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Research Article

Incidence of Cisplatin Induced Ototoxicity in Adults with Head and Neck Cancer

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Objective. To elucidate the incidence of cisplatin induced ototoxicity in adult patients, with a focus on an adult population. *Study Design*. IRB approved retrospective study. *Methods*. The charts of patients who underwent cisplatin therapy from 1995 to present were reviewed. Inclusion criteria were (1) cisplatin as the primary chemotherapeutic agent and (2) hearing evaluation performed prior to and after treatment. Audiometric thresholds were measured by presenting pure-tone stimuli at 0.25 to 10.0 kHz. Criteria for hearing loss were based on the Chang criteria. Cochlear radiation doses were also calculated in patients with primary tumors in their head and neck or brain. *Results*. There were 1565 patients that had undergone therapy with cisplatin from 1995 to 2014, which 30 met inclusion criteria. Eight were patients treated for head and neck or brain cancer. Evaluation with ANOVA testing identified statistically significant decline in audiometric scores for WRS and pure tone frequencies 500, 2000, 4000, 6000, and 8000 Hz in the right ear. Overall, hearing loss was noted with 63% incidence and in patients who received radiation to their cochlea and cisplatin. *Conclusion*. The incidence of cisplatin induced ototoxicity was significant and even more prevalent in those patients receiving both cisplatin and radiation to their cochlea.

1. Introduction

Cisplatin based treatment regimens have long been the gold standard in the treatment of various soft tissue neoplasms, specifically ovarian, testicular, cervical, non-small cell lung, bladder, and head and neck. Although several mechanisms have been proposed, it has generally been believed to work through depletion of the tumors' endogenous antioxidant system and activate its own apoptosis [1]. Despite the many beneficial features of cisplatin, serious side effects are nephrotoxicity, neurotoxicity, and ototoxicity. In regard to ototoxicity, it is believed that cisplatin selectively damages the outer hair cells within the organ of Corti, spiral ganglion cells and cells within the stria vascularis [2, 3]. Ototoxicity can occur anytime from hours to days after treatment. The loss is considered permanent and dose related and cumulative and affects the higher frequencies [4]. The hearing loss can progress for up to 2 years in 15–20% of patients [5].

Recent studies have suggested the importance of measuring pretreatment hearing thresholds in predicting the outcome following therapy with cisplatin. Brock et al. designed one of the first classification schemes, created to classify pediatric patients into subgroups of hearing loss after receiving cisplatin [6]. This was further modified to yield the Chang classification, which was more sensitive at detecting hearing loss than its predecessor [7, 8]. Johnson et al. subsequently showed that the Chang classification scheme was a useful tool in adults to show how pretreatment hearing thresholds may predict response to cisplatin treatment [9].

Despite all of these advancements in prediction methods and classification schemes, there has been little documentation on the frequency of hearing loss in adults undergoing cisplatin therapy. To our knowledge, there has been no reported incidence of cisplatin based hearing loss in the head and neck cancer population. Within the pediatric population, there has been report of as much as 30% clinically significant

Table 1: Patient demographics.

Age	17–81 (average 59.2) years
Sex	Male 14 (47%)
	Female 16 (53%)
Tumor location	Lung 13 (44%)
	Head/neck & brain 8 (27%)
	Kidney/bladder 5 (16%)
	Uterus/ovarian 3 (10%)
	Unknown 1 (3%)
Cisplatin cumulative dose	55–260 mg/m^2 (average: 148 mg/m^2)
Comorbidities	Hypertension 12 (40%)
	Diabetes 3 (10%)

hearing loss [10]. In head and neck cancer, chemotherapy is also combined with radiation for advanced tumors which may work synergistically with cisplatin to increase the risk of hearing loss. There have been reports that cochlear radiation doses greater than 45 Gy may cause hearing loss [11, 12]. Therefore, the goals of our study were to determine a relative incidence rate of cisplatin induced ototoxicity in the adult population and to specifically examine rates in head and neck cancer patients. It is our hope that this data will help otolaryngologists, oncologists, and radiation-oncologists realize the importance of pre- and post-cisplatin therapy audiologic testing.

2. Patients and Methods

Approval was obtained from our hospital institutional review board for a retrospective chart review. A total of 1565 medical records from 1995 to 2014 were reviewed for all patients who have received cisplatin. Inclusion criteria were (1) that cisplatin was used as the primary chemotherapeutic agent and (2) that hearing evaluation must have been performed prior to and after cisplatin treatment The most common reason for exclusion was lack of either pretreatment or posttreatment hearing evaluation. Based on these criteria, 30 subjects were included in the study (Table 1).

Baseline hearing thresholds were assessed prior to the start of cisplatin. Audiometric hearing thresholds were measured by presenting pure-tone stimuli at 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, and 10.0 kHz. The criteria for classification of hearing loss were based on the results from audiograms. Severity of hearing loss was graded according to the Chang criteria, that is, designated and validated specifically for cisplatin induced hearing loss (Table 2).

In those patients with tumor locations in the head/neck and brain, who received radiation in addition to cisplatin, their cochlear radiation doses were examined.

3. Results

Over a nineteen-year span from 1995 to 2014, 1565 patients underwent chemotherapy with cisplatin. Two hundred and three patients underwent audiometric testing before *or* after therapy. Only 30 of those patients had appropriate pre- and posttherapy hearing tests to be included in this study. Eight of the 30 patients were treated for head and neck or brain cancer. Twelve patients were treated for lung cancer, seven were treated for bladder/uterus or pelvic cancer, one was treated for ovarian cancer, and 2 were treated for unknown primaries. Table 1 demonstrates the breakdown of cancer type

Table 2: Chang classification of cisplatin induced hearing loss [7].

Grade	Sensorineural hearing threshold (db HL)
0	≤20 dB at 1, 2, and 4 kHz
1a	≥40 dB at any frequency 6–12 kHz
1b	>20 and >40 dB at 4 kHz
2a	≥40 dB at 4 kHz and above
2b	>20 and <40 dB at any frequency below 4 kHz
3	≥40 dB at 2 or 3 kHz and above
4	≥40 dB at 1 kHz and above

Table 3: Pretreatment versus posttreatment hearing examination using the Chang criteria. Worsening posttreatment hearing is written in bold.

Pretreatment (right/left)	Posttreatment (right/left)
2a/2b	2b/2b
1a/2b	1a/2b
3/3	3/3
0/4	**1a**/4
4/4	4/4
2b/1a	**4**/1a
2b/2b	2b/2b
0/0	0/0
0/0	**1b**/0
0/0	0/0
4/4	4/4
3/4	3/4
2b/2b	**3/3**
2b/2a	2b/**2b**
3/3	**4**/3
4/2b	4/**3**
2a/2a	2a/**2b**
0/0	**1a/1a**
0/1a	**1b/1b**
0/4	**1b**/4
2b/2b	**3/4**
2b/2b	2b/2b
4/4	4/4
1b/2b	**3**/2b
2b/2a	2b/**2b**
1a/1a	**2b/2b**
2b/3	2b/**4**
4/2b	4/**4**
4/4	4/4
2a/1b	2a/**2b**

Table 4: Cochlear radiation doses and associated hearing examination classified with the Chang criteria.

Cochlear max dose (Gy), left	Cochlear mean dose (Gy), left	Left pretreatment/posttreatment Chang classification	Cochlear max dose (Gy), right	Cochlear mean dose (Gy), right	Right pretreatment/posttreatment Chang classification
53.9	42.2	4/4	48.6	39.5	0/1a
6.3	2.9	1a/1a	14.1	9	2b/4
3.2	2.2	4/4	3	2.1	3/3
2.7	2.4	2a/2b	3.3	2.8	2b/2b
65.3	47.6	4/4	64.8	46.8	0/1a
30	30	2b/4	30	30	2b/3

Table 5: ANOVA analysis of changes in posttreatment hearing evaluation; highlighted values represent statistical significant worsening values.

Variable	Ear	p value
SRT	R	0.125
	L	0.395
WRS	R	**0.004**
	L	0.755
250 Hz	R	0.606
	L	0.176
500 Hz	R	**0.049**
	L	0.465
1000 Hz	R	0.165
	L	0.294
2000 Hz	R	**0.013**
	L	0.614
4000 Hz	R	**0.002**
	L	0.202
6000 Hz	R	**0.001**
	L	0.191
8000 Hz	R	**0.001**
	L	0.426

and highlights other patient factors in treatment. Nineteen out of the thirty patients (63%) had some hearing loss in either one or both ears based on the Chang criteria (Table 3). The mean cisplatin dose for each of the 30 patients was 55–260 mg/m^2 (average: 148 mg/m^2). The average cisplatin dose in the eight head/neck/brain patients was 113.3 mg/m^2 (range 50–190 mg/m^2). Of the eight patients with tumors located in the head/neck and brain, six received radiation in addition to cisplatin. The amount of radiation (max and mean) given to the cochlea is highlighted in Table 4. Based on the Change criteria, there was hearing loss in 5/6 (83.3%) of the head/neck and brain patients who received both cisplatin and radiation to their cochlea.

An analysis of variance (ANOVA) was used for the repeated measures. Each analysis had a factor for pre- and posttreatment for each ear (Table 5). Using a significance factor of 0.05, there was a significant decline in audiometric scores for WRS and pure-tone frequencies 500, 2000, 4000, 6000, and 8000 Hz in the right ear. The hearing at 250 Hz and the change in SRT were decreased after treatment but did not reach significance.

Multiple other factors were compared in the pre- and posttreatment analysis. Five out of 30 patients admitted to having vertigo symptoms prior to treatment while 6 additional patients developed vertigo during therapy. One patient's vertigo resolved during treatment. Half of the patients complained of tinnitus prior to therapy, while 5 patients developed tinnitus during therapy. One patient's tinnitus improved during the duration of therapy.

4. Discussion

This study demonstrates that there was 63% incidence of hearing loss after cisplatin therapy in adults. Furthermore, it demonstrates 62.5% incidence of hearing loss in patients with head and neck cancer that had concomitant radiation therapy. This result is similar to what Chen et al. found in 2006 when they showed that a cochlear radiation dose greater than 48 Gy was noted to have significantly increased risk of ototoxicity [13]. The difference seen in the current paper is that only two out of the eight of the patients had a cochlear radiation dose greater than 48 Gy and both of them had post-cisplatin treatment hearing loss. The value of this current study was highlighting the inadequate audiologic testing prior to and after cisplatin therapy. Thirty patients out of 1565 (1.9%) had appropriate testing with both pre- and post-audiologic testing.

Cisplatin therapy is known to cause hearing loss due to a variety of factors. The charged platinum molecule is highly reactive and integrates into nucleophilic groups (G-C rich) in DNA. This causes intrastrand and interstrand DNA cross-links that result in apoptosis and cell-growth inhibition. It is thought to target the organ of Corti, especially the outer hair cells, the type 1 spiral ganglion cells causing detachment of the myelin sheaths as well as the stria vascularis causing cell rupture in that area. Cisplatin also binds to sulhydryl groups and depletes copper, selenium, glutathione, and NADPH, increasing reactive oxygen species and oxidative stress [14].

Patients with head and neck cancer are at an increased risk for ototoxicity for many factors including concomitant cochlear radiation, disruption of vascular flow, and increased cisplatin doses. Head and neck patients need to have proper pretreatment and peritreatment audiologic testing to monitor for hearing loss. If patients demonstrate evidence of hearing

loss, then their treatment can be modified or terminated. Our institution had dismal 1.9% of patients that had adequate pre- and posttreatment audiologic testing. During the study, our institution realized this inadequacy and initiated a protocol for all patients undergoing cisplatin therapy. This included high frequency audiograms up to 12 kHz and DPOAEs on all patients prior to cisplatin therapy, directly after treatment and at six months after treatment.

5. Conclusion

In patients receiving platinum base chemotherapy and/or radiation to the cochlea, hearing loss remains a common side effect of the treatment. Although it has been found with high incidence, many institutions (including the present authors' one) have lacked ototoxicity protocol for these patients. New large scale studies must be conducted to evaluate for true incidence of hearing loss, in order to get to a point of earlier identification and prevention of this outcome.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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