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ORIGINAL ARTICLE

Platinum-Induced Ototoxicity in Children and Adolescents with Cancer

Dilek Gunes, Gunay Kirkim, Pinar Demiral, Kamer Mutafoglu Uysal, Bulent Serbetcioglu, Nur Olgun

Dokuz Eylul University Institute of Oncology, Dept. of Pediatric Oncology, Izmir, Turkey. (DG, KU)
Dokuz Eylul University Medical School, Dept. of Otolaryngology, Hearing, Balance and Speech Section, Izmir, Turkey. (GK, BS)
Dokuz Eylul University Medical School, Dept. of Pediatrics, Izmir, Turkey. (PD)

Objective: To evaluate hearing impairment in children with cancer who received platinum compounds.

Materials and Methods: There were 149 children who had received platinum-containing chemotherapy (cisplatin, carboplatin or both), and 62 of them were eligible in terms of medical and audiologic data. These patients were divided into three groups; cisplatin-only group (30 children), carboplatin-only group (15 children) and cisplatin + carboplatin group (17 children).

Results: Sixty-two patients were analyzed. Audiological assessments included pure tone audiometry, transient oto-acoustic emissions and auditory brainstem response testing. Medical records were analyzed for patient characteristics, details of platinum containing treatment, co-administration of other ototoxic drugs as well as head/neck radiotherapy. The median age at treatment was 9.4 years, and M:F ratio was 0.8. Ototoxicity incidence was 56% in cisplatin-only group (n=30), and 47% in cisplatin+carboplatin group (n=17). No patients had ototoxicity in carboplatin-only group (n=15). Majority (84%) of patients having ototoxicity was older than 5 years of age at the initial cancer diagnosis. Of the patients with moderate-severe ototoxicity, 90% was female, and 56% was pubertal/postpubertal girls.

Conclusion: The results of this study is in agreement with previous reports showing that ototoxicity is a potential side effect of cisplatin, but the standard dose of carboplatin-only usually does not cause ototoxicity. In this study, children older than 5 years of age and adolescents were also susceptible to develop platinum-induced ototoxicity. Primary tumor site was a risk factor for ototoxicity in this group of patients. Children with germ cell tumors, particularly the intracranial germ cell tumors tended to develop ototoxicity more frequently. Collaboration of pediatric oncology and audiology departments is mandatory in order to monitor platinum induced ototoxicity to avoid further insult and also to rehabilitate when mutilating toxicity occurs.

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Late effects of anticancer therapy have gained more attention as a result of the significant improvements in survival of childhood cancers. Cisplatin and carboplatin are both effective and widely used chemotherapeutics for the treatment of pediatric solid tumors with a similar spectrum of antitumor activity. Although both agents can cause ototoxicity, cisplatin-induced ototoxicity is more common and more severe than others [1 - 6]. Platinum induced ototoxicity is characterized by bilateral, usually permanent, high frequency sensorineural hearing loss (HFHL) that can progress to the lower frequencies [4 - 8]. Because of the speech and language development occurs in early ages, consequences of ototoxicity are more important especially for younger children at diagnosis [6, 7]. However, the potential platinum ototoxicity can sometimes be underestimated in clinical practice, despite its serious morbidity. In this study, we aimed to evaluate the hearing impairment in children with cancer who were treated with cisplatin and/or carboplatin at University Hospital, Pediatric Oncology Center.

Materials and Methods

There were 575 children with malignant lymphoma and solid tumors treated at our pediatric oncology center between 1988 and 2007. Medical records of these children were evaluated retrospectively regarding the treatment regimens that contained platinum compounds (cisplatin and/or carboplatin).

Corresponding address:
Bulent Serbetcioglu
Dokuz Eylul Tıp Fakültesi KBB ABD, İşitme- Konuşma-Denge Ünitesi, İnciraltı-İzmir 35340, Turkey
E-mail: serbetcioglu@gmail.com

There were 149 (26%) children who received platinum compounds as part of their anticancer treatment.

Medical records of these 149 children were evaluated for the availability of baseline and follow up audiologic assessments. Twenty-seven (18%) patients had baseline audiologic assessments before the first platinum-based treatment; and 34 (23%) patients had follow-up audiological assessments (Figure 1). Eligible 40 patients were invited for follow-up audiologic examination and 32 of them underwent audiological testing (Figure 1). Of the 66 patients who had completed the audiological assessments, four patients younger than 3 years of age were not included in the analysis since no grading could be established for these young patients according to the Brock's hearing loss criteria (Figure 1).

A total of 62 patients who were ≥3 years of age at the follow-up audiologic assessments were included in this study (Figure 1). Medical records of these 62 patients were evaluated for patient characteristics, details of the treatment regarding platinum compounds, other known ototoxic drugs (furosemide, aminoglycoside, bleomycin), head or neck radiotherapy and follow-up audiological assessment results.

Renal function tests (serum BUN, creatinine) were found normal in all patients before each course of platinum based chemotherapy. Standard

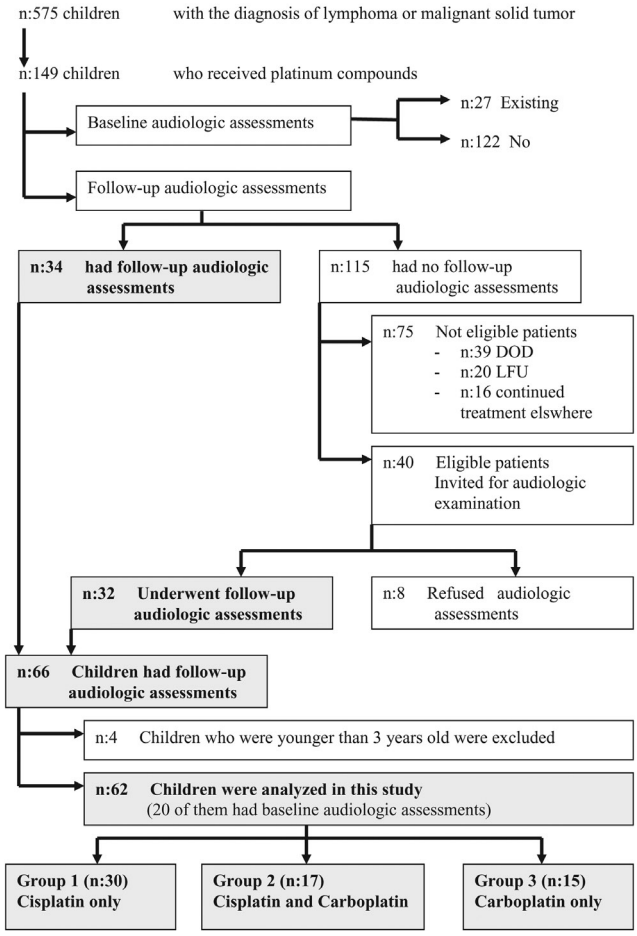

Figure 1. Summary of patients
DOD: Died of disease, LFU: Lost to follow up
* Four children with neuroblastoma were younger than 3 years old, and hearing was normal in free field conditions at frequencies of 250 to 8,000 Hz warble tones, by using COR audiometry technique. Otoscopic examination and acoustic immitance measurements were performed to exclude serous otitis media, which is a common entity in this age group. The results were justficated by ABR TEOAEs. We couldn't make grading according to the Brock's Scale in these four patients. Thus, these four children were excluded.

hyperhydration (3,000 ml/m^2/day) was given to all patients. Patients received 20 - 160 mg/m^2 per course dose of cisplatin by single dose schema or by divided doses schema during 5 days. Cisplatin was administered over one, 4 to 6 hours or 24 hours with mannitol diuresis. Carboplatin was given 300 - 600 mg/m^2 per course dose by single dose schema, over one hour. No regular records were available on furosemide treatment in medical records.

Hearing Assessment

Audiological assessment included otoscopic examination, standard pure tone audiometry (PTA), conditioned orientation reflex (COR) audiometry, speech audiometry (monitored live voice or picture identification technique), acoustic immitance measurements, transient oto-acoustic emissions (TEOAEs) and auditory brainstem response (ABR) testing. All audiologic evaluations were carried out by the same certified audiologist.

The audiometric techniques took into account child's age, medical status, capabilities and cooperation level. All procedures were performed in a sound-proof chamber (Industrial Acoustic Company). Interacoustics AC-40 audiometer with TDH 49 MX 41/AR headphones were used for air conduction measurements, and B-71 vibrator was used for bone conduction measurements. Air-conduction thresholds were obtained in octave frequencies from 250 to 8,000 Hz; whereas bone-conduction thresholds were obtained from 500 to 4,000 Hz. Hearing thresholds were measured using standard pure tone audiometry testing procedure for children over 3 years old.

All PTA results were analyzed, and ototoxicity was scored according to the Brock's ototoxicity criteria with a threshold level of 40 dB at targeted frequencies of 1,000, 2,000, 4,000 and 8,000 Hz [6]. The Brock's grades 3 and 4 hearing loss correlate with hearing loss in the speech frequency range. Post-treatment audiologic results were assigned numeric grades using the classification system of Brock et al [6]. In case of asymmetrical hearing loss, the numeric grade assigned corresponded to audiometric results obtained from the worse ear.

All the follow-up audiologic assessments were performed after cessation of platinum containing chemotherapy.

Statistical Methods

Descriptive statistics were performed for patient characteristics. Relationship between cumulative dose of cisplatin and the Brock's hearing loss grades was analyzed by using correlation analysis with Spearman correlation coefficients. Comparisons of categorical variables were analyzed using chi square analyses including Fisher's exact test. Nonparametric variables were compared among whole groups by the Kruskal-Wallis variance analysis, and between two independent groups by the Mann-Whitney U test. A value of $p < 0.05$ was accepted as statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11.0.

Results

There were 149 (26%) patients who received platinum-based treatment from 1988 to 2007.

Patients with baseline audiologic assessments:

Twenty-seven (18%) children had baseline audiological assessments, and 20 of them also had follow-up audiological assessments.

i) Seven children were younger than 3 years old and their hearing levels were within normal levels in free field condition testing at frequencies of 250 to 8,000 Hz warble tones, by using COR audiometry technique as well as TEOAE and ABR testings.

ii) Remaining 20 patients were older than 3 years and tested using standard PTA and TEOAEs. Three children had conductive hearing loss due to otitis media which resolved spontaneously.

Baseline audiologic assessment could not been done in 122 (82%) patients, and 106 of them were over 3 years old age.

Patients with follow-up audiological assessments:

The follow-up audiological testings were already available in 34 (23%) patients and an additional 32 (21%) patients underwent audiological testings during

this study. Four patients who were younger than 3 years at the follow-up audiological assessments were excluded. There were 62 eligible patients who were ≥ 3 years age at the follow-up audiological assessments.

Of the 62 patients, 30 received cisplatin-only (group 1), 17 received cisplatin and carboplatin (group 2), and 15 received carboplatin-only (group 3). The median age at diagnosis was 9.4 years (ranging from 0 to 19), and male to female ratio was 0.8. There was no significant difference among the groups for age at diagnosis and age at follow-up audiologic testings. There was a female predominance (70%) in cisplatin receiving group. Clinical characteristics of patients, details of anticancer treatment including platinum compound, dose, schedule, and also additional treatment with other ototoxic drugs and/or head-neck radiotherapy are shown in Table 1. The median age at control audiological assessments was 13.5 years (ranging from 3 to 26). The median time between the last platinum dose and the follow up audiological examination was one year (1 month - 17 years).

Baseline audiological assessment was available in 20

Table 1. Characteristics of patients

	Group 1 (n: 30)	**Group 2 (n: 17)**	**Group 3 (n: 15)**
Male / Female	9 / 21 =0.43	10 / 7 = 1.43	9 / 6 = 1.5
Median age at cancer diagnosis (range)	11 y (0 – 19)	11 y (1.5 –18)	4 y (5 mos–17 y)
Age at diagnosis, n (%)			
< 5 years old	9 (30)	5 (29)	8 (53)
≥ 5 years old	21 (70)	12 (71)	7 (47)
Diagnosis (n)	n	n	n
GCTs (n:11)	9*	1	1
SNS tumors (n:11)	7	4	–
Osteosarcoma (n:7)	4	3	–
Lymphomas (n:6)	3	2	1
Retinoblastoma (n:6)	–	–	6
NPC (n:4)	3	1	–
Hepatoblastoma (n:4)	1	3	–
STSs (n:4)	1	–	3
ESFTs (n:3)	1	1	1
CNS tumors (n:3)	–	2	1
Wilms tumor (n:2)	–	–	2
Squamous cell carcinoma (n:1)	1	–	–
Baseline audiologic assessment +, n (%)	10 (33)	9 (53)	1 (7)
Median time of control audiometry since the last platinum dose, years (range)	2y (0 – 17)	1 mos (1mos – 1.5 y)	2.8 y (1mos – 9.5 y)
Median individual dose of cisplatin, mg/m^2 (ranges)	100 (20 – 160)	100 (30 – 150)	–
Median number of cisplatin courses per child	4 (1 – 8)	5 (1 – 10)	–
Median cumulative dose of cisplatin, mg/m^2 , (ranges)	405 (100–800)	445 (120–1,000)	– –
Cumulative dose of cisplatin, n (%)	n (%)	n (%)	
< $400mg/m^2$	12 (40)	3 (18)	
≥ $400mg/m^2$	18 (60)	14 (82)	–
Cisplatin administration schema, n (%)			
by single dose	13 (43)	9 (53)	–
by divided doses	17 (57)	8 (47)	–
Median duration of cisplatin infusion, hours (ranges)	4 (1 – 24)	4 (1 – 24)	–
Median individual dose of carboplatin, mg/m^2 (ranges)	–	500 (300 – 600)	500 (400 – 600)
Median number of carboplatin courses per child	–	4 (1 – 13)	6 (1 – 12)
Median cumulative dose of carboplatin, mg/m^2, (ranges)	–	1,890 (300–4,200)	2800 (1120–8,400)
Cumulative dose of carboplatin, n (%)			
< $2,000mg/m^2$	–	9 (53)	8 (47)
≥ $2,000mg/m^2$		3 (27)	12 (73)
Additional aminoglycoside	18 (60)	14 (82)	10 (67)
Additional bleomycin	10 (33)	3 (18)	-
Additional HN-RT	7 (23)	5 (29)	5 (23)

* Three patients had intracranial GCTs.

mos: months; y: year, GCTs: Germ cell tumors; SNS: Sympathetic nervous system; NPC: Nasopharyngeal carcinoma; STSs: Soft tissue sarcomas, ESFTs : Ewing Sarcoma family of tumors; CNS: Central nervous system, HN-RT: Head/neck radiotherapy

of these 62 patients, and all of them were within normal levels. Among these 20 patients, HFHL was detected in 6 of 10 patients in group 1, and 4 of 9 patients in group 2 at follow-up evaluations (Table 2). There was no statistically significant difference between group 1 and group 2 for the occurrence of HFHL.

At the follow up audiological assessments, 15 patients had mild (grade 1) and 10 patients had moderate to severe (grades 2 - 4) HFHL (Table 3).

Average values for air conduction hearing thresholds in octave frequencies of 0.25, 0.5, 1, 2, 4, and 8 kHz are presented in Figure 2. Because there were no statistically significant changes in pure tone average values for air conduction hearing thresholds between left and right ears, only the left air conduction thresholds are presented in Figure 2.

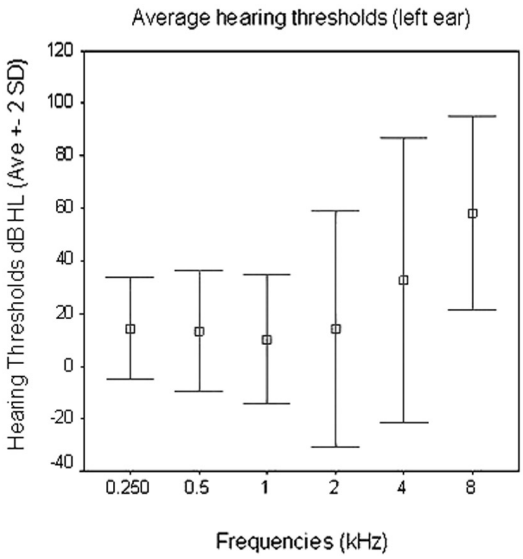

Figure 2. The mean and standard deviation values for air conduction hearing thresholds in octave frequencies (kHz)

Table 2. Patients with baseline and follow-up audiological assessments

	Age at Baseline audiological assessments (years)	Baseline audiological assessments	Median time of follow-up audiological assessments (month)	Follow-up audiological assessments
Group 1* (n:10)	<3	Normal (n:2)	32 (3 - 83)	Normal (n:1) Grade 1 HFHL (n:1)
	≥3	Normal (n:8)		Normal (n:3) Grade 1 HFHL (n:5)
Group 2* (n:9)	<3	Normal (n:3)	20 (7 - 23)	Normal (n:3)
	≥3	Normal (n:6)		Normal (n:2) Grade 1 HFHL (n:3) Grade 2 HFHL (n:1)
Group 3 (n:1)	≥3	Normal (n:1)	29	Normal (n:1)

* There was no significant difference between groups 1 and 2 for occurrence of HFHL (Chi square p= 0.65).

Table 3. Hearing loss according to the Brock's hearing loss grading system

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)
Normal hearing	13 (44)	9 (53)	15 (100)	37 (60)
Grade 0	–	–	–	–
Grade 1	9 (30)	6 (35)	–	15 (24)
Grade 2	6 (20)	1 (6)	–	7 (11)
Grade 3	1 (3)	1 (6)	–	2 (3)
Grade 4	1 (3)	–	–	1 (2)
Total	30	17	15	62

HTs: Hearing thresholds; HL: Hearing level

Normal hearing: HTs 0 – 25 dB HL at all frequencies; Grade 0 : HTs less than 40dB HL at all frequencies; Grade 1 : HTs 40dB HL or greater at 8,000Hz; Grade 2 : HTs 40dB HL or greater at 4,000 - 8,000Hz; Grade 3 : HTs 40dB HL or greater at 2,000 - 8,000Hz; Grade 4 : HTs 40dB HL or greater at 1,000 - 8,000Hz

There was a significant difference among groups for the occurrence of ototoxicity (Kruskal-Wallis, p: 0.001). No patient had hearing loss in carboplatin-only group 3. Occurrence of HFHL was not different between cisplatin-only and cisplatin + carboplatin groups. Characteristics of patients with or without HFHL, according to the Brock's hearing loss grades, are shown in Table 4.

Table 4. Characteristics of patients with or without ototoxicity

	n	Normal Hearing* n (%)	Grade 1** HFHL n (%)	Grades 2 – 4** HFHL n (%)
Number of patients (%)	**62**	**37 (60)**	**15 (24)**	**10 (16)**
Male	28	19 (51)	8 (53)	1 (10)
Female	34	18 (49)	7 (47)	9 (90)
Median age at diagnosis years (ranges)		6 (0 – 18)	9 (0 – 17)	14 (4 – 19)
Age at diagnosis & treatment				
< 5 years old	22	18 (49)	3 (20)	1 (10)
≥ 5 years old	40	19 (51)	12 (80)	9 (90)
Hearing evaluation time				
just after the end of treatment	23	12 (33)	7 (47)	4 (40)
within two years of the last platinum dose	13	9 (24)	3 (20)	1 (10)
after the 2nd year of the last platinum dose	26	16 (43)	5 (33)	5 (50)
Group 1 (cisplatin)	30	13 (35)	9 (60)	8 (80)
Group 2 (cisplatin + carboplatin)	17	9 (24)	6 (40)	2 (20)
Group 3 (carboplatin)	15	15 (41)	–	–
Additional aminoglycoside	42	22 (60)	14 (93)	6 (60)
Additional bleomycin	13	5 (14)	5 (33)	3 (30)
Additional HN–RT	18	8 (22)	4 (27)	6 (60)
Diagnosis				
GCTs (n:11)	11	6 (16.2)	1(6.7)	3 (30)
Extracranial GCTs	7	5	1	1
Intracranial GCT	3	1	–	2
SNS tumors (n:11)	11	7 (18.9)	4 (26.7)	–
Osteosarcoma (n:7)	7	4 (10.8)	2 (13.3)	1 (10)
Retinoblastoma (n:6)	6	6 (16.2)	–	–
NPC (n:4)	4	–	2 (13.3)	2 (20)
Hepatoblastoma (n:4)	4	2 (5.4)	1 (6.7)	1 (10)
STSs (n:4)	4	4 (10.8)	–	–
Hodgkin's lymphoma (n:4)	4	–	4 (26.7)	–
Non Hodgkin's lymphoma (n:2)	2	1 (2.7)	–	1 (10)
ESFTs (n:3)	3	2 (5.4)	1 (6.7)	–
CNS tumors (n:3)	3	2 (5.4)	–	1 (10)
Wilms tumor (n:2)	2	2 (5.4)	–	–
Laryngeal squamous cell carcinoma (n:1)	1	1 (2.7)	–	–
Cumulative dose of cisplatin				
< 400mg/m^2	14	9 (41)	2 (13)	4 (40)
≥ 400mg/m^2	33	13 (59)	13 (87)	6 (60)
Cisplatin administration				
Single dose schema	22	10 (46)	5 (33)	7 (70)
Divided doses schema	25	12 (54)	10 (67)	3 (30)
Duration of cisplatin infusion				
1 hour	17	9 (41)	4 (27)	4 (40)
4 to 6 hours	21	8 (36)	8 (53)	5 (50)
20 to 24 hours	9	5 (23)	3 (20)	1 (10)
Cumulative dose of carboplatin				
< 2,000 mg/m^2	15	11 (46)	2 (33)	2 (100)
≥ 2,000 mg/m^2	17	13 (54)	4 (67)	
Cumulative dose of cisplatin mg/m^2 median (ranges)		405 (120 – 675)	420 (240 – 1000)	400 (100 – 800)
Individual dose of cisplatin mg/m^2 median (ranges)		100 (30 – 150)	100 (20 – 150)	100 (70 – 160)
Cumulative dose of carboplatin mg/m^2 median (ranges)		2,500 (600 – 8,400)	2,850 (300 – 3,900)	1150 (1,000 – 1,300)
Individual dose of carboplatin mg/m^2 median (ranges)		500 (300 – 600)	450 (300 – 500)	500 (500 – 500)

* Normal hearing: hearing thresholds 0 – 25 dB hearing level at all frequencies
** Brock's hearing loss grades
GCTs: Germ cell tumors; SNS: Sympathetic nervous system; NPC: Nasopharyngeal carcinoma; STSs: Soft tissue sarcomas, ESFTs : Ewing Sarcoma Family of tumors; CNS: Central nervous system, NPC: Nasopharyngeal carcinoma; HN–RT: Head/neck radiotherapy

The median cumulative dose of cisplatin was 420 mg/m^2 (120 - 1,000) for all patients (n: 47) who had received either cisplatin-only or cisplatin+carboplatin. The median cumulative dose was 433 mg/m^2 (100-1,000) for children <5 years of age at diagnosis (n: 14), and 420 mg/m2 (120 - 750) in > 5 years of age at diagnosis (n: 33).The median cumulative dose of carboplatin was 2,500 mg/m^2 (300 - 8,400) for all patients who received either carboplatin-only or cisplatin+carboplatin (n: 32). It was 3,200 mg/m^2 (600 - 8,400) in children less than 5 years age at diagnosis (n: 13), and 2,000 mg/m^2 (300 - 4,900) in > 5 years of age at diagnosis (n:19). There were no significant differences regarding mean cumulative doses of carboplatin and cisplatin in patients <5 years old and >5 years old.

The mean cumulative dose of cisplatin in groups 1 and 2, and the mean cumulative dose of carboplatin in groups 2 and 3 showed no significant differences.

Group 1; - Cisplatin- only group (n:30)

The incidence of ototoxicity was not different between males and females and between patients who were younger or older than 5 years of age at the initial tumor diagnosis. The mean age of tumor diagnosis showed no difference between patients with and without ototoxicity.

The mean cumulative dose of cisplatin was not significantly different among patients with and without hearing loss, and also among patients with grade 1 and grades 2-4 ototoxicity. Incidence of ototoxicity was not different between patients who received a total dose of cisplatin < 400 mg/m^2 and ≥ 400mg/m^2; and between patients who received cisplatin as a single dose or as a divided-dose schema in five days. There was no significant correlation between HFHL regarding the Brock's scale and the cumulative dose of cisplatin.

Among patients with ototoxicity (n: 17), 13 (76%) patients also received aminoglycosides, 6 (35%) also received bleomycin, and 5 (29%) received head or neck radiotherapy. Four of these 8 patients who developed grades 2-4 ototoxicity had also received radiotherapy.

Group 2; Cisplatin and carboplatin received group (n: 17)

The mean cumulative doses of cisplatin and carboplatin were not different among patients with and without hearing loss. Of the 8 patients with ototoxicity, all received cumulative dose of cisplatin ≥ 400 mg/m^2, and four received carboplatin ≥ 2,000 mg/m^2.

Aminoglycoside antibiotics, and bleomycin were given in 7 (88%) and 2 (25%) of the patients who developed ototoxicity; and were given in 7 (78%) and 1 (11%) of the patients without ototoxicity, respectively. Head or neck radiotherapy was performed in 4 (50%) patients with HFHL and in one (11%) patients without HFHL. There was no significant difference among patients with or without ototoxicity in terms of receiving aminoglycoside antibiotics, bleomycin, and head-neck radiotherapy.

Group 3; Only - Carboplatin received group (n: 15)

No one had HFHL in the carboplatin-only group. Characteristics of this group and details of the chemotherapy are shown in Table 1.

Patients with the Brock's Grades 3 - 4 Hearing Loss

Only 3 patients with grades 3 - 4 ototoxicity had complaints of hearing difficulties. The Brock's grade 3 HFHL developed in a 10 years old girl with intracranial germ cell tumor (GCT), and in a 10 years old girl with medulloblastoma. Both of them received cisplatin as well as cranial irradiation, the second case additionally received carboplatin. The first patient died with progressive disease within 6 months. The second one had been followed up for 10 years at our center without disease and without any clinical progress of hearing loss, and then lost to follow up. Bilateral hearing aids were recommended for the latter patient, but, she was not willing to follow the advice.

The Brock's grade 4 ototoxicity developed in a 13 years old girl with anaplastic large cell lymphoma (stage 3 according to the Murphy staging system) whose baseline audiologic assessment was normal. Some severe and uncommon neurotoxic side effects including a short term memory loss, flaccid paraplegia, and anal sphincter tonus loss occurred after the first course of chemotherapy consisting dexamethasone,

etoposide, cytarabine, methotrexate, ifosfamide and triple intratechal therapy (methotrexate, cytarabine, prednisolone). These neurotoxicities considered to be related to anticancer chemotherapy. Cisplatin 20 mg/m^2/day was given for five days by one hour infusion. Complaints of hearing loss developed just after the last dose of cisplatin. She died with disease after 10 days of the occurrence of ototoxicity.

Discussion

Nowadays, survival rates of childhood cancer have been improved by multimodal treatment strategies including multi-drug / intensive chemotherapeutic regimens, irradiation, and surgery. Anticancer therapy can seriously lead to adverse effects in many organ systems particularly in still growing and developing children. In pediatric oncology, besides the aim of cure, acute and late toxicities and subsequent quality of life should be taken into account while treating children with cancer. Long-term follow up of the survivors of childhood cancer necessitates monitoring and management of late effects.

Hearing impairment is a serious side effect of platinum compounds, particularly cisplatin [1-6]. Cisplatin induced HFHL in children was firstly reported by McHaney et. al.[4]. It is characterized by bilateral, irreversible, sensorineural HFHL which can progress to the lower frequencies [4-8]. As a result of the platinum induced hearing loss, speech and language development can be impaired and this may influence learning and school performance, psychosocial and emotional status of child [6, 7, 9]. Practical hearing loss grading system for platinum induced ototoxicity has been developed by Brock's et. al.[6]. Patients can be clinically asymptomatic although certain degree of hearing impairment can be detected by audiological testing [6, 7].

Our pediatric audiology unit has been established at 1994, and capable to perform PTA, ABR since 1994, and capable to examine younger children by performing COR audiometry, speech audiometry and TEOAEs since 1998. This condition seems to contribute to the low rates of baseline and control audiological evaluations in earlier patients. In a vast majority of childhood cancers, pediatric oncologists need to start anticancer treatment as soon as possible in order to not to sacrifice the chance of cure over academic curiosities. If the neurological examination is satisfying in terms of a normal hearing, we are willing to start chemotherapy immediately. Therefore, some of the cases presented in this study may not have baseline audiological testing prior to treatment. However, we did our best in order to obtain the audiological evaluation as soon as possible during the treatment course. Recently, we established an ototoxicity monitoring protocol for the evaluation of hearing in patients receiving platinum. According to this protocol, all children receiving platinum containing chemotherapy, despite the absence of baseline audiological assessments, underwent serial posttreatment follow-up audiological assessments. During this study, we performed some additional follow-up audiological tests by inviting survivors for audiological evaluation and this rate was increased from 23% to 44%.

Brock's grade 1 to 4 HFHL was detected in 40% of all 62 patients receiving any platinum compound. The incidence of grade 1 to 4 HFHL was 56.6% in patients receiving cisplatin, and 47% in patients receiving both cisplatin and carboplatin. No HFHL was observed in carboplatin-only group. Our results were consistent with the reported experience. In previous studies, ototoxicity had been reported in 42 - 70% of patients receiving cisplatin [6 - 12]. Standard dose of carboplatin has been reported to cause ototoxicity in only a few patients during childhood [4, 6 -12].

Seven patients who achieved a long term survival underwent audiological evaluation over 5 years since the last platinum dose. Persistent hearing loss in these patients is supporting the permanent feature of platinum induced ototoxicity[6]. Since we do not have serial measurements in these patients, we can not comment on worsening of HFHL in long term follow up. Bertolini et al. [8] reported progression in platinum induced HFHL during follow-up of their patients. This topic necessitates further investigating.

The results of the previous studies showed several risk factors for the development of platinum induced ototoxicity in children including young age at diagnosis, high cumulative or individual dose of cisplatin, high dose carboplatin, head or neck radiotherapy, and other ototoxic drugs [6 - 14].

Young age at diagnosis and treatment has been identified as a patient related risk factor [6, 7, 8, 12]. However cisplatin ototoxicity has also been reported in higher median age groups as it happened in our patients [6, 7, 13]. In this study, median age at the initial platinum treatment was 9 and 14 years for grade 1 and grades 2 - 4 HFHL, respectively. Approximately 70% of patients were older than 5 years at the initial diagnosis in both groups 1 and 2. In groups 1 and 2, hearing loss was detected in 28.6% of patients younger than 5 years, and 63.6% of patients older than 5 years at the diagnosis. Although the age at diagnosis and treatment details showed no significant difference among patient with or without hearing loss, the majority (84%) of patients who developed grades 1 - 4 HFHL were older than 5 years. Li et. al.[12] reported that children younger than 5 years were particularly susceptible to ototoxicity, in this study. In their study group, only 14% of patients were older than 14 years and, among patients with moderate to severe ototoxicity, only 4% were older than 15 years at diagnosis [12]. However 50% of our patients with grade 2 - 4 HFHL was older than 15 years. Although the number of patients is small, this result suggests that children older than 15 years of age during the treatment are also susceptible to platinum induced moderate to severe HFHL.

Previously no significant effect of gender on cisplatin induced HFHL has been reported [10, 12]. In this study 90% of patients with grade 2 - 4 HFHL were females. Median age of these girls was 14 years (4 -18), and 5 (56%) of them were postpubertal. In our patients, platinum induced HFHL occurred 7 (64%) of 11 post-pubertal girls, and 3 (33%) of 9 post-pubertal boys, in groups 1 and 2 respectively. However, this female predominance might be incidental. A higher number of patients should be evaluated to draw a conclusion about the effect of gender on this particular toxicity.

Higher individual and cumulative doses of cisplatin have been reported as a risk factor for ototoxicity[6, 7, 12]. Majority of our patients received 100 mg/m^2/course dose of cisplatin and only 4 patients received greater than 120 mg/m^2/ course. Ototoxicity was detected in 36% of 14 patients who received < 400 mg/m^2, and in 61% of 33 patients who received ≥ 400 mg/m^2 cumulative dose of cisplatin (and also in 67% of 12 patients who received ≥ 600 mg/m^2 cumulative dose). Although ototoxicity was more frequent and severe in patients treated with higher cumulative doses of cisplatin, herein this difference was not statistically significant. Limited number of each group and limited number of younger children at diagnosis might be the reason for this insignificance.

In this study, the risk of HFHL was not significantly related to the age of treatment, the cumulative dose of cisplatin, its administration schema, receiving other ototoxic drugs, and prior head and neck irradiation. Small number of patients and heterogeneity of cisplatin administration schemas are the limitations of our study.

Due to less number of patients who received aminoglycosides, it was not feasible to investigate the effects of aminoglycosides on ototoxicity. Coradiani et. al.[11] reported similar results. In this retrospective study it was not feasible to analyze administration details (time, duration, total dose) of aminoglycosides because of no available data on patients' records.

In our study, head or neck radiotherapy was part of the treatment in some patients (n:18). Ototoxicity occurred in 55.5% of them, and all of these cases received cisplatin containing chemotherapy. No ototoxicity was observed in patients treated with carboplatin and radiotherapy. Herein, radiotherapy didn't adversely affect hearing of patients receiving carboplatin only; however the number of patients was limited. Ototoxicity was detected in 5 of 7 patients receiving cisplatin and 4 of 5 patients receiving cisplatin + carboplatin. The tumor diagnosis in these 9 patients with ototoxicity were nasopharyngeal carcinoma (NPC) (n: 4), intracranial germ cell tumor (GCT) (n:

2), and Hodgkin's lymphoma (HL) (n:2). Patients with HL and GCTs also received bleomycin. Combined treatment with cisplatin and radiotherapy as well as bleomycin might contribute to cisplatin induced ototoxicity in these four children.

Previously, greater hearing impairment has been reported in patients with NPC who had been treated with cisplatin and radiotherapy rather than radiotherapy only [15]. Gupta et. al. reported cisplatin ototoxicity in 5 (12.8%) of 39 children with GCTs who received cisplatin, and only one of them (2.5%) had grade 2 HFHL. They had no patients with intracranial GCTs in this report [16]. In our study, 11 patients had GCTs. Nine children with GCTs (3 of them had intracranial GCTs) received cisplatin only, and HFHL occurred in 4 (44.4%) of 9 patients. Of the 9 patients, 8 received cisplatin 20mg/m^2/day for 5 days by one hour infusion. All three patients who had intracranial GCTs also received cranial irradiation. Grades 2 - 4 HFHL was detected in two patients with intracranial GCTs who received 400 mg/m^2 and 300 mg/m^2 cumulative dose of cisplatin; and in one patient with extragonadal GCT who received 800mg/m^2 cumulative dose of cisplatin. The other patient with intracranial GCT had normal hearing although he received 300 mg/m^2 cumulative dose of cisplatin, and cranial irradiation. This result suggests that primary tumor site may be another risk factor for the development of cisplatin ototoxicity in children with GCTs, and children with intracranial GCTs may be more susceptible to cisplatin induced ototoxicity. Higher cumulative dose of cisplatin, and cranial irradiation may induce hearing impairment in this group of patients.

Conclusion

Ototoxicity is a potential side effect of platinum-based, particularly cisplatin-based chemotherapy. The standard dose of carboplatin does not cause ototoxicity. Our data suggests that children who are older than 5 years during the platinum treatment are also susceptible to platinum induced moderate to severe HFHL.

Our results may also suggest that primary tumor site may be another risk factor for cisplatin ototoxicity in children with GCTs, and patients with intracranial GCTs may be more susceptible to platinum induced hearing loss. Additional insult due to cranial irradiation might be contributing to the hearing loss in these patients.

Because of platinum compounds are highly effective agents in the treatment of childhood cancers and there are no definite alternatives for these drugs, early diagnosis and rehabilitation of patients with moderate to severe platinum induced HFHL is critical. Hearing should be monitored in every children receiving platinum. Collaboration of pediatric oncology and audiology departments is mandatory in order to monitor toxicity during and after platinum-based treatment, to avoid further insult and also to rehabilitate when mutilating toxicity occurs.

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