ELSEVIER

European Journal of Cancer 40 (2004) 2352–2354

European Journal of Cancer

www.ejconline.com

Editorial Comment

Best practice in assessing ototoxicity in children with cancer

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Received 27 July 2004; accepted 2 August 2004
Available online 26 August 2004

The success of contemporary treatment in curing over 70% of children with cancer, including leukaemia [1], is tempered by the development of late adverse effects of treatment in many survivors, which are particularly important in growing and developing children. "Cure at least cost" has become an important tenet for those involved in the management of these children, with the aim of reducing the incidence and impact of chronic treatment-induced toxicity, thereby enhancing the quality of survival [2].

Although treatment-induced ototoxicity, unlike some other late adverse effects, does not endanger life it may lead to significant impairment of a child's development and future social and educational functioning. Meaningful assessment of ototoxicity requires an understanding of its clinical nature and consequences.

What is ototoxicity? The commonest cause of ototoxicity in children treated for cancer is hearing loss due to cisplatin [3]. Carboplatin may cause similar, but usually milder, toxicity [4], although severe hearing loss may occur after high-dose therapy [5]. High-dose radiotherapy (>50 Gy), to a field including the middle ear, may cause mixed sensorineural and conductive hearing impairment, but clinically significant deafness is uncommon unless platinum treatment is also administered [6,7]. *What are the clinical features of ototoxicity?* Cisplatin-induced ototoxicity is usually manifest by bilateral, symmetrical, sensorineural hearing loss first affecting higher frequencies ($\geqslant$ 6000 Hz); the lower frequency sounds (500–2000 Hz) that are important for speech discrimination become involved progressively with higher cumulative doses [3,8]. Although many children with documented auditory toxicity are asymptomatic, a few complain of tinnitus [9]. Despite the absence of symptoms, moderate or severe deafness detected by audiometry is common [10]. Vestibular toxicity is described in adults, but has not been investigated adequately in children. *Why is ototoxicity important?* The most important clinical outcome of cisplatin-induced ototoxicity is the risk of considerably delayed speech development in infants and younger children due to impaired recognition of higher frequency consonant sounds [10]. *How common is ototoxicity?* The incidence varies according to the patient group studied, the treatment (and dose) received, and the criteria used to define toxicity. Several paediatric series have shown that hearing loss of $\geqslant$ 15–25 dB at high frequencies ($\geqslant$ 4000 Hz) occurs in 50–70% of children receiving cisplatin doses above 450–600 mg/m^2, whilst up to 30% may develop similar loss at 2000 Hz after a dose of 720 mg/m^2 [3,6,10]. In contrast, only 6% of children developed hearing loss of >25 dB at 6000 Hz or lower frequencies after radiotherapy without platinum chemotherapy [6]. *What causes ototoxicity?* The pathological lesion underlying platinum-induced ototoxicity is outer hair cell degeneration in the lower turns of the cochlea [7]. In contrast, several mechanisms may underlie radiation-induced hearing loss, including chronic otitis with tympanic membrane and external auditory canal damage [11]. *Is ototoxicity reversible?* Unsurprisingly, given the pathological lesions observed, most reports of cisplatin otoxicity in children have found no evidence of recovery up to 4 years post-treatment [10]. Indeed, occasional cases of hearing loss presenting years after cisplatin or radiotherapy have been described [7,12].

Can ototoxicity be predicted? Several patient- and treatment-related risk factors have been described for

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.08.002

the development of cisplatin otoxicity in children. Younger age has been associated with increased severity of hearing loss in some [3,6,8], but not all [9,12], studies. Higher cumulative and individual doses have been reported to cause more frequent and severe hearing loss in most studies [6,8–10]. Prior, but not subsequent, radiation involving the ears appears to increase the risk of cisplatin-induced ototoxicity [6,13]. Although it has been suggested that adults receiving cisplatin may be vulnerable to additive damage from the previous or concurrent use of other potentially ototoxic drugs, such as aminoglycosides, frusemide and bleomycin [14], this has not been confirmed in most paediatric studies [6,9,10]. In contrast, and although it is not regarded as ototoxic in its own right [15], one brief report has suggested that concurrent ifosfamide may exacerbate cisplatin-induced ototoxicity [16].

The use of clinical factors influencing the risk of ototoxicity has been limited in practice by considerable inter-individual variation [9,10]. The model constructed by *Li and colleagues* in their report in this issue of the European Journal of Cancer [17] offers precise information about the risks of ototoxicity in defined clinical circumstances. The authors determined Brock ototoxicity scores in 153 children and adolescents using pure tone audiograms (PTAs) performed after completion of cisplatin chemotherapy. Initial univariate analysis of several risk factors (including age, gender, ethnicity, dose and time elapsed since treatment), followed by logistic regression, showed that age <5 years at treatment and cumulative dose >400 mg/m^2 were associated with an increased risk of moderate to severe ototoxicity (Brock grades 2–4). A novel feature of this report is the construction of a model to enable prediction of the risk of developing grade 2–4 ototoxicity at any given age and cumulative cisplatin dose. However, as the authors admit, the functional consequences of particular degrees of hearing loss are still uncertain. Nevertheless, this model represents an important first step in providing evidence to allow the rational design of future treatment protocols incorporating cisplatin, with the aim of maximising efficacy whilst reducing the long-term consequences of ototoxicity.

Can ototoxicity be prevented? One randomised study has found a considerably reduced incidence of cisplatin-induced ototoxicity in adults given amifostine cytoprotection, and paediatric trials are in progress.

Given this information, how should a child at risk of ototoxicity be assessed? (Table 1) Any child treated with cisplatin or high-dose carboplatin chemotherapy should undergo hearing assessment on completion of treatment. Most paediatric experience and research has relied on PTAs. Older children can usually cooperate with PTAs, whilst other behavioural audiometry techniques can provide very satisfactory evaluations in younger (pre-school) children. Electrophysiological testing (auditory brainstem responses (ABRs)) and otoacoustic emissions (OAEs) may be useful in younger children or older ones who are unwell or whose compliance is suspect [18]. However, although OAEs are much easier to perform than ABRs and may be more sensitive for the detection of moderate deafness than behavioural audiometry, interpretation may be difficult, especially in the presence of concomitant middle ear disease. OAEs are generally a screening test, being either detectable or not, but the threshold (i.e., severity of hearing loss) for their absence displays inter-individual variability of 20–30 dB. Furthermore, frequency-specific information may be limited, although distortion product OAEs may be more useful than transient evoked OAEs in this respect. Therefore, OAEs have, at best, a restricted role in the evaluation of ototoxicity. Skilled paediatric audiological and ENT (Ear, Nose and Throat) assessment is therefore still essential for optimum assessment.

Table 1
Assessment of auditory function in children treated for cancer[a]

Risk factors	
(1)	Cisplatin
(2)	Carboplatin (ototoxicity uncommon and usually less severe, but may be clinically significant after high-dose carboplatin)
Other risk factors that may *cause* or *increase* hearing impairment:	
(3)	Prior cranial radiotherapy to field including middle ear
(4)	Treatment with other ototoxins (e.g., aminoglycosides)
(5)	Impaired renal function at time of platinum treatment (leading to higher systemic platinum exposure)
Clinical assessment	
(1)	Hearing acuity
(2)	Speech development
(3)	School and social functioning with respect to hearing and speech
Clinical investigation	
On completion of treatment, perform:	
(1)	Pure tone audiogram
(2)	Paediatric ENT/audiology assessment (infants) – including behavioural audiometry, and rarely, otoacoustic emissions
Management of high-risk patients	
(1)	Symptomatic patients – refer to paediatric ENT/audiology, and to speech therapy (where appropriate)
(2)	Infants and pre-school children treated with cisplatin or high-dose carboplatin – consider referral to paediatric ENT/audiology
(3)	Children with significant hearing impairment – liaise with education and community paediatric services

ENT, ear, nose and throat.

[a] Adapted with permission from Long-Term-Therapy-Based Follow-up Guidelines, 2nd edition, in preparation, edited by Skinner R, Wallace WHB, on behalf of United Kingdom Children's Cancer Study Group Late Effects Group.

Many treatment protocols require monitoring of auditory function during cisplatin treatment, but there is no clear published evidence to inform clinicians about how they should respond to evidence of early subclinical ototoxicity, demonstrated by either PTAs or OAEs. Although some paediatric oncologists do modify chemotherapy in patients with abnormal PTAs in the hope of reducing the risk of more severe hearing loss, we do not yet know whether this strategy is justifiable. At worst it might carry an unacceptable risk of reducing survival rates in the (unproven) hope of improving auditory outcome.

How should children with documented high frequency hearing loss be managed? Although many children are asymptomatic, it is important to identify those at higher risk of functional impairment. They include younger children who are still developing their speech skills, as well as those with other risk factors (e.g., higher cisplatin dose, prior radiotherapy, aminoglycosides). Whilst severe carboplatin ototoxicity is much less common, children given high doses, or conventional doses after previous cisplatin, may be at higher risk. These children may require expert paediatric ENT, audiological and (where indicated) speech therapy assessment. Those with symptomatic hearing loss or speech impairment require similar evaluation. Affected children may need hearing amplification and speech therapy, but hearing aids do not restore normal hearing function, and these children often need support from community paediatric and educational services.

What does the future hold? Ideally, new and equally efficacious non-ototoxic treatments, or alternatively effective otoprotective strategies, will be developed. The reduced ototoxicity of carboplatin is a step in the right direction, but in some cancers, carboplatin is not as effective a drug as cisplatin [19]. In the meantime, since cisplatin therapy is needed to maximise the prospects of cure of many children with cancer, the information provided by *Li*'s study is very valuable.

Conflict of interest statement

None declared.

Acknowledgements

I am indebted to Mr. David Meikle and Mr. Clive Elliot for their expert audiological advice in the production of this manuscript.

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