Carboplatin-Associated Ototoxicity in Children With Retinoblastoma

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Submitted May 9, 2011; accepted November 2, 2011; published online ahead of print at www.jco.org on February 27, 2012.

Supported in part by Grants No. CA21765 and CA23099 from the US Public Health Service and by the American Lebanese Syrian Associated Charities, Research to Prevent Blindness, and St Giles Foundation.

Both I.Q. and J.K.B. contributed equally to this work.

Presented in part at the International Congress of Ocular Oncology, Cambridge, United Kingdom, September 8-12, 2009, and at the Annual Meeting of the American Academy of Ophthalmology, San Francisco, CA, October 24-27, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/12/3010-1034/\$20.00

DOI: 10.1200/JCO.2011.36.9744

A B S T R A C T

Purpose

Carboplatin-induced ototoxicity remains poorly defined but is of potential great consequence in children with retinoblastoma. We retrospectively assessed the incidence of ototoxicity and its risk factors in children with retinoblastoma who were treated with carboplatin.

Patients and Methods

We reviewed the audiologic test results of 60 patients with retinoblastoma who received front-line treatment with systemic carboplatin and vincristine according to the St Jude RET-3 protocol (n = 23) or best clinical management (n = 37). Ototoxicity was evaluated by three different grading systems.

Results

Twelve patients (20%) developed ototoxicity at some time after treatment initiation; however, ototoxicity resolved in two patients, and thus, 10 patients (17%) had sustained hearing loss as documented at their most recent audiologic evaluation. Nine of these 10 patients had grade 3 or 4 ototoxicity, and nine patients were less than 6 months of age at the start of chemotherapy. Age at the start of chemotherapy was the only risk factor identified as a significant predictor of sustained hearing loss. Younger age was associated with an increased incidence of hearing loss. The different ototoxicity grading systems showed good overall agreement in the identification of patients with ototoxicity. Agreement was greatest between the Brock and Children's Cancer Group systems.

Conclusion

We found that young patients with retinoblastoma who were treated with systemic carboplatin had a higher incidence of ototoxicity than previously reported. Younger patients (< 6 months of age at the start of treatment) were more likely to have ototoxicity than were older patients. Children treated with carboplatin should routinely undergo thorough, long-term audiologic monitoring.

J Clin Oncol 30:1034-1041. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy in children. The unilateral, nonhereditary form of the disease is diagnosed at an average age of approximately 2 years; because intraocular disease is usually advanced at diagnosis, patients usually undergo enucleation.¹ The bilateral, hereditary form of retinoblastoma is typically diagnosed before 1 year of age when there is hope of saving one or both eyes.

Systemic chemotherapy has moved to the forefront in the treatment of intraocular retinoblastoma.¹⁻⁵ Because the survival rate for retinoblastoma is greater than 95% in developed countries,^{2,3} the ben-

efit of chemotherapy aimed at saving the vision of a child must be carefully weighed against its potential complications.¹

Carboplatin is the principal agent in all retinoblastoma chemotherapy protocols reported to date. Platinum-induced ototoxicity manifests as bilateral high-frequency sensorineural hearing loss,^{6,7} the incidence and severity of which increase with the cumulative dose. Carboplatin, although considerably less ototoxic than cisplatin, has been linked to sensorineural hearing loss. However, the few available reports that described the ototoxicity of carboplatin are contradictory. Although some articles describe no ototoxicity,³⁻⁵ one article reported ototoxicity in 4.5% of treated children.² Therefore,

we retrospectively studied the incidence and risk factors of ototoxicity in patients with intraocular retinoblastoma who received systemic carboplatin.

PATIENTS AND METHODS

Patients and Treatment

With the approval of the St Jude Institutional Review Board, we retrospectively reviewed an institutional Health Insurance Portability and Accountability Act (HIPAA) –compliant database to obtain information that is relevant to hearing loss in patients diagnosed with retinoblastoma between February 1996 and January 2005 and who received systemic carboplatin as part of a chemoreduction regimen for intraocular disease.

Between 1996 and 2001, patients were treated according to the institutional Retinoblastoma-3 (RET-3) protocol,¹ which comprised 8 cycles of vincristine and carboplatin administered at 3-week intervals. The carboplatin dose was calculated according to the body-surface area (560 mg/m^2) for patients with a glomerular filtration rate (GFR) $\geq 50 \text{ mL/min/m}^2$; for patients with a lower GFR, the dose was adjusted to achieve an area under the curve (AUC; systemic exposure) of $6.5 \text{ mg/mL} \times \text{h}$. A modified Calvert formula was used to calculate the AUC, and the carboplatin dose was calculated to achieve the specified AUC by using the measured GFR and the following regression equation that was previously evaluated in older pediatric patients^{8,9}:

$$\text{Dose}(\text{mg/m}^2) = \text{AUC} \times \{[0.93 \times \text{GFR}(\text{mL} \cdot \text{min}^{-1} \cdot \text{m}^2)] + 15\} \quad (1)$$

The GFR was determined by measuring technetium 99-diethylenetriaminepentaacetic acid serum clearance.¹⁰ Twenty patients treated by using RET-3 protocol received eight cycles of therapy, whereas two patients received six and seven cycles. A third patient received six cycles of carboplatin and vincristine and two cycles of vincristine only.

After the closure of RET-3, patients were treated off-protocol according to best clinical management (BCM) regimens individualized to the intraocular tumor burden and response to chemotherapy; 31 patients were treated with vincristine and carboplatin as in the RET-3 protocol (26 patients received eight cycles, four patients received seven cycles, and one patient received five cycles). Three additional patients received six cycles of vincristine, carboplatin, and etoposide, two patients received eight cycles of vincristine and carboplatin followed by three additional cycles of vincristine, carboplatin, and etoposide, and one patient received eight cycles of carboplatin and three cycles of vincristine and topotecan. Details regarding the chemotherapy type and number of cycles received are listed in Table 1.

Hypothetical cumulative carboplatin doses were calculated for patients with sustained hearing loss to compare these to the actual cumulative doses given (as fixed per square meters or by using the modified Calvert formula). These hypothetical doses were calculated as if all cycles had been administered as fixed per kilogram and dosed at 18.6 mg/kg/cycle . For six cycles (in three patients) in which weights were not available, linear interpolation was used to estimate the weight.

Audiology testing was conducted by using standard procedures (Appendix, online only). The examining audiologist used the following three grading systems (Table 2): the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3 to grade ototoxicity¹¹ and the Children's Cancer Group (CCG)¹² and Brock systems to grade ototoxicity.¹³ A five-point grading scale was used in which grade 0 ototoxicity indicated no evidence of hearing loss. Grades 1 through 4 ototoxicity indicated increasing severity of hearing loss.

All audiologic tests were included in this study to capture cases of hearing loss that were documented at some point but resolved. The first audiologic test of each patient established the baseline. Patients were typically tested at an interim point (usually after four cycles of chemotherapy) and after completion of chemotherapy. Thereafter, patients were followed annually unless hearing loss was detected. Patients with hearing loss were followed more frequently until hearing stabilized.

Statistical Methods

The presence of hearing loss was defined as grade 1 or higher on any of the three grading systems. The proportion of patients with hearing loss at the most recent evaluation was estimated and reported with a 95% Blyth-Still-Casella CI. Logistic regression was used to examine potential risk factors of sustained hearing loss. An odds ratio was reported for significant findings. The cumulative incidence of first hearing loss (hearing loss between the date of treatment initiation and the date of first detection of hearing abnormality and the date of last contact) was estimated by using the method of Kalbfleisch and Prentice.¹⁴ Gray's test¹⁵ was used to compare cumulative incidence curves.

RESULTS

Patients

Between February 1996 and January 2005, 67 patients were treated by using RET-3 or BCM regimens. Seven patients were excluded from this study. One patient was transferred to another facility and was lost to follow-up, three patients received no audiology testing, one patient had only a baseline evaluation, one patient was completely deaf at baseline, and one patient had grade 3/4 hearing loss at baseline that persisted without change.

Characteristics of the 60 patients studied are listed in Table 1. Forty-eight patients (80%) had bilateral retinoblastoma. Most patients were boys ($n = 34$; 57%) and white ($n = 40$; 67%). The median age at diagnosis was 8.6 months (range, 7 days to 13.6 years). Fifty-nine patients (98%) were 3 years of age or younger at diagnosis. All patients were alive, and the median time from the start of treatment to the most recent audiologic evaluation was 73 months.

Twenty-eight of 60 patients (47%) received external beam radiation therapy (EBRT) at a median of 8.7 months (range, 2.5 to 52.8 months) after the start of treatment. Ten patients received bilateral EBRT, and 18 patients received unilateral EBRT. For 41 of 60 patients, the carboplatin dose was based on the body-surface area in all cycles; for six patients, the carboplatin dose was calculated by using the modified Calvert formula in all cycles. For the remaining 13 patients, a combination of the two methods was used. The median cumulative dose of carboplatin for 58 patients with available data was 3850 mg/m^2 (range, 2580 to 4480 mg/m^2). The median cumulative carboplatin dose was 3590 mg/m^2 (range, 2580 to 4480 mg/m^2) in patients less than 6 months of age at the start of treatment and 4032 mg/m^2 (range, 2609 to 4480 mg/m^2) in older children ($P = .016$). Forty percent of carboplatin cycles were administered on the basis of the modified Calvert formula in patients less than 6 months of age compared with only 11% of cycles in older patients.

Incidence of Hearing Loss

The median number of audiologic evaluations per patient was five (range, two to 16 evaluations). A total of 12 patients developed hearing loss at some time after the start of treatment (median, 14.3 months; range, 5.9 to 82.2 months). The cumulative incidence of any hearing loss was estimated to be $20.3\% \pm 5.3\%$ (estimate $\pm 1 \text{ SE}$) at 10 years (Fig 1A). In 2 patients, hearing loss (grade 4 and 1) resolved with continued follow-up. Thus, 10 of 60 patients (16.7%; 95% CI, 8.3% to 27.6%) had sustained hearing loss as documented at the most recent audiologic evaluation.

The median time from treatment initiation to the most recent evaluation was 6.1 years (range, 3.5 months to 13.3 years). Patients

Table 1. Patient Demographics and Treatment Characteristics

Patient Demographics and Treatment Characteristics	All Patients (N = 60)		Most Recent Audiology Outcome			
			Hearing Loss (n = 10)		No Hearing Loss (n = 50)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex						
M	34	57	7	70	27	54
F	26	43	3	30	23	46
Race						
White	40	67	8	80	32	64
African American	16	27	1	10	15	30
Hispanic	4	7	1	10	3	6
Tumor laterality						
Bilateral	48	80	9	90	39	78
Unilateral	12	20	1	10	11	22
Age at diagnosis, months						
Median	8.6		2.2		10.3	
Range	0.2-163.3		0.2-8.3		0.5-163.3	
Age at treatment initiation, months						
Median	8.6		2.3		10.3	
Range	0.4-163.3		0.4-8.3		0.5-163.3	
No. of audiologic examinations						
Median	5		9.5		4	
Range	2-16		5-16		2-10	
Treatment regimen						
RET-3	23	38	2	20	21	42
BCM	37	62	8	80	29	58
Chemotherapy						
VC × 5	1	2	0		1	2
VC × 6	1	2	0		1	2
VC × 7	5	8	1	10	4	8
VC × 8	46	77	7	70	39	78
VC × 6 and VCR × 2	1	2	0		1	2
VCE × 6	3	5	0		3	6
VC × 8 and VCE × 3	2	3	1	10	1	2
VC × 8 and VT × 3	1	2	1	10	0	
Cumulative carboplatin dose, mg/m ² *						
Median	3,850		3,576		3,920	
Range	2,580-4480		2,580-4,480		2,609-4,480	
Dose-calculation method						
All cycles per square meters	41	68	5	50	36	72
All cycles per modified Calvert	6	10	2	20	4	8
Combination	13	22	3	30	10	20
EBRT						
None	32	53	7	70	25	50
Right eye only	10	17	1	10	9	18
Left eye only	8	13	0		8	16
Both eyes	10	17	2	20	8	16
Time from start of treatment to EBRT, months						
No. of patients	28		3		25	
Median	8.7		9.0		8.7	
Range	2.5-52.8		7.8-17.0		2.5-52.8	

Abbreviations: BCM, best clinical management; EBRT, external-beam radiation therapy; RET-3, Retinoblastoma-3 protocol; VC, vincristine + carboplatin; VCE, vincristine + carboplatin + etoposide; VCR, vincristine; VT, vincristine + topotecan.

*Cumulative carboplatin dose was calculated for 58 of 60 patients with available data.

with hearing loss had received more audiologic evaluations (median, 9.5 evaluations; range, five to 16 evaluations) than patients without hearing loss (median, four evaluations; range, two to 10 evaluations).

Among patients with sustained hearing loss, hearing loss was observed to be grade 3 or 4 (Table 3) in nine of 10 patients.

Treatment and audiologic characteristics of the 10 patients who had hearing loss at the most recent evaluation are listed in Table 3. Nine of 10 patients with hearing loss were less than 6 months of age at the time treatment began. Nine of 10 patients had bilateral hearing loss; one patient (patient 4) had grade 1 hearing loss in the right ear only. Six of 10 patients wore hearing aids, and one patient

Table 2. Definition of Ototoxicity/HL Grades According to System Used

Grade	NCI-CTCAE (ototoxicity)	Brock (HL)	CCG (HL)
0	Not defined	< 40 dB HL at all frequencies	No HL
1	Threshold shift or loss of 15-25 dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear	≥ 40 dB HL at 8,000 Hz only	≥ 40 dB HL at 6000 and/or 8000 Hz
2	Threshold shift or loss of > 25-90 dB, averaged at two contiguous test frequencies in at least one ear	≥ 40 dB HL at 4,000 Hz and above	> 25 dB HL at 3,000 and/or 4,000 Hz
3	Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (eg, ≥ 20 dB bilateral HL in the speech frequencies, ≥ 30 dB unilateral HL, and requiring additional speech-language related services)	≥ 40 dB HL at 2,000 Hz and above	> 25 dB HL at 2000 Hz
4	Audiologic indication for cochlear implant and requiring additional speech-language related services	≥ 40 dB HL at 1,000 Hz and above	≥ 40 dB HL at 2,000 Hz

NOTE. Ototoxicity/HL was defined as a change from baseline at the specified frequency.
Abbreviations: CCG, Children's Cancer Group; HL, hearing loss; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

wore a frequency-modulation receiver. Hearing aids and a frequency-modulation system, respectively, were recommended for two patients. Thus, at the time of the study, 90% of our patients with hearing loss were currently using or would have benefited from hearing devices, which indicated significant hearing loss. The remaining patient had unilateral, low-grade hearing loss and did not require a hearing-assistance device.

Risk Factors for Hearing Loss

Potential risk factors for sustained hearing loss examined in our study included sex, race, age at the start of treatment, cumulative carboplatin dose, treatment protocol (RET-3 v BCM), method of calculation of carboplatin dose, and use of EBRT. In univariate logistic regression models, the only significant risk factor observed was age at the start of treatment. Patients younger than 6 months of age were 21 times more likely to have sustained hearing loss than patients 6 months of age and older ($P = .006$). When examined as a continuous variable, age at the start of treatment was also a significant predictor of sustained hearing loss ($P = .008$); increases in age corresponded to lower odds of hearing loss. Cumulative incidences of hearing loss by age group are shown in Figure 1B. The 10-year cumulative incidence of hearing loss was $39.0\% \pm 10.6\%$ for patients younger than 6 months of age versus only $8.3\% \pm 4.7\%$ for patients 6 months of age and older at the start of treatment ($P = .004$; Fig 1B).

To investigate whether our dosing method contributed to the higher hearing loss in our study, we calculated the hypothetical fixed dose per kilogram for the 10 patients with sustained hearing loss and compared it with the actual cumulative carboplatin dose prescribed (Table 3). The hypothetical cumulative fixed dose per kilogram was less than the actual cumulative carboplatin dose prescribed in patients who received a fixed dose per square meters ($n = 5$) or mixed doses according to the Calvert formula and a fixed dose per square meters ($n = 3$). For two patients^{8,9} who received all doses per the Calvert formula, the hypothetical cumulative fixed dose per kilogram was slightly higher.

Agreement Among Audiologic Methods

Grading criteria of each of the three audiologic methods used in our study are listed in Table 2. Two methods were considered to be in agreement if they produced equal grades for both ears at the most recent audiologic evaluation.

The Brock and CCG grading systems of hearing loss showed the greatest agreement (56 of 60 patients; 93.3%). Among the 10 patients with hearing loss at the most recent evaluation, the Brock and CCG grades were the same for both ears in six patients. The four remaining patients had CCG grades that were higher than Brock grades.

The Brock and NCI-CTCAE grading systems were in agreement in 52 of 60 patients (86.7%), but these two systems agreed in only two of 10 patients with hearing loss at the most recent evaluation (Table 3). In the remaining eight patients, seven ears were 1 grade higher in the Brock system, and seven ears were 1 grade higher in the NCI-CTCAE system.

The NCI-CTCAE and CCG grading systems showed agreement in 50 of 60 patients (83.3%), but no agreement was observed in patients with hearing loss at the most recent evaluation. Grades were generally higher when the CCG system was used.

DISCUSSION

The incidence of carboplatin-associated ototoxicity in patients with retinoblastoma has not been well established. We found age at the start of treatment to be a statistically significant risk factor for hearing loss. Younger patients had a greater risk of ototoxicity than did older patients.

Twelve patients in total (20%) had hearing loss at some time after the start of treatment; the 10-year cumulative incidence of any hearing loss was $20.3\% \pm 5.3\%$. With additional follow-up, the hearing losses observed in two patients resolved, but 10 patients (17%) had sustained hearing loss as documented at their last audiologic evaluation. Most ototoxicity was grade 3 or 4 (90%) and bilateral (90%), which underscored its potential impact on quality of life. Because damage to either hearing or vision reduces quality of life,¹⁶⁻¹⁸ partial or total loss of both senses could synergistically impair development, cognition, and rehabilitation, especially in young children.^{19,20} Hence, ototoxicity is a crucial issue in patients with bilateral retinoblastoma.

Four studies in patients with retinoblastoma who received carboplatin reported 0% to 5.6% rates of ototoxicity (Table 4),²⁻⁵ but the studies were difficult to compare because of differences in methodology. We believe that the sensitivity and accuracy of our study were enhanced by the number of hearing tests (median, five tests; range, two to 16 tests), the use of three different grading systems, and the use

Fig 1. (A) Cumulative incidence of hearing loss in all patients. (B) Cumulative incidence of hearing loss by age at treatment initiation (< 6 months [$n = 24$] v ≥ 6 months [$n = 37$]; $P = .004$).

of a lower threshold to define ototoxicity. In addition, our study had the longest follow-up (Table 4). Our institutional protocols have been built on the two-drug regimen of vincristine and carboplatin, and eight cycles of this combination have been usually given.¹ This regimen results in a higher cumulative dose of carboplatin than most other regimens, which usually include six cycles (Table 4). Although it is possible that this higher cumulative exposure to carboplatin increases the risk of ototoxicity, we did not find a direct correlation between dose and hearing loss within our cohort.

Another potential contributing factor to the high ototoxicity rate noticed in our study could be the dosing method of per square meters used by our group. As noted by Kearns et al,²¹ infants in the first 6 months of life have markedly expandable total body water and extracellular water, which is expressed as a percentage of total body weight, and for this reason, many protocols include dosing of anticancer agents (including carboplatin) according to body weight and not surface area. In a previous study by our group that included all patients in the current study, we noticed that the fixed dose per square meters

Table 3. Clinical Characteristics of 10 Patients With Hearing Loss at the Most Recent Evaluation

Patient Number	Age at Treatment Initiation (months)	Protocol Group	Cumulative Carboplatin Dose (mg/m ²)	Actual Cumulative Carboplatin Dose (mg)	Hypothetical Cumulative Carboplatin Dose (mg)*	Chemotherapy	Dosing Method	GFR at Treatment Initiation (mL/min/m ²)	Age at Detection of Hearing Loss (years)
1	8.3	RET-3	4,144	1,761	1,284	VC × 8	F	58.3	3.4
2	2.8	RET-3	4,480	1,914	1,311	VC × 8	F	30.1	7.1
3	0.6	BCM	3,330	1,122	872	VC × 8	F and C	29	5.9
4	4.5	BCM	3,693	1,418	1,127	VC × 8	F and C	69.7	3.9
5	0.6	BCM	3,460	1,303	1,053	VC × 8	F and C	34.3	0.7
6†	3.5	BCM	4,480	1,843	1,388	VC × 8	F	55	0.8
7	1.5	BCM	3,020	1,166	956	VC × 7	F	39.3	0.8
8	1.8	BCM	2,712	989	1,040	VC × 8 + VCE × 3	C	31	0.8
9	0.4	BCM	2,580	806	826	VC × 8	C	34.5	0.8
10	2.8	BCM	4,340	1,552	1,008	VC × 8 + VT × 3	F	55	0.8

Patient Number	Time From Treatment Start to Detection of Hearing Loss	Age at Most Recent Exam (years)	Grade at Most Recent Evaluation						Current Hearing Status
			NCI (R)	NCI (L)	Brock (R)	Brock (L)	CCG (R)	CCG (L)	
1	2.7 years	12.1	3	3	4	4	4	4	Wears hearing aids
2	6.8 years	11.6	3	3	3	2	4	2	Wears hearing aids
3	5.8 years	7.9	3	3	2	2	2	3	Hearing aids recommended
4	3.5 years	5.9	0	0	1	0	1	0	No device
5	8.0 months	7.7	3	3	4	4	4	4	Wears hearing aids
6†	5.9 months	6.6	3	3	3	3	4	4	Wears hearing aids
7	8.5 months	6.5	3	3	3	3	4	4	Wears hearing aids
8	7.2 months	5.4	3	3	2	2	2	2	Wears an FM system
9	9.5 months	6.4	3	3	4	4	4	4	Wears hearing aids
10	6.8 months	3.3	3	3	2	2	2	2	FM system recommended

Abbreviations: BCM, best clinical management; C, Calvert; CCG, Children's Cancer Group; F, fixed per square meters; FM, frequency modulation; GFR, glomerular filtration rate; L, left ear; NCI, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3; R, right ear; RET-3, Retinoblastoma-3 protocol; VC, vincristine + carboplatin; VCE, vincristine + carboplatin + etoposide; VT, vincristine + topotecan.

*If all carboplatin cycles were administered as fixed per kilogram and dosed at 18.6 mg/kg.

†Only patient 6 had unilateral retinoblastoma.

delivered the highest carboplatin dosing for our patients.²² For cycles administered by using the modified Calvert formula, patients received approximately 70% of the hypothetical fixed per square meters. However, compared with the hypothetical fixed dose per kilogram (only one patient received the actual per-kilogram dose in the study), the median difference with the modified Calvert formula was only 13 mg.²² In this study, only two of 10 patients with sustained hearing loss received all of their doses per the Calvert formula. The actual cumulative carboplatin dose prescribed was not higher than the hypothetical fixed dose per kilogram.

The decision of dosing for chemotherapy is generally guided by achieving a response and decreasing toxicity when possible.²³ Targeting systemic exposure by means of AUC dosing provides reliable carboplatin exposure and minimizes inpatient and outpatient variations,²² seems to be a good predictor of hematopoietic toxicity and tumor response in some malignancies²⁴; however, such a correlation has not been well established for ototoxicity.

The incidence of carboplatin-induced ototoxicity in other pediatric cancers is also controversial; reported rates range from no ototoxicity⁷ to one of 25 patients (4%),²⁵ one of 12 patients (8%),²⁶ three of eight patients (38%),¹⁶ and 50% (11 of 22 patients).⁶ Again, the heterogeneity of these studies limits conclusions about the factors that may influence the risk of ototoxicity.

We found young age to be an independent, significant predictor of ototoxicity. Previous studies have found that, with the use of cisplatin, age less than 3 years,²⁷ less than 5 years,²⁸ or less than 7 years²⁹ was

associated with ototoxicity, whereas other studies found that younger age had no effect¹⁶ or even reduced ototoxicity risk.⁷ None of these studies, however, evaluated children in early infancy (< 6 months of age) separately. It should be noted that three of our patients with ototoxicity were diagnosed in the first month of life as a result of familial history and had a low GFR at diagnosis (Table 3), which could have contributed to their ototoxicity. The age distribution at initiation of therapy and cumulative dose for all retinoblastoma patients with and without hearing loss is shown in Figure 2. In addition, the young age of children at risk is delineated in Figure 2.

Our study is the second to use three different grading systems¹⁶ to evaluate ototoxicity but the first study, to our knowledge, to demonstrate a good level of agreement among the three systems. Knight et al¹⁶ used the NCI-CTCAE, Brock, and American Speech-Language-Hearing Association systems but found inadequate agreement and concluded that the NCI-CTCAE, which is the most used system, underestimates the frequency of platinum-associated ototoxicity. Our study did not include the American Speech-Language-Hearing Association system because it requires repeat testing to confirm a significant change in hearing,³⁰ and repeat testing would have imposed extra risk on young patients who required general anesthesia.

Recently, the Children's Oncology Group (COG) published valuable recommendations for the evaluation and management of pediatric patients at risk of hearing loss as a result of disease or treatment modality. The COG task force recommended that childhood-cancer survivors should receive at least yearly hearing tests. More

Table 4. Reports of Carboplatin-Induced Ototoxicity in Retinoblastoma Studies

	Jehanne et al ²	Lambert et al ³	Friedman et al ⁵	Smits et al ⁴	This Study
No. of patients	175	116	47	25	60
With bilateral RB	136	71	38	19	48
Ototoxicity					
No. of patients	8	None	None	None	10
%	5.6				16.7
Age, months					
Median	8	10	Bi, 5; Uni, 7.5	7	8.6 (0.2-163.3)
Range	0-60	0-87	Bi, 0-33; Uni, 0.4-79.2	0.5-41	
FU, months					
Median	60	40	13	25	73
Range	21.6-132	3-127	0.7-34.8	1-94	3.5-159
Time to ototoxicity, months					
Median	44.4	Pre-existing*	NA	NA	9
Range	0-91.2				6-82
Grading system	Brock	NA	NA	NA	Brock, CCG, NCI-CTCAE
Grades reported	All grades				All grades
Dose calculation method	Varied†	Per kilogram	560 mg/m ² or per kilogram‡	Fixed but varied§	Fixed and Calvert
Median carboplatin dose in patients without ototoxicity, mg/m ²	2,880	3,348	NA	2,240	3,920
Median carboplatin dose in patients with ototoxicity, mg/m ²	3,120	NA	NA	NA	3,576

Abbreviations: Bi, bilateral; CCG, Children's Cancer Group; FU, follow-up; HL, hearing loss; NA, not available/not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3; RB, retinoblastoma; Uni, unilateral.

*Three patients had abnormal hearing tests before treatment. Results of these patients results remained abnormal, but no patients developed ototoxicity during treatment.

†The dose of carboplatin varied according to age, weight, and treatment phase.

‡For patients ≤ 36 months of age, the dose was calculated per kilogram.

§A total of 560 mg/m² of carboplatin every 4 weeks or 450 mg/m² every 3 or 6 weeks according to the regimen used.

||Extrapolated from a median of six cycles (each cycle, 18.6 mg/kg).

frequent testing is required if any change is noticed or if hearing loss is suspected.³¹ Also, special testing, such as a distortion product otoacoustic emissions test, is recommended if a conventional audiogram is inconclusive, and testing of auditory brainstem response is recommended for infants. In addition, we recommend testing before each

cycle for patients with retinoblastoma who are less than 6 months of age.

In summary, treatment with carboplatin carries a significant risk of ototoxicity in children with retinoblastoma, especially in children younger than 6 months of age. The dosing of carboplatin should be

Fig 2. Scatter plot of age at treatment initiation and cumulative carboplatin dose.

adjusted for body weight or by using an AUC-dosing method such as the Calvert formula or its variants. Close monitoring during therapy and long-term follow-up and screening should be implemented according to the COG recommendations. Finally, the identification of new strategies to treat retinoblastoma that minimize long-term complications such as ototoxicity is essential.³²

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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