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Incidence of Platinum-Induced Ototoxicity in Pediatric Patients in Quebec

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Background. The antineoplastic agents cisplatin and carboplatin are widely-used and highly-effective against a variety of pediatric cancers. Unfortunately, ototoxicity is a frequently encountered side effect of platinum-based chemotherapy. There is currently no treatment or prevention for platinum-induced ototoxicity and development of hearing loss may lead to devastating consequences on the quality of life of pediatric cancer survivors. The objective of this study is to determine the incidence of platinum-induced ototoxicity in a large series of pediatric patients and to evaluate the incidence of progression of ototoxicity after completion of treatment. ***Procedures.*** A retrospective chart review of pediatric patients treated with cisplatin or carboplatin between 2000 and 2012 was conducted. The incidence of ototoxicity was determined based on the American-Speech-Language-Hearing Association (ASHA) criteria and severity was based on the Chang classification. ***Results.*** Four hundred and sixty-six patients received platinum-based chemotherapy. Patients were excluded due to congenital hearing loss (n = 1) and insufficient data for calculating the platinum dose (n = 24) or for assessing ototoxicity (n = 135). Three hundred and six patients were included in the analysis. Post-chemotherapy ototoxicity was detected in 148 (48%) patients, and clinically-significant ototoxicity was present in 91 (30%). In addition, based on the ASHA criteria, 48% of patients (97/204) with long-term follow-up had further deterioration of their hearing after completion of treatment. ***Conclusions.*** Ototoxicity following chemotherapy with cisplatin or carboplatin is common and can frequently progress after the completion of treatment. Long-term follow-up is strongly recommended. Pediatr Blood Cancer 2014;61:2012–2017. © 2014 Wiley Periodicals, Inc.

Key words: late effects of cancer treatment; ototoxicity; pediatric oncology; platinum; progressive hearing loss

INTRODUCTION

The chemotherapeutic agents cisplatin and carboplatin are widely-used and highly-effective against a variety of pediatric malignancies. Despite their effectiveness, however, platinum compounds may also lead to nephrotoxicity, neurotoxicity, and ototoxicity [1]. Platinum-induced ototoxicity manifests clinically with tinnitus and hearing loss, which is often permanent, bilateral, and progressive [1,2]. There is currently no treatment or prevention for platinum-induced ototoxicity and development of hearing loss may lead to devastating consequences on the quality of life of pediatric cancer survivors [3,4]. While fortunately earlier detection and improved treatment have contributed to an increasing number of cancer survivors over the past decade, a large proportion of these survivors have to live with permanent hearing loss.

There is large variability in the reported incidence of hearing loss following platinum administration. In children, the reported incidence ranges from 4% to 80% depending on the study [5–10]. Without an accurate estimate of the incidence of ototoxicity, it is difficult to appreciate the impact of platinum-based chemotherapy on children. A retrospective chart review was conducted in children who had received platinum-based chemotherapy in two major oncology centres in Quebec, Canada, in order to determine the incidence of platinum-induced ototoxicity in these patients.

METHODS

This retrospective cohort study was approved by the Montreal Children's Hospital and Sainte Justine Hospital Research Ethics Boards. Oncology pharmacy records were used to identify patients treated with platinum-based chemotherapy at the Montreal Children's Hospital between January 2000 and July 2011, and at the Sainte Justine Hospital between January 2000 and January 2012. These major tertiary centres in Montreal receive approximately 75–80% of all new cases of cancer in children in the province of Quebec.

Review of the medical records was undertaken by two independent reviewers, with all differences being resolved. Patients with congenital hearing loss or with insufficient data for calculating cumulative platinum dose were excluded before reviewing other clinical and audiological data. Variables recorded for the remaining patients included: gender, diagnosis, age at start of platinum-based chemotherapy, platinum doses (doses in mg/kg were converted to mg/m^2 by multiplying by 30) [11], surgeries, radiotherapies, and administration of other ototoxic medications, including tobramycin, vancomycin, vincristine, cyclophosphamide, mannitol, and furosemide. Results from hearing tests and recommendations for amplification by the audiologist were also documented.

Audiological Evaluations

All audiograms were performed by a licensed audiologist. The test technique was determined by the age, physical status, and cooperation of the patient and included: visual reinforcement audiometry (VRA), conditioned play audiometry, and conventional audiometry. Hearing thresholds recorded included 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz. To distinguish between sensorineural and conductive hearing loss, the air-bone gap was evaluated. If results from an ear indicated an air-bone gap $\geq$15 dB, bone-conduction measurements were used in the assessment of ototoxicity. For

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patients using hearing aids, the unaided audiograms were used. The test battery sometimes included impedance audiometry, Distortion Product Otoacoustic Emission (DPOAE) tests, and Transiently-Evoked Otoacoustic Emission (TEOAE) tests; however, only audiometry results were used in determining the incidence of ototoxicity in this study.

The time interval between audiological assessments was not standardized across patients. All audiological tests were logged into a database. The following tests were included in the analysis: the test conducted before the start of platinum-based chemotherapy (baseline), and the first and last audiograms performed following completion of treatment (post-chemotherapy and follow-up, respectively).

Assessing Ototoxicity

The incidence of ototoxicity was based on sensorineural hearing loss between baseline and post-chemotherapy audiograms at conventional frequencies (0.25–8 kHz). Due to their sensitivity and widespread use, the American Speech-Language-Hearing Association (ASHA) criteria were used, which define hearing loss as 20 dB or greater decrease in pure-tone threshold at a single test frequency, 10 dB or greater decrease in threshold at two adjacent frequencies, or loss of response at three consecutive frequencies where responses were previously obtained [12].

The severity of ototoxicity was determined using the Chang classification, which has been shown to be sensitive and clinically accurate in detecting ototoxicity and appears to have good correlation with clinical outcome [13]. As recommended by Chang and Chinosornvatana [13], Grades 2a and higher are considered clinically significant hearing loss and the higher grade of both ears was used. The Chang grade assigned was based on audiometric frequencies up to 12 kHz.

Patients were excluded from analysis if there was sensorineural hearing loss at baseline, missing post-chemotherapy audiograms, or if normal baseline hearing could not be confirmed. Progressive hearing loss is defined as a change in hearing thresholds based on the ASHA criteria between the post-chemotherapy and follow-up audiograms. The follow-up audiogram must have been performed at least six months after the completion of platinum-based chemotherapy in order to be included.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and audiological results. A standard binary logistic regression was used to model ototoxicity following cisplatin chemotherapy. The outcome binary variable for the regression analysis was the incidence of clinically significant hearing loss (versus non-significant hearing loss), based on the Chang classification. The predictor variables in the regression were the binary variable of gender and the quantitative variables of age of treatment (in months) and single maximum cisplatin dose (in mg/m^2).

RESULTS

Patient Characteristics

The preliminary search through pharmacy records revealed 466 patients treated with cisplatin or carboplatin at the two centres. After excluding one patient with congenital hearing loss and 24 patients with insufficient data for calculating the platinum dose, the audiological, and clinical data for 441 patients was reviewed. Of these, 135 patients were excluded: 74 patients had no post-chemotherapy audiogram, 46 patients had no audiological follow-up, 11 patients had no baseline audiograms, and four patients had pre-existing hearing loss. From the patients with no post-chemotherapy data, 26% (19/74) had documented hearing loss prior to completion of the chemotherapy regimen. In two of the patients with pre-existing hearing loss, this was likely caused by radiotherapy, and was then exacerbated due to platinum administration.

Demographic and clinical data for included and excluded patients is summarized in Table I. Out of the 441 patients, 93 (21%) patients were >2 years old, 93 (21%) patients were 2–5 years old, 86 (20%) patients were 5–10 years old, 82 (19%) patients were 10–15 years old, and 87 (20%) patients were 15–24 years old. In children younger than 5 years old (n = 186), the most frequent diagnoses were neuroblastoma (36%), retinoblastoma (10%), and medulloblastoma (10%). In patients older than 15 years (n = 87), the most frequent were osteosarcoma (32%), Hodgkin lymphoma (14%), medulloblastoma (11%), and extra CNS germ cell tumors (11%). Only four patients (5%) presented with neuroblastoma. In the younger group (<5 years old), only eight patients (4%) were diagnosed with extra CNS germ cell tumours and one with osteosarcoma.

Incidence of Ototoxicity

The incidence of ototoxicity according to the ASHA criteria was 48% (148/306), with 30% (91/306) of patients having Chang grades 2a and higher. Forty-six patients (23%) were recommended amplification, including frequency modulation (FM) systems (n = 12), hearing aids (n = 14), or both (n = 16).

Factors Influencing the Incidence of Ototoxicity

The incidence and severity of ototoxicity is presented by chemotherapy regimen in Table II.

Sample size for the logistic regression analysis was determined by the number of patients who received cisplatin (N = 218). Using clinically significant ototoxicity as the outcome variable, the logistic analysis indicated that the predictor model provided a statistically significant prediction of the severity of hearing loss, $\chi^2(3, N = 218) = 16.67$, $P = 0.001$. The overall prediction success rate of the model was 61.5%; however, correct prediction rates for patients experiencing significant hearing loss was only 26.7%, but 84.1% for those with non-significant hearing loss.

Table III summarizes the partial regression coefficients, Wald test, and odds ratios for each predictor. The Wald test indicated that the age of treatment and single maximum cisplatin dose were significant predictors for hearing loss. For each single-unit increase in age of treatment, there was a 99.4% chance that patients would experience hearing loss, controlling for gender, and single maximum cisplatin dose. Each single-unit increase in maximum cisplatin dose resulted in 1.02 times (95% CI = 1.01–1.03) greater likelihood of significant hearing loss, controlling for gender, and age of treatment.

Progression of Ototoxicity

Two hundred and four patients had long-term follow-up for hearing. Out of these, 97 patients (48%) had progressive hearing loss, defined as a change between post-chemotherapy and follow-up

TABLE I. Demographic and Clinical Data

	Included (n = 306)	Excluded (n = 135)	*P*-value[a]
Age at Tx			
Mean ± SD	7.8 ± 5.8 y	8.8 ± 6.8 y	0.13
Range	2 mo–21.4 y	0.5 mo–23.3 y	
Gender, n (%)			
Male	162 (53%)	75 (56%)	0.61
Female	144 (47%)	60 (44%)	0.61
Received, n (%)			
Cisplatin	147 (48%)	53 (39%)	0.09
Carboplatin	88 (29%)	56 (42%)	0.01*
Both	71 (23%)	26 (19%)	0.36
Cisplatin, in mg/m^2			
Cumulative			
Mean ± SD	380 ± 126	352 ± 167	0.18
Range	20–720	89–750	
Highest single dose			
Mean ± SD	64 ± 25	66 ± 31	0.64
Range	16–120	20–150	
Carboplatin, in mg/m^2			
Cumulative			
Mean ± SD	2,581 ± 1,970	1959± 1,021	<0.01*
Range	450–14,820	168–6,300	
Highest single dose			
Mean ± SD	444 ± 132	445 ± 123	0.95
Range	35–840	28–667	
H&N RT, n (%)	105 (34%)	28 (21%)	<0.01*
Other ototoxic drugs, n (%)			
Any	302 (99%)	130 (96%)	—
Tobra/vanco	231 (76%)	109 (81%)	0.23
VCR	201 (66%)	75 (56%)	0.04*
CPM	183 (60%)	69 (51%)	0.09
Diuretics	247 (81%)	106 (79%)	0.59
Tumor type, n (%)			
Neuroblastoma	69 (23%)	22 (16%)	0.13
Medulloblastoma	48 (16%)	5 (4%)	<0.01*
Osteosarcoma	39 (13%)	25 (19%)	0.11
GC tumor (extra CNS)	18 (6%)	7 (5%)	0.77
PNET	16 (5%)	8 (6%)	0.77
Retinoblastoma	15 (5%)	5 (4%)	0.58
GC tumor (CNS)	14 (5%)	3 (2%)	—
Hodgkin lymphoma	12 (4%)	9 (7%)	0.21
Astrocytoma	11 (4%)	4 (3%)	—
Hepatoblastoma	11 (4%)	2 (1%)	—
Wilms tumor	8 (3%)	12 (9%)	<0.01*
Other[b]	45 (15%)	33 (24%)	0.01*

Age at Tx, age at start of platinum-based chemotherapy; mo, months; y, years; H&N RT, radiotherapy to the head or neck; tobra/vanco, tobramycin or vancomycin; VCR, vincristine; CPM, cyclophosphamide; Diuretics, mannitol and furosemide; GC, germ cell; CNS, central nervous system; PNET, primitive neuroectodermal tumor. [a]Two-tailed *P*-values. [b]This group includes 25 different tumor types. *Statistically significant ($P < 0.05$).

TABLE II. Post-Chemotherapy Evaluation of Ototoxicity (n = 306)

	Chang grade								
	0	1a	1b	2a	2b	3	4	ASHA	Total
Carbo only	81 (92%)	2 (2%)	0 (0%)	0 (0%)	3 (3%)	1 (1%)	1 (1%)	6 (7%)	88
Cis									
≤200*	14 (48%)	2 (7%)	1 (3%)	1 (3%)	3 (10%)	5 (17%)	3 (10%)	17 (59%)	29
200–400*	20 (36%)	8 (14%)	4 (7%)	1 (2%)	12 (21%)	11 (20%)	0 (0%)	38 (68%)	56
≥400*	46 (35%)	28 (21%)	9 (7%)	11 (8%)	10 (8%)	27 (20%)	2 (2%)	87 (65%)	133
All patients	161 (53%)	40 (13%)	14 (5%)	13 (4%)	28 (9%)	44 (14%)	6 (2%)	148 (48%)	306

The post-chemotherapy evaluation consists in the first audiogram performed following completion of treatment. Carbo, patients receiving carboplatin-only; Cis, patients receiving cisplatin. *Cumulative cisplatin doses in mg/m^2.

TABLE III. Logistic Regression

	b	SE-b	Wald	df	Exp (B)	95% CI Exp (B)
Intercept	−0.928	0.498	3.486	1	0.395	
Gender	−0.042	0.283	0.023	1	0.958	0.551–1.668
Age of treatment	−0.006	0.002	6.717	1	0.994	0.990–0.999
Max. cisplatin dose*	0.017	0.006	7.431	1	1.017	1.005–1.029

The dependent variable was hearing loss based on the Chang criteria with significant hearing loss (Grades $\geq$ 2a). b, partial regression coefficients; SE-b, standard error of the coefficient; Wald, Wald test; Exp (B), odds ratio; 95% CI Exp (B), 95% confidence intervals for the odds ratio. *$P < 0.05$.

audiograms based on to the ASHA criteria. The Chang grades at the post-chemotherapy and follow-up audiograms are summarized in Table IV.

Patients underwent audiological testing at different time intervals. Post-chemotherapy audiograms were performed between zero and 42 months (mean 4 months, SD 5 months) after completion of treatment, while follow-up audiograms ranged from six to 125 months (mean 39 months, SD 28 months) after treatment. In order to evaluate whether the time interval had an effect on the incidence of progression reported, results were stratified based on the time to audiogram (Table V). It was observed that patients with longer follow-up periods had greater incidences of progression. Progression of platinum-induced ototoxicity was highest, or 70% (55/79), in the patients with the longest (>60 months) follow-up. Post-chemotherapy Chang grades in this group were grade 0 in 19 patients (41%), grade 1a in six patients (13%), grade 1b in three patients (7%), grade 2a in two patients (4%), grade 2b in two patients (4%), grade 3 in nine patients (20%) and grade 4 in one patient (2%).

Dose Reductions

Sixty-three patients (21%) did not receive the entire planned dose of platinum. In 25 patients, the dose reductions or omissions were due to detection of ototoxicity during audiological monitoring, as per current practice. At the time of dose reduction, 14/25 (56%) of these patients already had clinically significant hearing impairment (Chang Grades 2a or greater). By the post-chemotherapy and follow-up audiograms, the incidence of clinically significant hearing loss had risen to 76% (19/25) and 83% (19/23), respectively. Other reasons for dose reductions included nephrotoxicity (n = 10), infection/neutropenia (n = 4), carboplatin allergy (n = 1), low weight (n = 1), and myelosuppression (n = 1). The reason was unknown in 21 patients (7%).

DISCUSSION

Cisplatin and carboplatin ototoxicity lead to irreversible hearing loss, which can have severe consequences on communication, academic performance, overall health, and the quality of life of survivors [14–17]. In this study, 42% (186/441) of patients receiving platinum-based chemotherapy were younger than 5 years, which has been associated with greater risk of developing ototoxicity [18]. Not only are younger children more susceptible to ototoxicity, but hearing loss is especially devastating in these patients [11].

In this study, there were more male than female patients. Approximately one-third of patients (133/441) received radiation to the head and neck. Most patients received other ototoxic medications concomitantly with platinum-based chemotherapy. Male gender, irradiation to the brain or skull base, and co-administration with vincristine, aminoglycoside antibiotics, and diuretics are all associated with greater risk of developing platinum-induced ototoxicity [19–22]. One third (33%) of patients received carboplatin only, which is less ototoxic than cisplatin [23]. It must also be noted that different genetic polymorphisms may also influence the incidence of ototoxicity [24–26].

The incidence of hearing loss following platinum administration is highly variable depending on the study and ototoxicity criteria used. The definition of hearing loss used in pediatric studies is not always adequate for the detection of platinum-induced ototoxicity [27]. Furthermore, a limitation of most studies is their small sample size. In the present study of 306 patients, it was found that 48% (148/306) had ototoxicity according to the ASHA criteria, with 30% (91/306) developing clinically significant ototoxicity according to the Chang classification. Other studies using the ASHA criteria have also reported incidences of ototoxicity of 50–60% [3,28,29].

The incidence of ototoxicity seemed to be dependent on chemotherapy regimen used. In patients receiving carboplatin-only (n = 88), there was an incidence of only 7% (6/88) according to the ASHA criteria. Other pediatric studies have reported similar incidences of carboplatin-associated ototoxicity [5,7]. The incidence rose to 59% (17/29), 68% (38/56), and 65% (87/133) in patients receiving cumulative cisplatin doses of $\leq$200 mg/m^2, 200–400 mg/m^2, and $\geq$400 mg/m^2, respectively. Logistic analysis showed that age and maximum single cisplatin dose were

TABLE IV. Long-Term Evaluation of Ototoxicity (n = 204)

Grade	0	1a	1b	2a	2b	3	4
Post	91 (45%)	34 (17%)	9 (4%)	10 (5%)	20 (10%)	37 (18%)	3 (1%)
Follow-up	88 (43%)	30 (15%)	8 (4%)	9 (4%)	17 (8%)	41 (20%)	11 (5%)

Chang grades for the post-chemotherapy and follow-up evaluations (the first and last audiograms performed following completion of treatment, respectively). Post, post-chemotherapy audiogram; Follow-up, follow-up audiogram.

TABLE V. Effect of Time of Evaluation on the Reported Incidence of Progression

	Total no. of patients	No. with progression[a]
All patients[b]	204	97 (47%)
Post <6 months[c]	163	77 (47%)
Post <3 months[d]	129	66 (51%)
Post <1 months[e]	72	41 (57%)
FU >12 months[f]	171	88 (51%)
FU >24 months[g]	121	67 (55%)
FU >36 months[h]	86	53 (62%)
FU >60 months[i]	46	32 (70%)

[a]According to the American Speech-Language-Hearing Association (ASHA) criteria; [b]All patients with follow-up audiograms; patients with post-chemotherapy audiograms performed at less than [c]6 months, [d]3 months, or [e]1 month after completion of chemotherapy; patients with follow-up greater than [f]12 months, [g]24 months, [h]36 months, or [i]60 months after completion of treatment.

significant predictors for the incidence of significant hearing loss. Although cumulative dose of cisplatin is a well-known risk factor for ototoxicity [18,22], this was not statistically significant.

Several studies have suggested that platinum-induced ototoxicity can manifest or progress long after the completion of treatment [5,9,10,23,29]. In this way, even minimal hearing loss during chemotherapy may have detrimental effects in patients' quality of life over time. A study performed by our group including long-term follow-up for 21 patients, found that one third of patients had progression of hearing loss following the completion of chemotherapy according to the ASHA criteria [30]. In this study of a larger-scale, we found that 48% (97/204) of patients had progression of hearing loss. When the severity of ototoxicity was evaluated, there was an increasing trend in the proportion of patients with severe hearing loss: Chang Grades 3 or 4 increased from 20% (40/204) post-chemotherapy to 25% (52/204) at follow-up.

Progression of hearing loss was determined based on the post-chemotherapy and follow-up audiograms (the first and last audiograms performed following completion of treatment). Since these were performed at variable time intervals, the incidence of progression may be underestimated by including patients with post-chemotherapy audiograms performed long after completion of treatment or patients with a short follow-up. For instance, in patients with post-chemotherapy audiograms performed within one month after completion of chemotherapy, the incidence of progression was higher (57%) compared to patients whose post-chemotherapy audiograms were performed up to six months after completion of treatment (47%). This suggests that progression may occur soon after completion of chemotherapy in some patients. Furthermore, patients with longer audiological follow-up had greater incidence of progression (70% incidence with follow-up >60 months). The latter was not due to patients with more severe post-chemotherapy ototoxicity being more likely to undergo long-term follow-up for hearing loss, as these patients had a similar distribution of post-chemotherapy Chang grades as the overall cohort.

In many of the currently-used chemotherapeutic protocols, development of ototoxicity results in dose reductions, with the aim of preventing further hearing loss. At least 25 patients in the present study had dose reductions or omissions following detection of ototoxicity. Despite this, 14 of these patients (56%) already had clinically significant hearing loss (Chang Grades 2a or higher) upon detection, with the incidence rising to 83% (19/23) at follow-up. Dose reductions may be more effective in lowering the progression of hearing loss if ototoxicity is detected earlier, before ototoxic damage has progressed to the frequencies involved in speech. This may be achieved through use of high frequency (HF) audiometry (>8 kHz) audiometry.

Although, HF audiometry is not currently used in most centres, numerous studies have shown that HF audiometry is feasible and is more sensitive in detecting early platinum-induced ototoxicity than conventional audiometry (≤8 kHz) alone [28,31–35]. High test-retest reliability has recently been demonstrated for children 7 years and older [36]. Prospective studies should use HF audiometry for more sensitive detection of ototoxicity. Further research is needed to determine whether dose reductions based on HF monitoring protocols could effectively decrease the incidence of platinum-induced ototoxicity.

An inherent limitation due to the retrospective nature of this study is the variability in timing and completeness of audiometry data. Some patients were excluded due to incomplete data. It was noted that patients receiving low-dose carboplatin regimens were less likely to have complete audiological follow-up since they are at lower risk of developing ototoxicity, while patients receiving head and neck radiotherapy were more likely to receive close follow-up. Other baseline clinical characteristics among included and excluded patients were similar. Although, audiological evaluation was fairly consistent between the two centres, there were multiple evaluators. The reviewed records spanned a time period of 12 years in order to maximize the number of patients included in the study; however, oncology protocols have been fairly consistent over this time period.

CONCLUSION

As long as cisplatin and carboplatin remain widely-used chemotherapy agents, ototoxicity will continue to be a major concern for clinicians and patients. This study provides strong evidence that ototoxicity is a common side-effect of platinum based chemotherapy in the pediatric population. Furthermore, it was found that many patients suffer from progression of ototoxicity following completion of treatment. This raises concern, as current ototoxicity monitoring protocols do not always include long-term follow-up for hearing changes. Long-term follow-up for ototoxicity and use of high-frequency audiometry to detect early ototoxicity is strongly recommended in all patients undergoing treatment with platinum-based chemotherapy.

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REFERENCES

1. Rybak LP, Mukherjea D, Jajoo S, et al. Cisplatin ototoxicity and protection: Clinical and experimental studies. Tohoku J Exp Med 2009;219:177–186.
2. Campbell KCM. Pharmacology and ototoxicity for audiologists. Clifton Park, NY: Delmar; 2007.

3. Rybak LP, Whitworth CA, Mukherjea D, et al. Mechanisms of cisplatin-induced ototoxicity and prevention. Hear Res 2007;226:157–167.
4. van As JW, van den Berg H, van Dalen EC. Medical interventions for the prevention of platinum-induced hearing loss in children with cancer. Cochrane Database Syst Rev 2012;5:CD009219.
5. Jehanne M, Lumbroso-Le Rouic L, Savignoni A, et al. Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. Pediatr Blood Cancer 2009;52:637–643.
6. Kushner BH, Budnick A, Kramer K, et al. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer 2006;107:417–422.
7. Dean JB, Hayashi SS, Albert CM, et al. Hearing loss in pediatric oncology patients receiving carboplatin-containing regimens. J Pediatr Hematol Oncol 2008;30:130–134.
8. Massimino M, Spreafico F, Riva D, et al. A lower-dose, lower-toxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma. J Neurooncol 2010;100:65–71.
9. Kolinsky DC, Hayashi SS, Karzon R, et al. Late onset hearing loss: A significant complication of cancer survivors treated with cisplatin containing chemotherapy regimens. J Pediatr Hematol Oncol 2010;32:119–123.
10. Einarsson EJ, Petersen H, Wiebe T, et al. Long term hearing degeneration after platinum-based chemotherapy in childhood. Int J Audiol 2010;49:765–771.
11. Orgel E, Jain S, Ji L, et al. Hearing loss among survivors of childhood brain tumors treated with an irradiation-sparing approach. Pediatr Blood Cancer 2012;58:953–958.
12. American Speech-Language-Hearing Association (ASHA). Audiologic management of individuals receiving cochleotoxic drug therapy [Guidelines]. http://www.asha.org/policy/GL1994–0000 3/. Published 1994. Accessed April 20, 2013.
13. Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. J Clin Oncol 2010;28:1788–1795.
14. Umansky AM, Jeffe DB, Lieu JEC, et al. Quality of life questionnaire for children with hearing loss. J Am Acad Audiol 2011;22:644–653.
15. Varni JW, Limbers C, Burwinkle TM. Literature review: Health-related quality of life measurement in pediatric oncology: Hearing the voices of the children. J Pediatr Psychol 2007;32:1151–1163.
16. Wake M, Hughes E, Collins CZP. Parent-reported health-related quality of life in children with congenital hearing loss: A population study. Ambul Pediatr 2004;4:411–417.
17. Notteghem P, Soler C, Dellatolas G, et al. Neuropsychological outcome in long-term survivors of a childhood extracranial solid tumor who have undergone autologous bone marrow transplantation. Bone Marrow Transplant 2003;31:599–606.
18. Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: The influence of age and the cumulative dose. Eur J Cancer 2004;40:2445–2451.
19. Bokemeyer C, Berger CC, Hartmann JT, et al. Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer 1998;77:1355–1362.
20. Dell'Aringa AH, Isaac ML, Arruda GV, et al. Audiological findings in patients treated with radio- and concomitant chemotherapy for head and neck tumors. Radiat Oncol 2009;4:53.
21. Rybak LP, Ramkumar V. Ototoxicity. Kidney Int 2007;72:931–935.
22. Yancey A, Harris MS, Egbelakin A, et al. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer 2012;59:144–148.
23. Bertolini P, Lassalle M, Mercier G, et al. Platinum compound-related ototoxicity in children: Long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol 2004;26: 649–655.
24. Mukherjea D, Rybak LP. Pharmacogenomics of cisplatin-induced ototoxicity. Pharmacogenomics 2011;12:1039–1050.
25. Ross CJD, Katzov-Eckert H, Dube M-P, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet 2009;41:1345–1349.
26. Oldenburg J, Kraggerud SM, Cvancarova M, et al. Cisplatin-induced long-term hearing impairment is associated with specific glutathione S-transferase genotypes in testicular cancer survivors. J Clin Oncol 2007;25:708–714.
27. Neuwelt EA, Brock P. Critical need for international consensus on ototoxicity assessment criteria. J Clin Oncol 2010;28:1630–1632.
28. Knight KR, Kraemer DF, Winter C, et al. Early changes in auditory function as a result of platinum chemotherapy: Use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol 2007;25:1190–1195.
29. Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: Underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol 2005;23:8588–8596.
30. Al-Khatib T, Cohen N, Carret AS, et al. Cisplatinum ototoxicity in children, long-term follow up. Int J Pediatr Otorhinolaryngol 2010;74:913–919.
31. Dreschler WA, van der Hulst RJ, Tange RA, et al. Role of high-frequency audiometry in the early detection of ototoxicity. II. Clinical Aspects. Audiology 1989;28:211–220.
32. Fausti SA, Henry JA, Schaffer HI, et al. High-frequency monitoring for early detection of cisplatin ototoxicity. Arch Otolaryngol Head Neck Surg 1993;119:661–666.
33. Arora R, Thakur JS, Azad RK, et al. Cisplatin-based chemotherapy: Add high-frequency audiometry in the regimen. Indian J Cancer 2009;46:311–317.
34. Singh Chauhan R, Saxena RK, Varshey S. The role of ultrahigh-frequency audiometry in the early detection of systemic drug-induced hearing loss. Ear Nose Throat J 2011;90:218–222.
35. Abujamra AL, Escosteguy JR, Dall'Igna C, et al. The use of high-frequency audiometry increases the diagnosis of asymptomatic hearing loss in pediatric patients treated with cisplatin-based chemotherapy. Pediatr Blood Cancer 2012;60:474–478.
36. Beahan N, Kei J, Driscoll C, et al. High-frequency pure-tone audiometry in children: A test-retest reliability study relative to ototoxic criteria. Ear Hear 2012;33:104–111.