AUDITORY FUNCTION AND QUALITY OF LIFE IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY IN HEAD AND NECK CANCER: A CASE SERIES FOLLOW UP STUDY

BY

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IN
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UNDER THE GUIDANCE OF
Dr.SARALA. N M.D

DEPARTMENT OF PHARMACOLOGY
SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

APRIL 2013

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled, **"AUDITORY FUNCTION AND QUALITY OF LIFE IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY IN HEAD AND NECK CANCER: A CASE SERIES FOLLOW UP STUDY"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr.SARALA.N**, **M.D** Professor and HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Kolar.

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This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved **Dr.K.Balamurali,** post graduate student in the Department of Pharmacology of Sri Devaraj Urs Medical college, to take up the dissertation work entitled "**AUDITORY FUNCTION AND QUALITY OF LIFE IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY IN HEAD AND NECK CANCER: A CASE SERIES FOLLOW UP STUDY"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

MEMBER SECRETARY **PRINCIPAL**

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Gratitude is the memory of the heart. *~ Jean Baptiste Massieu.*

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Above all I am proud of my parents Mr. V.K. Kalyanam and Mrs.K. Arul Selvi for their constant encouragement, love and attention which has made me accomplish this work. They have formed the basis of this work without which it would not have seen the light of the day .In the end, I thank The Almighty for conferring in me the confidence, skill and ability to successfully complete this work.

Date: *Signature of the Candidate*

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Dedicated to….

My parents for their unconditional love,

inspiration, support

and the innumerable sacrifices they have made.

My beloved teachers for their guidance.

LIST OF ABBREVIATIONS

AC & BC	-	Air Conduction & Bone Conduction
BUN	-	Blood urea nitrogen
CRT	-	Chemoradiotherapy
Cys	-	Cysteine
dB	-	Decibel
EP	-	Endolymph potential
GFR	-	Glomerular filteration rate
Gy	-	Gray
HSA	-	Human serum albumin
Hz	-	Hertz
IHC	-	Inner hair cells
MHC	-	Monohydroxy cisplatin
OHC	-	Outer hair cells
OAE	-	Otoacoustic emissons
PTA	-	Pure Tone Audiometer
ROS	-	Reactive oxygen species
RT	-	Radiotherapy
SCCHN	-	Squamous cell carcinoma of head and neck cancer
SL, SV	-	Spiral ligament, Stria vascularis

ABSTRACT

Background and objectives

Cisplatin is one of the anti-cancer drugs used for head and neck cancers. Though some studies have shown that cisplatin can cause ototoxicity,[1] periodic audiometric assessments have not been extensively studied in the Indian rural population. Early detection of hearing loss by audiometric assessment and management in time can to some extent prevent the irreversible ototoxicity and thus improve quality of life. Hence this study has been undertaken to evaluate the effects of cisplatin on hearing.

1. To study the auditory functions in patients receiving cisplatin for head and neck cancers
2. To establish a relationship between serum albumin levels and ototoxicity of cisplatin
3. To assess the quality of life in patients receiving cisplatin therapy

Materials & Methods:

Fifty nine patients with squamous cell carcinomas of head and neck who received cisplatin chemotherapy were recruited and 54 completed the study. Demographic details of all the patients were collected. Serum creatinine, blood urea, serum proteins and audiometry was assessed before and after the first, second and third chemotherapy cycle. The cochleotoxic effect of cisplatin was assessed by pure tone audiometry at conventional audiometric frequencies (125, 250, 500, 1000, 2000, 4000, and 8000 Hz).

Hearing loss was graded as mild (25-40 db), moderate (41-55 db), moderately severe (56-70 db) and profound - greater than 91 db. All patients were administered a quality of life questionnaire at baseline and at the end of the third cycle. The resulting data was statistically analyzed.

Results:

Hearing loss was observed in 12 patients at Fisher's scale (speech frequencies) and the number of patients having hearing loss at higher frequencies were 12 (4000Hz), 18(6000Hz), 28(8000Hz). The hearing loss was symmetrical and sensorineural. There was a strong correlation observed between the low serum albumin levels and hearing loss at the end of the third cycle of chemotherapy. Dizziness was seen in eight patients, at the end of the study. The commonly noticed adverse effects were nausea, vomiting, hair loss, fatigue and tinnitus.

Conclusion:

There are studies which show hearing loss in higher frequencies, but in our study we have observed hearing loss at speech frequency in 22.2% of patients undergoing cisplatin chemotherapy for head and neck cancer. These patients also had low serum albumin levels. These findings were observed at the end of the 3rd cycle of chemotherapy, so intervention at this juncture is essential. This is an important aspect which has to be considered seriously because this will affect their hearing and also may deteriorate their quality of life.

Key words: Cisplatin, audiometry, serum albumin, hearing loss.

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INTRODUCTION

1. **INTRODUCTION**

Over one third of all cancers in India occur in the head and neck region. In the western world in general, head and neck cancers account for less than 10% of all cancers (4% in theUSA). The primary reason for this unusually high incidence in India is the indiscriminate use of tobacco in its various forms.[1] Use of tobacco in its different forms has been directly implicated as a risk factor in lung, stomach, bladder, head and neck cancers. Squamous Cell Carcinoma of the Head and Neck (SCCHN) affects 550,000 new patients worldwide annually.[2]The vast majority of head and neck cancers are squamous cell cancer type. Traditionally surgery and radiotherapy (RT) either alone for early stage disease or in combination for loco-regionally advanced disease were considered to have curative potential.[3] Although the dominant presentation as well as pattern of failure for patients with SCCHN remains loco-regional, an increasing number of patients are being diagnosed with distant metastases.[4] The commonly employed strategies for improving outcome in SCCHN i.e. chemo-radiotherapy (CRT) and altered fractionation, are attempts at treatment intensification. Although chemotherapy, not considered curative by itself, can be used to enhance the effect of radiotherapy, and can also be used as a palliative measure.[5]

Among the chemotherapeutic agents, Cisplatin was one of the earliest developed platinum containing anti-cancer drug. [2] In 1965, Rosenberg et al observed that inorganic platinum compounds inhibited cell division in *Escherichia coli*. *Cis*- diamminedichloroplatinum II (cisplatin) has been the most extensively used derivative.[6] Cisplatin is a complex of a central platinum atom, two chlorides and two ammonia molecules in the "*cis*" position. It inhibits tumor growth by interfering with DNA synthesis. It is cell cycle unspecific and it is combined with other anticancer drugs and is being used in metastatic tumours of testis, ovary, urinary bladder,

prostate, osteogenic sarcoma, neuroblastoma, medulloblastoma,head and neck squamous cell carcinomas.[7,8] It has demonstrated antitumor activity as a single agent and also in combination with other antitumor drugs in the head and neck cancers. Cisplatin has been advocated as a radiosenstizer to achieve synergistic effects with radiotherapy. Adelstein *et al*. performed a randomized phase III trial in stage 3 and 4 head and neck cancer patients adding concurrent chemotherapy with cisplatin and 5-FU to definitive radiation. The result was increased disease clearance, increased disease free interval and increased primary site preservation at long term follow up.[9] Recent advances in translational and clinical research have led to a paradigm shift wherein radical radiotherapy with concurrent chemotherapy (3-weekly cisplatin) is now considered the contemporary standard of care in the non-surgical management of loco-regionally advanced SCCHN.[10] Despite compelling evidence regarding the benefit of adding chemotherapy, there exists considerable difficulty in combining chemotherapy with RT. The major dose related toxicities of cisplatin are renal toxicity, gastrointestinal and neurotoxicity. Though some studies have shown that cisplatin can cause ototoxicity,[11] the exact degree, time of onset and relation to the dosage schedule, duration of chemotherapy and periodic audiometric assessments have not been extensively studied in the Indian rural population. Cisplatin induced ototoxicity has shown to have inter-individual variations. Though the etiology for this is not clearly known, difference in pharmacokinetics, genetic factors and metabolic status of the individual could be a possibility. In one study serum albumin level has been implicated to alter the severity of toxicity.[12]As there is a paucity of data on audiometric monitoring during cisplatin chemotherapy, its relation to dosage schedule, protein level, early detection of hearing loss by audiometric assessment an

management in time can to some extent prevent the irreversible damage to cochlear apparatus and thus improve quality of life.

The assessment of needs for cancer care is a critical step in providing high quality care and achieving cancer patients' and families' satisfaction. Instruments like the quality of life questionnaire can be used to assess their needs and guide cancer care planning.[13]The quality of life questionnaire will help us assess and understand the needs of the patients, relationships between needs, satisfaction and review the assessment instruments of needs experienced by cancer patients and their families. This will help cancer care providers to improve performance and reduce costs, not as a one-time event but as a way of life.[14] Hence this study has been undertaken.

AIMS AND OBJECTIVES

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1. To study the auditory functions in patients receiving Cisplatin for head and neck cancer

2. To establish a relationship between serum albumin levels and ototoxicity of Cisplatin

3. To assess the quality of life in patients receiving Cisplatin therapy

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Sense of hearing is very important to communicate effectively, imagining a deaf life is difficult, as the use of the ear is more instinctive than the use of the eye. A deaf person not only loses the ability to hear the other person but also loses the ability to control his or her own voice to make it comprehendible. Sometimes, the perception of meaningful sound is not replaced by a peaceful silence but instead by tinnitus which distracts thoughts and disturbs sleep. Although hearing impairment from chemotherapy can occasionally result in severe consequences, it is of clinical importance to detect the early ototoxicity, induced by cisplatin.

ANATOMY OF THE EAR

The ear is the sensory organ responsible for hearing. It is composed of three parts termed the external ear, the middle ear and the inner ear.[16] The external ear includes the auricle (pinna) and external auditory canal. The auricle is composed of elastic fibrocartilage covered by perichondrium and skin.The middle ear is composed of the tympanic membrane, the tympanic cavity, the ossicles and the eustachian tube. The tympanic membrane is oval in shape, about 0.1 mm thick and lies at an angle of 40 degrees in the sagittal plane and 8 mm wide and 10mm high. The umbo marks the middle of the tympanic membrane and corresponds to the attachment of the tip of the malleus to the tympanic membrane. The middle ear contains three bones or ossicles which transmit sound vibrations to the inner ear.

CROSS SECTION OF THE EAR

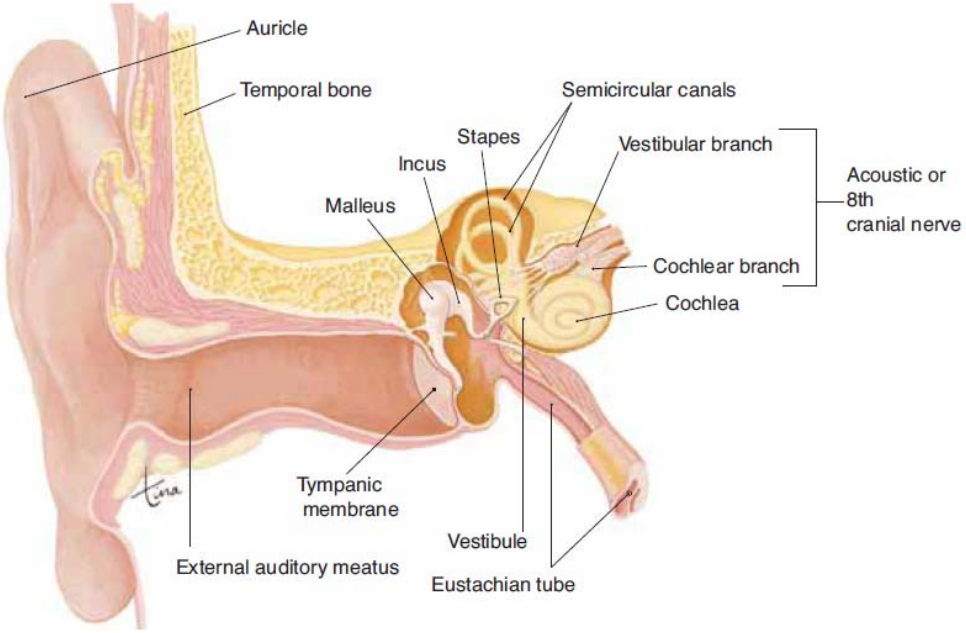
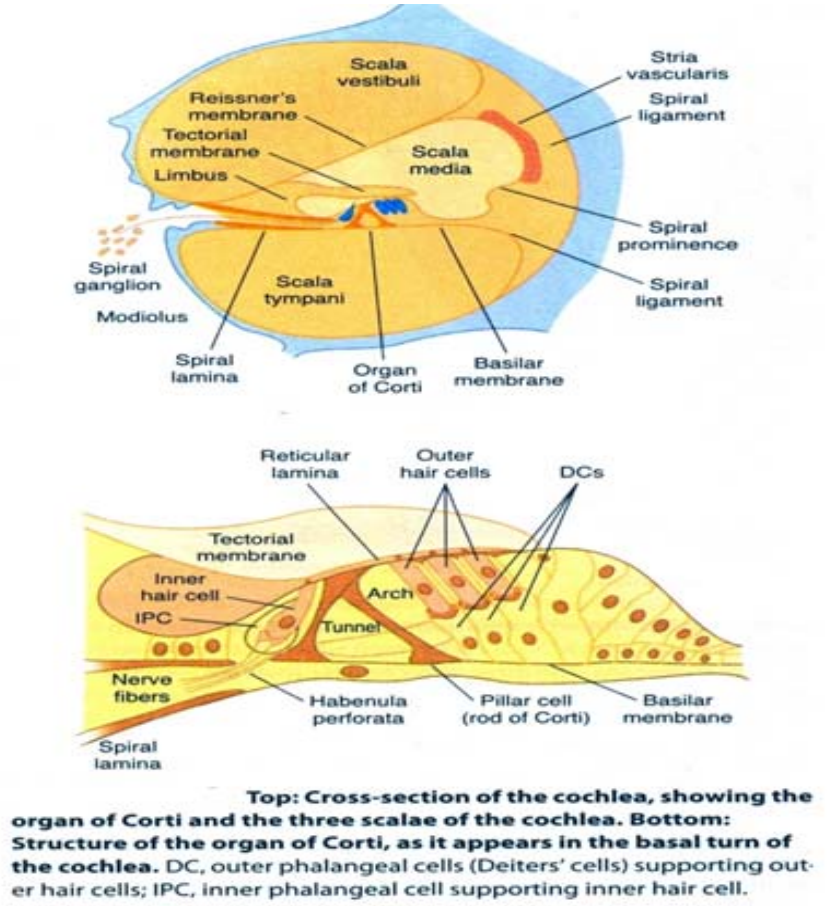


Figure 1. Anatomy of the ear

They are from lateral to medial, the malleus, the incus and the stapes as seen in Figure 1.[16] The malleus is firmly attached to the tympanic membrane and the stapes sits within the oval window of the cochlea. Between them lies the incus. The ossicles are held in place by their attachments mentioned above, by their joints with each other, by ligaments and two muscles; the tensor tympani to the malleus and the stapedius muscle to the stapes.[16] The inner ear consists of two main parts, the cochlea (end organ for hearing) and the vestibule and semicircular canals (end organ for balance). The inner ear can be thought of as a series of tunnels or canals within the temporal bone.

CROSS SECTION OF THE COCHLEA



Top: Cross-section of the cochlea, showing the organ of Corti and the three scalae of the cochlea. Bottom: Structure of the organ of Corti, as it appears in the basal turn of the cochlea. DC, outer phalangeal cells (Deiters' cells) supporting outer hair cells; IPC, inner phalangeal cell supporting inner hair cell.

Figure 2. A cross section of the cochlea illustrating the organ of Corti

Within these canals are a series of membranous sacs (termed labyrinths) which house the sensory epithelium. The membranous labyrinth is filled with a fluid termed endolymph; it is surrounded within the bony labyrinth by a second fluid termed perilymph (Figure 2).[17] The cochlea can be thought of as a canal that spirals around itself similar to a snail. It makes roughly 2.5 to 2.75 turns.[17] The bony canal of the cochlea is divided into an upper chamber, the scala vestibuli and a lower chamber, the scala tympani by the membranous (otic) labyrinth also known as the cochlear duct.

The scala vestibuli and scala tympani contain perilymph. The scala media contains endolymph. Endolymph is similar in ionic content to intracellular fluid (high K^+, low

Na+) and perilymph resembles extracellular fluid (low K^+, high Na^+) (Figure 3).[17] The cochlear duct contains several types of specialized cells responsible for auditory perception. The floor of the scala media is formed by the basilar membrane, the roof by Reissner's membrane. Situated on the basilar membrane is a single row of inner hair cells medially and three rows of outer hair cells laterally. The cells have specialized stereocilia and kinocilia on their apical surfaces. Attached to the medial aspect of the scala media is a fibrous structure called the tectorial membrane. It lies above the inner and outer hair cells coming in contact with their stereocilia. Synapsing with the base of the hair cells are dendrites from the auditory nerve. The auditory nerve leaves the cochlear and temporal bone via the internal auditory canal and travels to the brainstem.

SHOWING THE POTENTIALS ACROSS THE VARIOUS COMPARTMENTS OF THE COCHLEA

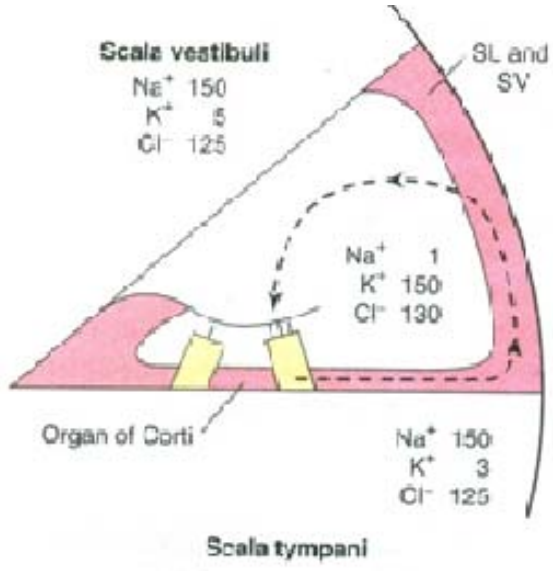


Figure 3. Ionic composition of perilymph in the scala vestibuli, endolymph in the scala media, and perilymph in the scala tympani.

SL - spiral ligament, SV- stria vascularis. The dashed arrow indicates the path by which K^+ recycles from the hair cells to the supporting cells to the spiral ligament and is then secreted back into the endolymph by cells in the stria vascularis.

SEMICIRCULAR CANALS

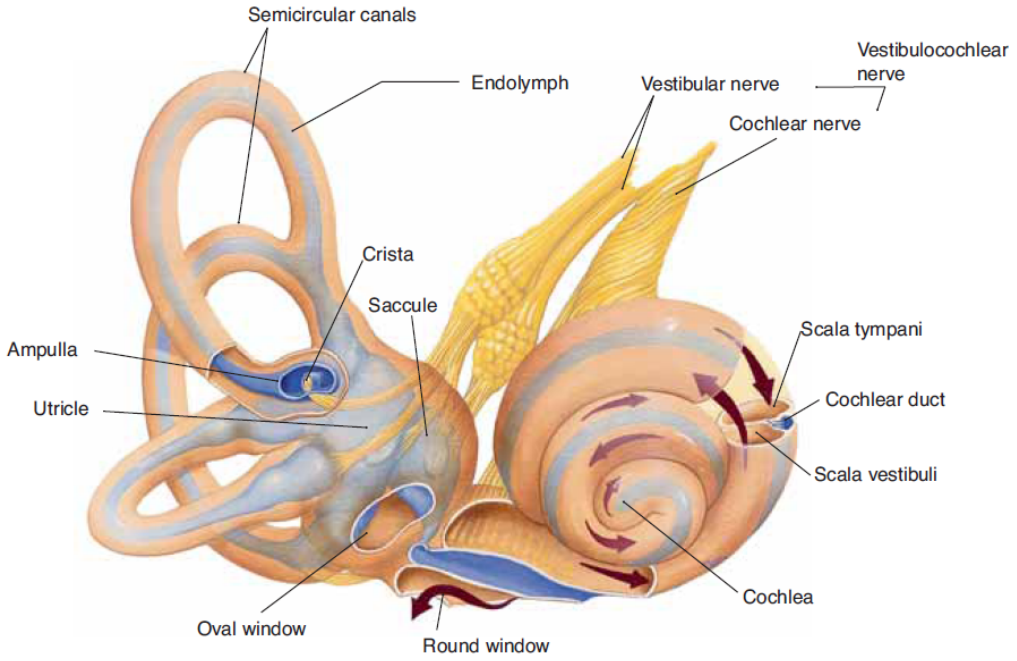


Figure 4. Semicircular canals

PHYSIOLOGY

Sound can be conducted to the sensory cells in the inner ear through the outer and the middle ear or directly through bone. Air conducted sound enters the external ear and travels through the ear canal to the tympanic membrane.The pressure difference across the tympanic membrane causes it to vibrate and these vibrations are conducted through the bones of the ossicular chain (malleus, incus and stapes) to the fluids of the cochlea (Figure 4).[18] Big movements of the tympanic membrane are transformed to small movements in the inner ear fluid, in effect an impedance matching.The arrangement of these systems improve transmission considerably, especially in the

frequency region important for speech perception in noisy environments i.e 2-5 kHz. The movements of the tympanic membrane and ossicles are controlled by tensor tympani and stapedius muscles. In the inner ear, movements of the fluid are transmitted through the tectorial and basilar membranes to the primary sensory cells—the inner hair cells (IHC).[18]

The cochlea acts as a mechanical demodulator, transforming sound frequency to a physical location along the basilar membrane. In addition to the IHCs there are also outer hair cells (OHC). These are believed to have dynamic micromechanical properties contributing to the high sensitivity, high frequency selectivity and wide dynamic range of the human ear. Movement of the hair-bundles on the IHCs causes depolarisation of the cell and neurotransmitter release, which stimulate the associated nerve endings. The neuronal signals initiated by the IHCs are conducted through afferent nerves with connecting stations in the cochlear ganglion, cochlear nucleus, superior olivary complex, the inferior colliculus, the medial geniculate body and the auditory cortex. At each of these stations neuronal processing of the auditory stimulus takes place, and as the neuronal signal reaches the primary auditory cortex it causes a sensation of sound. Chloride is the principal anion with a concentration of approximately 130 mM similar to that in plasma, thus theoretically not promoting the biotransformation from cisplatin to monohydrated complex of cisplatin, which is toxic. With regard to the perilymph and the surrounding tissues there are potential differences between the different cells and compartments. The interior of the HCs and the stria vascularis carry a negative potential, which is bigger than in most normal cells whereas the endolymph itself has a positive potential, the endolymph potential (EP). This potential is believed to be at least partially generated in the stria vascularis by an electrogenic Na^+ K^+ ATPase. According to the Davis

resistance theory, the potential across the hair cell membrane helps depolarise the hair cell when the resistance across the hair cell top membrane is changed through movement of the hair-bundles (Figure 5).[18] When the EP is lowered, for example from asphyxia, the micromechanical properties of the basilar membrane are changed and the frequency selectivity and sensitivity is lowered. Thus in some ways the stria vascularis seemingly act as a power source for the sensory cells through the EP. The human ear is sensitive to sound with frequencies roughly between 20 Hz and 20000 Hz. The dynamic range of reception is very large, spanning 10^7 times, from what is barely audible to what is painful. The corresponding sound pressures range from $2x10^{-5}$ to 200 Pa.[18]

MOVEMENT OF BASILAR MEMBRANE CAUSING STEREOCILIA TO BEND

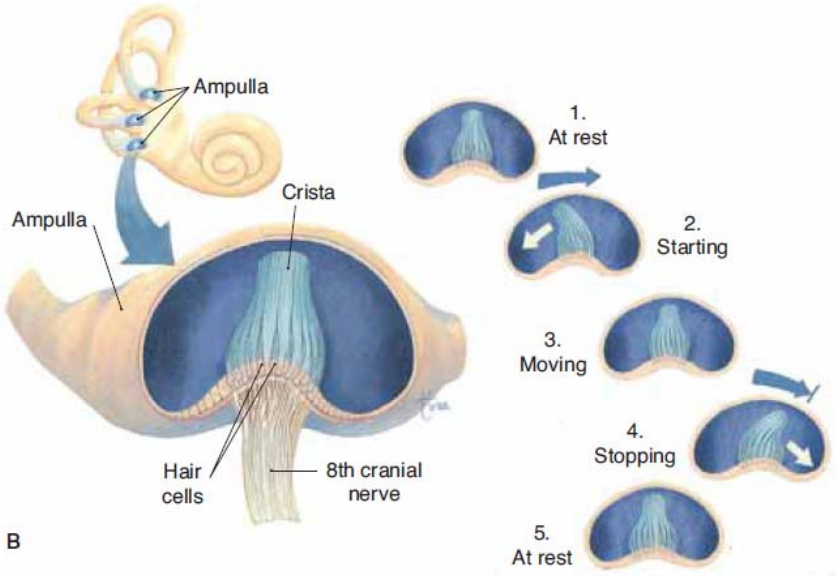


Figure 5. Movement of hair cells

AUDIOLOGY AND ACOUSTICS

Some of the terms which are frequently used in audiology and acoustics:

Sound: It is a form of energy produced by a vibrating object. A sound wave consists of compressions and rarefactions of the molecules of the medium (air, liquid, or solid) in which it travels. Velocity of the sound is different in different media. In the air, at 20°C at sea level, sound travels 344 metre/ second and it is faster in the liquid and still faster in the solid media.

Frequency: It is the number of cycles per second. The unit of frequency is Hertz (Hz), named after German scientist Heinrich Rudolf Hertz

Pure tone: A single frequency sound is called a pure tone.

Pitch: It is the subjective sensation produced by the frequency of the sound. Higher the frequency greater is the pitch.

Complex sound: Sound with more than one frequency is called a complex sound. Human voice is a complex sound.

Intensity: It is the strength of the sound which determines its loudness. It is measured in decibels. At a distance of one metre intensity of Whisper = 30 dB, Normal conversation = 60dB, Shout = 90 dB, Discomfort of ear = 120dB, Pain in ear = 130dB

Decibel: It is 1/I0th of a bel, and is named after Alexander Graham Bell, the inventor of telephone.

Formula for decibel is Sound in decibel = 10 Log power of S l/power of S2

OR

10 Log (SPL OF S1)2 /SPL OF S2

S1 = Sound being described

S2 = Reference sound

SPL = Sound pressure level

Sound can be measured in watts/cm2 or dynes/cm2.

In audiology, sound is measured as sound pressure level (SPL).

Frequency range in normal hearing: Normal persons can hear frequencies of 20 to 20000Hz but in routine audiometric tests only 125 to 8000Hz are evaluated.

Speech frequencies: Frequencies of 500, 1000, and 2000Hz are called speech frequencies as most of human voice falls within this range. Pure tone average is the average threshold of hearing in these three frequencies. It roughly corresponds to the speech reception threshold.

Hearing loss:

Hearing loss can be of three types.

1.**Conductive hearing loss** is caused by any disease process interfering with the conduction of sound from the external ear to stapedio-vestibular joint, Thus the cause may lie in the external ear (obstructions), tympanic membrane (perforation), middle ear (fluid), ossicles (fixation or disruption) or the Eustachian tube (obstruction).

Characteristics of conductive hearing loss

1. Negative Rinne test, i.e. BC>AC (BC- Bone conduction , AC – Air Conduction)

2. Weber lateralized to poorer ear

3. Normal absolute bone conduction

4. Low frequencies affected more

5. Audiometry bone conduction better than air conduction with air bone gap. Greater the air bone gap, more is the conductive loss

6. Loss is not more than 60 dB

7. Speech discrimination is good

2. **Sensorineural hearing loss** from lesion of the cochlea (sensory type) of VII th nerve and its central connections (neural type). The term retrocochlear is used when hearing loss is due to lesions of VIIth nerve and central deafness, when it is due to lesions of central auditory connections. It may be congenital or acquired. Acquired causes are infections of labyrinth-viral, bacterial or spirocheatal, trauma to the labyrinth or VIIth nerve, e.g. fractures of temporal bone or ear surgery, noise induced hearing loss, ototoxic drugs, presbyacusis, meniere's disease, acoustic neuroma, sudden hearing loss, familial, systemic disorders, e.g. diabetes, hypothyroidism, kidney disease.

Characteristics of sensorineural hearing loss

1. A positive Rinne's test, i.e. AC>BC

2. Weber laterlised to better ear

3. Bone conduction reduced on Schwabach and absolute bone conduction tests

4. More often involving high frequencies

5. No gap between air and bone conduction curve on audiometry

6. Loss may exceed 60 dB

7. Speech discrimination is poor

8. There is difficulty in hearing in the presence of noise

3 **Mixed hearing loss**: In this type, elements of both conductive and sensorineural deafness are present in the same ear. There is air-bone gap indicating conductive element, and impairment of bone conduction indicating sensorineural loss. Mixed hearing loss is seen in some cases of otosclerosis and chronic suppurative otitis media (CSOM).[18]

PURE TONE AUDIOMETER

An audiometer is an electronic device which produces pure tones, the intensity of which can be increased or decreased in 5 dB steps. Air conduction thresholds are measured for tones of 250, 500, 1000, 1500, 2000, 4000 6000 and 8000 Hz. Bone conduction thresholds are measured for 250, 500, 1000, 1500, 2000, 4000 hertz. The amount of intensity that has to be raised above the normal level (15-25dB) is a measure of the degree of hearing impairment at that frequency (Table 1).[17] It is charted in form of a graph called the' audiogram'. The thresholds of bone conduction are a measure of the cochlear function.The difference in the thresholds of air and bone conduction (A-B gap) is a measure of a degree of conductive deafness. The audiometer is so calibrated that hearing of a normal person,

both of air and bone conduction is at 0 db and there is no A-B gap. The procedure for audiometry is based on American Society for Speech and Hearing Association [ASHA] 1978 guidelines for manual pure tone audiometry (PTA).

DEGREE OF HEARING LOSS [WHO Classification 1980]

Normal	**0-25 dB**
Mild	**26-40 dB**
Moderate	**41-55 dB**
Moderately severe	**56-70 dB**
Severe	**71-91 dB**
Profound	**>91 dB**

Table 1: WHO classification of hearing loss

CANCER CHEMOTHERAPY

Cancer chemotherapy was introduced in the 1940s when the chemical warfare agent nitrogen mustard was first used in clinical practice. The addition of chemotherapy to locoregional treatment has revolutionized the treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). The treatment of head and neck cancer mainly consists of surgery and radiation therapy with or without chemotherapy. Although chemotherapy, not considered curative by itself, can be used to enhance the effect of radiotherapy and post surgically chemotherapy can be used as an adjunct, and as a palliative measure. [19] Evidence from a large meta-analysis demonstrated that adding chemotherapy led to a survival advantage of around 4% at 5 years over that seen with locoregional treatment alone.[19] Among the chemotherapeutic agents, Cisplatin was one of the earliest developed platinum containing anti-cancer drug. It has demonstrated antitumor activity as a single agent and also in combination with other antitumor drugs. In the metastatic tumors cisplatin chemotherapy is associated with severe dose dependent side effects. The toxicities associated with its treatment are an increasingly worrying aspect, with acute and late toxicities bringing their own problems, in terms of treatment compliance, safety, and quality of life.There needs to be a balance maintained between improving efficacy and minimizing what seems to be the inevitable greater rate of toxicity associated with more aggressive, active chemotherapy. Thus it can be said that a chemotherapeutic agent is thus not characterised only by its efficacy but to a great extent also by its side effects.

CISPLATIN HISTORY

Cisplatin (*cis*-$PtCl_2(NH_3)_2$) was first synthesised in 1845 by Peyrone[20] and was known for a long time as Peyrone's salt. [21] Its structure was deduced by Alfred Werner in 1893.[22] However it was only after another 120 years that the biological activity of the substance was discovered during an experiment designed to elucidate the effect of electrical fields on growing bacteria. In 1965, Barnett Rosenberg, van Camp et al. of Michigan State University discovered that electrolysis of platinum electrodes generated a soluble platinum complex which inhibited binary fission in Escherichia coli (E. coli) bacteria. Although bacterial cell growth continued, cell division was arrested. [22] The bacteria grew filaments up to 300 times their normal length. [23] The square planar Pt(II) complex, cis $PtCl_2(NH_3)_2$ turned out to be even more effective at forcing filamentous growth.[24] This finding led to the observation that cis $PtCl_2(NH_3)_2$ was indeed highly effective at regressing the mass of sarcomas in rats.[25] Confirmation of this discovery, and extension of testing to other tumour cell lines launched the medicinal applications of cisplatin. The results from the first clinical trials were published in 1972.[24] Cytotoxic effect of cisplatin was identified which did not affect the growth of cells and hence a new class of antitumour agent was proclaimed.[26] Cisplatin was approved for use in testicular and ovarian cancers by the U.S. Food and Drug Administration on December 19, 1978.[27]

Although two more platinum analogues had reached the market and were introduced for clinical use, cisplatin might still be considered the most useful platinum among compound carboplatin and oxaliplatin on the basis of versatility, experience of use and documentation.[26]

CISPLATIN CHEMISTRY

Cisplatin (cis-diammine-dichloroplatinum) is a highly reactive compound with only 11 molecules and electrophilic properties. Its formula is $H_6Cl_2N_2Pt$ as shown in Figure. 6 [24] and it has a molecular mass of 301.1 g/mol.[28]

CISPLATIN

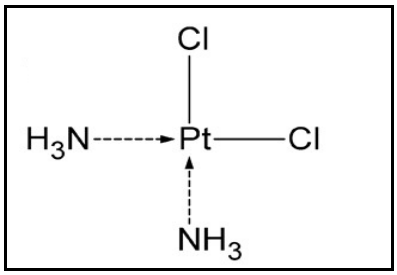


Figure 6. Structure of cisplatin

It is a rather small uncharged molecule and is believed to enter cells mainly through passive and partly through facilitated diffusion.[29] It gets hydrolysed in water losing a chloride ion and gaining a water molecule forming the monohydrated complex (MHC).

DIFFERENT FORMS OF MHC

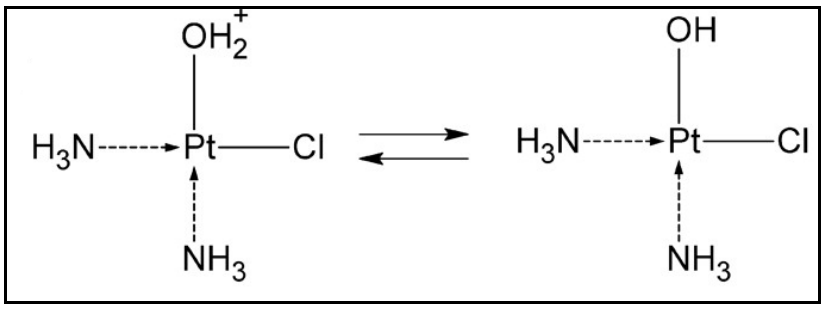


Figure 7: The protonated and deprotonated forms of cisplatin

MHC in its protonated form, monoaqua cisplatin, is positively charged and highly reactive with a pKa of 6.56, i.e. close to physiological pH. At physiological pH (7.4) 85% MHC will be in its deprotonated form, the much less reactive monohydroxo cisplatin (Figure 7)[24].This equilibrium between the two forms is affected by both pH and chloride concentrations in the body fluids. In plasma, cisplatin is the dominant form but in the low chloride intracellular environment MHC is favoured, which may be the form ultimately causing cytotoxicity. The positive charge of the MHC may cause it to be electrostatically attracted to the negatively charged DNA and thereby increasing the chance of a reaction. Indirect evidence suggests that formation of MHC in the circulation may contribute to the side effects of cisplatin.[30] Modification of the content of MHC in the solution of administration affects the toxicity of the treatment. Reconstitution in a hypertonic solution lowers the amount of MHC and cause less toxicity .[31]The high reactivity between cisplatin and nucleophilic sites on circulating endogenous substances makes covalent binding an important route of elimination. Cisplatin is bound to circulating high and low molecular complexes causing it to lose most of its cytotoxic properties and is slowly excreted.

Transplatin, the trans stereoisomer of cisplatin, has formula *trans*$[PtCl_2(NH_3)_2]$ and does not exhibit a comparably useful pharmacological effect. Its low activity is generally thought to be due to rapid deactivation of the drug before it can arrive at the DNA. It is toxic, and it is desirable to test batches of *cis*-platin for the absence of the trans isomer.[30]

CYTOTOXIC MECHANISMS

The main action has been assumed to be analogous to that of the alkylating agents, implying that cytotoxicity would mainly be caused by interaction with specific

DNA base sequences, G-G intrastrand link formation being the most frequent.[32] Along with interstrand DNA cross-links it inhibits DNA replication, transcription, and ultimately cell division. It is non specific on the cell cycle phase.

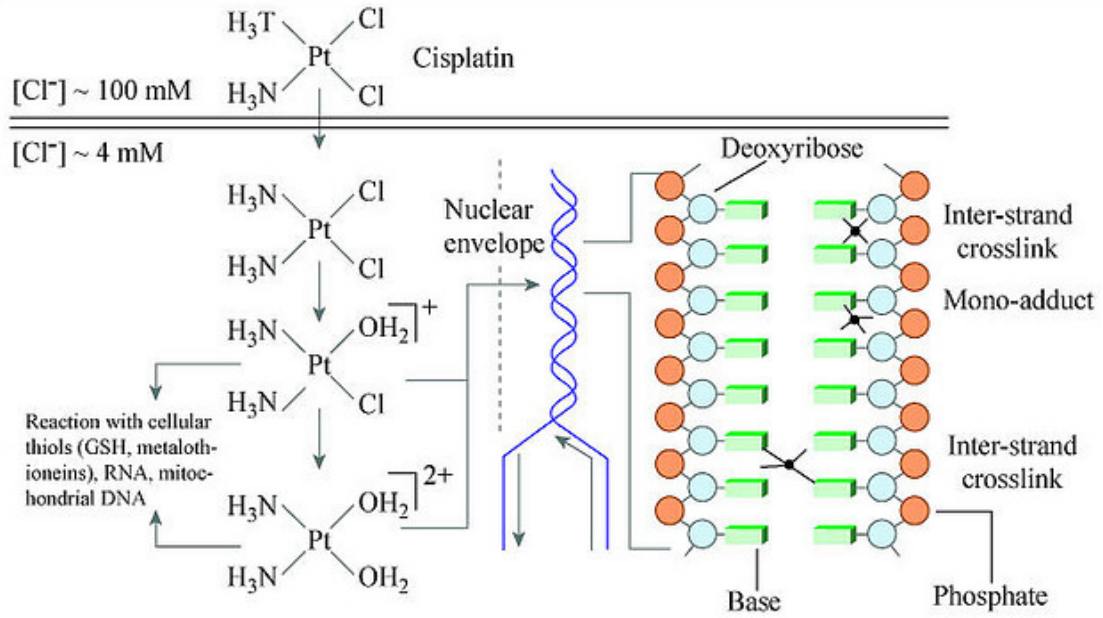


Figure 8: Mechanism of action of cisplatin

However, a number of other possible mechanisms have been suggested such as interaction with RNA and mitochondrial DNA as well as with proteins involved in the antioxidant systems, energy production and cell signalling and apoptosis. Induction of apoptosis has been attributed to its antitumour effect. [32]Dosing schedules may, apart from host factors, determine whether cell death occurs by apoptosis (programmed cell death) or necrosis (disorderly cell death). Cisplatin causes dose dependent inhibition of DNA synthesis. Preferential binding to mitochondrial DNA has also been suggested and mitochondrial damage is an early feature of cisplatin cytotoxicity. Mitochondrial transmembrane potential may be decreased and mitochondrial toxicity can be increased in cisplatin-induced necrosis than apoptosis.[33]Cisplatin has a high affinity

to proteins with crucial cellular functions and its cytotoxicity may also be exerted by its interaction with the sulfhydryl groups. Cisplatin can deplete the intracellular antioxidants related to the glutathione system and thus manifest with cytotoxicity.[34] Mitochondrial injury in renal cells is associated with dysfunction in glutathione peroxidase. Glutathione prevents peroxidation of cellular constituents. Cisplatin is associated with cellular death in the inner ear. The differences in the apical to base levels of intracellular antioxidants in the cochlea have been suggested as a cause of the observed apical to base difference in outer hair cell (OHC) sensitivity to ototoxic substances such as cisplatin and aminoglycosides .[35]

CISPLATIN RESISTANCE

Although initial platinum responsiveness is high, majority of cancer patients will eventually relapse with cisplatin-resistant disease. Many mechanisms of cisplatin resistance have been proposed.

These include :

1) Changes in uptake and efflux of the drug,
2) Increased intracellular concentration of neucleophilic thiol substances like gluthathione which conjugate and detoxify the drug.
3) Inhibition of apoptosis and increased DNA repair pathways.[36]

Oxaliplatin is active in highly cisplatin-resistant cancer cells in the laboratory, however there is little evidence for its use in the clinical scenario. The drug paclitaxel may be useful in the treatment of cisplatin-resistant cancer, the exact mechanism for which is unknown. [37]

CISPLATIN PHARMACOKINETICS

Absorption

Cisplatin gets absorbed following rapid IV injection over 1–5 minutes or rapid IV infusion over 15 minutes - 1 hour, peak plasma drug and platinum concentrations occur immediately.[38]

Distribution

Cisplatin is widely distributed and it achieves highest concentrations in the kidneys, liver, and prostate. A somewhat lower concentration is seen in the bladder, muscle, testes, pancreas, and spleen. Lowest concentrations in the small and large intestines, adrenals, heart, lungs, lymph nodes, thyroid, gallbladder, thymus, brain , ovaries, and uterus. It is also distributed minimally into leukocytes and erythrocytes.[39]It has been found that the platinum atom is present in tissues for as long as 180 days after administration of last dose.[39] Hence there is a possibility of accumulation of platinum complexes when administered on a daily basis. It also crosses the placenta and is distributed into milk and has been assigned to pregnancy category D by the FDA. Animal studies have revealed evidence of embryotoxicity and teratogenicity in mice. There is no controlled data in human pregnancy.[40] Cisplatin should only be given during pregnancy when there are no alternatives and benefits outweigh the risk.

Plasma Protein Binding

Platinum from cisplatin is 90% and irreversibly bound to mainly albumin, transferrin, and γ-globulin. Only non-protein bound platinum is cytotoxic. [41]

Metabolism and elimination

There is no evidence to date that cisplatin undergoes enzymatic biotransformation. Chloride ligands of the cisplatin complex are believed to be displaced by water, forming positively charged platinum complexes that react with nucleophilic sites.[32]Cisplatin is excreted principally in urine (predominantly via glomerular filtration) as intact cisplatin and platinum-containing product(s). Approximately 10–50% of dose is excreted within 24–48 hours.[42] Fecal elimination appears to be insignificant. Cisplatin may undergo enterohepatic circulation and it is minimally removed by hemodialysis. Intact cisplatin has an elimination half life of around 20–30 minutes (initial phase) and 30.5–107 hours or possibly longer (terminal phase) following rapid IV injection or infusion. [42]

USES OF CISPLATIN

1. **Testicular Cancer**

It is used as an adjunct to other antineoplastic agents for the treatment of metastatic testicular tumors (including non-seminomatous testicular carcinoma, seminoma testis, and extragonadal germ-cell tumors) in patients who have already received appropriate surgery and/or radiation therapy.[43] For induction of remissions, a regimen of cisplatin, bleomycin, and vinblastine has been used. For treatment of disseminated disease, a regimen of cisplatin, bleomycin, and etoposide has been used.

Regimen consisting of cisplatin, ifosfamide with mesna, and either vinblastine or etoposide considered standard initial salvage (i.e., second-line) regimen in patients with recurrent disease.[43]

2. Ovarian Cancer

Used alone or in combination therapy for the treatment of ovarian cancer. Platinum-based therapy has been used for adjuvant treatment following surgery in early-stage ovarian epithelial cancer. For initial (first-line) treatment of advanced ovarian epithelial cancer, combination chemotherapy with a platinum-containing agent (e.g., cisplatin, carboplatin) and paclitaxel currently is preferred regimen.[44] Carboplatin is as effective as but less toxic than cisplatin when used in combination with either paclitaxel or cyclophosphamide; therefore, carboplatin in combination with paclitaxel currently is a preferred regimen for initial treatment of advanced ovarian epithelial cancer. Regimen consisting of cisplatin and paclitaxel is superior to regimen consisting of cisplatin and cyclophosphamide,[44] as second-line therapy for the treatment of advanced epithelial ovarian cancer when retreatment is indicated in patients with platinum-sensitive disease. However, carboplatin monotherapy preferred to cisplatin monotherapy by some clinicians due to its more favorable toxicity profile. Cisplatin is used as adjuvant therapy of ovarian germ-cell tumors, combination chemotherapy with cisplatin, bleomycin, and etoposide currently is regimen of choice.

3. Bladder Cancer

Cisplatin is used alone or in combination therapy for the treatment of muscle-invasive and advanced bladder cancer that is no longer amenable to surgery and/or radiation therapy.[45]For adjuvant treatment of muscle-invasive bladder cancer, regimen

consisting of cisplatin, methotrexate, and vinblastine with or without doxorubicin (abbreviated as M-VAC or CMV, respectively) is currently is used.For palliative treatment of advanced or metastatic bladder cancer, a regimen consisting of cisplatin and gemcitabine currently is used.[45]

4. Head and Neck Cancer

Cisplatin is used as an adjunct to 5- fluorouracil or paclitaxel for the palliative treatment of recurrent or metastatic head and neck cancer. Regimen consisting of cisplatin, methotrexate, bleomycin, and vincristine also has been used.[46]

5. Cervical Cancer

Cisplatin is used alone or in combination as an adjunct to radiation therapy for the treatment of invasive cervical cancer (FIGO stages IB2 through IVA or FIGO stage IA2, IB, or IIA with poor prognostic factors).[47] It can also be a component of various combination chemotherapeutic regimens (e.g., bleomycin, cisplatin, and ifosfamide [BIP]; bleomycin, cisplatin, mitomycin, and vincristine [BOMP]) for the treatment of metastatic or recurrent cervical cancer.[47]

6. Non-small Cell Lung Cancer

Cisplatin is a component of various chemotherapeutic regimens for advanced non-small cell lung cancer. Currently preferred regimens include the combination of cisplatin with another agent, such as paclitaxel, vinorelbine, gemcitabine, or docetaxel. [48]For small cell lung cancer the regimen mainly consistsof cisplatin and etopside or irinotecan.[48]

7. Malignant Pleural Mesothelioma

Cisplatin is used in combination with pemetrexed for the treatment of malignant pleural mesothelioma in patients who are not eligible for surgery. It can also be used in monotherapy or as adjunct to other antineoplastic agents (e.g., doxorubicin, gemcitabine, mitomycin) for the palliative treatment of advanced malignant pleural mesothelioma.[49]

8. Esophageal Cancer

Some experts recommend combined modality treatment with combination chemotherapy (e.g., cisplatin and 5-fluorouracil) and concurrent radiation therapy with or without surgery for treatment of localized, resectable esophageal cancer.For palliative treatment of metastatic (local or distant) disease or recurrent or locally advanced disease not amenable to surgery or radiation therapy, combination therapy with cisplatin and 5-fluorouracil is considered the regimen of choice. [50]

9. Biliary Tract Cancer

The recommended (accepted) treatment for unresectable locally advanced or metastatic biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer) is cisplatin in combination with gemcitabine.[51]

10. Brain Tumors

Cisplatin is used as an adjunct for the treatment of astrocytic tumors, such as anaplastic astrocytoma and glioblastoma multiforme. It is also used in combination with lomustine and vincristine as adjuvant therapy following surgical resection and

radiation therapy for the treatment of medulloblastoma.[52]Monotherapy or in combination chemotherapy regimens (e.g., cisplatin and etoposide) as salvage therapy for recurrent oligodendroglioma. It can be an adjunct to etoposide for the treatment of intracranial germ cell tumors. It is also used as a component of combination therapy for high-risk neuroblastoma.[52] The uses of cisplatin mentioned above are all off label uses.

CISPLATIN DOSAGE AND ADMINISTRATION

General

- Pretreatment with antiemetics should be considered while giving cisplatin (e.g., selective inhibitors of type 3 [5-HT_3] serotonergic receptors) or combination antiemetic therapy (e.g., 5-HT_3 receptor antagonist and corticosteroid) to prevent nausea and vomiting.[53]

- Hydration with 1–2 L IV fluid 8–12 hours prior to administration is important to maintain adequate hydration and urinary output during and for 24 hours after to minimize nephrotoxicity.
- In adults, IV fluids are usually administered alone or with mannitol and/or furosemide to achieve a diuresis of 150–400 mL/hour (during and for at least 4–6 hours after administration of cisplatin).
- Potassium chloride (e.g., 10–20 mEq/L) is often added to IV fluids to replace losses and prevent K^+ deficiencies.

Care should be taken when cisplatin is administered so as not to use aluminum sets or instruments containing aluminium as it displaces cisplatin displaces platinum from cisplatin molecule, causing formation of a black precipitate and loss of potency.[54]

Cisplatin has to be handled cautiously by using gloves to avoid exposure to skin or mucosal surfaces.

Dilution

Dilution is done by mixing preservative-free solution with 2 L of 5% dextrose and 0.33 or 0.45% sodium chloride injection containing 18.75 g of mannitol/L (i.e., 37.5 g in 2 L). It should not be diluted with 5% dextrose injection and if it is not used within 6 hours, it should be protected from light.[55]

Rate of Administration

It is recommended to administer the dose by IV infusion over 6–8 hours. Apart from this continuous 24-hour or 5-day IV infusions also have been used. Rapid IV injection (e.g over 1–5 minutes) associated with increased risk of nephrotoxicity or ototoxicity.[55] Cisplatin dosages exceeding 100 mg/m^2/cycle once every 3–4 weeks are rarely used.[55] Inadvertent substitution of cisplatin for carboplatin can result in potentially fatal overdosage.

CISPLATIN SIDE EFFECTS

1.Nephrotoxicity

Risk of nephrotoxicity is dose-related (*cumulative*), severe nephrotoxicity manifests as increased serum creatinine, BUN, serum uric acid concentrations, and/or decreased creatinine clearance and gomerlar filteration rate(GFR). Nephrotoxicity is more common and severe than with carboplatin. Nephrotoxicity generally occurs during second week following initiation of therapy. High or repeated doses can increase severity and duration of renal impairment. Recovery generally

occurs within 2–4 weeks after administration of cisplatin, but if renal insufficiency occurs it may be irreversible and sometimes even fatal. Maintaining adequate hydration and urinary output during and for 24 hours after administration of cisplatin can help to minimize nephrotoxicity.[56]

2.Neurotoxicity

Cisplatin causes severe neuropathy (e.g., paresthesia, areflexia, loss of proprioception and vibratory sensation) in patients receiving higher single or cumulative doses, prolonged therapy (4–7 months), or greater dose frequency than recommended. The severity of neurotoxicity is more and it occurs more frequently than with carboplatin. The manifestations of cisplatin's neurotoxicity are as follows ossible motor (especially gait) difficulties, reduced or absent deep-tendon reflexes, leg weakness, or loss of motor function. Loss of taste, seizures, Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy reported. Muscle cramps reported, particularly in patients receiving high cumulative dose and at advanced symptomatic stage of peripheral neuropathy.[57] Peripheral neuropathy may be irreversible in some patients.

3.Ototoxicity

Cisplatin administration may cause transient or permanent tinnitus. Ototoxicity displays a rough dose dependence.Hearing loss can be unilateral or bilateral and becomes more frequent and severe with repeated doses. It may occasionally require dosage reduction or discontinuance of therapy.There is a high interindividual variability in ototoxicity, where some individuals may get a considerable hearing loss even after the first course.[58] Risk of vestibular ototoxicity (manifested as vertigo) or vestibular dysfunction.[58]

4.Fetal/Neonatal Morbidity and Mortality

Cisplatin may cause fetal harm. Teratogenicity and embryolethality has been demonstrated in animals. Pregnancy should be avoided during cisplatin therapy.[59]

5.Carcinogenic effects

Malignancies (like leukemia, renal fibrosarcoma) have been reported in rat.[59] Bladder cancer was reported in at least one patient, but causal relationship has not been established. Acute leukemia had been reported in humans but in such cases, cisplatin generally was given in combination with other leukemogenic agents and/or radiation.[59]

6.Anaphylactoid Reactions

Anaphylactoid reactions usually have occurred only after multiple cycles (e.g., at least 5 doses), but also can occur after the initial dose.[60]

Major Toxicities

Hematologic effects

In those receiving cisplatin the risk of cumulative myelosuppression which can manifest as leukopenia, thrombocytopenia, and anemia can exist. Leukopenia and thrombocytopenia are dose-related. Anemia not clearly dose-related but may be severe, sometimes even requiring transfusions.Nadir in circulating platelets, leukocytes, and hemoglobin occurs 18–23 days (range: 7.2–45 days) following a single dose but the levels return to pretreatment values in most patients within 39 days (range: 13–62 days). Hemolytic anemia has also been reported. If the repeat course

results in increased hemolysis then the benefit of therapy versus risk needs to be carefully weighed.[60]

Gastrointestinal effects

Marked nausea and vomiting occurs in virtually all patients and occasionally may require discontinuance of therapy. There has been an increase in the incidence and severity in females and young patients, especially following administration of high doses or rapid infusion, and/or following concomitant administration with other emetogenic drugs (e.g., doxorubicin). Also patients with history of chronic heavy alcohol use may experience less frequent and severe emetogenic effects. Nausea and vomiting generally begin within 1–6 (usually 2–3) hours after administration of cisplatin; persist for up to 24 hours or longer. Average of 10–12 vomiting episodes reported within first 24 hours after initial dose. Various degrees of nausea, vomiting, and anorexia may persist for up to 5–10 days.[60]

Cardiovascular and cerebrovascular effects

Bradycardia, left bundle-branch block, ST-T-wave changes with congestive heart failure, postural hypotension, myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, or cerebral arteritis have occurred and are very rare.[61]

Electrolyte disturbances

Hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia, and hyponatremia have also known to occur.Manifestations of hypomagnesemia and hypocalcemia include muscle irritability,cramps, clonus, tremor, carpopedal spasm, and tetany. Electrolyte disturbances may occur within several days after

administration of initial dose. Hypomagnesemia usually develops within 3–4 weeks and appears to increase in severity with progressive courses of treatment. Normal serum electrolyte concentrations generally restored by administration (usually parenteral) of appropriate supplemental electrolytes and drug discontinuance.[62]

Metabolic effects

Hyperuricemia (resulting from drug-induced nephrotoxicity) has been reported and it is more pronounced with doses >50 mg/m^2. Peak uric acid concentrations generally occur 3–5 days after administration of drug.[62]

Ocular effects

Optic neuritis (principally retrobulbar), papilledema, and cerebral (cortical) blindness has been reported infrequently. In such cases corticosteroids have been used, with or without mannitol, however efficacy of such treatment has not been established.[62]

Apart from the mentioned side effects it was seen that infusion of a solution with concentration >0.5 mg/mL resulted in tissue cellulitis, fibrosis, and necrosis.There can also be mild and transient elevations of serum AST (SGOT), ALT (SGPT), and bilirubin.[62]

Drug Interactions [62]

Drug	Interaction	Comments
Aminoglycosides	Increased risk of nephrotoxicity	Avoiding aminoglycoside for at least 2 weeks after cisplatin to minimize risk.
	Increased risk of ototoxicity	Monitor carefully for ototoxicity
Amphotericin B	Increased risk of nephrotoxicity	Avoid concomitant use
Bleomycin	Decreased elimination of bleomycin	Synergistic antineoplastic effects
Loop Diuretics, (ethacrynic acid, furosemide)	Increased risk of ototoxicity	Monitor carefully for ototoxicity
Etoposide	Decreased etoposide elimination.	Synergistic antineoplastic effects
Methotrexate	Decreased elimination of methotrexate	Synergistic antineoplastic effects

Table 2: Drug interactions of cisplatin

Solution Compatibility

Compatible

Dextrose 5% in sodium chloride 0.225, 0.45, or 0.9%

Dextrose 5% in sodium chloride 0.33 or 0.45% with mannitol 1.875%

Dextrose 5% in sodium chloride 0.33% with potassium chloride 20 mEq and mannitol 1.875%

Sodium chloride 0.225, 0.3, 0.45, or 0.9%

Incompatible

Sodium bicarbonate 5%

Variable

Dextrose 5% in water

Therapeutic index

Therapeutic index (TI) for a drug is the ratio of maximum tolerated dose to minimum effective dose .[62] A high TI indicates safety of the drug. It is difficult to actually calculate TI as the sensitivity of the normal tissue cells and tumour cells of the individuals, but the concept is useful when optimising treatments. Successful treatments are based on the presumption that the tumour cells are more sensitive than the normal cells of the host. In clinical practice treatment is often administered until critical toxicity is reached, then it is modified or discontinued. A side effect which cause the treatment to be modified or discontinued is termed dose limiting.

The ways that are currently used to optimise specific treatments:

1) Selection of suitable patients

2) Optimising the mode of administration

Selection of suitable patients

Selection of suitable patients is a strategy for risk/benefit assessment which is effectively used in every patient. The first step is the selection of patients with a drug-sensitive tumour and an acceptable performance status. Moreover, the patient should not have organ failures which most often present critical toxicities e.g. kidneys, heart/lung/liver or haematologic system, which could predispose the patient to serious side effects. The second step is to monitor the ongoing treatment on the individual, i.e. the tumour response and side effects.

Optimising the mode of administration

The mode of administration is believed to be important for dose response relationship and side effects. In radiation it is done by fractionation schedules. Possible alterations include the rate of drug administration, the timing of one drug in relation to the administration of other drugs and the interval between treatment courses. Common speculations pertaining to the role of mode of administration for cisplatin is that intermittent bolus injection may cause more gastrointestinal toxicity than repeated infusions whereas a slow infusion might be more myelotoxic.The AUC has been suggested to be more important than the peak for the nephrotoxic effect. Possible explanations might be differences in intracellular kinetics of uptake and binding or perhaps by the kinetics of reparative mechanisms. Hence, pharmacokinetics may affect cisplatin's action and its side effects in many different and unpredictable ways.

Cisplatin ototoxicity

The ototoxicity of Cisplatin is mainly evident in the turns of the cochlea and can be seen as degeneration of the OHCs and to some extent the IHCs and associated nerves. Sometimes the toxic effect of cisplatin may result in a degeneration of the vestibular organs. Cisplatin results in depletion of glutathione and antioxidant enzymes (Superoxide dismutase, catalase, glutathione-peroxidase and glutathione-reductase) in cochlear tissues, with a corresponding increase in the malondialdehyde levels.[63] These effects are mainly caused by the generated reactive oxygen species (ROS). Cisplatin chemotherapy also induces a decrease in the plasma antioxidant levels which may result in decreased levels in the cochlea too.[64]This may be due to utilization of antioxidants during oxidative stress and renal loss of low molecular-weight antioxidants. Peroxinitrites are formed when ROS interact with nitric oxide in the cells. When these peroxinitrites react with cellular proteins intracellular toxic products such as nitrotyrosine are produced. Increased nitrotyrosine may lead to the oxidation of membrane lipids resulting in membrane dysfunction and cell lysis.[65]

Ciplatin can also affect the mitochondrial membrane where it will result in the release of cytochrome C. This can activate caspase 9 and then caspase 3 that will end in apoptosis of the outer hair cells. Hence, apoptosis is also implicated in cisplatin-induced spiral ganglion ototoxicity.[66]A high dose of cisplatin is associated with an acute lowering of the endolymphatic potential. It is reported to cause a rather acute loss of auditory sensitivity, which can become stable after about three days. Multiple low dose administration may cause a more specific OHC loss, which appears more slowly. In man cisplatin ototoxicity is mostly irreversible. However, in the guinea pig there is a reversible component after treatment with cisplatin in multiple low doses,

which has been attributed to recovery of the function of the stria vascularis. One of the cause of the relative differences in ototoxicity between the different platinum compounds is the molecular size, less ototoxic compounds are larger molecules.

In body fluids, cisplatin is readily attacked by nucleophiles with exchange of one or both chloride ligands to form high and low molecular mass complexes. After rapid intravenous infusion of cisplatin, 65–98% of platinum in blood plasma is protein-bound in a day, while no unbound platinum has been detected at any time in blood plasma of patients after slow 20 hour infusions. Protein binding results in significantly lower urinary excretion and an increased tissue deposition of platinum. Cisplatin binding to albumin is essentially irreversible with less than 5% loss of protein-bound platinum after extensive dialysis.[6]

Serum albumin

Human serum albumin (HSA) is a single-chain 66-kDa protein, which is largely α-helical and consists of three structurally homologous domains, organized into a heart shape. HSA contains 17 disulfide bridges and one free thiol at Cys-34.[68] Binding of drugs to serum albumin affects their metabolism, efficacy, and body distribution.

Some studies have shown that

I. Hypoalbuminemic patients have more adverse effects to cisplatin treatment
II. The infusion of preformed cisplatin-albumin complexes significantly increases patient survival times, and
III. HSA-cisplatin complexes are cytotoxic to malignant cells.[65, 69]

Thus the antitumor activity of infused cisplatin may be determined by both free and albumin-bound drug. Additionally, it has also been noted that albumin binding may prevent some of the side effects of cisplatin treatment, especially its nephrotoxicity.[70]

Therefore to assess the correlation between Cisplatin induced ototoxicity and low serum albumin levels, as seen in malnourished population commonly seen in rural areas has been one of the objective of the study.[65]

MONITORING FOR OTOTOXICITY

Audiological evaluation in a clinical setup may be done to detect ototoxic changes in speech frequency range when communication is affected .The second purpose is to monitor the changes, even when it is known that the treatment regimen cannot be safely altered. In the latter situation, the purpose of monitoring is to assist the patient and their family in maintaining communication as hearing loss develops. This assistance may include counselling, communication strategies, amplification and assistive learning devices. Preventing hearing loss and maintaining communication is a major quality of life issue, particularly for patients and families dealing with serious and life threatening illness.Currently there are three main approaches to audiologic monitoring for ototoxicity : the basic pure tone audiometry, high frequency audiometry , and otoacoustic emissions (OAEs) .[71] Depending on the tests purpose and the patient needs they may be used separately or in combination. All these approaches require a baseline evaluation, preferably prior to any ototoxic drug administration, so that later findings can be compared. Given the high incidence of pre-existing hearing loss in the population at large, any assessment for ototoxicity without a baseline evaluation will be difficult to interpret in regard to cause .[72] In those cases, the patient or family may inaccurately attribute a long standing, but newly diagnosed hearing loss to the current medical treatment.

Occasionally an ototoxic medication may selectively cause low or mid frequency range hearing loss, best evaluated by testing the conventional frequency range. In case where the patient's treatment protocol cannot be altered despite ototoxic hearing loss being detected, pure tone audiologic assessment should be done, so that timely

intervention can be provided.Intrasubject variability over time for extended high frequency EHF (between 10000 Hz and 20000),[73] is similar to air- conduction threshold testing in the conventional frequency range.[74]

Oto- Acoustic Emissions (OAE) are another option for monitoring ototoxicity. OAE are aacoustic signals generated by the cochlear outer hair cells and transmitted from the cochlea thorugh the middle ear to the ear canal , where they can be detected and recorded with a sensitive low noise microphone .The advantages of this is that it doesn't require behavioural response from the patient and can be done even on comatose patient. Currently, it is not known whether high frequency audiometry and OAEs consistently provide the earliest indications of ototoxic changes , research in that area continues.[75]

MATERIALS AND METHODS

Materials and methods

This study was conducted by the Departments of Pharmacology, Otolaryngology Head and Neck Surgery and Medical Oncology at R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College,Tamaka, Kolar. Patients with squamous cell carcinoma of head and neck, receiving Cisplatin therapy after surgery, were recruited for the study. The duration of the study was from 1/12/2010 to 30/04/2012.

Inclusion criteria

1. Patients of either gender, above 40 years with squamous cell carcinomas of the head and neck receiving cisplatin
2. Patients receiving combination of cisplatin with 5-flurouracil
3. Patients receiving combination of radiotherapy and cisplatin

Exclusion criteria

1. Patients with past history of acoustic/noise induced trauma
2. Patients receiving other ototoxic drugs (like aminoglycosides, cyclosporine)
3. Patients with kidney disorders
4. Patients hypersensitive to cisplatin
5. Pregnant and lactating women

This study was approved by the institutional ethics committee. Informed consent to participate in the study was obtained from the patients. The subject's demographic details were collected as per the proforma (enclosed) (annexure pg 89)

The patients who were recruited had their serum creatinine, blood urea, serum albumin and audiometry tests done at baseline, that is after surgery and radiotherapy but before administration of chemotherapy. The above investigations

were repeated after each chemotherapy cycle. Every patient underwent a detailed history, clinical examination, hearing (tuning fork tests and vestibular functions assessment i.e positional tests). The dose of cisplatin and 5-flurouracil was calculated based on body surface area and administered. After the administration of chemotherapy the patients were followed up at the first, second and third chemotherapy cycle. During the follow up patients were asked for symptoms like hearing loss, tinnitus and vertigo. Serum albumin was assessed by the BCG (Bromo cresol green) method using Johnson and Johnson Vitros 250 auto-analyser. Serum creatinine was measured by Jaffe's method and blood urea levels were assessed by Diacetyl monoxime method.

The ototoxic (cochleotoxic) effects of cisplatin were assessed by pure tone audiometry at conventional audiometric frequencies (125, 250, 500, 1000, 2000,4000, and 8000 Hz). Grason-Stadler Inc GSI 68 Diagnostic Audiometer was used for the study which was installed in a sound proof room of the Otolaryngology department. Audiometry was done four times per patient, the first audiometry was done at baseline before starting cisplatin and repeated two weeks after the completion of each cycle. An increase by 10 dB in the speech frequencies (Fisher scale – 500, 1000 and 2000 Hz) and an increase of 20 db at higher frequencies from the baseline was considered significant.

The patients who complained of vertigo or dizziness were administered a Dizziness Handicap Index (DHI) questionnaire. This assessed the incapacities in physical, functional and emotional areas of a patient's life. DHI has an allotment of 28 points (7 items) for the physical aspect, 36 points (9 items) for each of the functional and emotional aspect. The answers were scored as "0" for "no" (absence of symptoms), 2 for "sometimes" (occasional presence of symptoms) and 4 for "yes"

(severe presence of symptoms). (enclosed: annexure pg 92) Reference. Thus, the minimum punctuation would be 0 points (not handicapped) and the maximum would be 100 (maximum handicapped). These scores were later classified as, 16-34 points (mild handicap),36-52 points (moderate handicap) and 54+ points (severe handicap)

All subjects were administered a modified European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30 before chemotherapy and at the end of the third cycle. This questionnaire consisted of 10 questions which evaluated the different parameters like physical functioning (pain in mouth, lacked appetite, diarrhoea), emotional functioning (feeling of depression), social functioning (contact with family), financial functioning (family support). This was rated on a scale of 1(not at all) to 4 (very much). The minimum and maximum scores on this scale were 10 and 40 respectively (enclosed see annexure:pg 91)

Statistics

The sample size was calculated by considering the incidence of hearing loss to be 6% in the general population and a sample proportion of 15% with power of the study fixed at 80% and an α error of 5%. The required sample was found to be 59 patients.Descriptive statistical analysis was carried out on the demographic data. Continuous variables were presented as mean $\pm$ standard deviation and categorical as percentages (%). Variables within the group and between the group were analysed by paired–t test and unpaired–t test. Pearson's correlation was used for establishing correlation between serum albumin and hearing loss. Quality of life scale was assessed using Wilcoxon Sign rank test. A p- value less than or equal to 0.05 was considered significant. The statistical tests were done with SPSS 11.0.

RESULTS

RESULTS

A total of 59 patients clinically diagnosed with squamous cell carcinoma of head and neck by the oncologists were recruited. All patients received three cycles of radiotherapy with 15 Gy, with a minimum gap of one week, before starting chemotherapy, and then the baseline parameters were taken. Fifty six patients received only cisplatin and three cisplatin with 5-fluorouracil. Out of 59 patients, 54 completed the required 3 cycles of chemotherapy. The remaining 5 patient's data was incomplete as they did not come for subsequent follow up hence were included only for demographic analysis.

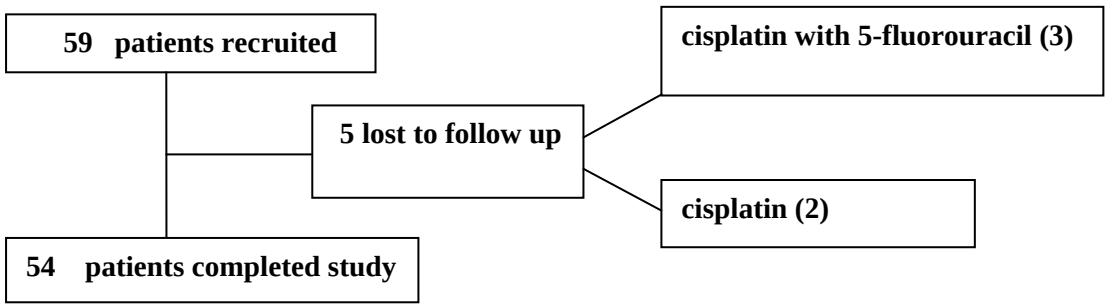


Figure 9. **Flowchart showing number of patients recruited.**

Table 3. **Gender and age distribution**

Gender	No of patients	Mean age ±SD (yrs)	Percentage
Male	26	55.25 ± 8.13	44.1
Female	33	54.73 ± 8.35	55.9
Total	59	54.94 ± 8.11	100.0

The youngest patient was 41 and the eldest was 70 years old.

Table 4. **Anatomical areas of squamous cell carcinoma tabulated genderwise**

Areas involved	Frequency	Percent	Males	Females
1 Buccal Mucosa	21	35.6	3	18
2 Retromolar Trigone	10	16.9	5	5
3 Supraglottis	10	16.9	10	0
4 Pyriform fossa	7	11.9	7	0
5 Tongue, floor of mouth	6	10.2	2	4
6 Oropharynx	3	5.1	3	0
7 Hard and soft palate	1	1.7	0	1
8 Upper alveolus	1	1.7	1	0
Total	59	100	33	26

Patients having cancer of the buccal mucosa were maximum in number 21 (35.6%), among them majority were females(18). Cancer of the supraglottis was seen only in males.

Table 5. **Cisplatin dose**

Dose (mg /cycle)	**Total dose received (mg)**	**Number of patients**	**Percentage(%)**
40.00	120	2	3.4
50.00	150	55	93.2
60.00	180	1	1.7
70.00	210	1	1.7
Total	-	59	100.0

Fifty four patients who received a dose of 50 mg per cycle only completed the study. Three patients also received 60 mg/cycle of 5- FU

Table 6. **Albumin levels at baseline and follow up visits**

Albumin	**Range (mg/dl)**	**Mean ± SD (mg/dl)**	**p value**
Baseline	2.90-5.90	3.85±0.54	-
Cycle 1	2.70-5.00	3.75±0.51	0.086
Cycle 2	2.50-5.10	3.63±0.49	0.005**
Cycle 3	2.10-4.90	3.53±0.50	0.005**

** 2^{nd} and 3^{rd} cycle values compared with baseline

When the serum albumin levels were compared between baseline and at the end of 1^{st}, 2^{nd} and 3^{rd} cycle, there was a significant reduction at the end of 2^{nd} and 3^{rd} cycle.

Table 7. **Pure tone audiometric findings in the right ear**

Right ear hearing loss	**Range (Decibels)**	**Mean ± SD (Decibels)**	**p value**
Baseline	13.33-50.00	22.48 ±8.53	-
Cycle 1	15.00-50.00	23.51±8.53	0.002*
Cycle 2	15.00-60.00	26.22±9.70	<0.001**
Cycle 3	15.00-63.33	29.53±11.70	<0.001**

* 1st , ** 2nd and 3rd cycle values compared with baseline

Table 8. **Pure tone audiometric findings in the left ear**

Left ear hearing loss	**Range (Decibels)**	**Mean ± SD (Decibels)**	**p value**
Baseline	11.60-45.00	23.23±9.02	-
Cycle 1	13.33-45.00	24.13±8.86	0.002*
Cycle 2	13.33-65.00	27.00±10.36	<0.001**
Cycle 3	13.33-75.00	30.95±13.30	<0.001**

* 1st, ** 2nd and 3rd cycle values compared with baseline

The hearing loss was evaluated using an audiometer, and values were expressed in decibels as shown in Tables 7 and 8. There was progressive worsening of hearing in the right and left ears after every cycle of chemotherapy. This deterioration of hearing from baseline was significant in the both the ears.

Table 9. **Data with respect to total number of ears (n = 108) tested**

(Total no. of patients = 54)

Frequency	**Follow up**	**0-20 dB**	**21-40 dB**	**41-60 dB**	**61-80 dB**	**81-100dB**
4000Hz	Baseline	14	80	12	2	-
	End of 3rd cycle	10	42	44	9	3
6000Hz	Baseline	9	68	26	5	-
	End of 3rd cycle	7	31	40	27	3
8000Hz	Baseline	7	47	39	14	1
	End of 3rd cycle	5	20	29	35	19
Fisher scale	**Follow up**	**0-25 dB**	**26-40 dB**	**41-55 dB**	**56-70 dB**	**71-90 dB**
	Baseline	78	24	6	-	-
	End of 3rd cycle	43	48	12	4	1

As shown in the above 54 patients with total number of ears tested being 108, the mean baseline hearing threshold tested at all frequencies was 34.5 dB which increased to 46.5 dB after the third cycle of chemotherapy. Towards the end of the third cycle of chemotherapy an increase in the number of ears with mild (26- 40db), moderate (41-55db) , moderately severe (56-70db), and severe (71-90db) hearing loss was observed. However none of the patients had profound hearing loss in either ear (i.e > 91 dB)

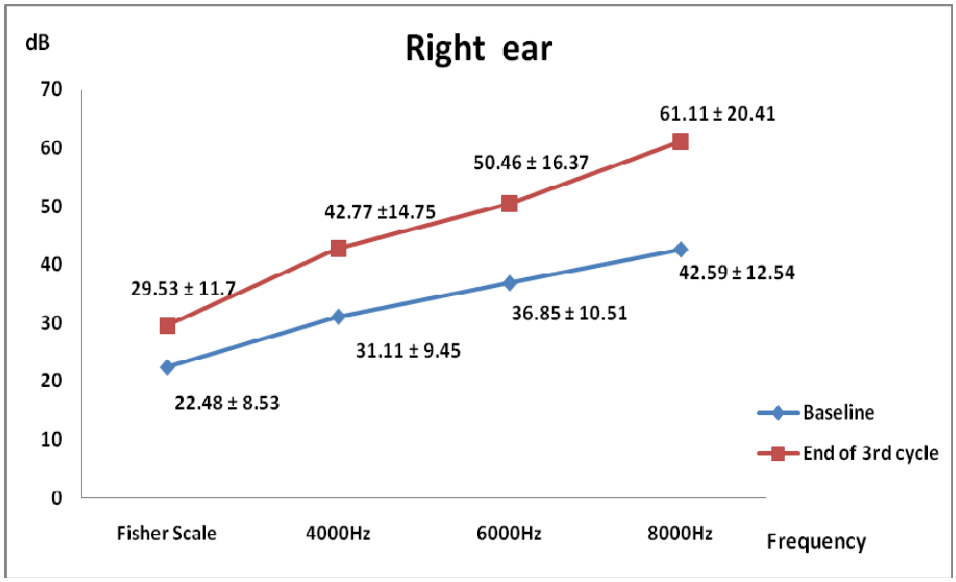


Figure 10. Mean decibel level of right ear at the corresponding frequencies at baseline and the end of the third cycle of chemotherapy

There is an increase in the mean decibel level from baseline to post chemotherapy assessment at all the frequencies, maximum being observed at 8000Hz (18.52 dB)

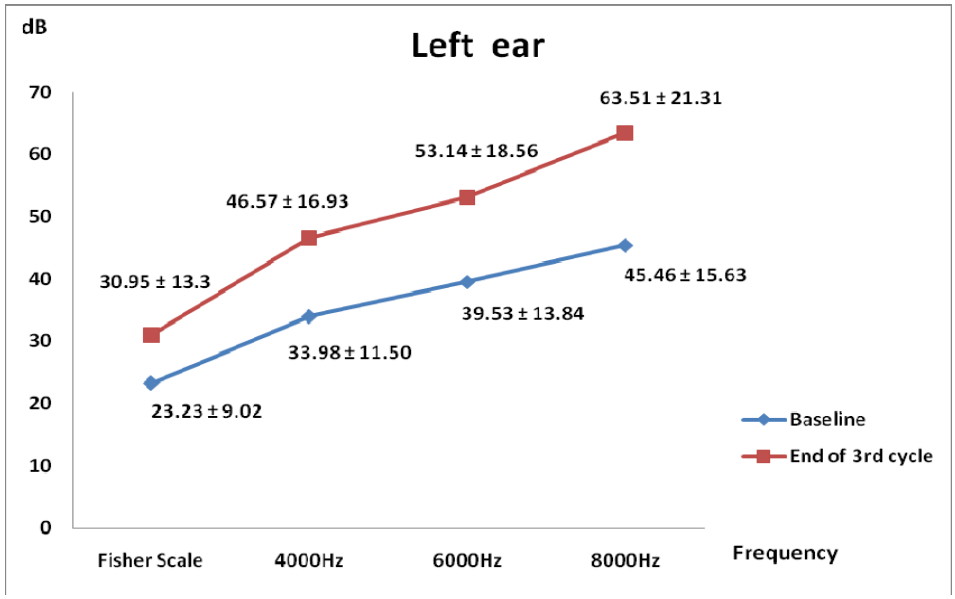


Figure 11. Mean decibel level of left ear at the corresponding frequencies at baseline and the end of the third cycle of chemotherapy

There is an increase in the mean decibel level from baseline to post chemotherapy assessment at all the frequencies, maximum being observed at 8000Hz (18.05 dB)

Table 10. **Hearing loss at different frequencies**

Frequency	**Significant**	**Non-significant**
Fisher's scale	12 (22.2%)	42 (77.8%)
4000 Hz	12 (22.2%)	42 (77.8%)
6000 Hz	18 (33.3%)	36 (66.7%)
8000 Hz	28 (51.8%)	26 (48.2%)

Increase in the number of patients showing high frequency (6000 and 8000Hz) hearing loss.

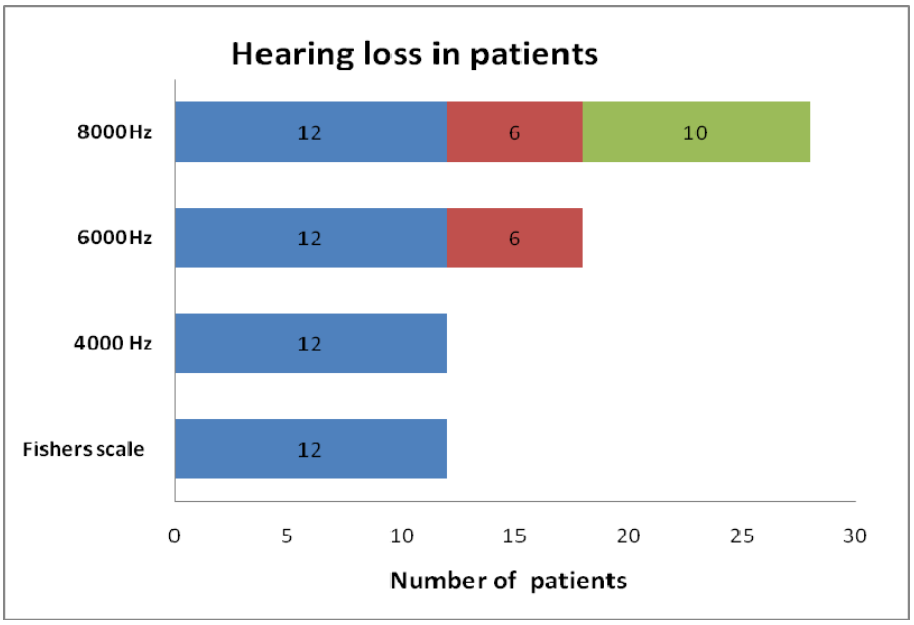


Figure 12. Number of patients with significant hearing loss increased from speech frequency (Fisher scale) to higher frequency

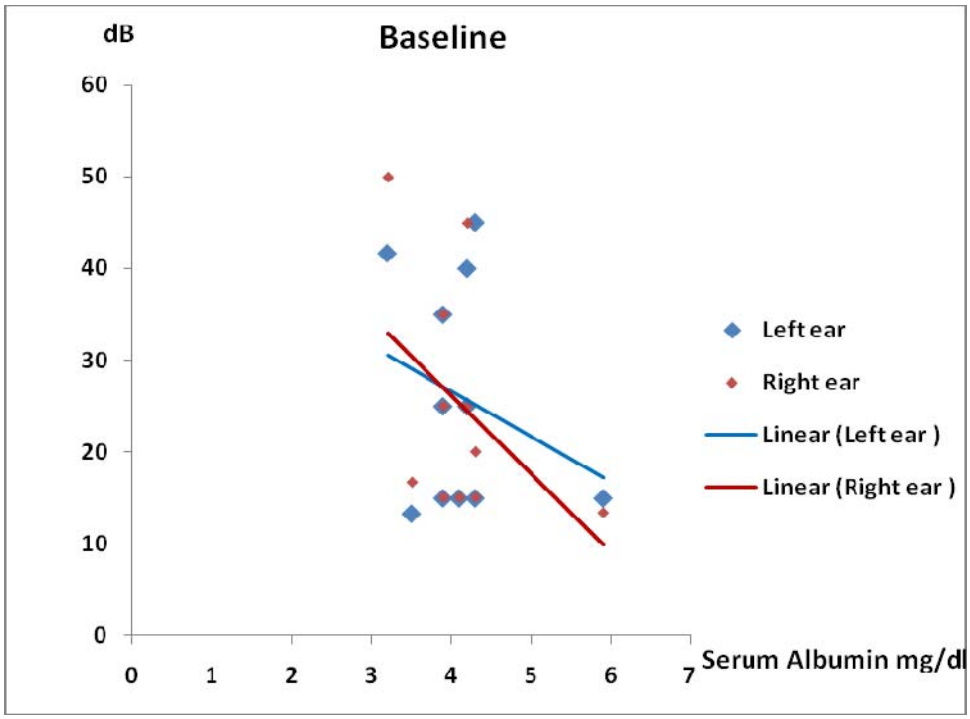


Figure 13. Correlation of serum albumin and hearing loss in both ears at baseline in Fisher's scale.(n = 12 patients)

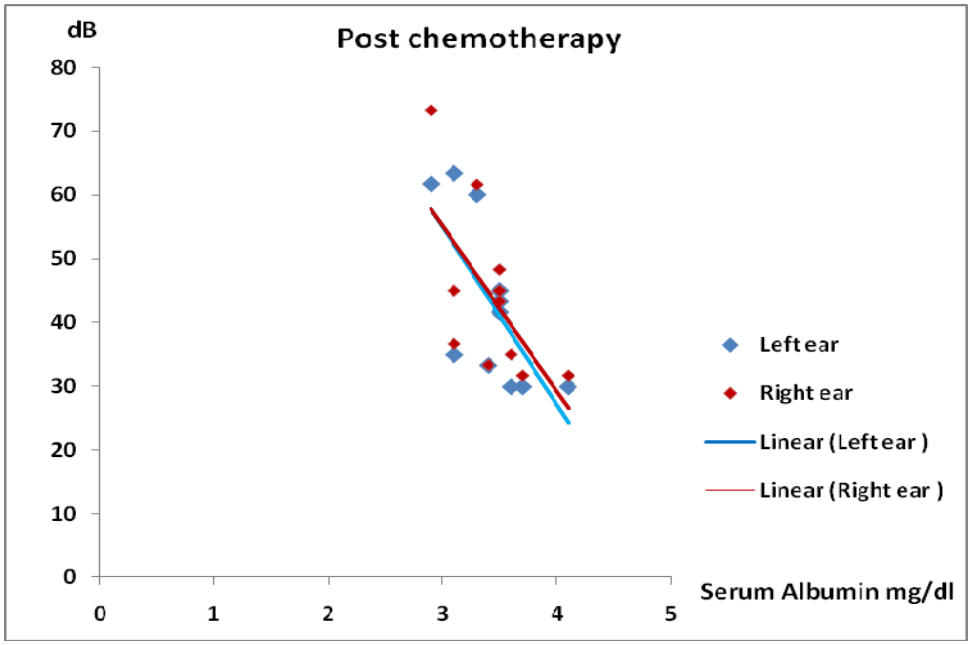


Figure 14. Correlation serum albumin and hearing loss in both ears after third cycle of chemotherapy in Fisher's scale.(n = 12 patients)

Table 11. **Correlation of serum albumin with hearing loss**

Parameters	**Right ear**	**r value**	**Left ear**	**r value**
Baseline albumin	0.16	-0.452	0.42	-0.271
Third cycle albumin	0.03*	-0.649	0.01*	-0.701

* p value <0.05 implies significant

There were 12 patients who suffered hearing loss in the Fisher scale at the end of the third cycle of chemotherapy, the correlation between low albumin levels and hearing loss in these patients was weak at baseline (Figure 13) but became stronger and significant at the end of the third cycle of chemotherapy (Figure 14). There was an inverse correlation (i.e as the levels of albumin decreased the hearing loss expressed in decibels increased)

Table 12. Levels of blood urea at baseline and follow up visits

Blood urea	**Range (mg/dl)**	**Mean ± SD (mg/dl)**	**p value**
Baseline	11.00-43.00	23.83±6.28	-
Cycle 1	14.00-50.00	26.14±7.36	0.029*
Cycle 2	15.00-71.00	27.66±7.94	0.001**
Cycle 3	16.00-51.00	28.05±6.66	<0.001***

* 1st , ** 2nd and ***3rd cycles values compared with baseline

The blood urea levels showed a progressive increase after every cycle of chemotherapy, which is statistically significant when compared to baseline

Table 13. Levels of serum creatinine at baseline and follow up visits

Creatinine	Range (mg/dl)	Mean ± SD (mg/dl)	p value
Baseline	0.47-1.50	0.91±0.23	-
Cycle 1	0.33-1.50	0.90±0.20	0.720
Cycle 2	0.62-2.50	0.97±0.27	0.210
Cycle 3	0.46-1.80	0.96±0.21	0.195

There was no significant change in the level of creatinine from the baseline after every cycle of chemotherapy

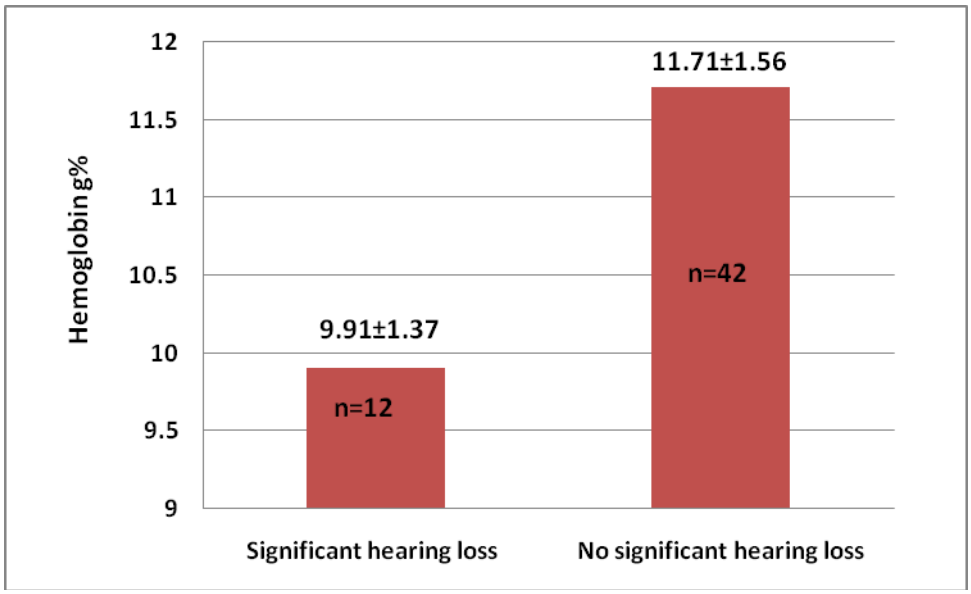


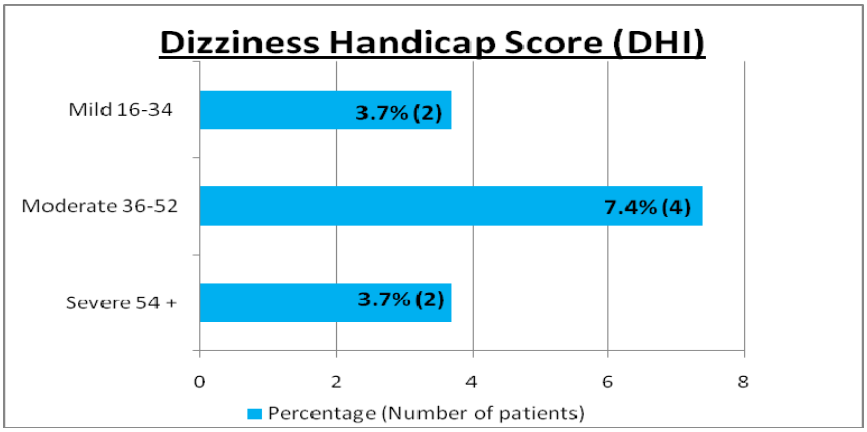
Figure 15. Haemoglobin levels in patients with hearing loss and without hearing loss at Fishers scale

The difference between the mean values in the two groups are significant (p = 0.001)

Table 14. **Assessment of quality of life (QOL)**

QOL	Range	Mean ± SD
Baseline	11.00-36.00	22.00±4.44
End of 3rd Cycle	16.00-34.00	24.37±4.44
p -value	-	<0.001**

There was a significant worsening of the quality of life as shown by the increased scores after the last cycle of chemotherapy. The minimum and maximum scores on this scale were 10 and 40 respectively.



Figue 16. DHI-score

The vestibulotoxicity was assessed by using the DHI score, only in those patients who complained about dizziness during follow-up. In the figure 18 the scores of 8 patients out of 54 who complained of dizziness are represented

Table 15. **Adverse effects seen in patient receiving cisplatin**

Adverse effects	**Number of patients**	**Percentage**
Nausea and vomiting	43	79.6
Fatigue	39	72.2
Hair loss	38	70.4
Tinnitus	36	66.7
Diarrhoea	13	24.1
Numbness in fingers	7	13
Rashes	5	9.3
Malena	5	9.3
Itching	3	5.6
Swelling of lips	1	1.9
Jaundice	1	1.9
Total	54	100

Commonly seen adverse effects listed in the above table.

Table 16. **Equation to predict the hearing loss based on baseline albumin levels**

	Prediction Equation	**r value**	**P value**
Baseline	Hearing loss =48.15 - 6.72 x baseline albumin	-0.379	0.005**
Chemotherapy Cycle 1	Hearing loss =54.42 - 7.91 x baseline albumin	-0.492	<0.001**
Chemotherapy Cycle 2	Hearing loss =58.27- 7.54 x baseline albumin	-0.532	<0.001**
Chemotherapy Cycle 3	Hearing loss =60.14 - 8.80 x baseline albumin	-0.539	<0.001**

The table indicates the linear equation with different constants as per the number of chemotherapy cycles and abumin level. If baseline albumin is known then the expected hearing loss can be predicted using the above equation. The above equation was generated by regression analysis after the correlation values were significant.

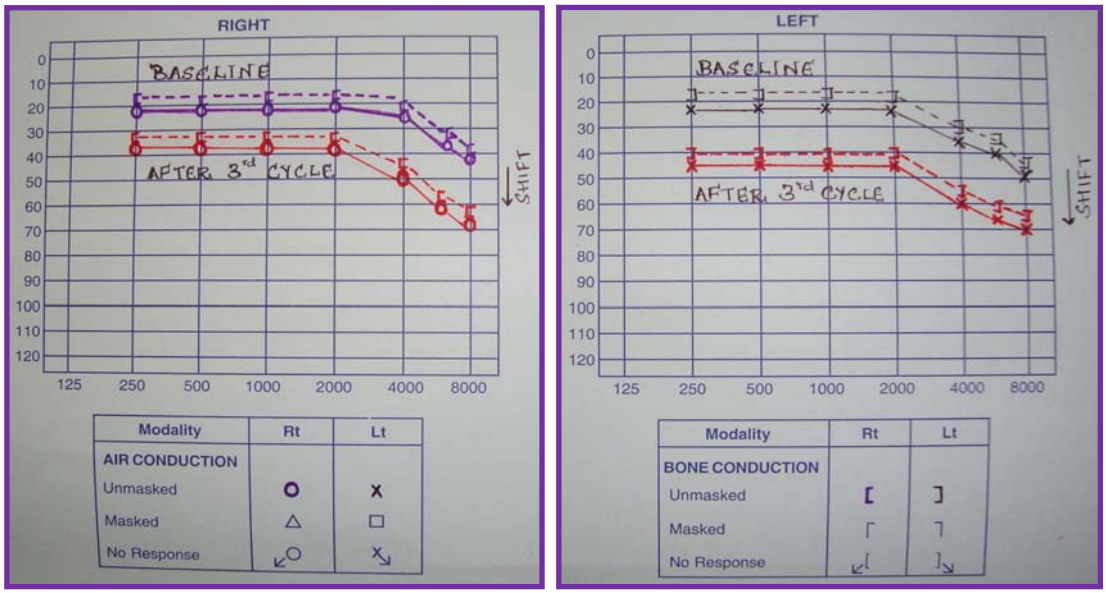


Figure 17. Audiogram of a 50 years old patient. Audiogram shows increase in decibel levels at all frequencies after the 3rd cycle of chemotherapy. PTA value has increased from 20 dB to 40 dB and 25 dB to 45 dB in the right and left ear respectively.

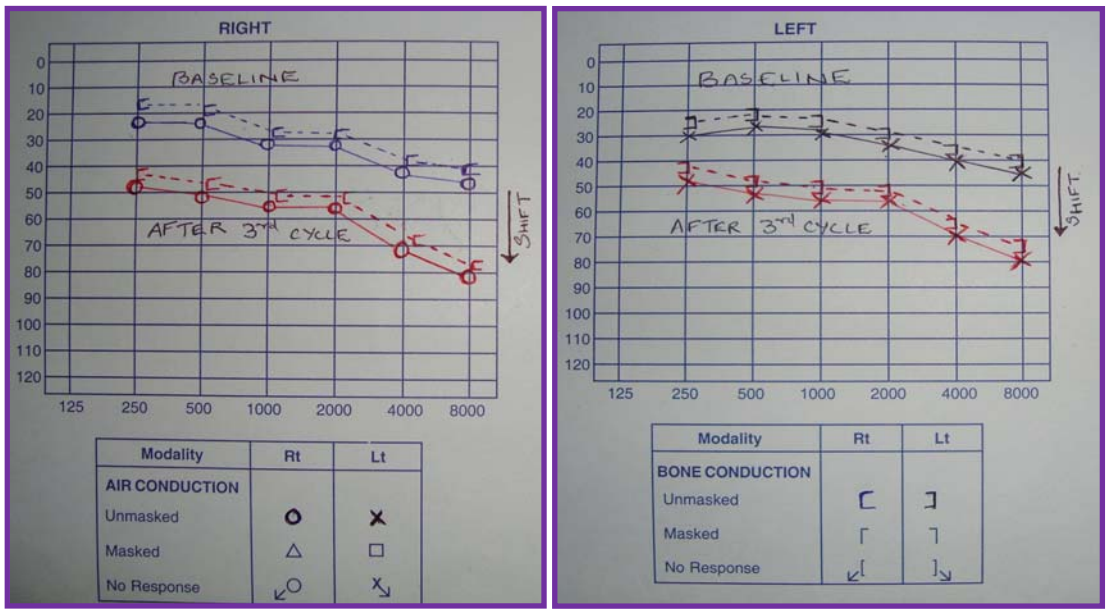


Figure 18. Audiogram of a 65 years old patient. Audiogram shows increase in decibel levels at all frequencies after the 3rd cycle of chemotherapy. PTA value has increased from 26.66 dB to 50 dB and 28.33 dB to 51.66 dB in the right and left ear respectively.

DISCUSSION

DISUSSION

In the present study 59 patients with squamous cell carcinoma of the head and neck region (SCCHN) were recruited (Figure 9). The occurrence of buccal mucosa carcinoma was found to be more in females, probably due to increased incidence of chewing tobacco. A study by Diaz EM et al. has shown that SCC of buccal mucosa is one of the most common cancers in Central and South East Asia because of the existence of habitual pan chewers (pan contains tobacco, nut and lime)[76]. All the patients were given three cycles of chemotherapy succeeding radiotherapy with 15 Gy. Although radiation can induce sensorineural hearing loss, it develops within 6 to 12 months and it is a dose-related phenomenon which affects hearing only in doses greater than 50–60 Gy.[77] In this study all patients who underwent radiation for head and neck cancers had their ipsilateral temporal bone and ear protected by beam –modification devices (shielding block made up of lead) so as to avoid any effect of radiation on hearing.

In our study 56 patients received only cisplatin and three patients 5-Flurouracil with cisplatin. Fifty four patients completed the study and five did not complete the follow up (Figure 9). The patients who received 5-FU and 40mg, 60 mg and 70 mg of cisplatin per cycle did not report for successive chemotherapy cycles.

Majority of patients were females (55.9%), and mean age of all, was 54.94± 8.11 years (Table 3). Although there is paucity of data related to gender predilection towards hearing loss, the influence of age on the effects of chemotherapy induced hearing loss is debatable. Aguilar -Markulis et al. reported that pre-existing hearing loss or advanced age were at increased risk of developing ototoxicity with cisplatin .[78, 79]

Our study involved patients only above the age of 40 years. As there was only one adult in our study with moderate hearing loss in both the ears at baseline, the effect of preexisting hearing loss is not being addressed here as the literature offers no clear consensus. However Kopelman et al described the "plateau" effect.[80,81] According to this effect in the presence of preexisting hearing loss administration of cisplatin chemotherapy will not worsen hearing at frequencies between 3000Hz and 8000Hz and hearing impairment of 40-60 dB. This is explained by the fact that once all outer hair cells of cochlea have been destroyed there can be no further hearing loss expected by subsequent administration of cisplatin. In our study three patients who had received a cumulative dose of 150 mg /m^2 showed this effect.

Cisplatin binds to serum albumin and only unbound form is active. It may be reasonable to assume that low protein binding of the drug may be responsible for greater toxicity which occurs at low serum albumin levels.[82] In our study it can be seen that the mean albumin level significantly decreased from the baseline value after every cycle of chemotherapy (Table 6). All patients had undergone routine urine analysis to rule out albuminuria. The reasons for the decreasing albumin levels could possibly be attributed to intolerance to chemotherapy.

The hearing loss was assessed in 54 patients using a Grason-Stadler Inc GSI 68 Diagnostic Audiometer. In pure tone audiometry it was observed that in the Fisher scale there was a shift in the mean decibel level in the right ear from the baseline value of 22.48±8.53 db to 29.53±11.70 db and in the left ear from 23.23±9.02 db to 30.95±13.30 db after the end of chemotherapy (Table 7, 8 , Figure 10, 11). Fisher's scale refers to the average of the decibel levels at 500Hz, 1000Hz and 2000Hz which is important for perceiving speech. Although in

many of our patients there were insignificant changes in the decibel levels from baseline in the Fisher's scale there were 12 (22.2%) who had significant hearing loss. These 12 patients also had significant hearing loss at 4000Hz, 6000 Hz and 8000Hz. Apart from the above mentioned patients an additional six patients had hearing loss at 6000Hz and 8000Hz and ten more patients had hearing loss at 8000Hz only (Figure 12). Among the 28 patients who had hearing loss at 8000Hz, three of them had maximum hearing loss and their hearing threshold after 3rd cycle was between 81-100db in both ears. These observations (Table 9, 10) were comparable to the studies by Laurall et al. who reported hearing loss in 22% patients at 4000-6000Hz and Fausi SA et al. who found significant high frequency (> 8000Hz) hearing loss in 71% patients.[79, 83]

Figure 17 and figure 18 illustrates the pattern of hearing loss due to cisplatin induced ototoxicity. These are audiograms from a 50 and 65 year old patient. The loss begins at high frequencies and then involves the lower frequencies. This hearing loss is bilateral, symmetrical and sensorineural. It typically affects the ultra high frequency (9000Hz -16,000 Hz) first, but we have restricted the assessment in this study to less than 8000Hz. Cisplatin ototoxicity appears rather quickly after drug administration and is fairly stable after three days. [84] However, the recovery of strial function and cochlear electrophysiology takes a considerably longer time. [85] The specific action of cisplatin on the inner ear may be related to the small size of the molecule enabling it to cross the blood-labyrinth barrier or the fact that cisplatin is not cell-cycle specific and thus can affect even the non-dividing cells of the inner ear such as the OHCs. Furthermore, mitochondria which are common in the OHCs and the metabolically active stria vascularis are known to be important cellular targets for cisplatin.

The association of serum albumin level with hearing loss was established by applying Pearson's correlation coefficient. The correlation between serum albumin and hearing loss was found to have inverse correlation in both, the right and left ear (Figure 13, 14). As the serum albumin levels decreased the hearing loss worsened as indicated by an increase in decibels. This fact is congruent with the study by Blakely BW et al. which assessed the association between albumin and cisplatin.[86] This correlation was found to be stronger and significant after the 3rd cycle of cisplatin chemotherapy (Table 11). By applying logistic regression we have found that the level of albumin is the salient factor affecting hearing in patients receiving cisplatin (p value 0.01). So it can be hypothesized that low serum albumin level means that fewer binding sites are available, so that more cisplatin is in the free form.

Some studies have found a relationship between free circulating cisplatin in plasma with time.[86,87] They found a diurnal variation in the plasma levels of cisplatin infusion. A low plasma level of free cisplatin was found during afternoon and evening, hence cisplatin administered during the early hours resulted in fewer side effects including ototoxicity. Measurement of correlation between time and plasma concentration was beyond the scope of this study.

A coincidental finding in our study was the significant difference in the hemoglobin level between the patients who had significant hearing loss at Fisher's scale (n=12, Figure 12) and those who did not have significant hearing loss at Fisher's scale (n=42). Figure 15 shows the mean hemoglobin values of both the groups. This decrease in hemoglobin value could also contribute to increased ototoxicity. The synthesis of hemoglobin requires globular proteins, low levels of albumin may alter protein synthesis and may adversely affect the

hemoglobin production, further studies may be required to establish this. It may be hypothesized that the ability of the blood to carry oxygen is decreased, the inner ear may be more susceptible to damage as show by Blakely BW et al.[88, 89]

As the heaing loss caused by cisplatin is irreversible, there has been a search for a chemopotectant that can be co-administered with chemotherapy to decrease hearing loss. Some of the drugs being tried out as otoprotectants are aspirin, intratympanic dexamethasone,[90] and antioxidants like vitamin E and tiopronin due its ability to suppress lipid peroxidation, thus attenuating tissue damage.[91] Strial vessels vasodilators like Ginkgo biloba extract [92] and hyperbaric oxygen therapy,[93] are being tried to improve the oxygen delivery to the inner ear as reduced oxygen levels has shown the inner ear to be more susceptibleThe other drugs which have been tried are lipoic acid,[94] adenosine agonist,[95]diethyldithiocarbamate,[96] and sodium thiosulfate.[97]

The involvement of the vestibular organ in cisplatin induced ototoxicity in humans is controversial. It has been proven that is affects the vestibular organs in studies on guinea pigs.[88] In our study among 54 patients eight of them had dizziness (Figure 16). Their disability due to dizziness was assessed using the DHI. This could indicate vestibulotoxicity in these patients and needs further monitoring and testing.

Cisplatin is known to cause nephrotoxicity and it has been the major reason for renal dysfunction in patients receiving it. In this study the blood urea levels increased after each cycle indicating early signs of renal involvement (Table 12).The creatinine values were however within the normal limit even at the end of the third cycle of chemotherapy (Table 13). There are several mechanisms that predispose to

renal impairment following administration of cisplatin. They are tubular epithelial cell damage, vasoconstriction of the renal blood vessels, and involvement of proinflammatory mediators.[98] In the body, cisplatin gets converted to an active compound, which reacts with glutathione in the cytoplasm and DNA in the nucleus in the dividing cells, resulting in cytotoxicity.[99] It achieves higher concentrations in the renal cortex to bring about the above mentioned changes. In our study the practices of hydration and administration of mannitol was used along with resumption of chemotherapy only upon return of the renal parameters (serum creatinine, blood urea) to normal values , which helped in reducing the incidence of renal dysfunction. There have also been studies testing the efficacy of the reducing agent Ethiofos (WR2721) to decrease the incidence of renal toxic reactions which however failed when it came to reducing ototoxicity.[100]

The patients were evaluated for QOL using modified EORTC- C30 QLQ-questionnaire, there was a significant worsening of QOL (Table 14). Patients experienced physical symptoms like persistent soreness in the mouth, difficulty in swallowing food and financial problems like funding their treatment. Lack of prolonged family support added to the worsening of quality of life score. The adverse effects of cisplatin also led to the worsening of quality of life.

Persistant nausea, vomiting, fatigue, hair loss and tinnitus were the frequently seen adverse effects (Table 15). Cisplatin is a highly emetogenic drug, the nausea and vomiting induced by it was treated using Ondansetron in a dose of 8mg i.v (0.15 mg/Kg) or Granisetron 1mg i.v (0.01 mg/Kg). These antiemetics were given along with 20 mg of dexamethasone, as it has a major role in the prevention of acute and delayed chemotherapy induced nausea and vomiting and is an integral component of almost all antiemetic regimens.[101]

The incidence of hair loss seen with alkylating agents are more than 60% in many studies.[102] Hair loss is a consequence of direct toxic insult on the rapidly dividing cells of the hair follicle.[102] Cisplatin induced ototoxicity is often present with transient or permanent tinnitus and shows high inter-individual variability.[102] Exact etiopathogenesis of even the high interindividual variability is still unknown but the differences in genetic factors and metabolic status of the individuals are implicated.[103]

Fatigue was seen in 39 patients. This could be due to many reasons like fall in haemoglobin levels, diarrhea or stress, and by a lesser known mechanism contributing to cancer-related fatigue involving abnormalities in adenosine triphosphate synthesis caused by carnitine deficiency as a result of cisplatin chemotherapy.[104]

Finally, for patients undergoing cisplatin chemotherapy the predicted hearing loss has been calculated using baseline albumin levels (Table 16). This can help patients in the future as we have found that if the base line albumin levels are low the chances of hearing loss in speech frequency will be more.

There are studies which show hearing loss in higher frequency, but in our study we have observed hearing loss at speech frequency in 22.2% of patients undergoing cisplatin chemotherapy. This is an important aspect which has to be considered seriously because this will affect their day to day activities and also may deteriorate quality of life. This finding was observed at the end of the 3rd cycle of chemotherapy so intervention at this juncture is essential.It can be in the form increasing the interval between the cycles, allowing the albumin level to return to normal or infusing proteins and reducing cisplatin dose without compromising the efficacy.

CONCLUSION

CONCLUSION

Cisplatin though discovered in 1970, still continues to be one of the common drugs effective in treatment of malignancies. Most of the treating physicians are well aware of the nephrotoxicity associated with it and also take precautions to check the renal status before drug administration. Others measures to minimize nephrotoxicity by administering fluids and diuretics are also followed. Similarly the oncologists should anticipate, evaluate and intervene to minimize the ototoxicity produced by cisplatin. Monitoring the auditory functions can be helpful in detecting hearing loss at an early stage and also adopting other preventive measures like reducing the dose or substituting cisplatin with carboplatin/oxaliplatin can be done. Therefore pretreatment and periodic audiograms should be done in patients receiving cisplatin. As patients with malignancy have to face a lot of mental agony and stress retlated to the disease, simple measures like audiometric testing at high and speech frequencies can assure them a better life to lead in their battle against malignancy.

SUMMARY

SUMMARY

- In the present study 59 patients with squamous cell carcinoma of head and neck were recruited of which 54 completed the study. These patients received three cycles of cisplatin chemotherapy.
- All patients were subjected to pure tone audiometer and successive serum albumin level estimation, at baseline and after each cycle of chemotherapy.
- The audiometric findings showed that cisplatin affected the higher frequencies first (i.e 8000 Hz, 6000Hz, 4000Hz).
- It was also observed that hearing loss in the speech frequencies were statistically significant in the patients with low serum albumin levels, and this relationship bears a strong inverse correlation. Monitoring serum albumin levels and auditory functions should be an essential part of the pre and post chemotherapy protocol for preventing the ototoxic effects of cisplatin.
- The involvement of the vestibular system due to the otoxicity of cisplatin can manifest as dizziness as observed in eight patients, and also haemoglobin levels may help in assessing the level of ototoxicity, however to substantiate these findings further studies are required.
- There was a significant deterioration in the quality of life at the end of the third cycle of chemotherapy.
- Nausea, vomiting, fatigue, hair loss and tinnitus were the commonly observed adverse effects to cisplatin in our study.

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ANNEXURES

PROFORMA

Name-

IP/OP No.-

Age: Address : Height:
Sex: Ph no: Body surface area:
Weight: Occupation:

PHYSICAL EXAMINATION

General Examination:

Pallor: Edema:

Icterus: Cyanosis:

Systemic Examination:

Cardiovascular System : Respiratory System:

Abdominal System: Central Nervous System:

Head and Neck: Ear Examination :

	Left ear	Right ear
Rinne's test		
Weber 's test		
Absolute bone conduction		

Tuning fork tests :

Vestibular functions :

Tumor Site : T Staging: Treatment status:

Examination Of Neck

Distant Metastasis:

Diagnosis:

Treatment plan :

INVESTIGATIONS

	BASELINE	1ST CYCLE	2ND CYCLE	3RD CYCLE
Urine analysis				
Serum Proteins				
Blood Urea				
Serum Creatinine				
Audiometry				

Commencement of treatment-

- 1ST CYCLE – (DATE):
- Drugs :
- 2ND CYCLE– (DATE):
- Drugs:
- 3RD CYCLE – (DATE):
- Drugs

CHECKLIST ON THE ADVERSE EFFECTS OF CISPLATIN

HYPERSENSITIVITY	RENAL	HEMATOLOGICAL	OTHERS
Breathing difficulty	No urine	Malena	Hair loss
Swelling of lips	Blood in Urine	Bleeding altered	Jaundice
Rashes	Reduced urine	Extreme fatigue	Blurred vision
Itching			Numbness in fingers or toes
			Nausea and vomiting
			Diarrhoea
			Tinnitus

Modified EORTC QLQ- C30 Questionnaire

Please indicate the extent to which you have experienced these symptoms or problems during the past week.

D**uring the past week** :	Not at all	A little	Quite a bit	Very much
1.Have you had pain/soreness in your mouth?	1	2	3	4
2.Have you felt weak ?	1	2	3	4
3.Have you had diarrhoea ?	1	2	3	4
4.Have you vomited ?	1	2	3	4
5.Have you felt nauseated ?	1	2	3	4
6.Were you short of breath ?	1	2	3	4
7.Did you feel depressed?	1	2	3	4
8.Have you had difficulty remembering things?	1	2	3	4
9.Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
10. Has your physical condition or medical Treatment caused you financial difficulties?	1	2	3	4

Dizziness Handicap Inventory [DHI]

INSTRUCTIONS: The patient should answer “YES,” “SOMETIMES,” or “NO” for each question as it pertains to their dizziness or unsteadiness problem only. To obtain a total score, add up the responses in each column, and then add the three column totals.

	Yes	Sometimes	No
1. Does Looking up increase your dizziness?	4	2	0
2.Because of your dizziness, do you feel frustrated?	4	2	0
3.Because of your dizziness, do you restrict your travel for business or recreation?	4	2	0
4.Does walking down the aisle of a supermarket increase your dizziness?	4	2	0
5.Because of your dizziness, do you have difficulty getting into or out of bed?	4	2	0
6.Does your dizziness significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	4	2	0
7.Because of your dizziness, do you have difficulty reading?	4	2	0
8.Does performing more ambitious activities like sports, dancing,or household chores such as sweeping or putting dishes away increase your dizziness?	4	2	0
9.Because of your dizziness, are you afraid to leave home without having someone accompany you?	4	2	0
10. Because of your dizziness, have you been embarrassed in front of others?	4	2	0
11. Do quick movements of your head increase your dizziness?	4	2	0
12. Because of your dizziness do you avoid heights?	4	2	0

13. Does turning over in bed increase your dizziness?	4	2	0
14. Because of your dizziness, is it difficult for you to do strenuous housework or yard work?	4	2	0
15. Because of your dizziness, are you afraid people may think you are intoxicated?	4	2	0
16. Because of your dizziness, is it difficult for you to go for a walk by yourself?	4	2	0
17. Does walking down a sidewalk increase your dizziness?	4	2	0
18. Because of your dizziness, is it difficult for you to concentrate?	4	2	0
19. Because of your dizziness, is it difficult for you to walk around your house in the dark?	4	2	0
20. Because of your dizziness, are you afraid to stay home alone?	4	2	0
21.Because of your dizziness, do you feel handicapped?	4	2	0
22. Has your dizziness placed stress on your relationships with members of your family and friends?	4	2	0
23. Because of your dizziness, are you depressed?	4	2	0
24. Does your dizziness interfere with your job or household responsibilities?	4	2	0
25. Does bending over increase your dizziness?	4	2	0

MASTER CHART

KEY TO MASTER CHART

Sln	- Serial number
OP NO	- Hospital Outpatient number
G	- Gender
C	- Type of cancer
D	- Dose of chemotherapy (kg/m^2/cycle)
BSA	- Body surface area
A0, A1, A2, A3	- Baseline albumin level,after 1^{st},$2^{nd,}$ 3^{rd} cycle(mg/dl)
RE0, RE1 RE2, RE3	- Right ear baseline (dB), after 1^{st}, 2^{nd} and 3^{rd} cycle
LE0, LE1, LE2, LE3	- Left ear baseline (dB), after 1^{st}, 2^{nd} and 3^{rd} cycle
R4,R6,R8, pc	-Right ear 4000Hz,6000Hz,8000Hz , postchemotherapy
L4,L6,L8, pc	- Left ear 4000Hz,6000Hz,8000Hz , postchemotherapy
ScrB, Scr1,Scr 2,Scr 3	- Serum creatinine baseline , after1^{st} ,2^{nd} ,3^{rd} cycle
BUB,BU1,BU2,BU3	- Blood urea baseline ,after after1^{st} ,2^{nd} ,3^{rd} cycle
Hb	- Hemoglobin value (g/dl)
QOL-base,PC	- Quality of life score baseline, Post chemotherapy
N&V	- Nausea and vomiting
Numbness	- Numbness in fingers
D	- Diarrhoea
BD	- Breathing difficulty
LS	- Lips swelling
B	- Bleeding altered
BV	- Blurred vision
1	- Present
0	- Absent
NFU	- No Follow up

	OP NO	G	Age	C	D	BSA	A0	A1	A2	A3	RE0	RE1	RE2	RE3	LE0	LE1	LE2	LE3	R4	R6	R8	R4pc	R6pc	R8pc	L4	L6	L8	L4pc	L6pc	L8pc	DHI-Scor	S.crB	Scr1	Scr2	Scr3	BUB	BU1	BU2	BU3	Hb	QOL-base	QOL-PC	hair loss	N & V	Fatigue	Numbness	D	BD	LS	Rashes	Itching	Malena	B	Urine	Jaundice	B V	Tinnitus
1	308211	1	35	1	40	1.5	3.9	3.6	4	3.6	16.7	16.7	25	25	16.7	16.7	25	25	20	25	30	30	35	40	15	20	40	25	35	50	0	1.5	0.56	0.68	0.91	32	14	22	28	13	14	32	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	
2	307573	1	49	2	50	1.7	3.9	3.8	3.8	3.7	15	25	25	31.7	15	25	25	30	25	25	25	40	40	50	15	15	20	40	40	55	0	0.77	0.73	0.63	0.46	18	20	24	21	9.6	16	24	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	
3	305641	1	45	2	50	1.8	3.6	2.7	2.7	2.8	25	25	25	33.3	25	25	25	33.3	30	40	45	45	50	60	30	35	50	30	35	55	0	0.67	0.92	0.94	0.96	18	22	23	21	13.7	16	26	1	0	0	0	1	0	0	0	0	0	0	0	0	1	
4	304763	1	45	6	50	1.3	3.5	2.8	2.5	2.1	16.7	20	23.3	36.7	13.3	20	23.3	35	15	30	35	35	45	55	15	20	30	35	45	50	0	0.68	0.62	0.62	0.57	17	23	25	28	10.6	17	16	0	1	1	0	1	0	0	0	0	0	0	0	0	0	
5	291716	2	54	3	50	1.7	4.2	4.4	4.1	3.9	13.3	20	20	21.7	11.6	20	20	21.7	35	35		40	45	55	40	55	75	50	60	95	0	1.1	1	1	1.13	15	24	27	25	13.2	18	26	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
6	307261	2	38	4	50	1.7	3.5	3.7	3.4	3.8	13.3	15	15	15	13.3	15	15	15	40	55	65	60	65	65	45	45	55	55	60	65	0	0.94	0.93	0.86	0.92	19	21	20	23	13.8	23	22	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
7	313526	2	55	5	50	1.8	4.1	4.1	3.7	3.2	23.3	25	30	30	23.3	25	30	30	30	35	40	30	35	45	30	35	30	35	40	45	0	0.77	0.91	0.98	0.98	27	23	28	25	14	17	29	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	
8	304649	2	35	2	40	1.5	3.9	3.4	3.5	3.2	15	18.3	18.3	20	15	18.3	18.3	20	15	20	20	15	20	20	20	20	20	20	20	20	0	1.5	0.63	0.72	0.87	32	14	26	28	10.8	17	16	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	
9	314216	2	58	5	50	1.8	5.9	4.8	4.4	4.1	13.3	15	25	31.7	15	15	25	30	40	50	60	65	70	80	50	50	60	65	70	80	0	1.1	1.2	1.1	0.99	34	27	28	21	8.7	19	29	0	0	1	0	0	0	0	0	0	0	0	0	0	0	
10	305117	1	60	2	50	1.7	3.2	3.1	3	2.9	50	50	60	73.3	41.7	45	45	61.7	65	70	70	85	90	95	65	70	75	85	90	95	54	0.47	0.63	0.69	0.72	20	24	27	23	12.3	19	21	1	1	0	1	0	0	0	0	0	0	0	0	0	1	
11	655433	1	65	2	50	1.6	3	3	2.9	2.9	35	41.7	41.7	41.7	25	30	30	30	40	55	70	50	60	100	40	55	70	50	70	90	48	0.71	0.89	0.88	0.91	23	26	27	30	11.4	11	20	0	1	1	0	0	0	0	0	0	0	0	0	0	0	
12	290055	1	52	2	50	1.6	3.8	3.7	3.4	3.6	15	15	15	20	15	15	15	20	25	30	30	25	35	40	25	25	30	25	25	35	0	0.91	0.94	0.99	0.95	15	22	24	21	14.2	13	18	1	0	1	0	0	0	0	0	0	0	0	0	0	1	
13	812076	2	60	3	50	1.8	4.2	4	3.7	3.3	45	45	50	61.7	40	45	45	60	50	55	60	75	80	90	60	60	60	75	80	95	46	0.84	0.93	1.1	0.9	24	28	23	31	8.3	19	22	1	1	0	1	0	0	0	0	0	0	0	0	0	0	
14	641506	2	63	4	50	1.6	3.8	4	4.3	3.2	15	15	15	15	15	15	15	15	35	40	50	40	50	60	40	55	65	50	65	70	0	1.5	1.3	0.84	0.97	23	32	15	21	11.3	36	34	0	1	0	0	0	0	0	0	0	0	0	0	0	1	
15	659360	2	64	3	50	1	3.6	3.8	3.4	3.3	16.7	16.7	25	25	41.7	41.7	65	75	25	25	25	30	35	40	45	55	60	85	85	90	42	0.95	1	0.8	1.4	24	43	16	16	12.8	26	26	1	1	1	0	1	0	0	0	0	0	0	0	0	0	
16	636462	2	65	3	50	1.2	4.3	4.2	4	3.1	20	20	30	45	45	45	45	63.3	50	60	70	65	80	95	55	70	80	90	95	100	0	1.1	1.17	1.29	1.32	15	23	30	32	11.7	28	24	1	0	1	0	0	0	0	0	0	0	0	0	0	1	
17	685839	2	60	3	50	1.1	4	4.2	4.3	3.8	15	15	15	15	13.3	13.3	13.3	13.3	25	40	45	30	45	50	30	35	40	30	35	45	0	0.74	0.9	1.1	0.95	22	23	21	40	10.6	25	29	1	1	1	0	1	0	0	1	0	0	0	0	0	1	
18	670373	2	49	4	50	1	5.1	5	4.7	4.3	20	20	20	25	20	20	20	25	25	35	40	35	35	55	30	35	35	40	40	50	0	0.95	0.97	1.1	1.2	43	19	28	27	13.1	23	27	0	1	1	0	1	0	0	0	0	0	0	0	0	1	
19	678860	1	35	2	70	1.1	3.7	3.5	3.5	3.2	40	43.3	43.3	43.3	40	40	43.3	43.3	45	50	55	55	55	75	50	55	65	45	60	85	0	1	1.1	1.3	0.97	25	28	26	27	11.7	23	34	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
20	639734	1	65	2	50	1.2	5	5	5.1	4.9	16.7	16.7	16.7	16.7	35	35	43.3	43.3	35	40	45	40	50	60	50	55	60	60	70	90	0	1.01	1.2	1.1	1.2	23	32	35	38	12.8	29	28	1	1	1	0	1	0	0	0	0	0	0	0	0	1	
21	679119	2	45	6	50	1.2	3.4	4.6	2.8	4.9	15	15	15	15	15	15	15	15	15	20	25	15	25	40	15	15	20	15	15	25	0	1.4	1.5	1.3	1.29	37	50	43	41	14.2	26	19	1	1	1	1	0	0	0	0	0	0	0	0	0	1	
22	672085	1	70	2	60	1.3	3.6	3.4	3.6	3.1	23.3	23.3	23.3	23.3	25	25	25	25	25	35	40	50	55	60	75	35	45	55	50	60	75	0	0.85	1.01	1.1	0.93	28	23	32	27	11.3	24	28	0	1	0	0	0	0	0	0	0	0	0	0	0	1	
23	270548	1	53	2	50	1.5	3.5	3.7	4	3.9	26.7	26.7	26.7	30	43.3	43.3	43.3	50	25	30	40	25	35	50	50	50	65	55	65	85	56	1.1	1	1.2	1.34	33	38	32	38	9.8	25	31	1	1	1	0	1	0	0	0	1	0	0	0	0	1	
24	688540	2	68	3	50	1.6	4	3.7	4.3	4.6	26.7	26.7	26.7	30	23.3	23.3	23.3	25	35	35	40	40	55	75	35	45	50	55	60	75	0	1.1	1.1	2.5	1.8	36	43	71	51	12.7	20	16	1	0	1	0	0	0	0	0	1	0	0	0	0	1	
25	685350	2	43	1	50	1.5	4.4	3	3.5	3.2	18.3	23.3	25	25	21.7	26.7	30	30	40	45	55	60	75	80	25	30	35	30	30	35	0	0.76	0.66	0.84	0.72	20	18	15	19	10.6	26	25	0	0	1	0	0	0	0	0	0	0	0	0	0	1	
26	286846	2	69	3	50	1.4	4.6	4.7	4	3.8	25	25	28.3	28.3	30	30	35	41.6	40	45	50	60	60	65	30	35	40	60	65	70	0	0.72	0.33	1.1	0.93	31	42	40	32	9.3	26	21	1	1	1	1	0	0	0	0	0	0	0	0	0	1	
27	696064	2	65	6	50	1.5	3.4	3.7	4.1	3.2	28.3	28.3	35	35	18.3	18.3	23.3	23.3	40	50	60	60	80	95	35	40	50	40	55	65	38	0.78	0.84	0.88	0.71	27	30	25	28	11.9	21	30	0	0	1	0	0	0	0	1	0	0	0	0	0	0	
28	686271	1	58	2	50	1.6	4.8	4.5	3.8	3.5	28.3	28.3	35	35	31.7	31.7	31.7	35	40	45	55	50	60	75	35	35	40	40	40	50	0	1.01	1.3	1.21	1.09	18	24	28	32	12.3	22	20	1	1	0	0	1	0	0	1	0	0	0	0	0	0	
29	626093	1	65	7	50	1.3	3.8	3.5	3.3	3.7	20	20	20	20	20	20	20	20	30	35	35	30	30	35	30	35	35	35	40	40	0	1.13	1.2	1.09	1.3	18	28	32	36	10.7	22	27	0	1	1	0	0	0	1	1	0	0	0	0	0	0	
30	736232	2	33	6	50	1.9	4.2	3.8	3.9	4.1	30	30	30	31.7	30	30	35	35	35	40	50	50	55	85	40	55	55	60	70	85	0	0.63	0.91	0.96	0.81	12	18	20	17	12.8	22	22	1	1	1	0	0	0	0	0	0	0	0	0	0	0	
31	266776	1	65	2	50	1.7	3.6	3.3	3.8	4.1	30	30	30	35	30	30	30	35	30	35	40	35	35	40	25	35	35	45	50	50	0	0.91	0.87	0.74	0.81	19	21	28	25	10.9	22	22	1	1	1	0	1	0	0	0	0	0	0	0	0	1	
32	719371	1	50	6	50	1.7	3.5	3.1	3.4	3.4	15	15	15	15	25	25	30	30	15	15	15	15	15	15	15	15	15	15	15	20	0	0.73	0.93	0.81	0.91	21	25	31	33	12.1	21	22	1	1	1	0	0	0	0	0	0	0	0	0	0	0	
33	305190	1	50	2	50	1.6	4	3.8	4	4.2	20	20	25	28.3	20	20	25	28.3	40	40	45	55	65	75	35	35	35	55	65	65	0	0.9	0.92	0.89	0.83	23	30	31	39	11.2	20	30	1	1	1	0	0	0	0	0	0	0	0	0	0	1	
34	764830	2	50	6	50	1.9	3.9	3.7	3.5	3.1	20	25	26.7	26.7	20	20	26.7	28.3	25	25	35	40	40	40	15	15	15	15	15	20	0	1.5	0.7	0.84	0.88	32	37	29	31	9	22	23	1	1	1	0	1	0	0	0	0	0	0	0	0	1	
35	785225	2	50	5	50	1.8	3.9	3.8	3.6	3.3	25	25	30	35	25	25	30	45	25	35	40	50	55	65	35	40	50	60	65	70	42	0.85	0.89	0.97	0.85	23	27	32	29	10.2	19	21	1	1	0	0	0	0	0	0	0	0	0	0	0	1	
36	392542	2	63	1	50	1.7	3.9	4	3.7	3.1	30	30	30	35	30	30	30	35	30	35	40	40	50	50	30	35	35	40	45	55	34	0.68	0.93	1.1	1.05	24	28	31	28	11.9	18	27	1	1	1	0	0	0	0	1	0	0	0	0	0	0	
37	688956	2	52	3	50	1.8	3.2	3.7	3.5	3.7	20	20	28.3	28.3	20	20	28.3	28.3	30	35	40	50	55	70	30	35	40	50	60	70	0	0.97	0.73	0.84	0.87	18	21	27	21	10.8	20	25	1	0	0	0	0	0	0	0	1	0	0	0	0	0	
38	797722	2	56	3	50	1.7	3.1	3.5	3.4	2.9	30	30	30	35	31.7	31.7	40	40	30	35	50	50	55	60	35	40	40	45	50	55	0	0.7	0.9	0.93	1.04	11	15	23	18	13.6	23	25	1	1	1	0	0	0	0	1	0	0	0	0	0	1	
39	773457	2	58	1	50	2	4.1	3.7	3.6	3.4	15	15	15	33.3	15	15	15	33.3	25	30	35	50	55	60	25	30	40	40	50	55	0	0.91	0.76	0.79	0.87	26	21	23	24	9.5	19	20	1	1	1	0	0	0	0	0	0	1	0	0	0	1	
40	319888	2	48	2	50	1.8	3.5	3.6	3.1	3	28.3	28.3	35	35	28.3	28.3	28.3	33.3	35	40	50	55	65	95	35	35	40	45	55	65	0	0.9	0.96	0.87	0.89	21	28	27	32	11.6	22	24	1	1	1	0	0	0	0	0	0	0	0	0	0	1	
41	741859	2	56	1	50	1.9	3.4	4.2	4.5	3.7	16.3	16.3	16.3	16.3	15	15	15	15	25	30	35	30	35	45	30	30	40	35	40	50	0	0.81	0.89	0.94	0.95	18	24	27	31	12.6	20	22	1	1	1	1	0	0	0	0	0	1	0	0	0	1	
42	524857	1	69	2	50	1.8	3.9	3.7	3.6	3.5	35	35	35	48.3	35	35	35	43.3	30	35	40	55	55	60	30	35	40	50	55	60	32	0.74	0.79	0.88	0.94	18	21	24	27	7.4	22	20	0	1	1	0	0	0	0	0	0	0	0	0	0	1	
43	716289	1	45	1	50	1.6	3.9	4	3.7	3.8	15	15	15	15	15	15	15	15	20	25	25	20	20	25	25	30	40	40	50	65	0	1.5	1.14	1.27	1.04	32	35	23	27	14.2	23	22	0	1	1	0	1	0	0	0	0	0	0	0	0	1	
44	633140	2	58	5	50	2	2.9	3.6	3.3	3.9	15	15	15	15	15	15	15	15	25	40	45	45	65	85	40	45	50	50	55	80	0	0.67	0.92	0.87	0.85	28	21	25	31	9.8	21	19	0	0	1	0	0	0	0	0	0	0	0	0	0	1	
45	718454	2	54	3	50	1.8	3.7	3.9	3.3	3.6	20	20	25	25	15	15	20	20	25	25	30	30	35	40	25	25	25	25	25	25	0	0.97	0.76	0.87	0.89	23	22	26	37	10.2	24	27	1	1	1	0	1	0	0	0	0	0	0	0	0	1	
46	305297	2	56	5	50	1.7	3.8	3.5	3.6	3.9	15	15	20	20	15	15	20	20	25	30	30	35	35	35	30	35	40	40	45	50	0	0.86	0.97	1.01	0.83	24	28	30	27	11.3	19	22	1	1	1	1	0	0	0	0	0	0	0	0	0	1	
47	727898	2	61	2	50	1.8	3.4	3.9	3.7	3.2	26.3	30	30	35	23.3	26.7	26.7	28.3	35	40	50	50	65	85	40	50	55	60	70	85	0	0.84	1.01	1.12	1.2	24	32	31	27	11.7	25	30	1	1	1	0	0	0	0	0	0	0	0	0	0	1	
48	727895	2	58	8	50	1.8	4.2	3.6	3.5	3.5	25	25	35	45	25	25	30	41.7	25	25	30	30	45	50	25	25	30	40	45	50	0	0.97	0.81	0.86	0.91	28	21	31	27	9.8	22	20	0	1	1	0	0	0	0	0	0	0	0	0	0	1	
49	723186	1	54	2	50	1.7	2.9	2.7	3.1	3.3	25	25	25	30	20	20	20	26.7	35	35	45	45	55	70	35	40	45	55	65	75	0	0.79	0.89	0.91	1.01	23	24	31	26	13.1	22	21	1	1	1	1	0	0	0	0	0	0	0	0	0	1	
50	760347	1	53	1	50	1.8	3.9	3.6	3.8	3.4	35	38.3	38.3	38.3	25	28.3	28.3	28.3	35	35	40	30	35	45	50	60	65	75	75	80	0	0.96	0.73	0.94	1.1	28	24	27	20	8.4	19	27	1	1	0	0	0	0	0	0	0	0	0	0	0	1	
51	800994	1	51	1	50	1.6	3.8	3.7	3.1	3.5	25	25	30	30	20	25	26.7	26.7	25	35	45	40	55	75	40	45	55	50	60	80	0	0.78	0.76	0.81	0.89	26	24	26	27	8.9	22	24	1	0	1	0	0	0	0	0	0	0	0	0	0	1	
52	802112	1	60	2	50	1.7	3.7	3.5	3.8	3.6	15	15	15	15	15	15	15	15	25	40	45	35	60	70	40	55	60	60	65	80	0	0.69	0.75	0.74	0.7	22	23	25	27	9.5	28	24	1	0	1	0	0	0	0	0	0	0	0	0	0	1	
53	790107	1	54	2	50	1.8	3.6	3.4	3.1	3.5	16.7	16.7	16.7	20	18.3	18.3	18.3	20	30	40	40	40	60	70	35	50	55	45	65	80	0	0.81	1.01	1.16	1.08	24	31	30	28	10.9	26	28	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
54	768953	2	62	5	50	1.8	4.3	4.1	3.9	3.6	15	15	21.6	35	15	15	21.6	30	30	30	35	50	60	70	30	40	45	50	65	80	0	0.69	0.73	0.81	0.76	24	27	23	26	10.1	31	29	0	1	1	0	0	0	0	0	0	0	0	0	0	1	
55	669382	2	47	5	50	1.9	3.6	NFU	NFU	NFU	30	NFU	NFU	NFU	30	NFU	NFU	LFU	NFU	LFU	NFU	LFU	NFU		NFU	NFU	NFU	NFU	NFU	NFU	NFU	0.87	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	25	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	
56	745632	2	51	1	50	1.8	3.3	NFU	NFU	NFU	25	NFU	NFU	NFU	25	NFU	NFU	LFU	NFU	LFU	NFU	LFU	NFU		NFU	NFU	NFU	NFU	NFU	NFU	NFU	0.91	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	21	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	
57	702545	1	59	2	50	1.6	2.9	NFU	NFU	NFU	30	NFU	NFU	NFU	30	NFU	NFU	LFU	NFU	LFU	NFU	LFU	NFU		NFU	NFU	NFU	NFU	NFU	NFU	NFU	0.75	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	22	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	
58	721925	1	49	1	50	1.7	3.8	NFU	NFU	NFU	35	NFU	NFU	NFU	35	NFU	NFU	LFU	NFU	LFU	NFU	LFU	NFU		NFU	NFU	NFU	NFU	NFU	NFU	NFU	0.65	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	30	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	
59	712641	1	55	2	50	1.4	3.2	NFU	NFU	NFU	25	NFU	NFU	NFU	25	NFU	NFU	LFU	NFU	LFU	NFU	LFU	NFU		NFU	NFU	NFU	NFU	NFU	NFU	NFU	0.78	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	27	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	NFU	