

# Ototoxicity: a worrying problem for survivors of high-risk neuroblastoma

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**Abstract:** Landier *et al.* report the results of a COG study about ototoxicity in children with neuroblastoma. The authors present the results of audiologic testing graded by four different scales [American Speech-Language-Hearing Association; Brock; Chang; and Common Terminology Criteria for Adverse Events version 3 (CTCAEv3)], in 333/489 evaluable neuroblastoma patients, treated with cisplatin alone (400 mg/m<sup>2</sup>) or after cisplatin (400 mg/m<sup>2</sup>) plus carboplatin (1,700 mg/m<sup>2</sup>) according to COG A3973 protocol. (Their conclusions are that severe hearing loss is prevalent among children with high-risk neuroblastoma. Exposure to cisplatin combined with myeloablative carboplatin significantly increases risk. The Brock scale underestimates severe hearing loss and should be used with caution in this setting). Hearing loss from cisplatin or carboplatin is permanent and may have a delayed onset, with progressive loss occurring many years after completion of therapy. Young children are particularly sensitive to this adverse effect. Children treated for high-risk neuroblastoma, for example, are likely to sustain moderate to severe therapy-related hearing loss, with high potential for difficulties in speech discrimination and language acquisition, diminished academic achievement compared with peers with normal hearing, the potential for lifelong impairment of language and academic skills, and diminished quality of life. Although often underappreciated, even hearing loss restricted to high frequency ranges (4,000–8,000 Hz) have a significant impact on language development, verbal abilities, and reasoning skills in young children. This is of particular concern because the ototoxic effects are concurrent with the developmental period in which the process of acquiring speech and language skills is so critical. The reported incidence of cisplatin ototoxicity in children ranges from 26% to over 90% with the variation influenced by treatment and patient-related factors, but it also depends to some extent on the grading system used. The absence of a practical and uniform system for grading ototoxicity has impeded assessment of results in prior studies, and another problem is that full compliance with complete audiological testing in these young patients remains a challenge.

**Keywords:** Ototoxicity; cisplatin; carboplatin; neuroblastoma

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In the issue of February 20, 2014, of the *Journal of Clinical Oncology*, Landier *et al.* report the results of a COG study about ototoxicity in children with neuroblastoma.

The authors present the results of audiologic testing graded by four different scales [American Speech-Language-Hearing Association; Brock; Chang; and Common Terminology Criteria for Adverse Events version 3 (CTCAEv3)], in 333/489 evaluable neuroblastoma patients,

treated with cisplatin alone (400 mg/m<sup>2</sup>) or after cisplatin (400 mg/m<sup>2</sup>) plus carboplatin (1,700 mg/m<sup>2</sup>) according to COG A3973 protocol (1).

Their conclusions are that severe hearing loss is prevalent among children with high-risk neuroblastoma. Exposure to cisplatin combined with myeloablative carboplatin significantly increases risk. The Brock scale underestimates severe hearing loss and should be used with caution in this setting (2).

Children with neuroblastoma, hepatoblastoma, retinoblastoma, germ cell tumors, osteosarcoma, medulloblastoma, and other brain tumors are routinely treated with cisplatin, and/or carboplatin.

Induction regimes for high-risk neuroblastoma include frequently both drugs. These agents are known to cause high-frequency hearing loss that is no reversible. The dose-limiting factors in the administration of platinum-based drugs are generally nephrotoxicity (cisplatin) or myelosuppression (carboplatin), but cisplatin in therapeutic doses is highly ototoxic (3). Carboplatin, although with substantially less ototoxic potential than cisplatin, is associated with a high risk for hearing loss when used in combination with cisplatin and when used in myeloablative doses as conditioning for hematopoietic stem-cell transplantation in children (3,4).

Cisplatin hearing loss is permanent, bilateral, dose dependent with significant increased severity in young children. It manifests initially as bilateral high frequency sensorineural hearing loss, progressing in severity to the speech ranges with increasing cumulative doses (5). The hearing loss is caused by sensory hair cell destruction that begins at the base of the cochlea, where high frequency sounds are processed, and continues toward the cochlear apex, where lower frequency sounds are affected (5).

Hearing loss from cisplatin or carboplatin is permanent and may have a delayed onset, with progressive loss occurring many years after completion of therapy (5). Young children are particularly sensitive to this adverse effect. Children treated for high-risk neuroblastoma, for example, are likely to sustain moderate to severe therapy-related hearing loss (6), with high potential for difficulties in speech discrimination and language acquisition, diminished academic achievement compared with peers with normal hearing, the potential for lifelong impairment of language and academic skills, and diminished quality of life (7). Although often underappreciated, even hearing loss restricted to high frequency ranges (4,000-8,000 Hz) has a significant impact on language development, verbal abilities, and reasoning skills in young children (7). This is of particular concern because the ototoxic effects are concurrent with the developmental period in which the process of acquiring speech and language skills is so critical (7).

The typical pattern of high frequency loss was first noted when high-dose cisplatin was used in young children with neuroblastoma at 200 mg/m<sup>2</sup> per dose (8). The typical fall off, affects consonants more than vowels which can severely affect speech and learning particularly in the young (6,8).

The Brock grading system (9) has been used in SIOPEL (hepatoblastoma) studies to assess the ototoxicity of different regimens since the 1990's, using institutional results. In the

most recent publications of the SIOPEL 3 standard risk study, approximately 30% of children had Brock grade 1-4 hearing loss (10). However when the standard risk ototoxicity results of SIOPEL 2 and 3 were pooled, only including data from countries with an audiology reporting rate of over 60% of patients, a larger proportion of patients were shown to have Brock grade 1-4 hearing loss (11,12). The alternating cisplatin/carboplatin and doxorubicin dose dense regimen used in the high risk SIOPEL 2 and 3 studies is more ototoxic confirming findings reported in other pediatric cancers where combined cisplatin/carboplatin regimens are used (13).

The young age of most neuroblastoma patients (around 50% are less than 1 year old at diagnosis), makes them particularly susceptible and the long-term consequences on speech development and learning are especially important (7,8). Platinum toxicity shows some interindividual variability since 20% or more of children are seemingly not affected, and there is some evidence to support ethnic/racial difference (14). These observations have led to the hypothesis that genetic factors may render certain individuals more susceptible to the adverse effects of cisplatin, but may be the characteristics of the language also influence the outcome (14).

All current induction protocols for high-risk neuroblastoma (COG, SIOPEL, N7) use cisplatin with cumulative doses inferior to 600 mg/sqm and some of them employ high-dose carboplatin as megatherapy (15-18).

The reported incidence of cisplatin ototoxicity in children ranges from 26% to over 90% with the variation influenced by treatment and patient-related factors (19) but it also depends to some extent on the grading system used. One of the key issues in designing a clinical research study to evaluate preventive interventions is having a valid and reliable outcome measure that is standardized, practical, and widely accepted. Such a hearing loss measure needs to reflect the unique aspects of testing children of different ages and capabilities. The absence of a practical and uniform system for grading ototoxicity has impeded assessment of results in prior studies, and another problem is that full compliance with complete audiological testing in these young patients remains a challenge.

Brock *et al.* published in 1991 a pediatric specific hearing loss scale for cisplatin exposure that has been widely used in European studies (9). In USA the measure used to monitor and categorize severity of hearing loss in therapeutic trials has been the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0 which requires a baseline evaluation before treatment initiation and then measures change in hearing level as treatment progresses (20). The NCI-CTCAE v3.0 scale was

not specialized to children and has many inherent problems, including the fact that baseline measurements are often difficult to obtain in pediatric patients, particularly in very ill patients. In addition, obtaining true auditory thresholds (response to lowest intensity level) can be challenging in pediatric patients. Instead, only minimal response levels are often obtainable, which makes calculating a true decrease in hearing sensitivity difficult and potentially inaccurate.

Although the most recent version of the NCI CTCv3, version 4.0 significantly improves on the previous 3.0 version by identifying specific test frequencies for pediatric patients and defining more objective measures, problems with measuring change in hearing compared with baseline measurements and the somewhat subjective nature of defining grades 3 and 4 still remain (21).

Several other hearing loss grading scales have been introduced, including a modification of the Brock *et al.* scale by Chang and Chinosornvatana in 2010 (22). The new International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Grading Scale (5), and the ASHA (23). This new SIOP scale is simpler and potentially better than the Chang and Chinosornvatana scale, but it does not solve all the difficulties: how grading be coded for incomplete testing and/or objective measurements such as otoacoustic emissions or auditory evoked potentials that are necessary for testing in the younger children, are problems not solved.

Up to now preventive measures for cisplatin ototoxicity has been of little efficacy. The role of amifostine in pediatric patients treated with cisplatin-based chemotherapy is uncertain (24). The COG is currently running a randomized Phase III study of another thiol, which has shown more potential to reduce ototoxicity *in vitro*, sodium thiosulfate (25).

Carboplatin is also ototoxic, especially when delivered at myeloablative doses for autologous bone marrow transplantation, and potentiate the ototoxicity of previous cisplatin (2,4).

The SIOPEN HR-NBL-1 trial has randomized patients for megatherapy to receive busulfan-melphalan (BUMEL) or carboplatin-etoposide-melphalan (CEM). The randomization was closed in August 2012, because the results demonstrated superiority of BUMEL, and now all patients in Europe do not receive high dose carboplatin. This can be an opportunity to decrease exposure to platinum derivatives in high-risk neuroblastoma and also to decrease ototoxicity (26).

In summary, Landier *et al.* has studied ototoxicity in a big series of high-risk neuroblastoma patients treated homogeneously. Prevalence of any hearing loss (Brock, CTCv3, and Chang, grades 1 to 4; ASHA, grades A to C) was comparable across the four grading scales, ranging from

64% to 71% for the patients treated only with cisplatin to 86% to 90% for those receiving cisplatin and high-dose carboplatin. Prevalence of severe hearing loss differed by scale, being the Brock scale less sensitive for the detection of severe toxicity. The new SIOP Boston scale has been recently published and still has to demonstrate with their use, its superiority to the previous ones and which are the problems it solves.

Anyway the most worrying conclusion is the high prevalence of severe ototoxicity in the survivors of high-risk neuroblastoma and the frequent need of hearing aides in so small children, with all the consequences of the permanent deficit.

Currently, the use of cisplatin cannot be avoided in induction regimes of high-risk neuroblastoma patients, but may be the inclusion of new drugs could diminish the cisplatin dose received. The results of SIOPEN HR-NBL-1 comparing CEM with BUMEL open the door to suppress high-dose carboplatin in PBSC transplantation, being substituted by BUMEL that has no ototoxicity.

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