

Original Research Article

A study of cisplatin chemotherapy and hearing loss

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ABSTRACT

Background: Various medications have been associated with ototoxicity. Platinum containing chemotherapeutic agents are associated with cochleotoxicity, characterized by high frequency hearing loss. Cisplatin and related agents are absorbed by the cochlear hair cells, resulting in ototoxicity through the production of reactive oxygen species.

Methods: About 67 patients, irrespective of the type of cancer, fit to undergo chemotherapy were considered for study after meticulous examination. Audiograms were taken prior to chemotherapy, at the end of each cycle of chemotherapy, and follow-up audiograms at 3 months and 6 months after completion of chemotherapy.

Results: Among 37% of the patients with normal hearing, 10% of the patients developed sensorineural hearing loss after treatment. Among 63% of the patients with prior mild sensorineural hearing loss, 11.8% developed worsening of hearing after completion of treatment.

Conclusions: Audiologic monitoring is important in patients undergoing cisplatin chemotherapy and post-chemotherapy auditory monitoring is essential to rehabilitate the patients with Sensorineural hearing loss.

Keywords: Cisplatin chemotherapy, Ototoxicity, Sensorineural hearing loss

INTRODUCTION

Chemotherapy drugs such as cisplatin are commonly used to treat several types of cancer. While chemotherapy has saved many lives, an unfortunate side effect can be ototoxicity, causing bilateral, progressive and permanent sensorineural hearing loss. Cisplatin is mainly cochleotoxic, affecting the outer hair cells first producing an oxidative stress. The hearing loss usually start with high frequencies, so it is not immediately obvious to the patient. As the chemotherapy treatment continues, the hearing loss become more severe and affects wider range of frequencies. When the speech frequency range is affected, patients may require amplification with hearing aids after completion of chemotherapy. Even though many drugs amifostine, vitamin E, N-acetyl cysteine, anti-inflammatory and anti-oxidant drugs have been used as trial, none appear to be a novel drug to prevent from

ototoxicity. As hearing loss after completion of chemotherapy are inevitable, patients getting chemotherapy with cisplatin needs Hearing rehabilitation.

Cisplatin is used for treatment of solid tumours like ovarian, testicular, cervical, lung, head and neck and bladder cancers. Cisplatin is a cell cycle – nonspecific cytotoxic drug and has a toxic profile different from other cytotoxic agents. High doses of cisplatin cause nephrotoxicity, gastro-intestinal toxicity, neurotoxicity and ototoxicity. Ototoxicity is one of the dose – limiting side effects of cisplatin, it increases with increase in dose. It shows higher inter-individual variability.¹ The etiopathogenesis of this inter-individual variability is unknown, but pharmacokinetic differences, genetic factors and metabolic status of the individuals has been implicated.² Identification of the susceptible individuals before treatment is not possible, however early ototoxic

effects can be detected by serial audiometry, and it helps in early management of these patients.

METHODS

A prospective study was conducted in the Department of ENT in Thoothukudi Medical College for a period of one year (January 2016 to December 2016). Around 67 patients between the age group of 15–80 years of age, irrespective of the type of cancer, fit and eligible to undergo chemotherapy with cisplatin, in the Department of Oncology were registered and considered for study. Patients with less than 15 years of age, with prior history of ear disease, ear surgery, noise exposure, trauma, suffering with chronic diseases such as diabetes/hypertension and undergoing chemotherapy with other platinum group of drugs were excluded from study. Patients with prior severe to profound sensori-neural hearing loss were not considered as study population. Patients were selected, admitted in Department of Oncology, evaluated with necessary investigations including complete haemogram, liver and renal function tests to undergo chemotherapy. Once the patient has become fit for chemotherapy, patients were further evaluated in Department of ENT, with relevant history taking, meticulous examination of ear is done, prior audiogram is taken before starting the first cycle of chemotherapy and patients were sent back to Oncology Department for starting chemotherapy.

Serial audiograms are taken at the end of each cycle up to 6 cycles of chemotherapy. Follow-up audiograms are taken at 3 months and 6 months after completion of chemotherapy. Among 67 patients, 6 patients were defaulters for further treatment and 7 patients died during the course of treatment. Among 54 patients, head and neck carcinoma patients were treated with the dose of 40–60 mg/sqm, lung, stomach and neuroectodermal carcinoma patients were treated with 60 mg/sqm, ovarian, nasopharyngeal carcinoma and patients with malignant Brenner tumour were treated with 75 mg/sqm, breast and pancreatic carcinoma patients were treated with a maximum of 50 mg/sqm, oesophageal and cervical carcinoma patients were treated with 40–60 mg/sqm. All patients were treated for 3 days with three divided doses.

RESULTS

Among 54 patients, 13 patients had head and neck carcinoma, 13 patients had lung carcinoma, 11 patients had stomach carcinoma, 4 patients had cervical carcinoma, 4 patients had periampullary carcinoma, 2 patients had ovarian carcinoma, 2 had oesophageal carcinoma, one patient had breast carcinoma, 2 patients had non-hodgkins lymphoma, one patient had Neuro-ectodermal tumour and one had malignant Brenner tumour (Table 1). Among 13 patients with head and neck carcinoma, 6 patients had carcinoma in oral cavity, 2 patients had carcinoma in oropharynx, one patient had carcinoma of nasopharynx and laryngopharynx each and

3 patients had carcinoma of larynx. Among 54 patients, 22 patients were in stage III, accounting to about maximum of 40.74%. 21 patients in stage IV, accounting to about 38.8%, 9 patients in stage II, resulting for 16.6% and 2 patients in stage I, resulting for 3.7%. Pathologically, 17 patients had grade II, 12 patients had grade III and 11 patients had grade I tumours. Histopathologically, 30 patients with lung, oesophagus, stomach and pancreas tumours were adenocarcinoma, 19 patients were squamous cell carcinoma and invasive ductal carcinoma noted in patient with breast carcinoma. Adenocarcinoma accounts for maximum, about 55.5%, Squamous cell carcinoma, about 35.18%, invasive ductal carcinoma about 1.85% and around 7.4% accounting for other tumours.

Table 1: Incidence of various types of cancer in the study.

Sl. No.	Types of cancer	No. of patients	%
1.	Head and neck carcinoma	13	24.07
2.	Lung carcinoma	13	24.07
3.	Stomach carcinoma	11	20.37
4.	Ovarian carcinoma	2	3.70
5.	Oesophageal carcinoma	2	3.70
6.	Carcinoma breast	1	1.85
7.	Non hodgkins lymphoma	2	3.70
8.	Neuro-ectodermal tumour	1	1.85
9.	Malignant Brenner tumour	1	1.85
10.	Carcinoma cervix	4	7.40
11.	Pancreatic carcinoma	4	7.40
	Total	54	

Among 67 registered patients, 6 patients were defaulters for further treatment and 7 patients died during the course of treatment. Among 54 patients under study, 20 patients had normal hearing at the initiation of treatment and 34 patients had mild pre-existing hearing loss at the initiation of treatment. Among 20 patients with normal hearing, 2 patients developed sensorineural hearing loss at the end of treatment and during the follow-up period, accounting for 5%. Among 34 patients with pre-existing hearing loss, 4 patients had worsened hearing after treatment. Among 37% of the patients with normal hearing, 10% of the patients developed sensorineural hearing loss after treatment, accounting for 8.82%. Among 63% of the patients with prior mild sensorineural hearing loss, 11.8% developed worsening of hearing after completion of treatment.

DISCUSSION

Numerous antineoplastic medications are known to be potentially ototoxic. Cisplatin has been the most thoroughly studied of the chemotherapeutic agents and is commonly included in multiple drug treatment protocol. The mechanism of cochlear injury in cisplatin chemotherapy is by generation of reactive oxygen species

in all three subregions of organ of corti: stria vascularis, spiral ligament and spiral ganglionic cells. This reactive oxygen species overload leads to the depletion of cochlear anti-oxidant enzyme system (e.g. superoxide dismutase– SOD, catalase– CAT, glutathione peroxidase– GSH-Px and glutathione reductase– GSH-R, that scavenge and neutralize the superoxides generated. Thus increase in reactive oxygen species (ROS) generation leads to increase in proinflammatory cytokines- leading to inflammation, superoxide formation- eventually forming peroxynitryls and 4-hydroxynoenol (4HNE) and activation and cleavage of pro-apoptotic enzymes such as caspases.³

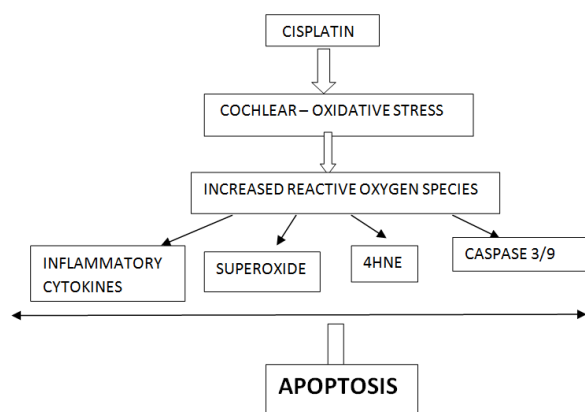


Figure 1: Mechanism of cisplatin.

The reported hearing loss with cisplatin therapy ranges from as high as 91% to as low as 9%.⁴ The potential for ototoxicity increases with bolus administration and may be reduced by low infusion a long time period. Dose limitation of cisplatin is usually based on renal impairment. Cumulative dose exceeding 400 mg, concomitant use with other ototoxic medications, previous sensorineural hearing loss and renal dysfunction appear to be predisposing factors increasing the possibility of hearing loss.⁵ Young patients tend to be more susceptible to audiological changes associated with cisplatin.⁶

Common symptoms associated with cisplatin ototoxicity include hearing loss (usually symmetrical but not always), tinnitus (ranging from transient to permanent), loudness recruitment and otalgia. Occasionally vestibular symptoms are also reported. Hearing loss initially occurs in high frequencies and may then progress to low frequencies, thus affecting intelligibility. Hearing loss may begin shortly after initiation of cisplatin therapy, or initially appear several days after treatment. Tange et al reported that 8 of the 23 cisplatin treated patients, demonstrated significant auditory changes above 8000 Hz. Inclusion of high frequency audiometry in monitoring these patients is advisable.⁷

Aguilar-Markulis et al encountered two patients with severe ontological changes. Follow-up testing 2 years

later, total recovery for one patient, but continued deterioration for another patient.⁸ Fausti et al reported on one patient whose audiogram indicated further deterioration of hearing across the frequency range during follow-up test 5 weeks post-treatment.⁹ Shulman et al recommended to assess the cochlear and vestibular function before, during and at the completion of parental drug treatment whenever possible.¹⁰ Sweetow et al in their study demonstrated the changes in auditory function following completion of chemotherapy. Schell et al prospectively tested a large group of patients who received either cisplatin, cranial irradiation or both. They reported that there was significantly greater potentiation of ototoxicity, when both therapies done together, but hearing acuity was either not affected or minimally affected for irradiation only group.¹¹

Few studies have found the relationship between free circulating cisplatin in plasma with time. They found that cisplatin infusion during afternoon and evening results in low plasma levels of free cisplatin, and hence fewer side effects including ototoxicity. Measurement of correlation between time and plasma concentration is beyond the scope of this study.

The risk of permanent hearing damage from platinum chemotherapy drugs has stimulated the development of otoprotectants for co-administration to reduce the hearing damage without affecting the anti-tumour activity. There are numerous otoprotectant agents under research, includes aspirin, antioxidants, intratympanic dexamethasone, hyperbaric oxygen, ginko biloba extract, diethyldithio carbamate, lipoic acid, vitamin E and sodium thiosulphate.¹²

CONCLUSION

Among 37% of the patients with normal hearing, 10% of the patients developed sensorineural hearing loss after treatment. Among 63% of the patients with prior mild sensorineural hearing loss, 11.8% developed worsening of hearing after completion of treatment. Hence, audiologic monitoring is important in patients undergoing cisplatin chemotherapy and post- chemotherapy auditory monitoring is essential to rehabilitate the patients with Sensorineural hearing loss. Auditory rehabilitation with hearing aid, ensures the patient to lead a meaningful and improves the quality of life.

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