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Original Article

Ototoxicity and long-term hearing outcome in pediatric patients receiving cisplatin

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ABSTRACT

Background. Hearing is essential in child development. Cisplatin which is a common chemotherapy used in many pediatric solid-tumor protocols cause various degrees of ototoxicity. Several risk factors for cisplatin-induced ototoxicity have been reported, including race and age. This study aimed to evaluate the incidence of ototoxicity and its long-term outcome in Thai pediatric solid-tumor patients receiving cisplatin and to determine the risk factors associated with hearing impairment.

Methods. A retrospective study was conducted in solid-tumor patients <15 years old from 2007 to 2019 at Siriraj Hospital, Bangkok, Thailand. Hearing was evaluated by an audiogram and/or auditory steady-state response and the impairment was graded according to the Common Terminology Criteria for Adverse Events version 5. Grade 2 and above was considered significant hearing loss.

Results. In total, the hearing of 47 patients was evaluated. At the end of treatment, hearing impairment and significant hearing loss were found in 66% and 48.9% of patients, respectively. A high median cumulative cisplatin dose was significantly associated with worse hearing impairment ($p = 0.039$) and a more progressive grading of ototoxicity ($p = 0.005$). A risk factor for significant hearing loss was a cumulative dose ≥400 mg/m^2 ($p = 0.014$). All 9 patients who received a cumulative dose >600 mg/m^2 and 5 patients who received aminoglycoside developed significant hearing loss. One patient had progressive hearing impairment at 8 months after the end of treatment and 1 patient developed grade 3 ototoxicity which required a hearing aid after bone marrow transplantation. The latter patient received a total cisplatin dose of 708.2 mg/m^2 and carboplatin 1400 mg/m^2.

Conclusions. The incidence of hearing impairment in pediatric patients receiving cisplatin is high. Regular hearing evaluation is essential for the early detection of ototoxicity. Long-term follow-up is recommended, especially in patients who have a combination of other risk factors for hearing loss.

Key words: cisplatin, ototoxicity, pediatric, oncology, long-term.

Cisplatin is incorporated in the treatment of many pediatric solid tumors, including hepatoblastoma, neuroblastoma, intra- and extracranial germ cell tumor (GCT), and osteosarcoma. Its mechanism of action is the activation of the apoptosis cascade and generation of reactive oxygen species, leading to cellular toxicity.[1,2] Cisplatin is well known to cause permanent sensorineural hearing loss especially in the high-frequency range. Previous reports of the incidence of cisplatin-induced ototoxicity revealed varying rates from 11-97% depending on the criteria used.[3-8] Several risk factors for cisplatin-induced ototoxicity have been reported, including an increasing cumulative dosage, prior cranial irradiation, co-administration with aminoglycosides, renal insufficiency, race, male gender, age <5 years old, and glutathione S-transferases genetic polymorphisms.[1,3,4,6-8] A previous study in Thai oncology patients showed that 79.5% had

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hearing loss at the end of treatment according to Brock classification, and a cumulative cisplatin dose >400 mg/m^2 was associated with an increased risk of ototoxicity.[6] The audiogram in that study was evaluated only once at the median time of 25.7 months between the last dose of cisplatin and hearing evaluation.[6] However, cisplatin-induced ototoxicity may be progressive if the patient is receiving repeated doses of chemotherapy and can occur up to 5 years later.[5,9]

Since hearing is essential for child development; hearing loss in early life can affect children in many aspects. Impairment of hearing, especially at 500 Hertz (Hz)–4 kiloHertz (kHz), which is the human speech frequency, can cause delayed speech, impaired cognitive function, and affect neurodevelopmental outcomes.[6,9,10] Long-term hearing loss, even if at high frequency, can also affect language development.[9] Therefore, we were interested to analyze Thai pediatric solid-tumor patients receiving cisplatin-based chemotherapy to address the ototoxicity effects of cisplatin, which may provide a recommendation for follow-up in future patients.

Material and Methods

Patients and objectives

This cohort study was a retrospective chart review of pediatric solid-tumor patients, including neuroblastoma, hepatoblastoma, osteosarcoma, and GCT, who were <15 years old and had received cisplatin-based chemotherapy at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand from January 2007 to December 2019. Their baseline hearing was evaluated by an audiogram and/or auditory steady-state response (ASSR) pre- or within 1 month of the initiation of cisplatin and then followed-up with further hearing tests for at least 2 sequential times. All the patients had an audiogram performed for both ears at the last hearing evaluation to quantify the change in hearing threshold. Patients who had an anatomical defect of the ear and renal dysfunction before treatment, which may be risk factors for hearing loss and cisplatin toxicity, were excluded. The primary objective was to study the effect of cisplatin on the incidence of ototoxicity throughout the course of treatment and after the end of therapy in Thai pediatric solid-tumor patients. The secondary objective was to determine the risk factors that may be associated with hearing impairment. This study was approved by the ethical committee of the Faculty of Medicine Siriraj Hospital (Si 052/2020) and was registered in the Thai Clinical Trial Registry (TCTR20210221001).

Data collection and analysis

Data collection included the patients' gender, diagnosis, age at diagnosis, dose of cisplatin (mg/m^2), co-administration of other chemotherapies and aminoglycoside, complications including infections that required hospitalization, and outcome at the end of treatment. The audiogram and/or ASSR results, including frequency and threshold of hearing, were recorded. The hearing impairment severity was assigned a numeric grade from 0–4 according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v.5) established by the National Cancer Institute.[11] Grade 0 is considered normal hearing. Grades 1, 2, 3, and 4 are considered to indicate mild, moderate and severe hearing loss indicating the need for therapeutic intervention including hearing aids, and very severe hearing loss indicating the need for a cochlear implant, respectively.[11] CTCAE grade 2 and above were considered to impact the hearing function in children because a hearing threshold shift at 4 kHz or less is in the range of human speech frequency.[9] These grading toxicities represented significant hearing loss in this study.

Data were analyzed with descriptive statistics using SPSS Statistics for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA). Data are presented as the mean±SD or median (range) for continuous variables and number (%) for

categorical variables. The Mann–Whitney U test, Chi-square test, and Kruskal–Wallis test were used, as appropriate, to compare and identify the association between factors, such as cisplatin dose and duration of follow-up with the grading of hearing impairment. Kaplan–Meier analysis was performed for each cumulative cisplatin dose range to determine the hearing loss-free duration from the first dose of cisplatin and the significance was assessed using the log-rank test. Univariable logistic regression was employed to analyze the covariables on the impact of hearing impairment. Significant factors were included in the multivariable analysis using a multiple logistic regression method. A p-value of <0.05 was considered statistically significant.

Results

In total, 47 patients were enrolled in this study. The median age at diagnosis was 7.1 (range 1.3–14.8) years old, and about one-third of the patients were <5 years old. Osteosarcoma was the most common disease (36.2 %). One patient with extracranial GCT received autologous bone marrow transplantation (BMT) after relapsed disease and 3 patients with intracranial GCT received cranial radiation (median dose 5,000; range 2,268–5,000 centigray). Infectious complications occurred in 19 patients (40.4%), which consisted of febrile neutropenia in 16, sepsis in 6 (among whom, 2 patients had septic shock), moderate to severe gastroenteritis in 5 (among whom, 1 patient was diagnosed with typhlitis), and urinary tract infection and respiratory syncytial virus pneumonia in 1 patient each. Five patients received aminoglycoside. The disease-free survival rate at the end of treatment was 68.1%. The chemotherapies for each type of malignancy are shown in Table I. The characteristic of the patients and diseases are summarized in Tables II and III. The median cumulative dose of cisplatin for all patients was 423.1 (range 118–1080) mg/m^2. No statistically significant difference in cumulative dose (p = 0.235) was found for each type of malignancy, as demonstrated in Table III. Overall, 28 patients (59.6%) received a cumulative dose of cisplatin ≥400 mg/m^2.

Audiologic evaluation

The results from the baseline hearing evaluation are demonstrated in Table II. Six patients (12.8%) had grade 2–3 hearing impairment at the first hearing evaluation. At the end of treatment, 31 patients (66%) had grade 1 or higher hearing impairment and 23 of them (48.9%) had significant hearing impairment (> grade 2). Patients who received a higher cumulative dose range of cisplatin had significantly worse hearing impairment at the end of treatment (p = 0.001; Table IV) and a significantly more

Table I. Chemotherapies for each type of malignancy in this study.

	Cisplatin	Bleomycin	Carboplatin	Doxorubicin	Etoposide	Cyclophosphamide	Ifosfamide	Methotrexate	Irinotecan	Topotecan	5-Fluorouracil	Vincristine	Remarks
Hepatoblastoma	√√		√	√	√		√				√	√	
Extracranial GCT	√√	√√	√		√√		√						
Intracranial GCT	√√		√		√		√						
Osteosarcoma	√√		√	√√	√		√	√√					√√ = all cases
Neuroblastoma	√√		√	√√	√√	√√	√		√	√		√	√ = some cases

GCT: germ cell tumor

Table II. Characteristics of the patients (n = 47).

Characteristics		Number	Percent
Gender	Female	24	51.1
	Male	23	48.9
Age at diagnosis (years)	0–5	15	31.9
	6–10	15	31.9
	10–15	17	36.2
Hearing grade at baseline evaluation	0	33	70.2
	1	8	17.0
	2	4	8.5
	3	2	4.3
Other medications	Doxorubicin	31	66.0
	Etoposide	29	61.7
	Methotrexate	16	34.0
	Carboplatin	15	31.9
	Ifosfamide	14	29.8
	Cyclophosphamide	10	21.3
	Vincristine	10	21.3
	Other chemotherapies†	17	36.2
	Aminoglycoside	5	10.6
Other treatments	Cranial radiation	3	6.4
	Surgical removal	33	70.2
	Bone marrow transplantation	1	2.1
Complications	Infections/ Febrile neutropenia	19	40.4
Outcome at the last follow-up	Survive without disease	32	68.1
	Palliative/Dead	15	31.9

†Other chemotherapies: 5- Fluorouracil, irinotecan, topotecan, bleomycin.

Table III. Number of patients in each range of cumulative cisplatin doses and median with range doses classified by diagnosis.

Diagnosis	Number of cases for each cumulative cisplatin doses range (mg/m^2)					Cumulative cisplatin doses (mg/m^2)	
	Total	0–200	201–400	401–600	>600	Median	Range
Osteosarcoma	17	1	5	11	0	427.4	118–596
Neuroblastoma	11	0	4	2	5	423.1	286–1080
Hepatoblastoma	8	0	5	0	3	395.5	230–1038
Extracranial GCT	8	1	1	3	3	523.7	172–1040
Intracranial GCT	3	0	2	1	0	384.6	316–411
Total	47	2	17	17	11	423.1	118–1080
						(p-value = 0.235)	

GCT: germ cell tumor.

progressive grading shift of hearing impairment during the course of treatment ($p < 0.001$; Table IV). The median cumulative cisplatin dose was significantly higher in patients who had worse hearing impairment ($p = 0.039$; Fig. 1) and a more progressive grading shift of hearing impairment ($p = 0.008$; Fig. 1). One of the 3 patients who received cranial radiation

Table IV. Number of patients in each range of cumulative cisplatin doses classified by Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v.5) for hearing impairment at the end of treatment (n = 47).

CTCAE v.5 for hearing impairment		Number of cases (%) in each cumulative dose range (mg/m^2)					*p*-value
		Total	0–200	200–400	400–600	>600	
Grading at the end of treatment	0	16	1 (6.3%)	9 (56.3%)	6 (37.5%)	0	
	1	8	0	3 (37.5%)	4 (50%)	1 (12.5%)†	
	2	16	1 (6.3%)	4 (25%)	4 (25%)	7 (43.8%)	
	3	6	0	1 (16.7%)	3 (50%)	2 (33.3%)	
	3 with hearing aids	1	0	0	0	1 (100%)	0.001*
Progression of grading until the end of treatment	Unchanged	25‡	2 (8%)	14 (56%)	7 (28%)	2 (8%)	
	+1	9	0	2 (22.2%)	4 (44.4%)	3 (33.3%)	
	+2	9	0	1 (11.1%)	4 (44.4%)	4 (44.4%)	
	+3	4	0	0	2 (50%)	2 (50%)	< 0.001*

CTCAE: Common Terminology Criteria for Adverse Events.
†At 8 months after the end of treatment, this patient had progressively impaired hearing from grade 1 to grade 2.
‡Six patients who had baseline hearing grade 2–3 showed no change in grading during the treatment course.
* Result statistically significant at P < 0.05.

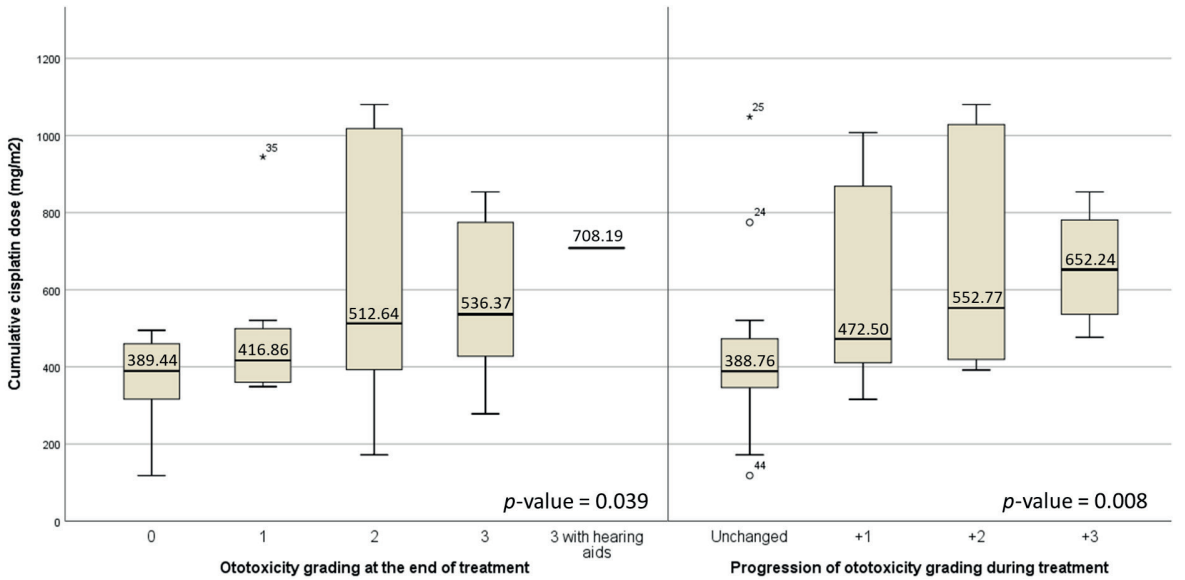

Fig. 1. Median and range of cumulative cisplatin doses classified by Common Terminology Criteria for Adverse Events version 5.0 for hearing impairment (n=47).

had normal hearing until the last evaluation. The other 2 patients had progressed hearing impairment from grade 1 to 2 and grade 0 to 3, respectively. The latter patient had recurrent GCT and received both cisplatin (total 411 mg/m^2) and carboplatin (total 6,570 mg/m^2). The median follow-up time from the first dose of cisplatin to the final hearing evaluation of these 3 patients was 36 (range 27-50) months. One patient who received a cumulative dose of cisplatin 708.2 mg/m^2 had hearing impairment grade 3, which required hearing aids. This patient was diagnosed with stage 1 testicular yolk sac tumor at 1 year 3 months old and total tumor removal was performed without chemotherapy. He had a recurrent tumor at 2 years old and received chemotherapy followed by tandem autologous BMT at 3 years 3 months old. His conditioning regimen consisted of carboplatin 700 mg/m^2 and etoposide 750 mg/m^2

in a 3-day course for a total of 2 courses, 6 weeks apart. During the course of BMT, he had *alpha-hemolytic Streptococci* septicemia but did not receive aminoglycoside. He received 3 cycles of oral etoposide 50 mg/m^2/day for 21 days of a 28-day course after BMT. His hearing evaluation was normal 1 month before BMT. However, his audiogram revealed an impairment >20 dB at 500 Hz–4 kHz 4 months after BMT when he was on oral etoposide (6 months after the last dose of cisplatin) and was classified as grade 3 ototoxicity. He started to use hearing aids 2 years after the BMT.

Risk factors affecting hearing outcome at the last follow-up

Patients were classified into 2 groups, namely grades 0–1 and 2–4 of hearing impairment, according to the clinical implication that a threshold shift >20 dB at 4 kHz and below in at least one ear may affect speech and language development in children.[9,10] Twenty-four patients (51.1%) had grade 2–4 hearing impairment at the last follow-up. Six patients who had baseline hearing grade 2–3 did not show a progression in hearing impairment during the treatment and were excluded from the risk factor analysis. The median cumulative cisplatin dose in these 6 patients was 391.4 (range 172–1048) mg/m^2. None of these patients received aminoglycoside. The association of the patient's characteristics and treatment, such as gender, diagnosis, cranial radiation, chemotherapy except for cyclophosphamide (p = 0.04), and infections that required hospitalization were not found to be statistically significant risks for hearing impairment when comparing grade 0–1 with grade 2–4. An age of ≤5 years old at diagnosis had a significant impact on hearing impairment compared to an older age (Odds ratio 6.67; 95% CI 1.45–30.64, p = 0.015). Patients receiving cumulative doses of cisplatin ≥400 mg/m^2 had a significantly higher risk of developing grade 2–4 hearing impairment compared with patients receiving lower doses (Odds ratio 8.727; 95% CI 1.62–46.93, p = 0.012). All the patients receiving a cumulative dose of cisplatin >600 mg/m^2 (n = 9, excluding 2 patients who had baseline hearing impairment > grade 2) developed significant hearing impairment (grade 2 in 7 and grade 3 in 2 patients; Fig. 2). All the patients who received aminoglycoside (n = 5) developed significant

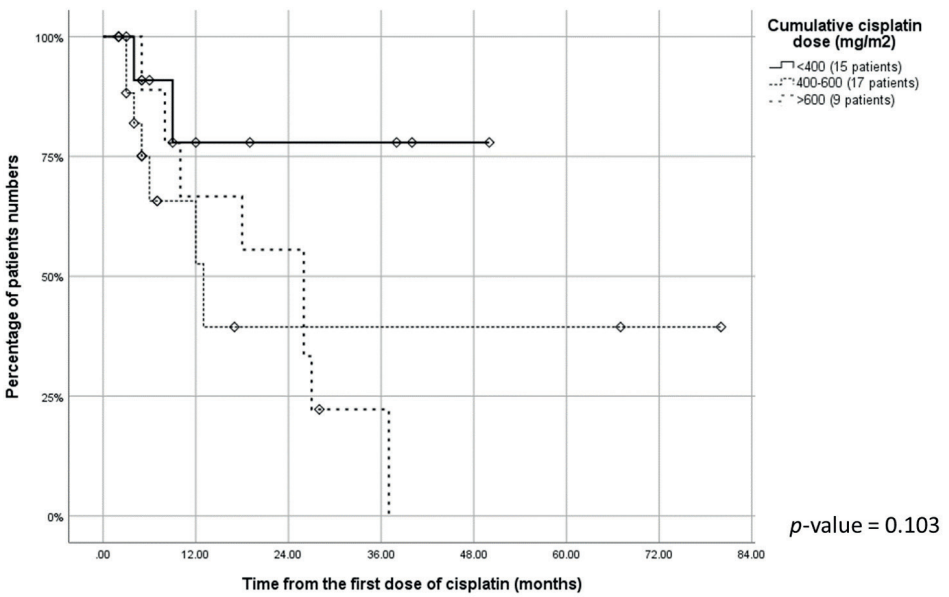

Fig. 2. Percentages of patients who progressed form grade 0-1 to grade 2-4 hearing impairment and duration (months) from the first dose of cisplatin to hearing impairment ≥grade 2 categorized by the cumulative dose ranges of cisplatin (n=41).

hearing impairment (grade 2 in 4 and grade 3 in 1 patient). From the multivariable analysis, the factor that significantly increased the risk of significant hearing impairment was a cumulative dose of cisplatin ≥400 mg/m^2 (Adjusted odds ratio 18.79; 95% CI 1.83–193.19, p = 0.014).

Long-term follow-up of hearing outcome

The median follow-up time from the first dose of cisplatin to the last hearing evaluation for all patients was 17.0 (range 4–121) months. Among the 41 patients who had baseline hearing grade 0–1, 18 (43.9%) progressed to grade 2–4 hearing impairment at the last hearing evaluation. The median time of progression to significant hearing impairment was 9.5 (range 3–37) months. Six patients with grade 2–3 hearing impairment at baseline evaluation had the same grade of hearing impairment until the last hearing evaluation. The median time from the first dose of cisplatin to the last hearing evaluation of these 6 patients was 24.5 (range 8-64) months. Thirty-two patients survived at the end of treatment. Fourteen patients underwent a followed-up audiogram after the end of treatment at a median duration of 35.5 (range 4–67) months. The median cumulative dose of cisplatin in this group of patients was 407.2 (range 172-944) mg/m^2. Thirteen patients did not have a change in hearing grade from the end of treatment to the last hearing evaluation. One patient, who was diagnosed with mediastinal ganglioneuroblastoma and had received a cumulative dose of cisplatin 944 mg/m^2, had hearing impairment grade 1 at the end of treatment but progressed to grade 2 at 8 months later. This patient had 4 episodes of febrile neutropenia, for which he received aminoglycoside at every episode. In total, 24 patients (51.1%) had significant hearing loss at the last hearing evaluation.

Nineteen patients who have hearing impairment received N-acetylcysteine. The time to starting medication and the duration of treatment varied, depending on the physicians' decision and the financial status of the patients, since the cost of N-acetylcysteine was not covered by the national healthcare system in Thailand. Because of the inconsistent data, we did not analyze the effect of N-acetylcysteine on the hearing outcome in this study.

Discussion

Hearing impairment impacts the quality of life of children, especially their speech and language development, which can also affect their academic achievement, cognitive function, and social integration.[9,10] Cisplatin-containing chemotherapy, which can cause ototoxicity and lead to hearing impairment, is incorporated as part of the standard treatment for many types of solid tumors in children. Our hospital applies the CTCAE v.5 classification established by the National Cancer Institute to classify hearing impairment from cancer treatment because each grade of audiological impairment correlates with hearing function and the need for an audiological intervention.[11,12] The reported incidence of hearing impairment from cisplatin depends on the criteria used to classify ototoxicity and the cumulative cisplatin doses received in the studies. Our study reported hearing impairment ≥grade 2 in 12.8% of patients at baseline which is higher than the prevalence of previous reports on hearing impairment in the Thai school-aged pediatric population (3.9-6.1%).[13,14] However, Thai children in rural areas had a higher prevalence of hearing impairment than in the capital city which was caused mainly by a higher incidence of ear infections and impact cerumen.[14] This may explain high prevalence of hearing impairment in our study since Siriraj hospital is a university hospital and a majority of patients were referred from rural areas. Fifty-one percent of our patients had hearing impairment at the last hearing evaluation, which was a similar rate to some previous studies[3,8] but lower than the study by Choeyprasert et al.[6] performed in Thai pediatric patients, which reported grade 2 or worse hearing loss according to Brock classification in 67.6% of their study patients. This discrepancy might be due to the lower doses of cisplatin in

our study than in Choeyprasert et al.'s study[6] (median dose 423.08 mg/m^2 vs. 525.5 mg/m^2, respectively) and the different criteria used for grading hearing impairment.

Risk factors influencing hearing outcome

Cisplatin causes high-frequency hearing loss, which is usually bilateral and permanent. However, higher cumulative doses may also affect hearing thresholds at lower frequencies.[1,2,4] Many risk factors for cisplatin-induced ototoxicity, such as male gender, younger age, high cumulative dose, radiotherapy to the head and neck region, and co-treatment with other ototoxic drugs, have been described.[4,7,15] Our study found that a cumulative cisplatin dose ≥400 mg/m^2 significantly increased the risk of significant hearing impairment. This result was similar to previous studies that demonstrated that a cumulative cisplatin dose >400 mg/m^2 was considered an independent risk factor for moderate to severe hearing impairment.[4,6,7] However, the dose of cisplatin correlated with high-frequency hearing loss was varied in different studies. McHaney et al.[16] reported an 88% incidence of high-frequency hearing loss in patients receiving >450 mg/m^2 cisplatin. The deteriorative effect on hearing ability in our study was noticeable when the cumulative cisplatin dose was >600 mg/m^2 since all the patients who had received this dose developed significant hearing loss. Our patients who received a greater cumulative dose of cisplatin showed a significantly more progressive grading shift of hearing impairment during the course of treatment and had worse hearing impairment at the end of treatment (Table IV and Fig. 1). This result confirms the dose-dependent effect of cisplatin in inducing ototoxicity that has been reported by others.[7,17] The progression of hearing impairment in our study occurred as early as 3 months after the first dose of cisplatin and 43.9% of patients progressed ≥2 grades of CTCAE v.5, which was associated with them having received a higher cisplatin dose. However, the progression of significant hearing impairment in our study occurred as late as 37 months. This emphasizes the importance of early and regular long-term hearing evaluation in this group of patients, especially for those who receive high cumulative cisplatin doses. Another significant risk factor in our study was a young age of ≤5 years old, which correlated with previous literature.[6,7,17] However, the multivariable analysis in our study did not show the younger age as significant. This could be due to the small number of this population (31.9%). Interestingly, all the patients who received aminoglycosides in our study showed impaired hearing function ≥grade 2 even though the statistical risk of this drug could not be calculated, but this should emphasize that patients who receive co-treatment with other ototoxic drugs, such as aminoglycosides, need to be closely evaluated for their hearing. If possible, ototoxic antibiotics should be avoided in patients who receive a high cumulative dose of cisplatin. Infections are common complications during the course of chemotherapy, as in our study, which revealed that 40.4% of patients had significant infections that required hospitalization. Infections that have been reported to cause hearing loss in children include chronic suppurative otitis media, meningitis, mumps, and measles.[18] We did not find that infections were associated with a higher risk of significant hearing loss. This might be because none of our patients had these types of infections. Cyclophosphamide and carboplatin were found to be risk factors for ototoxicity, especially when co-administered with cisplatin in the treatment protocol.[3,9,19-22] However, our study could not find any significant relationship between the co-treatment of carboplatin and cyclophosphamide with cisplatin ototoxicity. Other risk factors, such as male gender and cranial irradiation reported in previous literature, had no significant association with ototoxicity in our study.[4,22] This could be due to the small number of patients in our study.

Long-term follow-up of hearing outcome

Cisplatin-induced ototoxicity has mostly been reported to be irreversible[5,9,23,24], although some

studies have observed an improvement in hearing impairment over time post-therapy.[3,25,26] Our study revealed no improvement in hearing impairment after the cessation of therapy. All except one patient did not improve or show progress in their grading of hearing impairment after the end of treatment evaluation. This patient received a high cumulative dose of cisplatin (944 mg/m^2) and had a progression of hearing impairment from grade 1 to grade 2 at 8 months after discontinuing cisplatin. A similar progression of hearing impairment was reported by Bertolini et al.[20], whereby 120 pediatric patients with solid tumors showed no improvement of hearing impairment over the follow-up time after receiving cisplatin and/or carboplatin containing chemotherapy. On the contrary, a worsening or progression of hearing loss at lower frequencies was detected, and 5% of audiograms showed toxicity ≥grade 2 according to Brock's grading scale before the end of therapy. This grading of hearing impairment was observed in 11% of the early post-therapy evaluations and progressed to 44% after more than 2 years of follow-up.[20] Of note, one patient in our study who had recurrent GCT and had received a cumulative high dose of cisplatin (708.2 mg/m^2) followed by a cumulative carboplatin dose of 1,400 mg/m^2 in the BMT course developed grade 3 ototoxicity, which required hearing aids during follow-up after BMT. This finding correlated with the study by Parsons et al.[21] which reported that 9 out of the 11 study children with advanced stage neuroblastoma who underwent autologous BMT (82%) had evidence of speech-frequency hearing loss post-BMT. This group of patients received a high dose of carboplatin >2 g/m^2. This high dose of carboplatin is ototoxic, particularly in patients who have previously received cisplatin therapy or other ototoxic agents. All of these results emphasize the importance of the long-term evaluation of hearing function in pediatric patients who have received cisplatin-based chemotherapy.

In conclusion, this retrospective study demonstrated cisplatin toxicity, in terms of causing irreversible high-frequency hearing loss. A significant risk factor for grade 2-4 hearing loss was found to be a cumulative cisplatin dose ≥400 mg/m^2. Early and regular hearing evaluation during cisplatin treatment is essential for the early detection of hearing impairment. Long-term follow-up is recommended, especially in patients with a high risk of hearing impairment who have been receiving a high cumulative dose of cisplatin, have a young age at diagnosis, and their treatment involves the co-administration of other ototoxic drugs, such as aminoglycoside and high-dose carboplatin.

Our study has several limitations including its retrospective nature, which might lead to some missing data especially data on the ototoxicity of drugs other than aminoglycoside, carboplatin and cyclophosphamide; the limited study number, which might have prevented some parameters from achieving statistical significance in the analyses; and the lack of genetic study for analyzing the association with cisplatin-induced ototoxicity. However, our study highlighted the importance of early and regular audiologic monitoring during and long-term after cisplatin treatment, especially in high-risk patients. Further studies are needed to minimize this complication by the early detection of ototoxicity and the use of cooperative potential otoprotective medication to observe the benefit of hearing impairment recovery and to prevent the progression of this complication.

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Ethical approval

This study was approved by the ethical committee of the Faculty of Medicine Siriraj Hospital (Si 052/2020) and was registered in Thai Clinical Trial Registry (TCTR20210221001).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: TS, KT, KS; data collection: TS; analysis and interpretation of results: TS, KS, KT, KP; draft manuscript preparation: TS, KS, KP, NV, JB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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