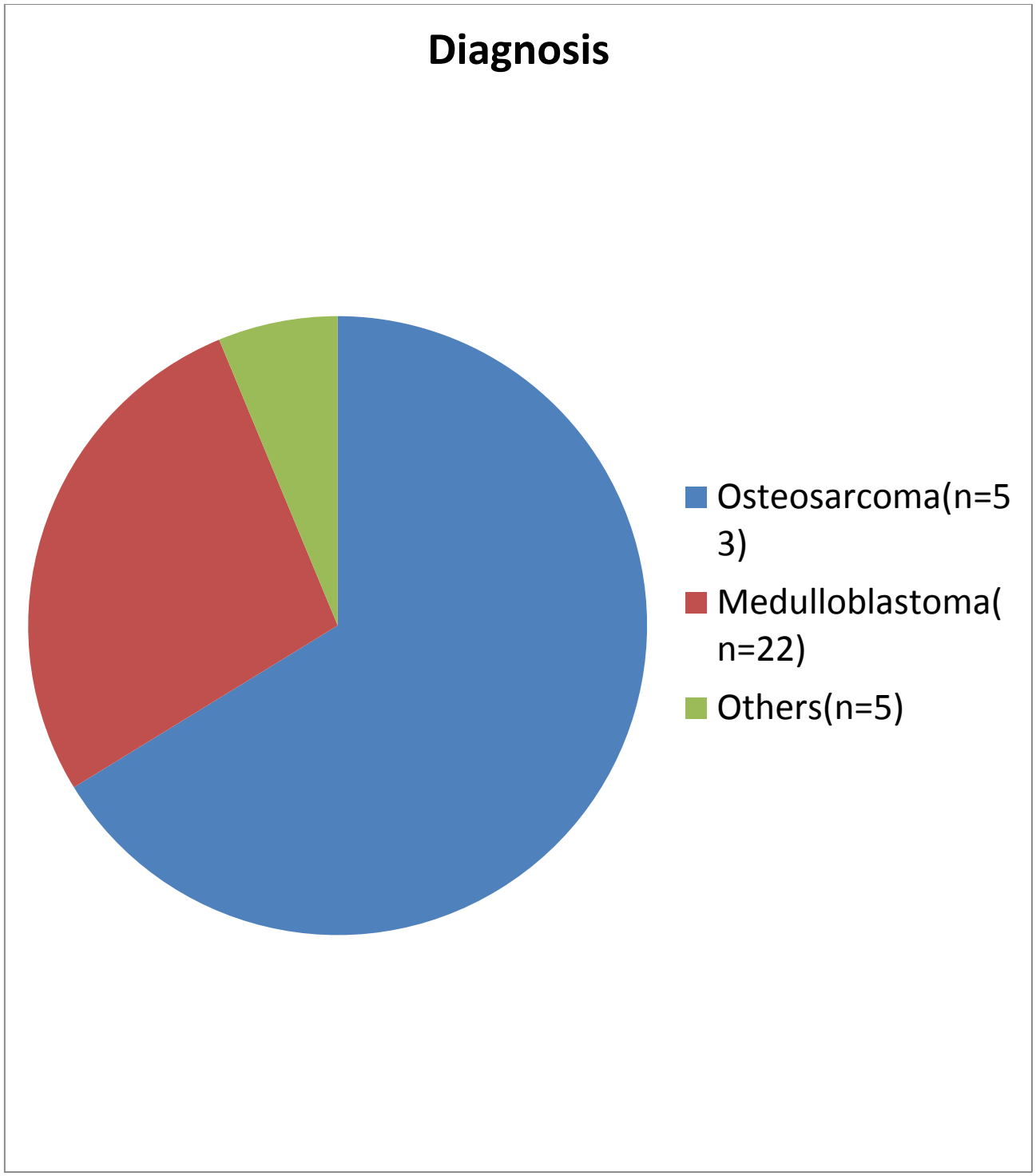
Those detected to have hearing loss above grade 3 were then examined. Paediatric oncologist would then replace cisplatin with carboplatin or any other drug suitable. The child would then be followed up and advised hearing aid if necessary so that speech development is not affected.

The hearing evaluation included a tympanometry and OAE to rule out middle ear causes.

RESULTS

The study was conducted among the paediatric population attending the paediatric oncology unit and with malignancies other than those involving the head and neck region, in whom cisplatin based chemotherapy was planned.

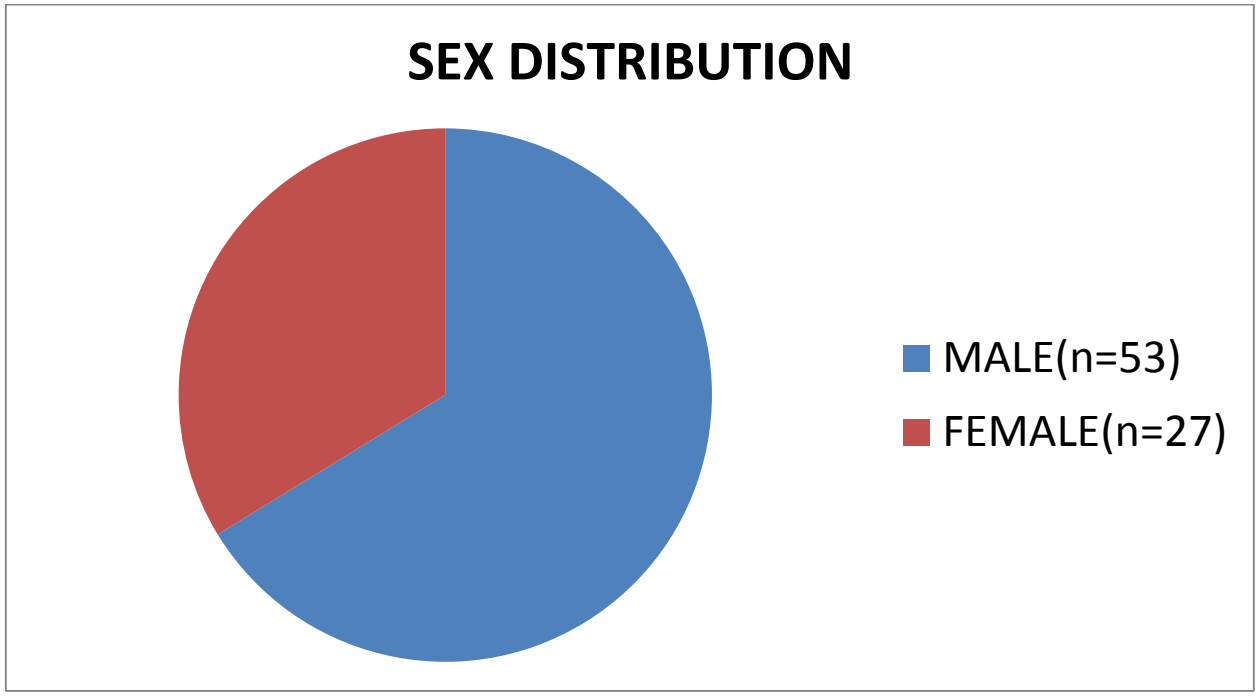
The study included children from all over India especially from the states of Bihar, West Bengal and Jharkhand. Of the 80 children studied, cisplatin based chemotherapy was used in all of them for various malignancies. The various malignancies included osteosarcoma, medulloblastoma and neuroectodermal tumours. A distribution of the diagnosis is given in Fig. 19


Diagnosis
Osteosarcoma(n=53)
Medulloblastoma(n=22)
Others(n=5)

Baseline characteristics of the study population

SEX DISTRIBUTION OF THE STUDY POPULATION

Of the 80 patients included in the study, there were 53 males and 27 females. The age distribution is illustrated in Fig.20



AGE OF THE STUDY POPULATION

The study patients had an age varying from 5 years to 17 years. For ease of analysis, they were grouped into three groups of- 5-10 years, 11-15 years and more than 15 years.

Children less than 5 years were excluded as it was thought that the hearing assessment would be unreliable before that.

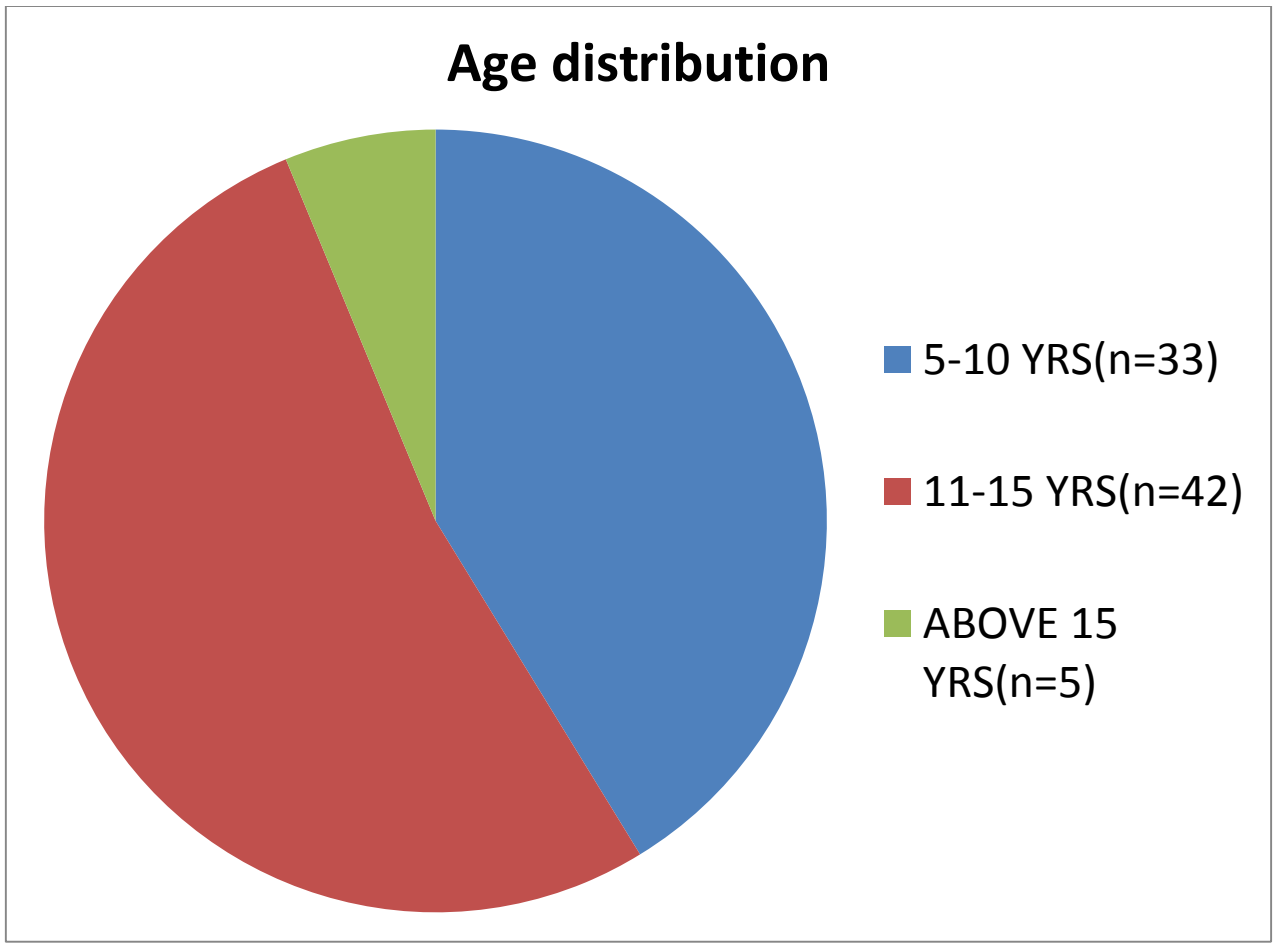
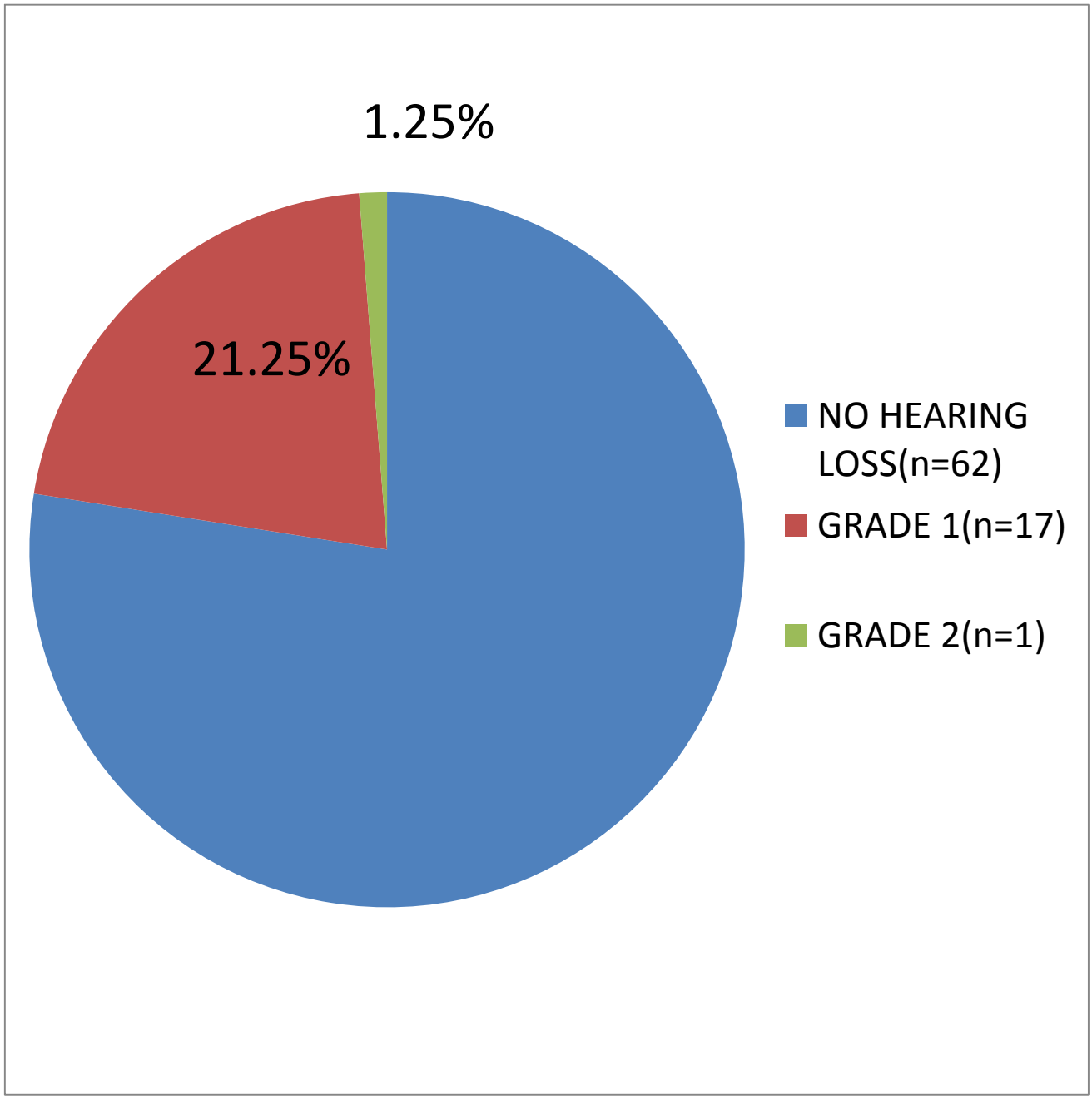


Figure 21.

All patients underwent an Audiogram, tympanometry and distortion product oto acoustic emission testing prior to inclusion in the study. All 80 patients had a normal hearing assessment.

This cohort was followed up for 6 weeks after the administration of cisplatin. The SIOP Boston ototoxicity grading system (Given above) was used. It was found that 62 out of the 80 patients still had a normal hearing. 17 of them developed a grade 1 hearing loss and 1 child was detected to have a grade 2 hearing loss. The data is illustrated in the following pie chart.

Figure 22 showing grade of hearing after 6 weeks.



HEARING	AT 6 WEEKS
No hearing loss	77.5%
Grade 1 hearing loss	21.25%
Grade 2 hearing loss	1.25%

This cohort was followed up for another 6 weeks i.e., a total of 12 weeks from the date of administration of cisplatin. A hearing assessment was done at the end of 3 months and it showed that only 9 children retained their normal hearing. 51 of them developed a grade 1 hearing loss. Grade 2 was seen in 16 children and grade 3 was seen in 4 patients.

This data is given in the following graph.

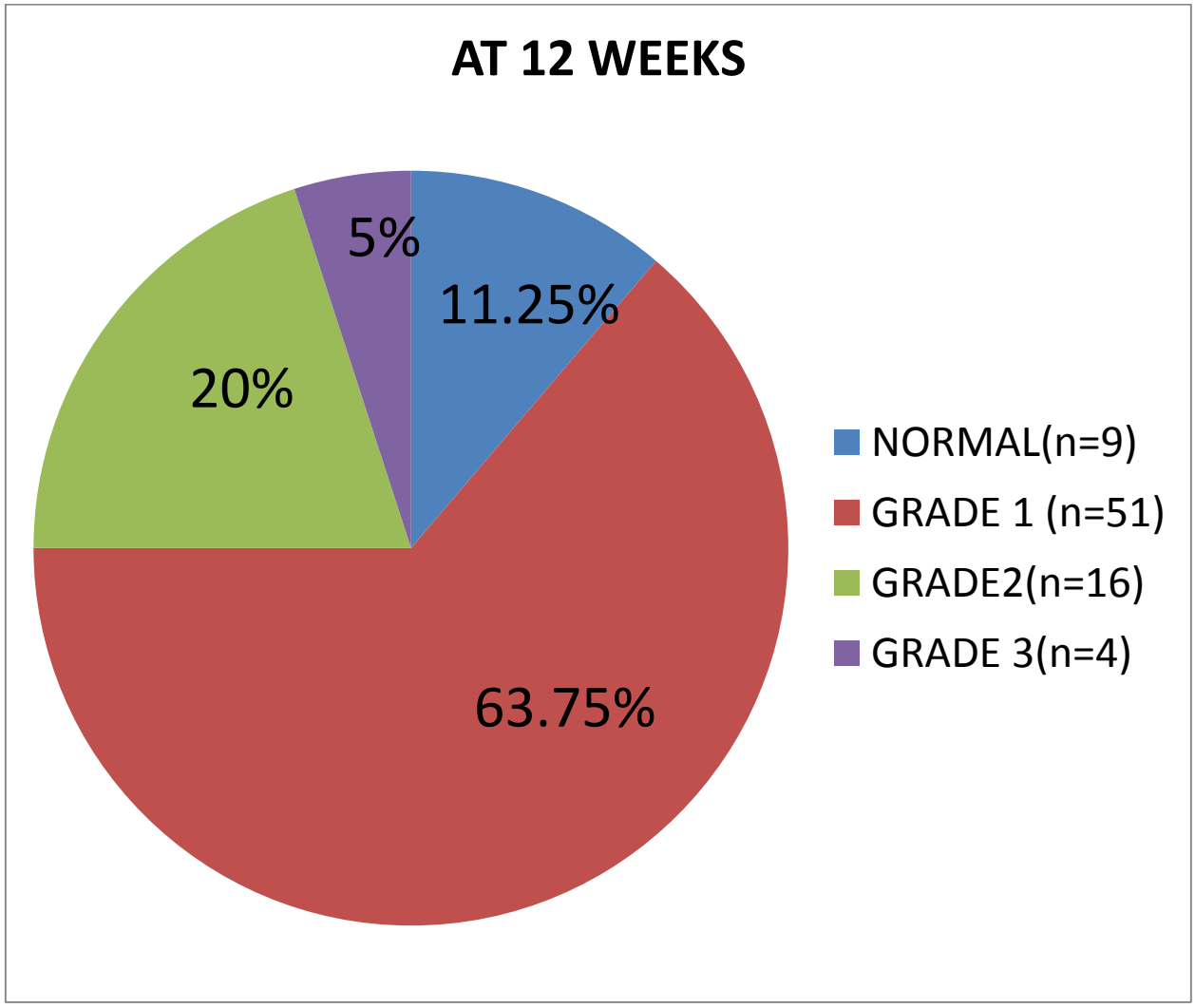


Figure 23. Audiogram at 3 months

HEARING	AT 12 WEEKS
Normal	11.25%
Grade 1	36.75%
Grade 2	20%
Grade 3	5%

The progression of hearing loss from 6 weeks to 12 week duration was studied. Of the 62 children who had normal hearing at the end of 6 weeks, only 9 of them still retained their normal hearing. 38 of the patients went on to develop grade 1 hearing loss, 14 of them grade 2 and one patient who was initially grade 0 developed a grade 3 hearing loss.

From the cohort who were Grade 1 at the end of 6 weeks, 13 of them still remained at grade 2 whereas 1 child each developed a grade 2 and grade 3 hearing loss respectively.

One child who had grade 2 hearing at the end of 6 weeks developed a grade 3 hearing loss at the end of the study.

The above data is illustrated in the following figure 24

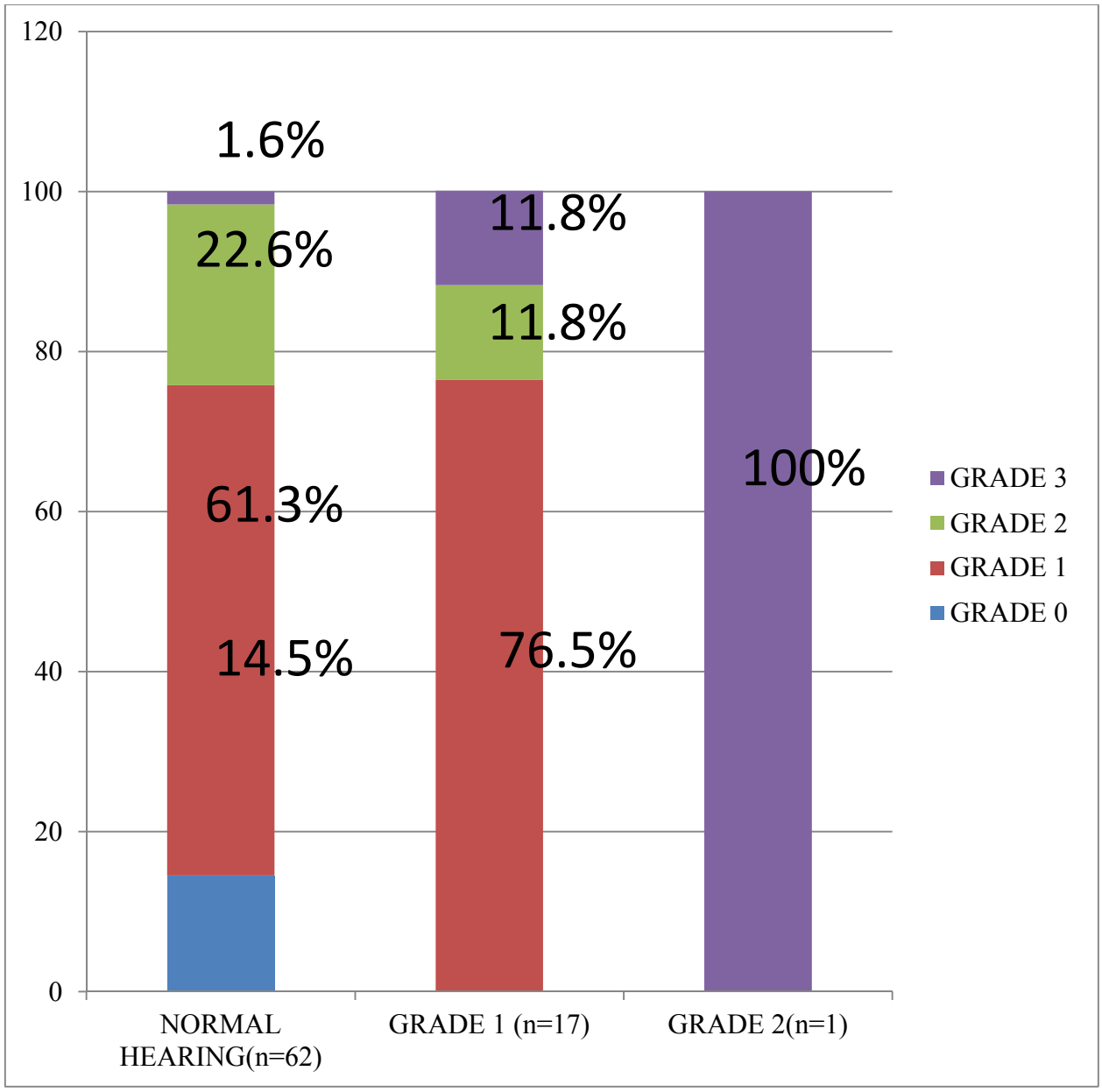


Figure 24 showing progression of hearing loss in children undergoing treatment with cisplatin from 6 weeks to 12 weeks.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	16.305[a]	4	.003	.042	
Likelihood Ratio	6.888	4	.142	.110	
Fisher's Exact Test	7.352			.079	
Linear-by-Linear Association	.168[b]	1	.682	.693	.409
N of Valid Cases	80				

Figure 25 showing statistical analysis of the progression of hearing loss. The p value was found to be 0.079.

The patients were categorized according to the age into 3 groups- patients ranging from 5 to 10 years, those between 11 and 15 years and ones above 15 years. A comparison was made between the age and hearing loss both at 6 weeks and at 12 weeks.

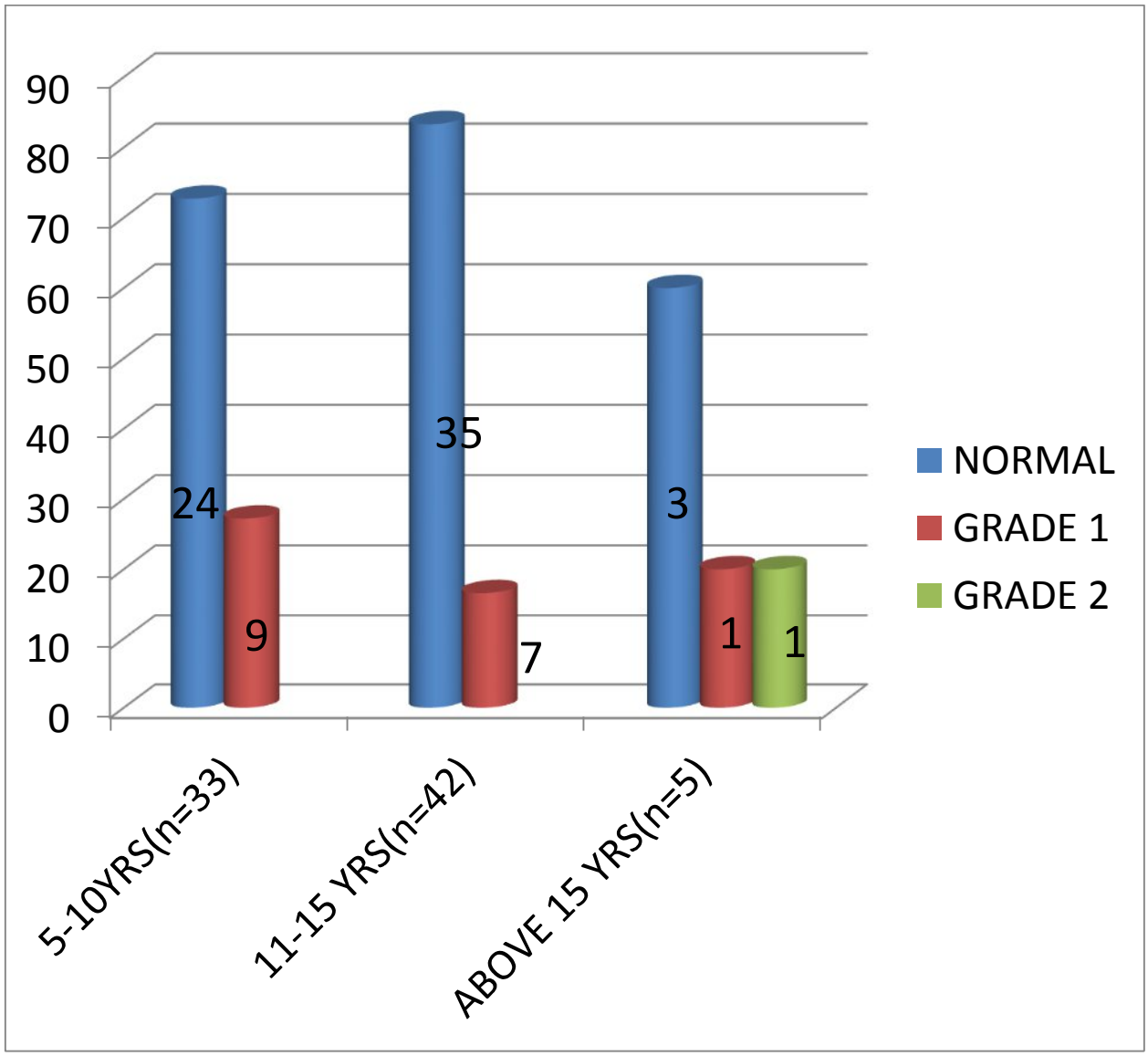
There were 33 patients in the age group of 5 to 10 years, 42 in the group of 11 to 15 years and 5 in the age group of above 15 years.

At the end of 6 weeks , it was found that in the age group of 5 to 10 years, 24 out of the 33 had normal hearing. The remaining 9 patients went on to develop Grade 1 hearing loss.

Among the 42 patients in the age group of 11 to 15 years, 35 patients had normal hearing and 7 had grade 1.

There were 5 patients above 15 years of age, of whom 3 had normal hearing , 1 developed a grade 1 hearing loss and one child developed a grade 2 hearing loss.

The results of age versus hearing loss at 6 weeks is depicted in Figure.26



Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	16.305[a]	4	.003	.042	
Likelihood Ratio	6.888	4	.142	.110	
Fisher's Exact Test	7.352			.079	
Linear-by-Linear Association	.168[b]	1	.682	.693	.409
N of Valid Cases	80				

The p value of this association was found to be 0.079

The same association was studied at the end of 12 weeks. Among the 33 patients in the 5-10 year age group, 3 patients had normal hearing, 22 developed Grade 1 hearing loss, 6 developed grade 2 hearing loss and 2 of them went on to develop a grade 3 hearing loss.

The above data is illustrated in the figure below.

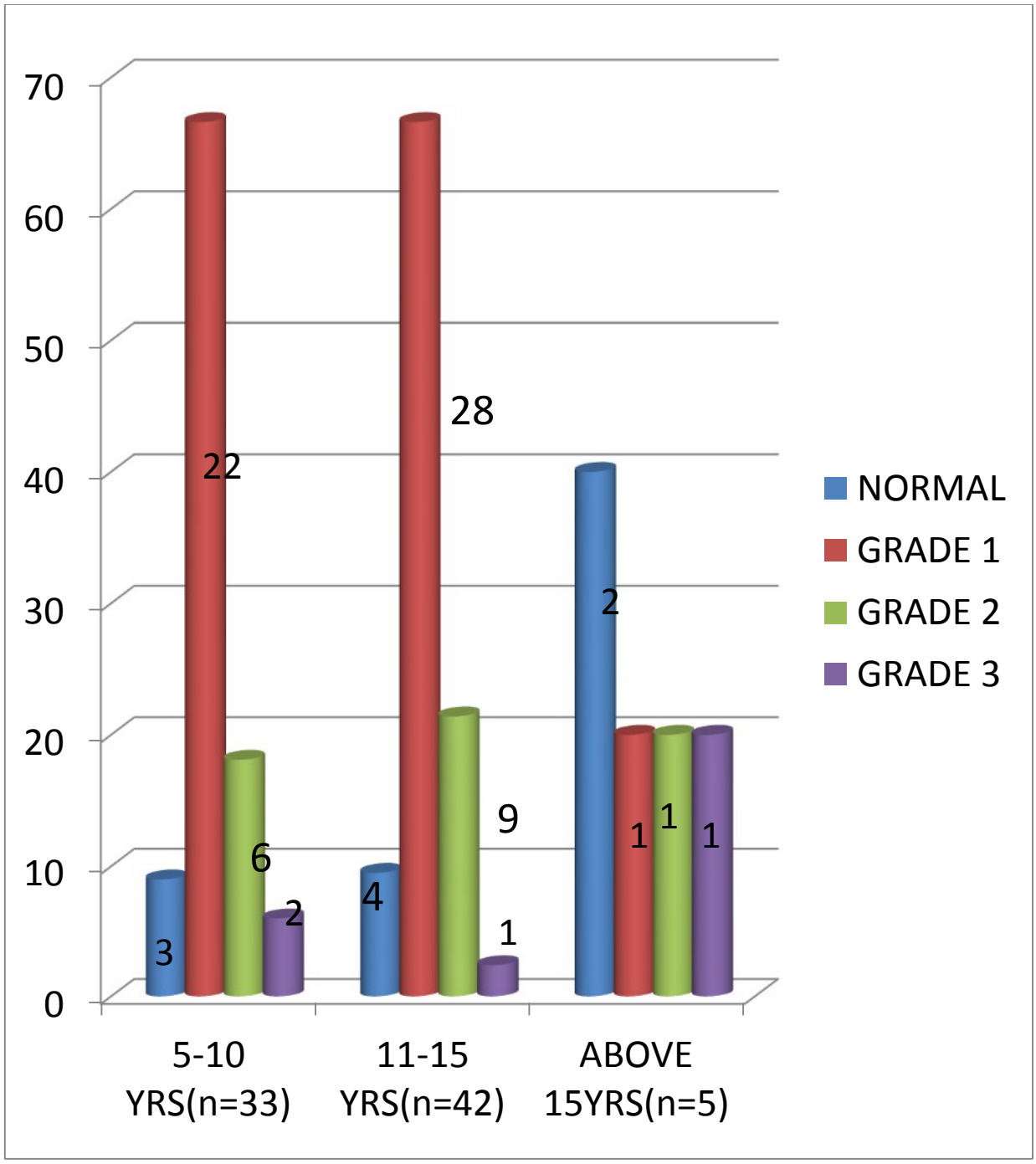

70
60
50
40
30
20
10
0
22
28
6
2
3
4
9
1
2
1
1
1
NORMAL
GRADE 1
GRADE 2
GRADE 3
5-10 YRS(n=33)
11-15 YRS(n=42)
ABOVE 15YRS(n=5)

Figure 27

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.653[a]	6	.100	.090	
Likelihood Ratio	9.520	6	.146	.171	
Fisher's Exact Test	10.469			.065	
Linear-by-Linear Association	.675[b]	1	.411	.434	.245
N of Valid Cases	80				

The p value was found to be 0.065 for this association.

The dose of cisplatin also makes an important contribution to the emergence of hearing loss. The dose is measured in mg/m2. The cumulative dose of Cis-platin given to the 80 study patients over the study period of 3 months were calculated.

For ease of calculation, the doses were classified into 3 groups. The first group consisted of patients who had received a total cumulative dose of 240- 290 mg per metered sq.

There were 24 patients who received this dose. Of them, 4 patients had normal hearing, 15 developed grade 1 hearing loss and 5 of them developed grade 2 hearing loss.

34 patients received a dose of 291 to 340 over the study period of 3 months. Of them, 4 had normal hearing, 26 developed grade 1 hearing loss and 4 children developed grade 2 hearing loss.

There were 22 patients who received a dose above 340 mg/m2. Of them, only one patient had normal hearing. 10 developed grade 1 hearing loss, 7 developed grade 2 and 4 developed grade 3 hearing loss.

This is illustrated in the following Figure.

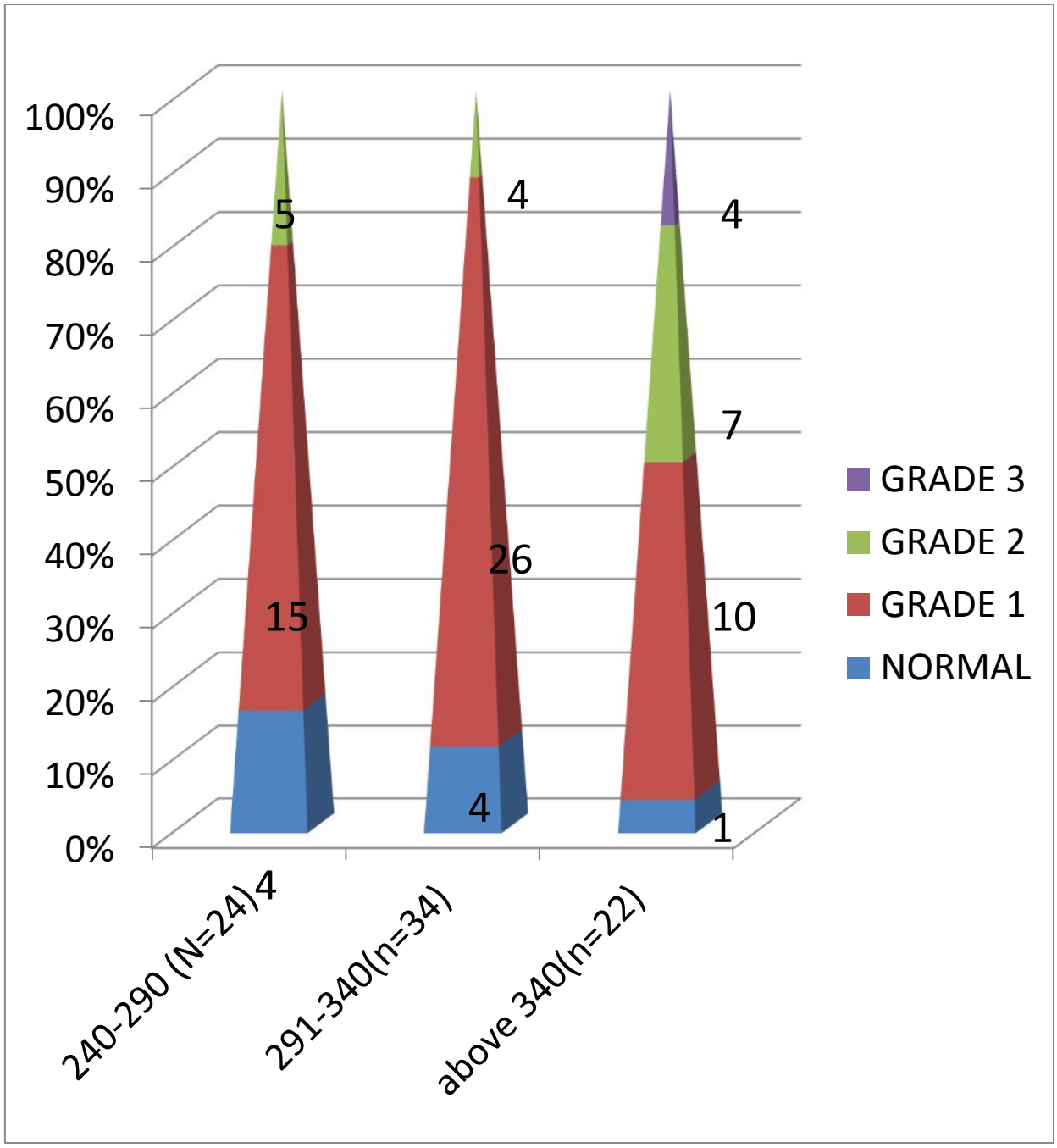

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
5
15
4
26
4
4
7
10
1
GRADE 3
GRADE 2
GRADE 1
NORMAL
240-290 (N=24)4
291-340(n=34)
above 340(n=22)

Figure 28

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	25.752[a]	6	.000	.004	
Likelihood Ratio	14.755	6	.022	.009	
Fisher's Exact Test	13.999			.014	
Linear-by-Linear Association	5.200[b]	1	.023	.032	.020
N of Valid Cases	80				

DISCUSSION

Cisplatin belongs to the class of platinum anti neoplastic drugs. It acts by the mechanism of alkylation. It is chemically known as cis-diamminedichloro-platinum.

Since its discovery, it has been of immense use in malignancy treatment, especially in the paedatric age group. However, its toxicities are a huge limitation.

The aim of this study is to find the incidence of sensorineural hearing loss among paediatric age group attending this tertiary care hospital. The hospital has a set protocol for cisplatin chemotherapy. The aim was to validate this and to also find the co relation between cumulative dose and age versus onset of hearing loss.

The patients (a total of 80) were studied over a period of 2 years and each child was followed for 3 months.

Our results show that at the end of 6 weeks, 17 children developed grade 1 hearing loss and 1 child developed grade 2 hearing loss. The hearing loss was graded according to the International society of Paediatric Malignancies, Boston grading system.

Knight et al studied children undergoing cisplatin chemotherapy for various malignancies for over a period of 26 months. They found 25 % hearing loss in their subjects. (1)

Our study period was for duration of 3 months. In this duration, we found that 63% of patients developed grade 1 hearing loss , 20 % developed grade 2, 5 % developed grade 3 and 11 % of the patients retained their normal hearing . Considering Grade 3 to be sensorineural hearing loss which affects the child physically, emotionally and in development of speech, our results showed an incidence of 5% hearing loss at the end of 3 months as opposed to 25% in the previously described study over a period of 26 months.

In another study by Anne Weissenstein et al, follow up of all children receiving chemotherapy was done for a period of 126 months. They found a 37% incidence of sensorineural hearing loss in their patients. (2)

A comparison was also made with age and hearing loss. Holmes et al found that the hearing outcomes were better in the age groups of 7 to 10(64). In our study we included children aged 5 years onwards. This was because accurate results of audiogram might not be obtainable before that.

In this study it was shown that, higher the age group better is the ability to tolerate ototoxicity. In the age group above 15 years, almost 40 % of the subjects had normal hearing as against only 9% children with normal hearing in age group 5-10 years. The 10-15 year age group showed a 9.5% incidence of hearing loss. Thus it can be concluded that higher the age group, the better.

Another striking feature in this study is that, there was progression of hearing loss from 6 weeks to the 3 months duration. Around 11 % of the children who were grade 1 at the end of 6 weeks developed grade 2 and grade 3 hearing loss respectively.

In a study conducted by Bertolini et al, almost 30 % of the subjects had hearing loss.(65) In another study, Berg et al followed up patients with paediatric malignancies undergoing cisplatin chemotherapy. He found that the median time to developing hearing loss in these subjects were about 5.6 months.

However, in this study, patients have been followed up only for a period of 3 months. Hence, it will be more yielding if the present cohort is followed up for some more time.

The cumulative dose given to the patient also has an impact on hearing loss. In this study, it was found that patients who received cumulative doses above 34 mg/m2 were found to have more ototoxicity than those that received fewer doses. Almost 49% of patients who were exposed to higher doses developed sensorineural hearing loss as against 11 % in other groups.

The impact of such hearing loss is profound. The auditory system is affected which means that the child's speech is also affected. This in turn affects their academic as well as social development.

When children do not hear well, they cannot connect sentences or phrases. Hence, this affects their vocabulary drastically.

The study has helped find out the incidence of sensorineural hearing loss among paediatric population undergoing cisplatin chemotherapy. It has helped find out risk factors. More importantly, Children at risk could be picked up early and their dose reduced or a different regime with a different drug started, so that these children will not develop a hearing loss that would affect their overall development.

Since more and more children undergoing cisplatin chemotherapy are surviving, they will live to see the effects of this drug. Thus it is imperative, that every hospital sets up such a protocol of hearing assessment at the start of every cycle, to overcome this untoward side effect. This study has shown that the onset of hearing loss due to chemotherapy can be detected early and the regimen may be modified to reduce the risk.

LIMITATIONS

Our study was also not without limitations. Many patients coming from Bihar and West Bengal after initial assessment and after charting out a chemo schedule, would go back to their hometown and hence was lost to follow up.

Also when children develop fever or any other complications, their chemo dates would be revised which does not give a correct assessment of the time duration.

CONCLUSION

Platinum based chemotherapy, especially with cisplatin offers a wonderful cure to many malignancies. However their ototoxic nature limits their use. Our study found a statistically significant relation between time duration and development of hearing loss. There was also a co relation between cumulative dose and hearing loss.

It is important to pick up this ototoxicity early so that the academic and social development of these children are not affected. This cohort will need to be followed up for some more period of time to see the complete effects of this drug and to pick out any ototoxicity early.

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PATIENT INFORMATION SHEET

STUDY TITLE- Cisplatin induced hearing loss in paediatric malignancies.

The purpose of the study is to find out the incidence of hearing loss in patients undergoing chemotherapy for cancers. The study also aims to find out the prevalence of hearing loss in different age groups. It will also determine the total dose of chemotherapy and amount of hearing loss. Hearing tests will be done before chemotherapy, 6weeks after start of treatment and 3 months after start of treatment.

The information collected from you will be kept confidential, analyzed separately and results published in standard medical books, without revealing your identity.

The results obtained from the study are expected to improve the understanding about hearing loss following chemotherapy, thereby guiding the doctor in improving the approach towards the management of such cases.

DATE:

INFORMED VALID CONSENT

Study number-

Hospital number-

Participant's name-

Date of birth/age

I, _____ son/daughter/wife of _____ have been explained in my own language about the proposed study. It has been explained that this study involves

doing hearing tests for checking the hearing of my child . These are tests which are routinely done and does not involve any invasive procedure. It has been explained to me that there is no additional risk in the study and that I am free to withdraw from the study any time I want and it will not in any way compromise the treatment, the Oncology doctors are giving me. I understand that my identity and participation will not be revealed in any information released to third parties. I am giving this consent on my own free will. I hereby give my full valid consent for participating in the proposed study.

Name of patient

Signature

Date

Name of Doctor

Signature

Date

Name of witness

Signature.

Date

CLINICAL RESEARCH FORM

CISPLATIN INDUCED HEARING LOSS IN PAEDIATRIC MALIGNANCIES

SERIAL NUMBER:

NAME: HOSPITAL NO:

AGE: SEX: PLACE: PHONE NUMBER:

DIAGNOSIS:

MODALITY OF TREATMENT:

IS RT PLANNED

PREVIOUS CHEMOTHERAPY/RT

CHEMO- AGENT: DOSE:

CYCLE: DAYS PER CYCLE:

PRE TREATMENT

AUDIO:

OAE :

TYMP:

AT 6 WEEKS FOLLOW UP:

CYCLE:

TOTAL DOSE RECEIVED:

AUDIO:

OAE:

TYMPS:

EVIDENCE OF HEARING LOSS: Y/N

IF YES, GRADE:

ACTION TAKEN:

COMMENTS:

AT 3 MONTHS FOLLOW UP

CYCLE:

TOTAL DOSE RECEIVED:

AUDIO:

OAE:

TYMPS:

EVIDENCE OF HEARING LOSS: Y/N

IF YES, GRADE:

ACTION TAKEN:

COMMENTS:

PATIENT NAME	HOSPITAL	AGE	SEX	DIAGNO	DATE OF STARTING CH	PRE CHEMO AUD	duration to 2nd audi	dose
LAXMI	769732F	13	1	2	Dec-13	0	6	1
MUNIRA	620768F	11	2	2	Sep-13	0	6	1
SUDIPTA	495022F	10	1	1	Oct-13	0	5	1
ROCKY GHOSH	493488F	16	1	1	Jun-13	0	5	1
LIANA JOBSY	639207F	5	2	3	Sep-13	0	6	1
ALEN THOMAS	727891F	10	1	3	Apr-13	0	6	1
ARPITA	330190F	10	2	1	Apr-13	0	6	1
MD.NOOR	718327F	14	1	2	Dec-13	0	6	1
FILZA	766220F	6	2	2	Jan-14	0	6	1
HUI PELLEN	378121F	15	1	1	Jan-13	0	6	1
AMISHA SINGH	760428F	6	1	1	Sep-13	0	6	1
MIZANUR	508691D	14	1	2	Jan-13	0	6	1
ANSARUL	809657F	6	2	3	Oct-13	0	6	1
SANGEETHA	908604D	14	2	1	Apr-14	0	5	1
SUBODH	766153F	6	2	1	Jan-14	0	6	1
CERIN	234207F	10	2	1	Feb-12	0	5	1
SHRI ATO BIDA	742953F	6	1	1	May-13	0	6	1
MARIYAM	848320F	15	2	2	May-11	0	4	1
Venkata Sai	690869F	16	1	2	Oct-13	0	5	1
HARSHVARDHA	464031F	11	1	1	Apr-13	0	6	1
VARUN	843772F	12	1	2	Jun-13	0	6	1
KARTHICK	637257F	11	1	2	Oct-13	0	6	1
BALLA KALYAN	637441F	12	1	1	May-13	0	6	1
JYOTI	791162F	13	2	1	May-14	0	6	1
SUMAN	791174F	6	1	1	Jun-13	0	6	1
PRAYENSHU	661270F	7	1	2	Jul-14	0	6	1
SIBASIS	398344F	12	1	2	Feb-13	0	5	1
SHORAV	186368F	8	1	2	Jan-13	0	6	1
MANAS SAHA	840711F	9	1	2	Jan-14	0	5	1
SAMBHAV	743822F	13	1	1	Nov-13	0	6	1
ADITI	869026F	12	2	1	Nov-14	0	5	1
SABANA	683736F	6	2	1	Oct-13	0	6	1
MD.YASIR	668606F	9	1	2	Nov-12	0	6	1
ASNA	484775F	8	2	2	Jun-13	0	6	1
PARAMITA	472309F	11	2	2	Mar-13	0	6	1
JUEL GEORGE	409451F	2	1	1	Mar-14	0	6	1
JOICY JAMES	402191F	7	1	2	Nov-13	0	6	1
ISHANI	392818F	9	1	2	Jul-13	0	6	
CHANDAN	341480F	8	1	2	Oct-14	0	5	1
JOSEPH	857071F	16	1	2	Jul-14	0	6	1

duration to 3rd a	dose 2	3rd Audi
12	380	1
12	360	1
11	240	1
12	380	2
12	260	1
13	300	0
12	340	0
12	320	1
12	260	1
13	360	1
12	280	1
12	300	1
12	360	1
12	340	3
12	320	3
12	240	1
12	280	1
12	300	1
12	360	1
12	320	2
12	380	1
12	320	1
12	240	2
12	280	1
12	300	1
12	260	2
12	300	1
12	340	1
12	320	2
12	260	2
12	380	2
12	240	3
12	240	1
12	260	1
12	300	1
12	360	0
11	320	1
10	160	0
12	340	1
12	260	0

PRIYA	653738F	15	2	2	Aug-13	0	5	1
GOUTHAM	048022D	13	1	1	Nov-14	0	6	1
RAYALA	841603D	8	2	1	Jul-12	0	5	1
HIBA	897458F	16	2	2	Jun-13	0	6	1
REKHA	837641F	14	2	2	Aug-12	0	5	1
KASHIF NAWAB	800671F	13	1	2	Mar-12	0	6	1
MAHADI HASAN	793813F	16	2	2	Sep-13	0	5	1
MAGESH	913121F	7	1	2	Jan-14	0	6	1
PAWAN	999161D	7	1	2	Aug-12	0	6	1
SHAHANAZ	849064F	9	1	2	Nov-13	0	6	1
MUBTASIM	855669F	10	1	2	Jan-12	0	6	1
DEBASIS	822175F	12	1	2	Apr-13	0	6	1
SNEHA	839848F	14	2	2	Jul-14	0	6	1
ROHIT	775942F	7	1	2	Jan-12	0	6	1
SUSHEELA	888624F	9	2	2	Jun-12	0	6	1
AMIT	894582F	9	1	2	Jun-13	0	6	1
DHARANIDHAR/	722589F	15	1	3	Oct-13	0	6	1
IAN JOBIN	111824G	13	1	1	Jan-12	0	6	1
SAHANA	757433F	8	2	2	Feb-13	0	6	1
DEVASHISH	087768G	9	1	2	Feb-12	0	6	1
DEVENDRAN	136596F	11	1	2	Oct-14	0	6	1
MD ADIL	704210F	10	1	2	Jan-12	0	6	1
VADIA	096322G	11	1	2	Feb-13	0	6	1
THEJAS	267965F	7	1	2	Mar-13	0	6	1
MD NASIM LASK	888021f	6	1	2	Sep-12	0	5	1
SAHIDHAFEZEE	352363F	9	1	2	Aug-13	0	6	1
SANTANU	001808G	10	1	2	Oct-12	0	6	1
TANISHA	919763F	13	2	2	Jul-13	0	6	1
ANAND	423589C	11	1	1	Mar-12	0	6	1
NAFEES ANSARI	690533C	8	1	3	Jun-12	0	6	1
DEB SEBAK MAN	973390C	10	1	2	Jul-14	0	6	1
NEEL KANT SINC	271297D	8	1	2	Jul-12	0	6	1
ASIF RAJA	403179D	11	1	2	Jun-12	0	6	1
JOEL FRANKO	321164D	15	1	2	Mar-12	0	5	1
PRATIBHA	274708D	9	2	2	Jan-13	0	6	1
AHMED RAJA	238431D	13	1	1	Mar-12	0	6	1
IPSITA	682261D	11	2	2	Sep-13	0	6	1
ANU PRADHAN	732478C	10	2	2	Oct-12	0	6	1
KARPAGA	786078D	7	2	2	Jan-11	0	6	1
ANUPAM	726529D	9	1	2	Jan-11	0	6	1

140	0	12	280	1
120	0	12	240	2
150	1	12	300	1
190	2	12	380	3
190	0	12	380	1
120	0	12	240	2
130	0	12	260	0
140	0	12	280	1
150	0	12	300	2
170	0	12	340	2
160	0	12	320	1
140	0	12	280	0
130	0	12	260	1
120	0	12	240	1
190	0	12	380	1
150	0	12	300	0
170	0	12	340	1
130	0	10	260	2
120	1	12	240	1
130	1	12	260	2
180	0	12	360	1
190	0	12	380	2
160	0	12	320	1
140	0	12	280	1
150	0	12	300	1
140	0	12	280	1
150	0	12	300	1
170	0	12	340	2
130	0	12	260	1
160	0	12	320	2
140	0	12	280	1
190	0	12	380	0
140	0	12	280	1
170	0	12	340	1
160	0	12	320	1
140	0	12	280	1
190	0	12	380	1
180	0	12	360	1
120	0	12	240	1
150	1	12	300	1