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Ototoxic Hearing Loss and Retinoblastoma Patients

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1. Introduction

Chemotherapy is often used in the conservative management of retinoblastoma. Chemotherapy drugs, while ameliorative, can produce long-lasting side effects that potentially can affect survivor quality of life. Carboplatin is a common chemotherapy agent with known ototoxic side effects that is used in the treatment of retinoblastoma (Rodriguez-Galindo et al., 2003). The potential for carboplatin-induced hearing loss is of concern to the medical professional, given that retinoblastoma is often diagnosed in early childhood and children with retinoblastoma have visual impairments. This chapter will outline the mechanisms underlying carboplatin ototoxicity. The extent of knowledge concerning the pathophysiology of carboplatin-induced hearing loss will be explained, and descriptions of the progression of hearing loss on the audiogram will be provided. The types of hearing tests administered to patients receiving carboplatin chemotherapy and monitoring regimens will be reviewed in the chapter. Physiological hearing tests, including the auditory brainstem response (ABR) and otoacoustic emissions (OAE) will be described. Knowledge of these tests will assist the medical professional in understanding if a particular chemotherapy regimen is potentially causing a hearing loss.

The impact of high-frequency hearing loss on the development of speech and language in young children will be discussed, which is of particular relevance in children with an existing visual loss. In the context of this discussion, the academic and social development of children with hearing loss will be addressed. Future directions, including the potential use of otoprotective agents that can be given concurrently with chemotherapy treatment, will be highlighted at the end of the chapter.

2. Pathophysiology of carboplatin-induced hearing loss

Carboplatin (*cis*-diammine [1,1-cyclobutanedicarboxylate]-platinum [II]) is a second-generation platinum compound that initially was reported to have less nephrotoxic and ototoxic side effects than its analog, cisplatin (Bacha et al., 1986). It is a common chemotherapy agent used in the treatment of a wide range of pediatric malignancies. More recently, higher incidences of carboplatin ototoxicity have been reported compared with what was previously described in the literature. The pathophysiology of carboplatin ototoxicity is not completely understood, but evidence from experimental animal models

suggests dose-dependent and species-specific effects of carboplatin. Chinchillas are rodents that are commonly used as animal models in experimental studies. In chinchillas, administration of low doses of carboplatin results in the progressive loss of inner hair cells and spiral ganglion neurons from the apex to the base of the cochlea, and outer hair cells are largely unaffected (Takeno et al., 1994; Hofstetter et al., 1997a; Wang et al., 2003; Bauer & Brozoski, 2005). At higher doses of carboplatin, extensive loss of inner hair cells is exhibited across all cochlear turns, and loss of outer hair cells is exhibited most prominently in the basal turn (Hofstetter et al., 1997a; Bauer & Brozoski, 2005). Studies of high-dose carboplatin administration in guinea pigs revealed that primarily outer hair cells were destroyed (Saito et al., 1989), and both outer and inner hair cells were affected in rats (Husain et al., 2001).

3. Methods of hearing assessment in young children

Retinoblastoma is one of the most common intraocular malignancies in young children and it is usually diagnosed before children reach three years of age (Broaddus et al., 2009). Until recently, suspicion of childhood hearing loss was primarily based on behavioral observations by physicians or anecdotes provided by concerned parents. However, reliance on behavioral observations is often confounded by the fact that hearing-impaired infants often seemingly respond to environmental sounds and can babble in a manner similar to normal-hearing infants (Marschark, 1997). These factors often resulted in delays in identifying children with hearing loss. In the past, the typical age of identification of hearing loss in the United States was 11-19 months for children with risk factors for hearing loss and 15-19 months for children with no known risk factors (Mauk et al., 1991; Parving ,1993; Stein, 1995; Harrison & Roush, 1996). In the United Kingdom, the average age of suspicion of hearing loss was 18.8 months and hearing loss was confirmed at an average age of 26 months (Davis et al., 1997). It is crucial that young children with retinoblastoma experiencing vision loss be monitored appropriately while they undergo chemotherapy, as undetected ototoxic hearing loss can impact the development of speech and language.

Hearing is a complex psychological process involving the detection, identification, and comprehension of sound. Assessment of hearing in infants and young children has evolved from reliance primarily on behavioral observations alone to combining behavioral observations with computer-based measurements of auditory physiology. As infants and young children often cannot respond reliably during behavioral hearing assessments, modification of the testing protocol often includes physiological tests of auditory function. While physiological measurements do not test the psychological aspects of hearing directly, they provide information on the status of anatomical structures believed to be crucial for hearing. The major advantage of these physiological tests is that they do not require a behavioral response from the infant, and can be completed rapidly. Most importantly for screening purposes, physiological test results are highly informative in distinguishing between normal-hearing infants and infants with hearing loss. The Joint Committee on Infant Hearing recommended inclusion of ABR and/or OAE tests in screening programs designed to detect hearing loss in infants (Joint Committee on Infant Hearing, 2000). Although these tests are not true tests of hearing, they may provide evidence of a change in cochlear function during the administration of potentially ototoxic medications including carboplatin.

Study	Behavioral Audiometry	ABR	OAE	# of patients studied
Smits et al. (2006)	**Yes**	**Yes**	**Yes**	**25**
Lambert et al. (2008)	**Yes**	**Yes**	**No**	**164**
Jehanne et al. (2009)	**Yes**	**No**	**No**	**175**
Bhagat et al. (2010)	**No**	**No**	**Yes**	**10**
Pecora Liberman et al. (2011)	**Yes**	**No**	**Yes**	**15**

Table 1. Recent studies investigating carboplatin ototoxicity in children with retinoblastoma,the monitoring methods used, and the number of patients examined. Yes indicates the test (behavioral audiometry, ABR, OAE) was evaluated in the study and No indicates the test was not evaluated.

3.1 Behavioral assessment of hearing

Assessment of infant hearing involves presentation of sounds through loudspeakers and observing the infant's behavior. If a change in behavior (i.e. the infant is startled) occurs following presentation of a sound, a positive response is noted. The sound level is lowered and the procedure is repeated until no change in behavior is observed. Many infants can respond reliably at sufficiently low levels of sound, and this is suggestive of normal hearing. However, the response of other infants for similar sound levels may be ambiguous. This procedure requires a subjective judgment on whether or not a response has occurred. In addition, many infants cease to respond behaviorally after repeated trials, even though they may be aware of sound in their environment. For these reasons, response detection levels for many infants only provide a gross estimate of hearing sensitivity. However, behavioral observation of infant hearing is useful in corroborating the results of physiological screening tests. For example, if an infant fails an OAE and/or ABR screening, and does not exhibit a behavioral response at sound levels indicative of normal hearing, a hearing loss can be confirmed. In addition, observation of developmental auditory behavior in infants can provide a guideline for comparative purposes. At three months of age, most normal-hearing infants are able to follow the direction a sound is coming from with their eyes. By six months of age, they can turn their heads to determine the source of sounds. If an infant exhibits delays in development of auditory behavior, a hearing loss may be indicated. For older children, hearing may be assessed by visual reinforcement audiometry (VRA) or conditioned play audiometry(CPA). In VRA, a sound is presented through loudspeakers and the child is directed to turn their head in the direction of where the sound came from. Following a correct response, the child is rewarded by seeing an animated toy. This form of reinforcement serves to help the clinician to orient the child to participate in the task and to determine the child's hearing sensitivity. By lowering the sound level until no response is provided by the child, the clinician can obtain an estimate of the hearing threshold on a frequency-by-frequency basis. In CPA, sounds may be presented through loudspeakers or through headphones, and a child is conditioned to drop a block in a bucket (or similar task)

every time a sound is heard. Hearing thresholds can be tracked by noting the transitions between sound levels where the child performs or does not perform the task. For both VRA and CPA, the clinician makes a subjective decision to determine whether or not a response occurred, and these methods typically are reserved for children up to 4 years of age. Most older children can participate in a conventional hearing test, whereby they raise their hand or push a button every time they hear a sound, and their responses are noted on a conventional audiogram.

Platinum-compound ototoxicity typically causes hearing loss at audiometric frequencies above 2000 Hz (Macdonald et al., 1994). There are guidelines in place that help to characterize shifts in behavioral hearing thresholds on the audiogram due to the administration of ototoxic medications. Common guidelines in use to characterize ototoxicity in the United States are shown in Table 2. In monitoring ototoxicity, it is vitally important to obtain baseline measurements of hearing before the patient undergoes

Brock	NCI CTCAE	CCG	Chang
Grade 0: < 40 dB at all frequencies		Grade 0: No hearing loss	Grade 0: ≤ 20 dB at 1, 2, and 4 kHz
Grade 1: ≥ 40 dB at 8 kHz only	Grade 1: Threshold shift or loss of 15-25 dB averaged at two contiguous frequencies in one ear	Grade 1: ≥ 40 dB HL loss at 6 kHz and/or 8 kHz	Grade 1a: ≥ 40 dB at any frequency from 6-12 kHz Grade 1b: >20dB and <40 dB at 4 kHz
Grade 2: ≥ 40 dB at 4 kHz and above	Grade 2: Threshold shift or loss >25-90 dB averaged at two contiguous frequencies in one ear	Grade 2: >25 dB HL loss at 3 kHz and/or 4 kHz	Grade 2a: ≥ 40 dB at 4 kHz and above Grade 2b: >20dB and <40 dB at any frequency below 4 kHz
Grade 3: ≥ 40 dB at 2 kHz and above	Grade 3: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g. > 20 dB bilateral loss in the speech frequencies)	Grade 3: >25 dB HL loss at 2 kHz	Grade 3: ≥ 40 dB at 2 or 3 kHz and above
Grade 4: ≥ 40 dB at 1 kHz and above	Grade 4: Indication for cochlear implant	Grade 4: ≥ 40 dB HL loss at 2 kHz	Grade 4: ≥ 40 dB at 1 kHz and above

Table 2. Common grading scales used in the United States for characterizing ototoxic hearing loss. dB= decibels, dB HL= decibels hearing level, kHz= kiloHertz.

chemotherapy, and then to monitor their hearing at prescribed time points once treatment commences. This allows for comparisons to be made between pre-treatment hearing and peri- or post-treatment hearing in the patient. The Brock grading scale (Brock et al., 1991) assigns a grade based on degree of bilateral hearing loss. The NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) uses threshold shifts to assign its grades based on comparisons between baseline and current hearing thresholds. The CCG (Children's Cancer Group) criteria are based on a loss as defined as a change from baseline at any one frequency. The Chang grading scale (Chang & Chinosornvatana, 2010) is the most recent of the grading scales that has been developed.

Clinical studies of carboplatin ototoxicity conducted in children with pediatric cancers other than retinoblastoma have revealed equivocal results. Macdonald et al. (1994) found that 50 % of children in their study had a sensorineural hearing loss in the 4,000-12,000 Hz range following treatment with carboplatin. They found that hearing losses could occur after the first dose of carboplatin, and that hearing losses could progress with subsequent doses. Similarly, Simon et al. (2002) reported that 40% of children treated with high-dose carboplatin developed a hearing impairment and Knight et al. (2005) found that 38% of children treated with carboplatin developed sensorineural hearing loss. In contrast, Stern and Bunin (2002) found that ototoxic complications from carboplatin chemotherapy were rare and mild in severity and other studies have found similar results (Bertolini et al., 2004; Dean et al., 2008). The variability of carboplatin ototoxicity seen across past studies may be related to insufficient control of confounding factors. Factors that may potentiate the severity of carboplatin ototoxicity include prior exposure to cisplatin or other ototoxic medications and high dosage of carboplatin associated with autologous stem cell reinfusion (Knight et al., 2005; Parsons et al., 1998). Another factor that may increase the severity of platinum-compound ototoxicity is patient age, with younger children being more

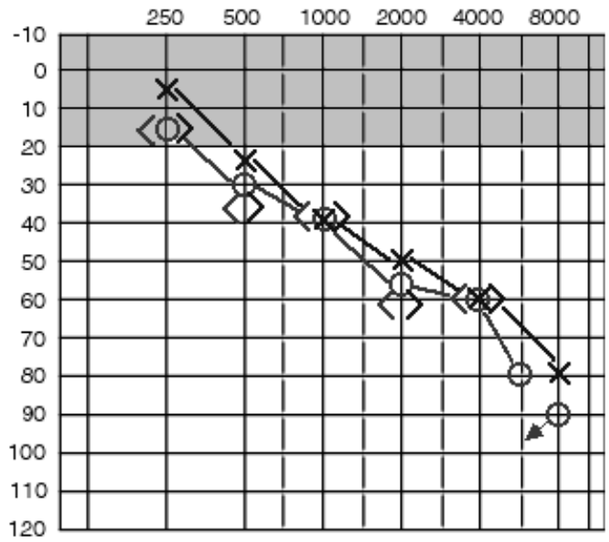

Fig. 1. An audiogram depicting a sensorineural hearing loss in both ears, often seen in ototoxicity. The x-axis is frequency in Hertz and the y-axis is level in decibels. The shaded region represents the normal-hearing range. The hearing loss depicted indicates a greater loss of sensitivity in the high frequencies compared to the low frequencies.

susceptible than older children (Li et al., 2004; Coradini et al., 2007). Studies examining carboplatin ototoxicity in children with retinoblastoma are less prevalent. Smits et al. (2006) studied 25 children diagnosed with retinoblastoma ranging in age from 1-41 months at the start of carboplatin chemotherapy and found no signs of ototoxicity. Lambert et al. (2008) reviewed audiometric data from 116 children (aged 1-87 months) treated for retinoblastoma with a multi-drug regimen including carboplatin. Most of these children were monitored with behavioral audiometry and 48 received ABR evaluations. Only one of the children was suspected of incurring progressive hearing loss due to carboplatin chemotherapy, but this child was diagnosed at less than 1 month of age. Other studies have also indicated a low incidence of carboplatin ototoxicity (4.5-6.6%) in children with retinoblastoma of various ages, although some children were found to have late-onset hearing loss (Jehanne et al., 2009; Pecora Liberman, 2011).

3.2 Auditory brainstem response

Behavioral hearing tests in children less than 12 months old can be unreliable and difficult to interpret. A common alternative method used to monitor auditory function in children receiving platinum-compound chemotherapy is the ABR test. During the ABR test, surface electrodes are attached to locations on the scalp and forehead, and these electrodes record electrical activity generated by the auditory nerve and neural centers in the brain responsive to auditory stimuli. Clicks or brief tones are stimuli presented to an ear while the ABR response is being recorded. The ABR test is a passive test in that the patient does not respond behaviorally to the sounds that are heard. The electrode leads connect to an amplifier box, and the ABR response is filtered and averaged by a computer. The resulting ABR waveform consists of a series of positive and negative voltages displayed on a computer monitor. Peak amplitudes and latencies of the ABR waveform are analyzed and compared to normative data. The lowest level of sound that can evoke a replicable ABR waveform is known as the ABR threshold. Previous research has established that the ABR threshold provides a reliable estimation of infant hearing sensitivity. Children with hearing loss typically have elevated ABR thresholds compared to children with normal hearing. When used as a screening test, a criterion stimulus level is selected and if an ABR waveform is successfully recorded at this level, the infant passes the screening test. If an ABR waveform is not recorded at the criterion level, a hearing loss may be suspected and the infant is referred for further diagnostic testing.

The ABR screening test is a well-established physiological measurement procedure that has been validated through years of clinical research. It is relatively easy to administer and is typically completed in a short period of time. However, as with any screening instrument it is not infallible. The ABR screening test will produce both false positive (incorrectly failing children with normal hearing) and false negative (incorrectly passing children with hearing loss) results. Confirmation of hearing loss is often enhanced when test results from OAE and/or ABR screenings are combined with reliable behavioral observations of infant hearing. In children less than 12 months old, the ABR test may be the only reliable means of examining if auditory function is being compromised by carboplatin, given that younger children receiving platinum compounds may be more susceptible to drug-induced hearing loss as estimated by ABR thresholds (Coupland et al., 1991). Previous research has shown that click-evoked ABR test results can accurately track permanent changes in cochlear

function due to administration of ototoxic medications in adults (DeLauretis et al.,1999). However, some studies have questioned the sensitivity of ABR test results in monitoring platinum-compound ototoxicity in children (Weatherly et al., 1991). It is known that carboplatin can cause a substantial amount of damage to inner hair cells and spiral ganglion neurons prior to a change being registered on an electrophysiological assessment, such as the compound action potential (El-Badry & McFadden, 2007). Because the ABR is a far-field potential that relies upon compound activity from an ensemble of neurons, it may not provide the best indication of early change in cochlear function. In addition, if a change is detected on the ABR test, it may reflect a permanent loss of auditory sensitivity.

3.3 Otoacoustic emissions

An alternative method of monitoring platinum-compound ototoxicity is the OAE test. Believed to be linked to the functional status of outer hair cells (Brownell, 1990), OAEs have been effectively used to monitor platinum-compound ototoxicity in children (Dhooge et al., 2006; Knight et al., 2007). OAEs are usually inaudible sounds produced by the healthy inner ear, and these sounds escape into the ear canal and are measured with an ear-canal probe containing a miniature microphone. The probe assembly interfaces with a computer, and a software program analyzes data being recorded by the probe microphone. Typically, OAEs are evoked by stimulating the ear with clicks or tones, and the recorded response is then measured and compared to normative data collected in children with normal hearing. No overt behavioral response from the child is required, and the test can be done while the child is asleep. This physiological test provides information on the functional status of middle and inner ear (outer hair cells) structures. Children with hearing loss have reduced or absent OAEs compared to normal-hearing children. A criterion OAE response is required in order to pass the test, and children who fail are typically referred for further testing to confirm potential hearing loss. The OAE test is a simple screening test to administer and can be completed rapidly, typically within 1-2 minutes per ear. However, a relatively quiet environment is required to complete a valid OAE test, as extraneous noise recorded by the probe microphone can interfere with testing. In addition, the degree of hearing loss cannot be determined by OAE testing alone, as both hard-of-hearing and deaf children typically exhibit absent OAE responses. The information provided by OAE testing is quite useful in determining if a child is a potential candidate for intervention programs.

In children, OAEs were found to be reduced prior to the onset of hearing loss on the audiogram in the conventional frequency range following cisplatin chemotherapy (Knight et al., 2007). DPOAE levels also exhibit high correlations with behavioral hearing thresholds in children suffering hearing loss due to platinum compound ototoxicity (Dhooge et al., 2006). High doses of carboplatin are known to damage outer hair cells and reduce the amplitude of OAEs in animal model (Hofstetter et al., 1997b). Based on these findings, the OAE test potentially is more sensitive at detecting early changes in cochlear function due to carboplatin ototoxicity than is the ABR test. Previous research has not compared the abilities of ABRs and OAEs to register changes in cochlear function throughout the entire course of carboplatin chemotherapy in young children with retinoblastoma. In fact, few studies have examined OAE tests in children with retinoblastoma. Smits et al. (2006) examined OAEs in evaluating children with retinoblastoma receiving carboplatin. They concluded that there were no signs of ototoxicity in the sample of children they examined, although no details

concerning what constituted a change in OAE level were provided. Bhagat et al. (2010) found different results in studying 10 children with retinoblastoma receiving carboplatin. They reported that when a criterion change in OAE level was utilized, four of the ten children studied had reductions in OAE level that met the criterion. These findings suggest that OAE tests are useful in identifying the deleterious effects of carboplatin chemotherapy on cochlear function in some children with retinoblastoma.

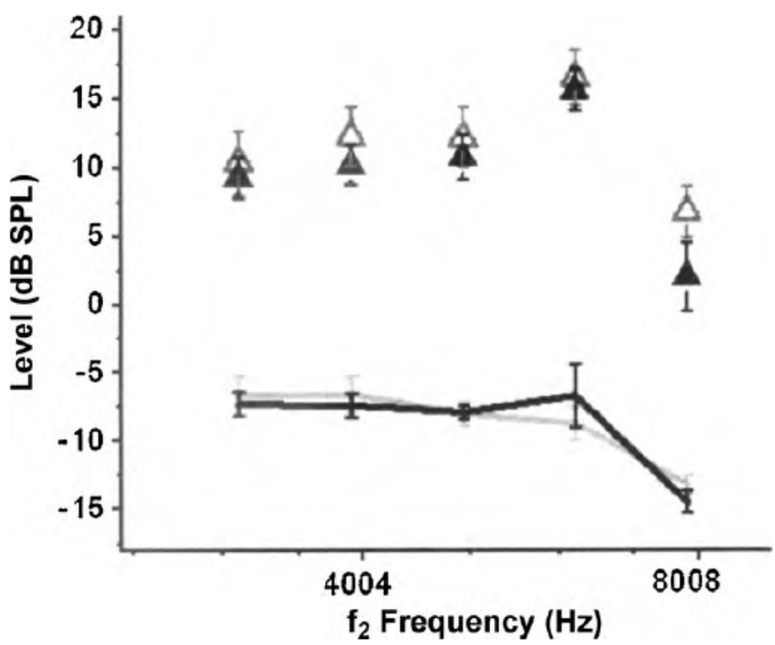

Fig. 2. Mean OAE levels in children with retinoblastoma before (open triangles) and after (filled triangles) carboplatin chemotherapy. Post-therapy OAE levels at the highest test frequency were reduced compared to pre-therapy OAE levels. Reprinted from the International Journal of Pediatric Otorhinolaryngology, Vol. 74/Issue 10, Bhagat, S.P., Bass, J.K., White, S.T., Qaddoumi, I., Wu. J. & Rodriguez-Galindo, C., "Monitoring carboplatin ototoxicity with distortion-product otoacoustic emissions in children with retinoblastoma", pp.1156-1163, 2010, with permission from Elsevier.

4. Impact of hearing loss on academic and social development

The degree of hearing loss associated with carboplatin ototoxicity can vary, but the initial onset of hearing loss typically begins in the high frequencies. High-frequency sensorineural hearing loss can be problematic for the development of speech and language in young children (Stelmachowicz et al., 2004). High frequency speech phonemes contribute to speech intelligibility, and high frequency sensorineural hearing loss reduces the audibility of important speech cues, limits speech understanding in noise, and increases the risk for academic failure (Stelmachowicz et al., 2001; Horwitz et al., 2002; Bess et al., 1998). With more courses or higher dosages of carboplatin, hearing may deteriorate further, and the hearing loss may involve a loss of sensitivity at lower frequencies on the audiogram (Parsons et al., 1998). In rare cases, the use of platinum compounds may result in deafness (Chu et al., 1993).

In most educational settings, the dominant mode of information transfer from teacher to student is oral instruction. Most normal-hearing children have little difficulty understanding oral instruction and have developed a sufficient language base to successfully progress academically. However, children with permanent sensorineural hearing loss are at a disadvantage compared to their normal-hearing peers. Oral instruction may be inaudible to hearing-impaired students, depending upon the degree of hearing loss. In addition, hearing-impaired students often lack language skills that are requisite for achievement in the classroom. While advancements in technology have increased the audibility of classroom instruction for many hearing-impaired students, their expressive and receptive language skills are often below those of children with normal hearing. These language skills form the foundation for word knowledge and verbal reading, which account for 90% of the variability in reading skills found in normal hearing children (Davis, 1972). The lack of an adequate language base in both hard-of-hearing and deaf children impacts their academic performance. Average reading ability for hard-of-hearing high school graduates has been measured at the fifth-grade level, while average reading ability for deaf high school graduates was at the fourth-grade level. Reading ability for both groups was below that of their normal-hearing peers (Allen, 1986). The overall academic performance of hearing-impaired students is negatively influenced by their reading ability (Quigley, 1979).

Once suspected, hearing loss in infants is confirmed through diagnostic tests. The degree of hearing loss can be determined with diagnostic physiological tests such as the ABR combined with behavioral auditory assessments. This information is important, as the type of intervention planned often depends on whether the infant is hard-of-hearing or deaf. Traditional amplification systems, including hearing aids, usually can benefit hard-of-hearing children (Gravel & O'Gara, 2003). When their residual hearing is aided and they are able to hear the acoustic cues of conversational speech, the language acquisition of hard-of-hearing children can be similar to that of normal-hearing children (Moeller, 2000). Factors which influence the language skills of hard-of-hearing children include the age at which their hearing loss was identified, when they received intervention and the amount of parental involvement in the intervention plan (Yoshinaga-Itano et al.,1998; Yoshinaga-Itano & Apuzzo, 1998).

For many deaf children, traditional amplification systems may not be a viable option. These children often do not have enough residual hearing to benefit from hearing aids. Alternative intervention in the form of cochlear implants designed to facilitate development of spoken language, or adoption of manual communication as the child's first language may be more appropriate options. The choice of which communication style to adopt for a deaf child can be a controversial one for many families. This choice can be influenced by the opinions of intervention professionals, who often view deafness as a condition to fix. However, individuals in the Deaf community have argued that deafness is indicative of a cultural difference, and that all deaf children should learn American Sign Language as their primary means of communication (Samson-Fang et al., 2000). The choice of communication style will certainly affect the future educational placement of the deaf child. Deaf children who receive cochlear implants are more likely to be mainstreamed with normal-hearing children in classrooms, while alternative educational placements may be required for children who communicate manually. Regardless of the communication style, evidence indicates that early intervention benefits linguistic outcomes. Children who receive cochlear implants

within the age range of 2-6 years perform well on speech reception and production tasks, with better performance seen in children implanted earlier rather than later in life (Brackett & Zara, 1998). Deaf children with early exposure to manual communication developed linguistic skills in a manner similar to normal-hearing children who received early exposure to spoken language (Bandurski & Galkowski, 2004). These findings underscore the importance of early intervention on the development of hearing-impaired children.

Substantial evidence concerning the effects of early identification of hearing loss and early intervention on the language development of hearing-impaired children has been provided by Yoshinaga-Itano and her colleagues. In a series of studies published in peer-reviewed journals, they examined the language skills of children between 13-40 months of age who were identified with hearing loss either before or after the age of six months. The expressive and receptive language development of children enrolled in intervention services before six months of age was significantly better than those of the children identified later in life. Both hard-of-hearing and deaf children benefited from early intervention. Most importantly, the language skills of the early-identified children approached those seen in age-matched normal-hearing children (Yoshinaga-Itano et al., 1998; Yoshinaga-Itano & Apuzzo, 1998). Moeller (2000) extended these results, finding that the benefits of early intervention on language development were maintained in children at five years of age. In addition, personal-social development and self concept are more advanced in children who were identified and enrolled in intervention early in life (Yoshinaga-Itano, 2003).

Another contributing factor to the development of language in hearing-impaired children is the degree of family involvement in the intervention plan (Moeller, 2000). The diagnosis of hearing loss in an infant can be a catastrophic event in the emotional lives of new parents. Parental reaction to this event can contribute significantly to the developmental outcomes for the child (Kurtzer-White & Luterman ,2003). Once they are informed about their child's hearing loss, many parents go through a series of emotions including anger, resentment, and guilt before acceptance of the hearing loss occurs. Recognition of these coping mechanisms by professionals including physicians and educators will enhance parental involvement in the intervention process. There is evidence that well-adjusted families contribute to academic achievement in hearing-impaired children (Feher-Prout, 1996). Educators of the deaf have received training in psychosocial issues of hearing-impaired children and their families, and this expertise can improve the quality of early intervention services.

5. Otoprotection and carboplatin-induced hearing loss

The ability to prevent ototoxicity in patients undergoing carboplatin chemotherapy with pharmaceutical agents is currently being investigated by several teams of researchers. The molecular mechanisms of cell death in the cochlea induced by ototoxic agents are currently being elucidated. Armed with this knowledge, researchers are developing substances that can interrupt the chain of events that lead to hearing loss. These substances are generally known as "otoprotectants". Sodium thiosulfate (STS) is an otoprotectant used to prevent carboplatin ototoxicity that has been evaluated in animal models and in human patients. In guinea pigs, STS was found to reduce the toxicity of carboplatin when it was given up to 8 hours after the ototoxic drug was administered (Neuwelt et al., 1996). Further, the ability of STS to lessen the cochlear toxicity of carboplatin did not interfere with the anti-tumor effectiveness of carboplatin in rats (Muldoon et al., 2000). In a study involving human

patients receiving carboplatin, Neuwelt et al. (1998) found that patients given STS 2 hours after carboplatin administration incurred a significantly lower average hearing loss compared with a control group of patients that did not receive STS. The benefits of delayed administration of STS were further revealed when it was shown that when STS is given 4 hours after carboplatin, it reduces ototoxicity rates (Doolittle et al., 2001). The beneficial effects of STS in adults were also seen in a study involving children, where trends indicated that STS provided protection against carboplatin ototoxicity while sparing the anti-tumor activity of the drug (Neuwelt, 2006). Another otoprotectant against carboplatin ototoxicity that has been evaluated in animal models is D-Methionine (D-Met). Lockwood et al. (2000) found that carboplatin-induced cell loss was reduced in chinchillas treated with D-met compared to untreated controls.

In the future, it is conceivable that otoprotectants such as STS or D-Met would be administered during carboplatin chemotherapy in order to reduce the cochlear toxicity of the drug. The use of these pharmaceutical agents to prevent hearing loss would be invaluable in children with retinoblastoma, as these children have existing visual impairments in one or both eyes.

6. Conclusions

Carboplatin is a chemotherapy agent with known ototoxic side effects that is widely used in the conservative management of retinoblastoma. Children with retinoblastoma have visual impairments that may impact their development. There is a risk of incurring additional sensory deficits (loss of hearing) when carboplatin is included in the treatment regimen. Although research to date has indicated a low incidence of carboplatin-induced hearing loss in children with retinoblastoma, additional study of this topic is required before definitive conclusions can be drawn. Factors such as exposure to other ototoxic agents including cisplatin and poor renal function may potentiate carboplatin-induced hearing loss. It is important that medical professionals remain vigilant about monitoring hearing during carboplatin chemotherapy, as conservation of hearing is a priority in children with retinoblastoma. If a change in hearing is noted during the monitoring regimen, it may be possible to alter the dosage of the drug to prevent further deterioration in hearing from occurring. If the carboplatin dose cannot be modified, monitoring hearing status during the treatment regimen can serve as an entry point into intervention programs, including the provision of hearing aids and family counseling. It is also important to note that late-onset hearing loss can occur years after completion of carboplatin chemotherapy. Therefore, long-term hearing assessments may be required in these cases. Recognition of the impact of ototoxic hearing loss on the lives of retinoblastoma survivors will lead to appropriate planning in cases when hearing loss is detected.

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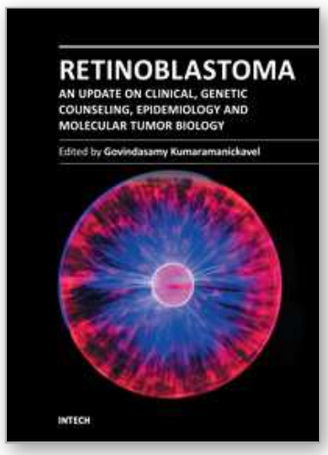

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Retinoblastoma is the first tumor suppressor gene discovered ever. The discovery opened a new avenue in the field of oncology leading to the identification of 35 tumor suppressor genes, till date in our genome. This book is an excellent compilation of both clinical and basic science information that meets the needs of a young clinician and a researcher at the same time. It also has abundant information on recent advances and cutting-edge knowledge in intracellular molecular cross-talking of retinoblastoma protein with various cellular viral-like proteins.

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