Hearing Loss in Pediatric Patients Receiving Platinum-based Chemotherapy

Sofia Waissbluth

Platinum-based chemotherapy

Platinum compounds are frequently used as part of an oncology regimen. The most commonly used compounds are cisplatin, carboplatin and oxaliplatin (Hartmann JP. & Lipp H-P, 2003). Cisplatin appears to be the most effective and has a wide-ranging spectrum of activity against multiple types of cancer including testicular, ovarian, medulloblastoma, osteosarcoma, hepatoblastoma, germ cell tumors and neuroblastoma (Bertolini P. *et al*, 2004). While nephrotoxicity and ototoxicity are considered dose limiting side effects for cisplatin use, myelosuppression can limit the use of carboplatin. Carboplatin can be used alone or before and after treatment with cisplatin, and is often considered an alternative treatment (Hartmann JP. & Lipp H-P, 2003).

Cisplatin

Cisplatin-induced ototoxicity is a predominant side effect of cisplatin chemotherapy yet its incidence is extremely variable in the current literature due to various factors including cumulative dose (Li Y. *et al*, 2004), infusion duration (Reddel RR. *et al*, 2004, van As JW. *et al*, 2016), genetic susceptibility (Mukherjea D. & Rybak LP, 2011), ototoxicity grading criteria, timing of hearing testing, follow-up and the presence of risk factors (Zuur C.L *et al*, 2007).

Risk factors for hearing loss secondary to cisplatin chemotherapy include age (< 5 years old) (Li Y. *et al*, 2004), renal insufficiency (Bokemeyer C. *et al*, 1998), cranial radiotherapy (Chen WC. *et al*, 2006), pre-existing hearing loss (Bokemeyer C. *et al*, 1998), and use of ototoxic medications (Kohn S. *et al*, 1991).

Clinically, cisplatin-induced ototoxicity presents as sensorineural hearing loss that is irreversible, bilateral and progressive, which begins at the high frequencies and progresses towards the lower frequencies (Rybak LP. *et al*, 2007). The severity of the hearing loss appears to be associated with the cumulative platinum dose (Bokemeyer C. *et al*, 1998). Patients can present with hearing loss weeks or months following the chemotherapy treatment, or even years after completion of the treatment (Bertolini P. *et al*, 2004). Tinnitus has also been described as a consequence of cisplatin chemotherapy (Dille MF. *et al*, 2010).

Mechanisms of cisplatin-induced ototoxicity

Cisplatin is believed to enter the cell by passive diffusion, and by various transporters including copper transporters Ctr1 and Ctr2, and organic cation transporter OCT2. It has also been suggested that channels belonging to the transient receptor potential channel family may play a role as well (Waissbluth S & Daniel SJ, 2013). Once cisplatin enters the cell, it can activate nuclear transcription

factor-kappa B (NF-kB) and stimulate the inflammatory cascade which generation of interleukin-1, interleukin-6 and tumor necrosis factor-α (Chung WH. *et al*, 2008, Barnes PJ. 1997). It causes oxidative stress with the resulting production of 4-hydroxynonenal and peroxynitrite, molecules known to be cytotoxic (Rybak LP. *et al*, 2007). Importantly, cisplatin can bind to RNA, proteins and DNA in an irreversible manner (Tanida S. *et al*, 2012, Zamble DB. *et al*, 1996). All of these mechanisms lead the activation of the apoptotic cascades, intrinsic and extrinsic.

Prevalence of platinum based chemotherapy ototoxicity

The prevalence of hearing loss following a pediatric platinum based chemotherapy treatment is extremely variable. A recent Cochrane review was performed in order to review this topic (van As JW. *et al*, 2016). The review included all-study designs except: case reports, case series and studies with fewer than 100 patients. Participants were aged up to 18 years at the time of cancer diagnosis and must have received platinum-based chemotherapy, and hearing assessments. With these inclusion criteria, 13 studies were evaluated. From these, it was observed that hearing loss varied between 0% and 90.1% (see **Table 1**).

As we can appreciate from table 1 (data extracted from the Cochrane review article), there is variability in terms of patient age, platinum analogue and cumulative dose, criteria used to define and grade hearing loss, follow-op periods, and presence of important risk factors such as concomitant use of aminoglycosides or radiotherapy.

Studies with patients receiving carboplatin had mostly 0% prevalence of hearing loss, except for Jehanne *et al* for which they found a 3.4% prevalence of hearing loss, in this case, some of the patients also had exposure to aminoglycosides and radiotherapy. Hudson *et al* 2013 has the longest follow up period and had a prevalence of 67.1% of hearing loss. Interestingly Landier *et al* as well as Peleva *et al*, both used two or more criteria to evaluate the prevalence of hearing loss. Landier *et al* used the Brock, Chang and CTCAE version 3.0 with a prevalence of 87, 90 and 86% respectively. While Peleva *et al* showed a prevalence of 48.4% with ASHA, and 29.7% with Chang grades ≥ 2a. None of the studies mention presence or absence of tinnitus for their patients. With these results, we can understand why it is difficult to specify the prevalence of platinum-based chemotherapy induced hearing loss in the pediatric population.

While the grading criteria are mostly based on audiogram results, it is not always possible to perform an audiogram depending on the patients age and cooperation. Because of this, ABR and OAE testing is also an option yet the criteria do no take these results into account. Of the criteria available, ASHA (American Speech-Language-Hearing Association) and POG (Pediatric Oncology Group) require a baseline measurement which is also not always possible depending on the hospital setting (Waissbluth *et al*, 2017).

Genetic susceptibility

Most recently, an important effort has been made by the research community to understand whether certain patients are genetically susceptible to cisplatin-induced ototoxicity. Maagdenberg H. *et al* have recently published an interesting review about pharmacogenomics in pediatric patients. They review the possible

candidate genes and the pitfalls that have limited the ability to make conclusions about cisplatin-induced ototoxicity. For now, it appears that the scientific evidence is strongest for the impact of genetic variants for the enzyme TPMT (thiopurine S-methyltransferase) (Maagdenberg H. *et al*, 2016).

Table 1. Summary of included studies in the Cochrane review

Study group	n	Age (m)	Analogue (mg/m2)*	Hearing test	Criteria	Follow-up (mean)	Risk factor	%
Mandell 1999	113	37-266	Cis (300)	Audiogram, ABR	POG ≥ 1	8 weeks & as needed	RT	15
Shields 2002	103	11	Carbo (3360)	nm	nm	29 months (2-63)	RT	0
Simon 2002	715	nm	Cis (1-800) 188 C+C (1500)	nm	WHO ≥3	At least 12 months		20.1
Bertolini 2004	120	2.6 yrs (median)	Cis (400), Carbo (1600), C+C	Audiogram	Brock ≥ 2	7 yrs (median)		32.5
Cushing 2004	295	0-20 yrs	Cis (400-1200)	Audiogram	NCI version? Grade 3,4	nm		7.1
Shields 2006	163	nm	Carbo	nm	Nm	6.2 yrs (1-10.6)		0
Lambert 2008	116	10 (median)	Carbo (111.6)	Multiple	nm	40 months (3-127)	AMG	0
Jehanne 2009	175	8 (median)	Carbo (2880)	Multiple	Brock ≥ 1	5 yrs (median)	RT, AMG	3.4
Perilongo 2009	168	13.5 (median)	Cis (480)	nm	Brock ≥ 1	nm		31.5
Hudson 2013	152	7.5 yrs	Cis, Carbo, C+C (556)	Audiogram	Chang ≥ 1a	25.6 yrs	RT	67.1
Kennedy 2014	144	nm	Cis (560)	Questionnaire	Hearing aid?	5.8 yrs (median)	RT	16
Landier 2014	267	3.9 yrs	Cis (400), carbo (1700)	Audiogram, ABR	Brock, Chang, CTCAEv3	480.1 days	RT	87, 90, 86
Peleva 2014	306	7.8 yrs	Cis (580), Carbo (2581), C+C	Multiple	ASHA, Chang ≥ 2a	nm	RT	48.4, 29.7

n: number of patients that had hearing assessment, nm: not mentioned, *cumulative platinum dose, AMG: aminoglycoside, RT: radiotherapy

Conclusions

As children are surviving cancer, many patients develop side effects to the chemotherapy treatments given which can be invalidating, and decrease their quality of life. Special consideration should be taken with hearing loss as children are deeply impacted when they cannot participate or communicate with other children and adults, it can limit their ability to develop and learn, and lead to social isolation. Further research is required in order to understand genetic susceptibility for cisplatin-induced hearing loss as personalized Medicine is the future.

References

1. Hartmann J.T., Lipp H.P. Toxicity of platinum compounds. Expert Opin Pharmacother 4, 889-901 (2003).
2. Bertolini, P. *et al*. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol 26, 649-55 (2004).
3. Li, Y., Womer, R.B. & Silber, J.H. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer 40, 2445-51 (2004).
4. Reddel, R.R. *et al*. Ototoxicity in patients receiving cisplatin: importance of dose and method of drug administration. Cancer Treat Rep 66, 19-23 (1982).
5. van As J.W., van den Berg H., van Dalen E.C. Different infusion durations for preventing platinum-induced hearing loss in children with cancer. Cochrane Database Syst Rev. Aug 8;(8):CD010885 (2016).
6. Mukherjea, D. & Rybak, L.P. Pharmacogenomics of cisplatin-induced ototoxicity. Pharmacogenomics 12, 1039-50 (2011).
7. Zuur, C.L. *et al*. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. Int J Radiat Oncol Biol Phys 68, 1320-5 (2007).
8. Bokemeyer, C. *et al*. Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer 77, 1355-62 (1998).
9. Chen, W.C. *et al*. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 106, 820-9 (2006).
10. Kohn, S. *et al*. Toxic effects of cisplatin alone and in combination with gentamicin in stria vascularis of guinea pigs. Laryngoscope 101, 709-16 (1991).
11. Rybak, L.P., Whitworth, C.A., Mukherjea, D. & Ramkumar, V. Mechanisms of cisplatin-induced ototoxicity and prevention. Hear Res 226, 157-67 (2007).
12. Dille, M.F., *et al*. Tinnitus onset rates from chemotherapeutic agents and ototoxic antibiotics: results of a large prospective study. J Am Acad Audiol 21, 409-17 (2010).
13. Chung W.H., *et al*., Proapoptotic effects of NF-kappaB on cisplatin-induced cell death in auditory cell line. Acta Otolaryngol 128, 1063-1070 (2008).
14. Barnes, P.J., Nuclear factor-kappa B. Int. J Biochem Cell Biol 29, 867-870 (1997).
15. Tanida S., *et al*. Mechanisms of cisplatin-induced apoptosis and of cisplatin sensitivity: potential of BIN1 to act as a potent predictor of cisplatin sensitivity in gastric cancer treatment. Int J Surg Oncol 862-879 (2012).
16. Zamble D.B., Mu D., Reardon J.T., Sancar A., Lippard S.J., Repair of cisplatin-DNA adducts by the mammalian excision nuclease. Biochemistry 35, 10004-10013 (1996).
17. van As, J.W., van den Berg, H., van Dalen, E.C. Platinum-induced hearing loss after treatment for childhood cancer. Cochrane Database Syst Rev Aug 3;(8):CD010181 (2016).
18. Waissbluth S., Peleva E., Daniel S.J. Platinum-induced ototoxicity: a review of prevailing ototoxicity criteria. Eur Arch Otorhinolaryngol 274, 1187-1196 (2017).
19. Maagdenberg H., *et al*. Pharmacogenomics in Pediatric Patients: Towards Personalized Medicine. Paediatr Drugs18, 251-60 (2006).