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Assessment of hearing in very young children receiving carboplatin for retinoblastoma

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ABSTRACT

Children with retinoblastoma have increasingly been treated with carboplatin in the past decade. Ototoxicity is a known, possible, side-effect of carboplatin. Since retinoblastoma patients are very young and frequently have impaired vision, the evaluation of hearing loss is very important. The hearing status of 25 children with retinoblastoma treated with carboplatin (median cumulative dose 2240 mg/m^2) was evaluated in detail. Median age at first carboplatin administration was 7 months. The evaluation of hearing loss was performed by an age-appropriate measurement protocol consisting of tympanometry, otoacoustic emission measurements, auditory brainstem responses and (high-frequency) visual reinforcement audiometry (VRA) or play-audiometry. The median follow-up time after last carboplatin dose was 25 months (range 1–94 months). In none of the children was hearing loss detected after carboplatin administration. A measurement protocol that includes tympanometry, distortion product otoacoustic emission measurements and high-frequency VRA is recommended for young children receiving carboplatin or other ototoxic drugs.

1. Introduction

Retinoblastoma is a malignant tumour of the retina, predominantly affecting young children below 4 years of age, with an incidence of 1:17000.[1] The disease can be hereditary (mostly bilateral) or non-hereditary (always unilateral). The genetic cause of retinoblastoma is a mutation or a deletion of the chromosome 13q14, which is detectable in approximately 80% of patients with hereditary disease.[2] Staging procedures of intra-ocular disease follow the Reese-Ellsworth (RE) classification, with five degrees of tumour extension referring to the chance to salvage the affected eye.[3] For advanced extra-ocular disease the Grabrowski–Abramson (GA) classification can be used.[4]

Treatment methods depend on the stage of disease. They can include enucleation, plaque radiotherapy, laser photocoagulation, cryotherapy, (chemo)thermotherapy, chemoreduction and/or chemotherapy and/or external beam radiotherapy. The treatment of choice for individual patients is based on the location, size and number of tumours, the number of eyes affected, absence or presence of extra-ocular tumour sites and the age of the patient.

Many patients with unilateral disease are treated with enucleation of the affected eye, although eye preservation is becoming more usual.[5,6] When invasive disease is observed post-laminar in the optic nerve or massive in the choroidea, additional chemotherapy is applied in order to prevent subsequent metastatic disease.[7,8] In the past, radiation therapy was

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often indicated in hereditary retinoblastoma. However, the risk of facial malformation and the high chance of second primary tumours urged to develop other treatment strategies.[9,10] Chemotherapy and local ocular treatment were combined in terms of chemoreduction facilitating local ocular treatment or in so-called thermochemotherapy, combining laser therapy with systemic carboplatin.[11,12] Finally, retinoblastoma requires intensive chemotherapy in extra-ocular disease.[8,13]

A diversity of chemotherapeutic agents is applied in retinoblastoma, most often including carboplatin. Since children with retinoblastoma often have an impaired vision, it is of major importance to detect ototoxicity due to carboplatin administration as early as possible. Even a minimal hearing loss is a risk factor for acquiring speech and language skills and has a negative impact on spatial awareness.

Carboplatin is a second-generation analogue of cisplatin. Cisplatin is well known to induce otoxicity with specific high-frequency hearing loss with progress to lower frequencies by increasing cumulative dosages. The severity of hearing loss seems to be related to patient age, initial and cumulative dosages, method of administration and cranial irradiation.[14]

While the ototoxicity of cisplatin has been investigated thoroughly, much less is known about the ototoxicity caused by carboplatin. Our overview of the literature summarises articles that report specified audiological evaluation after intravenous administration of a documented dose of carboplatin as single ototoxic drug (Table 1). Several factors appear to contribute to the severity of hearing loss: cumulative doses,[17,18] prior cisplatin exposure[19,21] and radiotherapy, but many studies are not conclusive about possible aggravating factors such as prior irradiation or simultaneous administration of other ototoxic agents (e.g., aminoglycoside antibiotics).

Furthermore, studies on carboplatin-induced ototoxicity in young children often show limited information on the audiological methods to assess ototoxicity at different ages. Those limitations also characterise the scarce data on ototoxicity in children with retinoblastoma receiving carboplatin.[11,13,29–31]

Therefore, the aim of this study is to evaluate the hearing status of infants and young children with retinoblastoma treated with carboplatin by using an age-specific audiologicial measurement protocol.

2. Patients and methods

2.1. Patients and treatment

Children diagnosed with retinoblastoma and treated in our hospital with carboplatin in their chemotherapy regimen were entered in the study. Parental informed-consent was given to participate in the study. Patients underwent initial ophthalmological examinations under general anaesthesia, and intra-ocular staging of the disease was performed according to the Reese–Elsworth classification.

A total of 25 children (12 boys and 13 girls) with retinoblastoma (19 hereditary, 6 non-hereditary disease) were included.

Four options for chemotherapeutic treatment were evaluated: thermochemotherapy with 560 mg/m^2 carboplatin in combination with diode-laser therapy 2 h after infusion (regimen A); chemoprevention with 450 mg/m^2 carboplatin every 6 weeks (regimen B); chemoreduction with 450 mg/m^2 carboplatin every 3 weeks (regimen C); and long-term chemotherapy with 450 mg/m^2 carboplatin every 6 weeks for a duration of at least 1 year (regimen D). All carboplatin doses were infused during 1 h. The different regimes are summarised in Table 2. All patient charts were reviewed regarding the administration of any other potentially ototoxic drugs. Table 3 lists the patient data.

2.2. Audiological procedures

The method of hearing evaluation in young children depends on the age and co-operation of the child. Therefore, various methods of hearing assessment were applied in this study. The measurement protocol is shown in Table 4. The complete audiological regime consisted of one test before each carboplatin dose and at least one test following completion of the chemotherapy.

Tympanograms (226 and 1000 Hz probe frequencies) were recorded by using a Capella system (Madsen Electronics, Denmark). In older children a Zodiac (Madsen Electronics, Denmark) was sometimes used to record 226 Hz tympanograms.

The Capella system was used for otoacoustic emission measurements. Both transient evoked otoacoustic emission (TEOAE) and distortion product otoacoustic emission (DPOAE) measurements were performed. TEOAE measurements were taken in non-linear mode at a stimulus level of 80 dB peSPL. In DPOAE measurements primary levels L1 and L2 were 60 and 50 dB, respectively, and measurements were taken at 2, 3, 4, 6 and 8 kHz.

In this study auditory brainstem responses (ABR) were used only in very young children at pre-treatment to confirm normal hearing by threshold determination. ABR measurements were performed using a Toennis system (Erich Jaeger GmbH, Germany) with alternating clicks presented by TDH-39 headphones at a rate of 21 Hz.

Visual reinforcement audiometry (VRA) with warbled tones in the sound field was used. Frequencies up to 12 kHz were measured.

A Madsen OB822 audiometer (Madsen Electronics, Denmark) with TDH-39 headphones was used for play audiometry and pure-tone audiometry (PTA).

2.3. Evaluating hearing status

An audiologist looked for signs of ototoxicity by comparing the outcome of all different measurements. In particular, changes in high frequency thresholds and high frequency DPOAE strength compared with lower frequency thresholds and DPOAE strength, were determined as signs of ototoxicity.

3. Results

For the 25 children entered in the study the different chemotherapy regimens were applied as follows: thermochemotherapy in 10 patients for 2–8 courses, chemoprevention in 7 patients, chemoreduction in 4 patients with large tumours (1 had to stop after only one course), while long-term chemotherapy was administered in 3 patients (1 fatal trilateral

Table 1 – Overview of relevant literature on ototoxicity of carboplatin

Study (year)	Patients (evaluated for ototoxicity)	Age[a] (years) (median)	Cumulative carboplatin dose, mg/m^2 (median) infusion dose and time	Relevant factors	Audiometric methods	Findings
Gaynon et al. (1990)[15]	95 (38)	1–20 (7)	560–12,880 (1020), 560 mg/m^2 in 1 h	12/38 received cisplatin previously information on prior radiation therapy not available	PTA or ABR	• 1/38 had hearing loss $\geqslant$40 dB at <4 kHz • 5/38 had hearing loss >40 dB at $\geqslant$4 kHz or 20–40 dB hearing loss at <4 kHz • 32/38 no significant hearing loss (i.e., hearing loss <20 dB at <4 kHz and <40 dB at $\geqslant$4 kHz)
Kennedy et al. (1990)[16]	27	20–72 (48)	300–2400, 300–400 mg/m^2 in 1 h		PTA	• 5/27 increase of $\geqslant$30 dB in threshold • No significant influence of pre-treatment threshold or cumulative dose
Bauer et al. (1992)[17]	65	49–76 (58)	1080, 120 mg/m^{2}d 1–3–5 infusion NM		PTA	• Hearing loss in 42/130 ears • No correlation between age and ototoxicity • No correlation between existing hearing loss and ototoxicity • Proportion of patients with reduced hearing increases with cumulative doses
Macdonald et al. (1994)[18]	22	4–17	1000–5500 (2500) infusion NM	3/22 received cranial irradiation	PTA up to 12 kHz	• After two doses (1000 mg/m^2) 12/21 patients showed hearing loss at 8 kHz • Proportion of patients with hearing loss and mean hearing loss increases with cumulative doses

Ettinger et al. (1994)[19]	117 (30)	1–23 (10)	560–at least 3920 (560), 560 mg/m^2 in 1 h	71 received cisplatin previously	PTA or ABR	• 1/30 had 30 dB hearing loss at 3 kHz and $\geqslant$60 dB hearing loss at $\geqslant$4 kHz • 1/30 developed an additional 40 dB hearing loss at 3 kHz. This patient had pre-existing severe high-frequency hearing loss • Both patients received cisplatin previously
Heideman et al. (1995)[20]	26 (23)	3.6–17.3 (9.5)	2800, 350 mg/m^2 in 1 h for 2 d	Pre-irradiation chemotherapy	PTA	• 1/23 had 35 dB hearing loss at 2 kHz • 1/23 had 45 dB hearing loss at 2 kHz
Freilich et al. (1996)[21]	11	17–63 months (43 months)	1500, 500 mg/m^2 in 4 h for 3 d	All received cisplatin previously, All received aminoglycoside antibiotics, One patient received cranial irradiation before final hearing evaluation	Behavioral, play and standard audiometry	• Hearing deterioration in 5/11 patients • 7/11 had high-frequency hearing loss after cisplatin treatment
Cavaletti et al. (1998)[22]	10 (9)	31–53 (44)	3500, 350 mg/m^2 in 2–3 h for 5 d (two courses) or continuous in 24 h (two courses)		PTA, ABR	• 8/9 had increase in threshold almost exclusively at 4 and 8 kHz • 1/9 had 30 dB increase at 4 kHz and 70 dB at 8 kHz • 1/9 had 65 dB increase at 2 kHz, 75 dB at 4 kHz and 90 dB at 8 kHz • 9/9 had unchanged ABR
Parsons et al. (1998)[23]	11	1.1–17.5 (3.9)	2000, 667 mg/m^2 in 1 h for 3 d	All received cisplatin previously 8/11 received carboplatin previously 9/11 had hearing loss prior to high-dose carboplatin 9/11 received radiation abdominal Majority of patients received aminoglycoside antibiotics and/or diuretics during their course	PTA, play audiometry, VRA or ABR	• All patients sustained worsening of hearing

(*continued on next page*)

Table 1 – (*continued*)

Study (year)	Patients (evaluated for ototoxicity)	Age[a] (years) (median)	Cumulative carboplatin dose, mg/m^2 (median) infusion dose and time	Relevant factors	Audiometric methods	Findings
Aquino et al. (1999)[24]	12	1–15 (9)	3360–10,080 (8400), 560 mg/m^2 in 1 h	One patient underwent radiation therapy prior to chemotherapy	PTA	• One patient developed unilateral high frequency hearing loss[b]
Wandt et al. (1999)[25]	21	30–59 (50)	4800–5200, 1600 or 1800 mg/m^2 continuous in 3 d	7/21 pre-treated with cisplatin or carboplatin	PTA	• NCI grade 1, 2 and 3 ototoxicity occurred in 6/21, 10/21 and 1/21, respectively
De Lauretis et al. (1999)[26]	12	51–71	Up to 2250, 250 mg/m^2 in 1 h		PTA, ABR	• None of the patients showed hearing loss • No significant changes in ABR results
Jillella et al. (2000)[27]	14 (11)	36–57 (48)	800, 800 mg/m^2 continuous in 4 d	All patients received diuretics 13/14 received gentamicin	PTA and DPOAE	• None had audiometric threshold shifts from 250 to 8000 Hz • 1/11 showed changes in DPOAEs (greater than 6 dB change in three adjacent frequencies)
Meyer et al. (2001)[28]	69 (33)	1.2–24.1 (14.1)	2800 mg/m^2, 560 mg/m^2 in 1 h	Multi-agent chemotherapy protocol, including ifosfamide, doxorubicin and methotrexate	PTA	• No hearing loss detectable by PTA in 33/33 patients

PTA, pure-tone average; ABR, auditory brain stem response audiometry; VRA, visual response audiometry; DPOAE, distortion product otoacoustic emissions.
a Age of diagnoses or initial carboplatin dose.
b In general, ototoxicity appears bilateral.

Table 2 – Cytostatic drug treatment schedules

Chemotherapy regimen	Cytostatic drugs and doses[a]		Duration of therapy
A. Thermochemotherapy	Carboplatin 560 mg/m^2[2b]		Ongoing until persisting flat tumour scars
B. Chemoprevention	Vincristine 2 mg/m^2	Day 1 + 8	3 courses
	Cyclophosphamide 500 mg/m^2	Day 1–3	
	Carboplatin 150 mg/m^2[2b]	Day 21–23	
	Etoposide 150 mg/m^2	Day 21–23	
C. Chemoreduction	Vincristine 1,5 mg/m^2	Day 1 + 8	At least three courses
	Carboplatin 300 mg/m^2[2b]	Day 1	
	Etoposide 225 mg/m^2	Day 1	
	or cyclophosphamide 300 mg/m^2	Day 1	
	additional cyclosporin A		
D. Long-term chemotherapy	Vincristine 2 mg/m^2	Day 1 + 8	1 year
	Cyclophosphamide 500 mg/m^2	Day 1–3	
	Carboplatin 150 mg/m^2[2b]	Day 21–23	
	Etoposide 150 mg/m^2	Day 21–23	

Four different treatment schedules including carboplatin in the treatment of children with retinoblastoma were used.
a In case of weight <10 kg, dose calculation per kg, 1 m^2 = 30 kg.
b Carboplatin infusion in 1 h.

Table 3 – Patient data

Patient number	Age at start treatment (months)	Hereditary	RE class		Enucleation	ERBT (E)/ plaque RT (P)	Carboplatin		Chemotherapy regimen	Follow-up time (months)
			OD	OS			Courses	Cumulative dose (mg/m^2)		
1	1	H	V	I a	OD	E	5	1240	D	94
2	27	H	I a	V	OS		9	3150	D	1
3	14	H	II a	II a		E	3	1350	B	55
4	34	H	V b	V b	OD	E	6	3280	C	24
5	13	H	II b	V	OS	E	3	1350	B	59
6	32	N	V		OD		3	1350	B	47
7	8	N		V	OS		3	1350	B	41
8	14	N	V		OD		3	1350	B	40
9	6	H	III	Ia			4	2860	C	32
10	0.5	H	II a	I a			5	2240	C	62
11	1	H	II a	I a		P	1	560	C	41
12	3	H, 13q –	I a				3	1680	A	
13	41	N	V		OD		3	1350	B	19
14	5	H	I b	II a			3	1680	A	37
15	2	H	II a	I b			4	1720	B + A	37
16	1	H	I a	I a			6	3360	A	18
17	1	N	I a	I a		P	6	5600	A	10
18	7	H	I b	V a	OS		5	2800	A	26
19	5	H	V b	I a	OD		4	2240	A	19
20	36	H	III a	V	OS	P	3	6580	D	6
21	9	H	III	V	OS	P	5	2800	A	12
22	15	N	V		OD		3	1050	B	15
23	30	H	V b	III	OD		4	2240	A	9
24	2	H	I a	III			7	3920	A	2
25	1	H	I a	I a			8	4420	A	21

An explanation of the chemotherapy regimen can be found in Table 2.
DOD, dead of disease; RE, Reese Ellsworth classification of retinoblastoma; 13q–, syndrome with 13q minus karyotype.

retinoblastoma, 2 systemic metastasis with 1 subsequent fatal central nervous system (CNS) disease). One patient received sequential treatment with thermochemotherapy and chemoprevention.

Besides the chemotherapeutic treatment, local therapy with cryocoagulation and diode laser-therapy was performed by the ophthalmologist in 20 patients, and prior enucleation of the eye was performed in 15 patients. External beam radiotherapy (EBRT) was necessary in 4 patients, while a radioactive plaque was administered in 5. The field of radiation in EBRT was limited to the eye without the risk for acquiring hearing loss.

Table 4 – Age-specific measurement protocol used for hearing evaluation in young children

Measurements	Age (months)		
	0–9	9–36	>36
Tympanometry (1000 Hz)	×		
Tympanometry (226 Hz)	×	×	×
Distortion product otoacoustic emission measurements (DPOAE)	×	×	×
Transient evoked otoacoustic emission measurements (TEOAE)	×	×	×
Auditory brainstem responses (ABR)	×		
(High-frequency) visual reinforcement audiometry (VRA)		×	
(High-frequency) play-audiometry			×

One child (patient 12) with 13q minus syndrome was treated with carboplatin and included in the thermochemotherapy, but she was excluded from further audiological analysis in this study, since she had severe hearing loss pre-treatment as was detected by ABR.

One child (patient 20) had extensive relapsing disease after a prior chemoprevention schedule for massive choroideal invasion. The chemotherapy schedule at relapse was continued including cisplatin. Still, the patients audiological test results remained normal until shortly before he died.

None of the patients received additional ototoxic drugs such as antibiotics or diuretics.

For the 25 children included, first carboplatin dose was administrated at a median age of 7 months (range 0.5–41 months). The median dose of carboplatin was 2240 mg/m^2 (range 560–6580 mg/m^2). Follow-up time after the last carboplatin dose ranged between 1 and 94 months (median 25 months).

None of the children or parents reported subjective hearing loss at the last evaluation. Although the aim was a regular follow-up, the measurement protocol could not be performed fully every time in every child due to lack of co-operation or, factors such as middle-ear pathology. On average, each child was evaluated 4.6 times, including a baseline visit. One child had a pre-existing hearing loss.

In 21 children the available audiological measurements were sufficient to conclude that there were no signs of ototoxicity. In 16/21 children the last audiological evaluation showed no hearing loss as confirmed by VRA or play audiometry, TEOAE and DPOAE measurements. 4/21 children could only be evaluated by play audiometry and showed normal thresholds. 1/21 child was evaluated by OAE measurements only because of its young age.

In 2 of the remaining 4 children it was not possible to make a reliable evaluation because of recurrent middle ear problems. One of these children received ventilation tubes. One child (patient 12) had 13q minus syndrome and had a severe hearing loss pre-treatment.

One child (patient 10) had a bilateral small high-frequency hearing loss. Air conduction thresholds ranged from 10 dB at 2 kHz to 50 dB at 8–12 kHz for the left ear and 5 dB at 2 kHz to 25 dB at 8–12 kHz for the right ear. The hearing loss of this child was judged as a sensorineural loss at the right ear and a mixed hearing loss at the left ear. Whether the small sensorineural hearing loss is due to ototoxicity of carboplatin remains unclear, because the pre-treatment hearing evaluation, at 1 month of age, consisted of ABR, which is incapable of detecting small hearing losses at 8 kHz.

Brock and colleagues[32] proposed a grading system of cisplatin-induced hearing loss that can also be applied to the data in the present study. In that grading system the hearing loss was graded according to the frequency at which the pure-tone threshold is worse than 40 dB. All of the children that were evaluated by VRA or play audiometry had a hearing loss of grade 0. Note that the child with a mild high-frequency hearing loss also had grade 0.

4. Discussion

Carboplatin is widely used in paediatric oncology, including the treatment of retinoblastoma. Although ototoxicity of carboplatin is much less common than ototoxicity of cisplatin, it is a well known side-effect. In general, retinoblastoma patients are very young at the start of treatment, which might make them more vulnerable to otoxicity of carboplatin. The correlation between age and ototoxicity of cisplatin has been suggested before[33–35] but has not been reported for carboplatin. Because of the young age of retinoblastoma patients, they are also in a vulnerable period for normal speech and language acquisition.

Even minimal sensorineural hearing loss, if not detected in time, can have far-reaching consequences. Crandell[36] showed that children with average pure-tone thresholds of 15–30 dB HL obtained significant poorer speech recognition scores in noise conditions. Bess and colleagues[37] found that even very small hearing losses can be associated with increased social and emotional dysfunction among school-aged children.

It is important to realise that children with retinoblastoma might suffer from impaired or no vision and thus are more dependent on hearing ability. Since carboplatin is accepted worldwide as a component of retinoblastoma treatment, its safety for the hearing of these young patients warrants a closer study. Our study investigated possible ototoxic effects of carboplatin in retinoblastoma patients. The young age of the children made the use of an extensive age-appropriate measurement protocol inevitable.

In older children and adults, pure-tone audiometry and speech audiometry are most frequently used for monitoring ototoxicity. Pure-tone thresholds can be measured reliably and ototoxic agents cause a bilateral sensorineural hearing loss that starts in the high frequencies and extends to lower frequencies. The sensitivity can be improved by using high-frequency audiometry.[38] Unfortunately, these methods are not suitable for young children. The audiological methods applied in this study have different advantages and disadvantages for detecting ototoxicity. The value of VRA, ABR and OAE measurements in monitoring ototoxicity depends largely on normal middle ear function. Tympanometry was performed at each evaluation to search for middle ear problems. In children less than 9 months of age both 226 and 1000 Hz tympanometry was used, since higher probe frequencies are more suitable in the young children. Otoacoustic emis-

sion measurements are probably the most promising objective method for monitoring ototoxicity in children.[39–41] Otoacoustic emissions (TEOAEs and DPOAEs) are signals generated by the outer hair cells of the cochlea in response to acoustic stimuli. OAEs are not age-limited and can be detected objectively by placing a probe in the outer ear canal. However they can not be used to determine hearing thresholds. DPOAEs are more frequency specific than TEOAEs. Although, it has been well established that cisplatin affects outer hair cells, this has not been confirmed for carboplatin and human inner ears.

In former days ABR was the only objective audiological method before the discovery of otoacoustic emissions. (Click-evoked) ABR measures the auditory system up to brainstem level and is suitable for infants. Disadvantages are the long test time and limited frequency specificity. In contrast with OAE measurements, ABR can be used for hearing threshold determination. Weatherly and colleagues[34] state that ABR testing alone for cisplatinum has limited diagnostic value due to the limited sensitivity.

VRA is only useful for children over approximately 6–9 months of age. Small changes in hearing loss can be difficult to detect because only response thresholds can be measured. In this study frequencies up to 12 kHz were measured. Measuring these high frequencies with VRA has proven its value in our clinic in detecting early stages of ototoxicity in children receiving cisplatin. As far as the authors know using these high frequencies in VRA has not been published before. For children from at least 2.5–3 years old, play audiometry can be used, which make high-frequency measurements and bone conduction measurements possible. Evaluation of hearing status in young children is hampered for several reasons. First, the occurrence of middle-ear problems may cause changes in hearing thresholds. Secondly, in children under approximately 9 months of age no ideal measurement procedure for frequency specific hearing thresholds is available. Furthermore, VRA thresholds are less reliable than PTA thresholds in adults. Thirdly, both VRA thresholds and OAE strength change over time in the first few years of life, making comparison of changes difficult.

We compared our results directly with previous published reports on carboplatin ototoxicity (Table 1). Differences in audiological methods, reported audiological findings, age of subjects, infusion time and use of other ototoxic treatments are present. The study of Freilich and colleagues[21] showed hearing deterioration in 5 out of 11 children receiving carboplatin, however all patients had cisplatin in preceding chemotherapy courses. Macdonald and colleagues[18] found a high rate of hearing loss in children receiving carboplatin, half of them after two courses. None of their children had received cisplatin or other ototoxic agents before. On the other hand, Meyer and colleagues[28] found no hearing loss in their study on 33 patients. Our patient group is the youngest described in the literature thus far. Although ototoxicity of cisplatin seems related to age,[14] our results from very young children suggest that this might be not the case for carboplatin. Our results might suggest a redundancy of regular audiometry in this patient group, however monitoring of hearing status remains to be recommended since this study group is too small to generalise the results and because it has been reported that carboplatin is ototoxic.

Carboplatin is very important in the reduction of EBRT in retinoblastoma treatment, in order to reduce facial malformation and the chance of second malignancies. Our results suggest that carboplatin can be safely administered at usual doses to the very young children suffering from retinoblastoma. Since this patient group harbours very young children and possibly acquiring some loss of vision we still recommend close monitoring for ototoxicity by using appropriate audiological measurement methods. It is proposed to include high-frequency VRA or play audiometry and DPOAE measurement methods. The measurement protocol is recommended as a general protocol for assessment of hearing in young children receiving ototoxic drugs, including carboplatin and cisplatin.

Conflict of interest statement

None declared.

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