RESEARCH ARTICLE

Analysis of Cisplatin-Induced Ototoxicity Risk Factors in Iranian Patients with Solid Tumors: a Cohort, Prospective and Single Institute Study

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Abstract

Background: Cisplatin has been associated with irreversible hearing damage. Up to now, there is no therapeutic intervention showing benefit in preventing Cisplatin-induced ototoxicity. The aim of this study was to determine risk factors contributing to hearing impairment after cisplatin administration in Iranian patients. **Methods:** Hearing thresholds of 124 patients before and after cisplatin administration were assessed with reference to pure-tone audiometry averages at several frequencies from 2006 to 2010. Mean values were calculated at each tested frequency in each ear at baseline and subsequent follow-up audiometry. Hearing impairment was assessed with the Münster score. **Results:** The mean age at diagnosis and the median cumulative Cisplatin dose were 47.3 years and 453.8 milligrams, respectively. Bilateral hearing loss, mostly of grade 1, and tinnitus were detected in 26% and 3.2% of patients. Logistic regression analysis showed that a high cumulative dose of cisplatin was the most important risk factor for developing hearing damage (P=0.034). The most significant changes in the status of the auditory system and the most severe threshold shift from base line (35 dB) were observed at a frequency of 8 kHz. Also, patients who received higher individual doses of Cisplatin showed significantly more tinnitus (P=0.002). **Conclusions:** The results are testament to benefits of routine audiometric monitoring program during cisplatin-based chemotherapy. Further research should be performed to understand other risk factors, such as genetic predictors of Cisplatin-induced ototoxicity.

Keywords: Cisplatin- hearing loss- risk factors- cancer

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Introduction

Cisplatin (cis-diamminedichloroplatinum) is the mainstay of systemic chemotherapy in many solid tumors. Serious dose-limiting adverse events such as nephrotoxicity, ototoxicity, myelosuppression and neurotoxicity have been evident during Cisplatin-based chemotherapy (Rybak et al., 2009). Some of them are manageable but in medical practice, no therapeutic intervention has been showed benefit to prevent ototoxicity and neurotoxicity.

Cisplatin is the most ototoxic drug in both adults and pediatrics (Rademaker-Lakhai et al.,2006). The exact mechanisms of Cisplatin-induced ototoxicity are not clearly evident but it seems reactive oxygen species (ROS) such as superoxide anion and genetic polymorphisms have a crucial role (Rybak et al., 2009; Cho et al.,2014; Mukherjea et al., 2011; Talach et al.,2016). Symptoms of Cisplatin-induced ototoxicity are subjective hearing loss, ear pain, and tinnitus that these symptoms are usually bilateral and irreversible (Reddel et al., 1982).

It believes that Cisplatin-induced hearing loss to be more sever in relation to higher cumulative dose, younger or older ages, history of noise exposure (Chirtes et al., 2014), cranial irradiation (Warrier et al., 2012), other ototoxic drugs administration, nutritional and metabolic status (Chirtes et al., 2014). Hearing loss following Cisplatin-based regimens has different ranges from 11% to 97% in different studies (Marshak et al., 2014).

The other main adverse effects of Cisplatin administration is tinnitus (Reddel et al., 1982). Tinnitus is an abnormal processing of signals generated in the auditory nervous and is probably caused by Cisplatin-induced degeneration of the hair cells of the cochlea (von Boetticher, 2011).

Cisplatin–based regimens carry with them an increased risk for acute and chronic sequel on hearing ability which may have a negative impact on patient's quality of life.

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Susceptible patients' identification before Cisplatin administration is not possible. Thus, early detection of Cisplatin- hearing loss by high-frequency audiometry is very necessary to prevent disability. Adequate knowledge of medical oncologists about ototoxicity complications may facilitate the early detection of hearing impairment as well as further damages prevention.

The study reported here aimed to assess contributed risk factors in developing Cisplatin-induced hearing impairment in consecutive Iranian adult patients.

Materials and Methods

This cohort, prospective, longitudinal, population-based, single institute and observational study with 124 patients was conducted in the National Institute of Tuberculosis and Lung Disease (NRITLD), from July 22, 2006 to March 20, 2010. Informed written consent was obtained prior to participating patients in the study according to Shahid Beheshti Medical University's ethics and scientific committees and was conducted in compliance with the Helsinki Declaration. Also, the local hospital ethics committee approved the study.

Eligibility Criteria

All patients who scheduled for Cisplatin-based chemotherapy regimens were eligible if aged ≥ 18 years old, had a performance status (PS) of 0 to 2 (WHO Eastern Cooperative Oncology Group)(Oken et al., 1982) and serum creatinine less than or equal to 1.5 mg/dl. Patients were excluded if they had symptomatic brain metastases, preexisting abnormal hearing loss, history of noise exposure, ototoxicity National Cancer Institute Common Toxicity Criteria (CTCAE, version 4.0, 2010) grade more than 1 at treatment initiation, Previous head and neck irradiation and Simultaneous use of other ototoxic drugs. For all included patients physical examination, hearing assessment (pure tone audiometry and tuning fork tests), blood tests and urine analysis were performed.

Treatment plans

For all eligible patients regarding to their diagnosis, appropriate treatments according to oncology guidelines were done. At all schedules Cisplatin was administered as a 3-hour intravenous infusion with pre-and post-hydration (consisted of Potassium chloride 20 meq in 1,000 ml 0.9% sodium chloride over 2-3 hours before treatment and 500 ml of 0.9% sodium chloride over 2 hours after Cisplatin administration). Furosemide was not used routinely unless patient had signs/symptoms of fluid overload.

Chemotherapy regimens administrated in study with number and percent were as follow

-Docetaxel plus Cisplatin (both: 75 milligrams per square meter [mg/m^2]) every 3 weeks: n=57 (45.9%).

-ESHAP protocol (including Etoposide 40mg/m2 plus Methylprednisolone 500mg/m^2 plus Cisplatin 25mg/m^2 for 4 days and Cytarabine 2000mg/m^2 in day 5) every 3 weeks: n=8(6.4%).

-BEP protocol(including Bleomycin 30 mg/m^2 in days 1,8 and 15 with Etoposide 100mg/m^2 plus Cisplatin 20mg/m$_2$ for 5 days) every 3 weeks: n=10(8.1%).

-EP regimen (including Etoposide 100mg/m^2 for 3 days plus Cisplatin 75mg/m^2, one day) every 3 weeks: n=19(15.3%).

-Gemcitabine 1250 mg/m^2 in days 1 and 8 plus Cisplatin 75mg/m^2, one day, every 3 weeks: n=9 (7.2%).

-Vinorelbine 25mg/m^2 in days 1 and 8 plus Cisplatin 75mg/m^2, one day, every 3 weeks: n=6 (4.8%).

-CAP regimen (including Cyclophosphamide 500mg/m^2 plus Adriamycin 50 mg/m^2 plus Cisplatin 50mg/m^2, one day) every 3 weeks: n=8 (6.4%).

-DCF regimen (including Docetaxel 75 mg/m^2 plus Cisplatin 75mg/m^2, one day plus 5-Fleoro Uracil 750 mg/m^2 for 3 days) every 3 weeks: n=5 (4.1%).

-Adriamycin 25mg/m^2 for 3 days plus Cisplatin 75mg/m^2, one day, every 3 weeks: n=2 (1.6%).

Audiometric Monitoring

The main parameter to assess ototoxicity was the audiogram. Basic audiometric evaluations for both ears were conducted within 1 week before Cisplatin infusion and were repeated before 3rd, 5th Cisplatin cycles and within one month post completion of all planned cycles. The study only included patients in whom pre- and at least one post-therapy audiograms were available. Audiometric evaluations were performed by a Diagnostic Audiometer AD22qe (Denmark) installed in a sound-proof room in audiometry department. The frequency spectrum of hearing loss was recorded for each case. The pure-tone averages (PTAs) thresholds in decibels (dB) hearing level were obtained through air conduction at frequencies 0, 1, 2, 4 and 8 kHz. These averages are clinically relevant because they are related to the understanding of speech and perception of music (Rademaker-Lakhai et al.,2006).

Hearing impairment was evaluated by Münster score (Schmidt et al., 2007) as below: Grade 1 (beginning hearing loss) encompasses > 10 dB up to 20 dB in at least one frequency or tinnitus. Grade 2 (moderate impairment) describes hearing loss > or = 4 kHz and differentiates 2a (> 20 to 40 dB), 2b (> 40 to 60 dB) and 2c (> 60 dB). Hearing loss < 4 kHz > 20 dB in grade 3 (severe impairment, hearing aids needed) is further classified according to grade 2 in a, b and c. Grade 4 (loss of function) finally describes average hearing loss <4 kHz of at least 80 dB. Patients that developed hearing loss more than 120dB from the baseline hearing thresholds were excluded.

Statistics

The primary end point was to assess hearing impairment after Cisplatin administration. The baseline and the post-treatment audiograms of 124 eligible patients (248 ears) were studied.

For testing the differences in categorical and continuous variables between two groups (with or without hearing loss), the chi-square test (or Fisher's exact test when appropriate) and Student's t-test were used, respectively. Non-parametric Mann-Whitney test was used to compare the difference between quantitative parameters of the 4 repeated measurements (eg, pre- and post-treatment audiogram measurements for the frequencies 0, 1, 2, 4 and

8 kHz) in each group, individually. Repeated Measures tested for significancy by ANOVA test using primary value of each thresholds. The dependent variable was the difference between hearing threshold (in dB) from the baseline audiogram and the post-treatment audiogram. Binary logistic regression was used to model hearing impairment following Cisplatin administration, estimate odd's ratios and their 95%confidence intervals (CIs) in respect to cumulative dose of Cisplatin (mg/m2 and is defined as total dose of Cisplatin that each patient received during his/her treatment), sex, PS, age, individual dose (mg/m2 of Cisplatin and defined as dose of Cisplatin in each cycle of chemotherapy) and cancer type. The analysis was the "intent to treat" and includes all eligible patients regardless of subsequent withdrawal from study or incomplete audiologic data for some patients.

All tests of hypotheses were descriptive and with assuming a 5% significance level and 80% power, 124 patients were entered to current study.

Analysis was performed using SPSS Inc version 16.0. All tests were two-sided and P values of less than 0.05 were considered significant.

Results

In 15 patients the audiogram at treatment initiation compared with two audiograms (after 3rd and 5th cessations of therapy). One audiogram at treatment initiation and only one audiogram after therapy were available in 9 patients. Overall, in 100 cases all audiograms were available. For all cases, there was a minimal difference between the threshold levels in the right and left ears; therefore, an average of the 2 ears was calculated. The mean age of patients was 47.32 years (media: 50 years,range 18-78, standard deviation: 13.54). Eighty patients were male and 44 patients were female. Most prevalent cancer was Lung cancer (63%). The median cumulative dose of Cisplatin was 453.79 mg (median:400 mg,range: 100-1450 mg, standard deviation: 277.79).

During follow up 4 patients (3.2%) complained of tinnitus. Importance of each patient's characteristics in relation to hearing loss is summarized in Table 1. Patients who received more than 300 mg Cisplatin during chemotherapy were more likely to develop significant

Table 1. Patients' Characteristics

Characteristics	Hearing loss (with any grades) as Münster score)		P-value	Tinnitus		P-value
	Yes n (%)	No n (%)		Yes n (%)	No n (%)	
Age						
<50	14 (20.5)	54 (79.5)	0.143	3 (4.4)	65 (95.6)	0.41
>51	18 (32.1)	38 (67.9)		1 (1.4)	55 (98.6)	
Gender						
Female	8 (18.1)	36 (81.9)	0.15	2 (4.5)	42 (95.5)	0.537
Male	24 (30)	56 (70)		2 (2.5)	78 (97.5)	
Individual dose of Cisplatin						
35 mg/m^2/cycle	1 (12.5)	7 (87.5)		1 (14.2)	6 (85.8)	
50 mg/m^2/cycle	2 (40)	3 (60)		0	5 (100)	
75 mg/m^2/cycle	26 (27)	70 (73)	0.657	2 (2)	95 (98)	0.002*
100 mg/m^2/cycle	3 (20)	12 (80)		1 (6.5)	14 (93.5)	
Cumulative dose of Cisplatin						
<300 mg	2 (7.5)	25 (92.5)		0	27 (21.7)	
≥300 mg	30 (31)	67 (69)	0.013*	4 (4.1)	93 (95.9)	0.283
Performance status[a]						
0	5 (17.8)	23 (82.2)		2 (7.1)	26 (92.9)	
1	14 (24.1)	44 (75.9)	0.3	1 (1.7)	57 (98.3)	0.399
2	13 (34.2)	25 (65.8)		1 (2.6)	37 (97.4)	
Cancer Type						
Lung cancer	24 (31)	54 (69)		2 (2.5)	76 (96.5)	
Lymphoma[b]	3 (25)	9 (75)		2 (1.5)	10 (98.5)	
Ovarian Cancer	0	2 (100)		0	2 (100)	
Mesothelioma	2 (28.5)	5 (70.5)		0	7 (100)	
Thymoma	1 (16.5)	5 (83.5)	0.468	0	6 (100)	0.163
Sarcoma	1 (50)	1 (50)		0	2 (100)	
Germ cell tumor	1 (10)	9 (90)		0	10 (100)	
GI malignancy[c]	0	7 (100)		0	7 (100)	

a, Performance status was considered as Eastern Cooperative Oncology Group; b, both Hodgkin and non-Hodgkin lymphoma; c, including esophageal and gastric cancer; *P value was significant

Table 2. Mean of Hearing Thresholds in Each Frequency in Baseline and During Treatment

	Hearing loss					
	No		Yes			
	Mean(in dB[a])	Standard Deviation	Mean(in dB)	Standard Deviation	P-value[b]	P-value[c]
Primary mean of hearing threshold at 0KHz	10.16	10.55	13.75	14.43	0.162	
Mean of hearing threshold at 0KHz after 3rd cessation of therapy	10.22	10.68	14.06	13.93	0.177	0.92
Mean of hearing threshold at 0KHz after 5th cessation of therapy	10.23	10.69	13.85	13.95	0.145	
Mean of hearing threshold at 0KHz after 1 month of therapy termination	9.64	10.7	13.67	14.2	0.138	
Primary mean of hearing threshold at 1KHz	9.51	11.29	7.5	7.3	0.741	0.001*
Mean of hearing threshold at 1KHz after 3rd cessation of therapy	9.45	11.34	10	8.37	0.428	
Mean of hearing threshold at 1KHz after 5th cessation of therapy	9.59	11.02	10	8.21	0.365	
Mean of hearing threshold at 1KHz after 1 month of therapy termination	8.8	10.52	11	7.61	0.124	
Primary mean of hearing threshold at 2KHz	11.9	11.76	11.25	11.76	0.986	0.033*
Mean of hearing threshold at 2KHz after 3rd cessation of therapy	12.03	12.36	13.13	14.13	0.606	
Mean of hearing threshold at 2KHz after 5th cessation of therapy	11.85	12.85	13.25	14.36	0.587	0.001*
Mean of hearing threshold at 2KHz after 1 month of therapy termination	11.87	13.31	13.67	14.45	0.386	
Primary mean of hearing threshold at 4KHz	18.53	17.22	28.44	23.22	0.081	
Mean of hearing threshold at 4KHz after 3rd cessation of therapy	19.51	17.95	36.25	27.84	0.012*	
Mean of hearing threshold at 4KHz after 5th cessation of therapy	19.58	18.32	32	29.21	0.065	
Mean of hearing threshold at 4KHz after 1 month of therapy termination	20	18.36	34	29.53	0.078	<0.001*
Primary mean of hearing threshold at 8KHz	21.25	19.69	35.31	28.13	0.053	
Mean of hearing threshold at 8KHz after 3rd cessation of therapy	21.59	20.57	45.63	29.55	0.002*	
Mean of hearing threshold at 8KHz after 5th cessation of therapy	21.65	20.74	45.36	31	0.002*	
Mean of hearing threshold at 8KHz after 1 month of therapy termination	21.98	20.53	46.00	30.19	0.002*	

A, dB, decibels; b, Mann-Whitney test; c, Repeated Measures ANOVA using Primary value of each thresholds as a covariate in the model; *Significant P value

hearing loss (P=0.013). Also, Tinnitus was significantly associated with Cisplatin dose more than 75 mg/m2/cycle (P=0.002).

Hearing impairment was identified in 32 (25.8%) cases (24 male and 8 female). In all cases hearing impairment was bilateral. Significant hearing impairment and hearing threshold shift in different frequencies were as follows:

Grade 1: 2(9%) patients at 0 KHz, 4 (18%) patients at 1 KHz, 7 (33%) patients at 2 KHz, 3 (13.5%) patients at 4 KHz and 6 (27%) patients at 8 KHz. Grade 2a: all of 8 patients at 8 KHz. Grade 3a: only one patient in 1 KHz. Grade 4: only one patient in 8 KHz. Most hearing loss occurred in 8 KHz. Mean of hearing thresholds in each frequency in baseline, during treatment and post treatment in patients with and without hearing impairment were showed in Table 2. By ANOVA test, it was observed that the shift was significant at 1, 2, 4 and 8 KHz but not in 0 kHz (P = 0.001, P =0.033, P = 0.001, P <0 .001, and 0.920 respectively, Table 2). Also, significant changes in hearings thresholds were seen at 4 and 8 KHz after Cisplatin administration by Mann-Whitney test (Table 2). At the lower frequency combination (0, 1, and 2 kHz), an average post-treatment threshold shift of 7.6 dB from base line was observed. For the other frequencies (4 and 8 KHz) a mean threshold shift of 7.2 and 14.6 dB was observed respectively. The most severe threshold shift from base line was 35 dB and observed at 8 KHz.

Linear regression was not preformed regarding to

Table 3. Results of Logistic Regression Analysis in Relation to Hearing Loss

Risk factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CIa for the odds ratio	P-value	Odds ratio	95% CIa for the odds ratio	P-value
Age group (<50 versus ≥ 50)	0.981	0.391-2.460	0.968	2.162	0.723-6.46	0.168
Gender (male versus female)	1.576	0.569-4.363	0.381	0.62	0.193-1.903	0.423
Performance status[b]		0.350-1.240	0.232			0.292
2 versus 0	0.672			1.856	0.412-8.356	
1 versus 0				2.554	0.790-8.264	
Cumulative Cisplatin dose(<300mg versus above)	7.269	0.933-58.620	0.058	10.796	1.203-96.863	0.034*
Individual dose of Cisplatin	0.6	0.127-2.835	0.519			
<75 mg/m^2/cycle versus ≥75 mg/m^2/cycle				0.512	0.046-5.724	0.587
Cancer Type (Lung cancer vs other types)	3.121	0.987-9.868	0.053	6.244	0.712-54.714	0.098

a, CI, confidence interval; b, Performance status was considered as Eastern Cooperative Oncology Group; *significant P-value in binary logistic regression analysis.

tinnitus due to small portion of patients with this adverse effect. The odds of developing Cisplatin-induced hearing loss were elevated for patients who received more than 300 mg Cisplatin [logistic regression, odds ratio (OR) 10.796; P=0.034] but did not differ significantly according to other factors (Table 3).

Discussion

At best of our knowledge, this is the first study that provides risk factor analysis of Cisplatin-induced ototoxicity in Iranian adult patients. Most of studies in Cisplatin hearing impairment were conducted in western countries and children. We observed an overall incidence of hearing loss of 25.8%. Patients who received higher individual dose of Cisplatin (>75mg/m^2 in each chemotherapy cycle) showed more tinnitus significantly. Most of hearing impairment and significant changes in hearing threshold occurred at 8 KHz PTA. Current result is notable because in presence of hearing impairment at high frequencies, speech understanding and perception of music can be impaired. After Cisplatin administration, most sever threshold shift from base line was seen at 8 KHz. In multivariate regression analysis, cumulative Cisplatin dose was found to be associated with ototoxicity development.

In some studies, age is the determining factor for Cisplatin-induced ototoxicity especially in pediatric and elderly patients (Li et al., 2004; Bakhit et al., 2012) but in our study similar result was not evident.

Yancey et al., (2012) demonstrated that male patients who treated with Cisplatin are more susceptible to develop ototoxicity but in agreement with the other study (Langer et al., 2013), we found no association between gender and the development of significant hearing loss.

Comparison of various study results is difficult because there is no globally consensus definition and agreement for ototoxicity evaluation. Among different grading systems for Cisplatin-induced hearing loss assessment, we chose Münster scoring system because it claimed that this classification can identify patients with a risk of severe impairment early (Beahan et al., 2012).

Prior works reported 11% to 97% hearing loss following Cisplatin-based regimens (Marshak et al., 2009). One explanation for this wide variation of Cisplatin induced ototoxicity may be different ototoxicity classifications and dosage schedules of Cisplatin in different cancer and protocol. On the other hand, different rates and grades of Cisplatin ototoxicity are seen in patients who receive similar therapies which may be related to some genetic and non-genetic risk factors (Dille et al., 2010). We observed an overall incidence of hearing loss of 25.8% which is partially in accordance with other studies (Olgun et al.,2016, Laurell and Jungnelius,1990; Yancey et al., 2012).

Cisplatin Cumulative dosages considered as the most important predictor of Cisplatin-induced ototoxicity in several studies (Frisina et al., 2016; Yancey et al., 2012; Zuur et al., 2007). It is claimed that cochlear hair cells death is impacted by platinum agents (including Cisplatin and Carboplatin) and is associated with dose of these agents (Brock et al., 2012). The cut off for cumulative dosage of Cisplatin varied between 200-400 mg/m^2 (Whitehorn et al., 2014). Our results demonstrated patients were more likely to develop significant hearing impairment when received higher cumulative Cisplatin dose especially above 300 mg/m^2 (both in univaraite and multivariate testing). In addition, in current study most patients whom hearing ability impaired by Cisplatin administration, received high dose of Cisplatin but in few patients ototoxicity was evident even at low doses, which may suggest a genetic predisposition may render certain patients more susceptible to hearing loss followed by Cisplatin administration.

Also, our results have highlighted that high individual doses of Cisplatin contribute to the development of ototoxicity but it was not statistically significant and may suggests that cumulating of platinum agents has a crucial role in Cisplatin ototoxicity.

Higher frequencies (≥4 kHz) are more affected after Cisplatin administration. Albeit later, can progress to involve speech frequencies (<4 kHz) with continued

exposure (Langer et al., 2013). Our result revealed that the severity of the hearing thresholds shift was greater at the higher frequencies which is in accordance with other studies (Langer et al., 2013; Callejo et al., 2015) Therefore, speech and perception of music can be impaired in presence of Cisplatin ototoxicity.

Patients who received ototoxic drugs especially Cisplatin, have a greater risk for tinnitus (Dille et al., 2010). It has been reported that 2% to 36% (Cho et al., 2014) of patients treated with Cisplatin complain of tinnitus. In the present study, tinnitus occurred in 3.2% of cases. The difference between rates of tinnitus in different studies may be related to different dose of Cisplatin used in various malignancies and regimens.

There was no statistically significant difference between different tumor types and hearing impairment in this study. Comparison of tumor types can be valuable if chemotherapy regimens were same and in our study different protocols were used.

Our study had some limitations: treatment cessation may have confounded the relationship between cumulative dose and hearing loss by underestimating the effect of escalating doses. Also, late audiometric data were not available to assess late ototoxic effect of Cisplatin or any improvement in hearing damage. Additionally, since not all patients treating with Cisplatin receive audioligical monitoring in Iran, our findings may under-represent the incidence of Cisplatin–induced hearing loss in Iranian population.

In this cohort, cumulative Cisplatin dose was found to be important risk factor for developing ototoxicity. Thus, audiological monitoring of patients receiving high-dose Cisplatin chemotherapy is very important for early detection of hearing loss. More ever, Otoprotective drugs during chemotherapy with Cisplatin may be beneficial in Cisplatin-induced ototoxicity. Further research should be focused to elucidate other risk factors, such as genetic predictors and identification of genotypes that are susceptible for ototoxicity as well as clinical use of otoprotectants.

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