Selected Summaries

Cisplatin-induced hearing loss in children with cancer

Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, Pollock BH, Ramdas J, Lange B, Van Hoff D, VanSoelen ML, Wiernikowski J, Neuwelt EA, Sung L. (Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA; Departments of Pediatrics and Medicine and Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA; Children's Oncology Group, Monrovia, CA; Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR; Department of Public Health Sciences, University of California Davis, Davis, CA; Pediatric Hematology/Oncology, Geisinger Medical Center, Danville, PA; Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA; and Helen DeVos Children's Hospital, Grand Rapids, MI, USA; Pharmaceutical Services, McMaster University, Hamilton, ON; and Hematology/Oncology, Hospital for Sick Children, Toronto, ON, Canada.) Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): A multicentre, randomised controlled, open-label, phase 3 trial. *Lancet Oncol* 2016;**18:**63–74.

SUMMARY

This study by Freyer *et al*. was a multicentre, randomized, open-label, phase 3 trial. They enrolled 1–18-year-old, newly diagnosed patients with various cancers (osteosarcoma, germ cell tumours, medulloblastoma, hepatoblastoma or any other tumour) receiving cisplatin-based chemotherapy. The inclusion criteria were: planned cumulative cisplatin dose of 200 mg/m^2 or more and infusion duration of 6 hours or less; performance score of 50 or more by the Karnofsky (>16 years) or Lansky (≤16 years) scales; no previous cisplatin or carboplatin treatment; no known thiol hypersensitivity and normal organ function. Normal hearing was required before enrolment as defined by hearing thresholds of 20 dB hearing level (HL) or less at 500–8000 Hz when measured with earphones, or 25 dB HL or less when measured in the sound field or as defined by brainstem auditory-evoked response thresholds equivalent to behavioural thresholds of 20 dB HL or less.

Patients were stratified by age (<5 and ≥5 years) and cisplatin infusion duration (<2 and ≥2 hours) and were randomized to sodium thiosulphate or control (observation) group. The sodium thiosulphate dose was 16 g/m^2 (or 533 mg/kg) and was administered as a 12.5% solution, and infused daily over 15 minutes beginning 6 hours after completion of each cisplatin dose. Hearing assessments were done at baseline, up to 8 days before each cisplatin course, 4 weeks after completion of the final cisplatin course and 1 year later. Hearing loss was determined according to the American Speech–Language–Hearing Association (ASHA) criteria.[1] The primary end-point was hearing loss at 4 weeks after final cisplatin treatment and secondary end-points were frequency-specific hearing loss at 4 weeks (for 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz), haematological and renal toxicity and survival (event-free and overall survival).

One hundred thirty-one participants were screened and 125 were enrolled (64 in the control group and 61 in the sodium thiosulphate group), and 105 patients were eligible for primary end-point analysis at the end of the study. The median cumulative cisplatin dose for the control group was 387 mg/m^2 and 393 mg/m^2 for the sodium thiosulphate group. Hearing loss at 4 weeks was identified in 14 (28.6%) participants in the sodium thiosulphate group compared with 31 (56.4%) in the control group (p=0.0002), and the benefit was more in patients younger than 5 years of age (21.4% [3/14] *v.* 73.3% [11/15]) in favour of sodium thiosulphate. ASHA-defined hearing loss at 1 year (*n*=67) was 28% (*n*=9/32) and 54% (*n*=19/35) in the sodium thiosulphate and control groups (p=0.001), respectively. Haematological toxicity was comparable among both groups (p=0.95), though nephrotoxicity was more common in the sodium thiosulphate group (25% *v.* 13%, p=0.006), as was hypokalaemia and hypophosphataemia. After a median follow-up of 3.5 years, there was no difference in event-free survival (hazard ratio [HR]=1.3, p=0.36), but there was a trend towards inferior overall survival (HR=2.03, p=0.07) in the sodium thiosulphate group, and the difference in overall survival was statistically inferior for the sodium thiosulphate group in those with disseminated disease (HR=4.1, p=0.009).

COMMENT

Cisplatin is an anticancer agent used commonly in various human cancers including most paediatric solid tumours. Cisplatin-induced hearing loss is progressive, irreversible and bilateral resulting in permanent functional disability with a poor quality of life.[2] The approximate incidence of cisplatin-induced hearing loss is 40%, but it can be as high as 100% in specific subsets of children.[3,4] The risk factors include younger age (>5 years) and higher cumulative dose of cisplatin (>200–400 mg/m^2). In a preclinical model, sodium thiosulphate, a thiol-containing antioxidant, is rapidly excreted by the kidney after intravenous administration and provided protection against cisplatin-induced hearing loss when injected 4–8 hours after cisplatin injection without compromising its anticancer effect.[5]

The study by Freyer *et al*. was conducted in a heterogeneous group of paediatric malignancies with heterogeneous chemotherapy protocols in a small number of patients. No previous phase 1 or phase 2 study was conducted in paediatric cancer patients with sodium thiosulphate to define its ideal dosage, pharmacokinetics and pharmacodynamics or drug interaction and its efficacy for the prevention of cisplatin-induced hearing loss before embarking on a randomized phase 3 study in a vulnerable population. Is the dose of sodium thiosulphate used in the current study (16 g/m^2) an ideal standard dose for children as no previous study exists? The authors did not stratify sodium thiosulphate dose according to cumulative cisplatin dose, concurrent ototoxic and nephrotoxic drug use, single-day versus multi-day cisplatin use, etc. Is dose modification required for sodium thiosulphate for the above-mentioned variables? We do not know about the interaction of sodium thiosulphate with other chemotherapy agents and that may influence the overall toxicity and survival outcome. Though the authors tried to evaluate the effect of sodium thiosulphate on event-free and overall survival, the evaluation was limited by small sample size, no information on chemotherapy (cisplatin as well) intensity maintained and subsequent line of therapy and heterogeneous nature of the malignancy included with difference in disease biology, etc. Difference in cisplatin intensity and chemotherapy combination will also influence the

primary outcome of the study—hearing impairment. This study did not address any underlying genetic susceptibility in cisplatin-induced hearing loss intensity including any hidden pharmacogenomics. Hence, until a properly conducted prospective study in a homogeneous, larger population of children with cancer using uniform treatment protocols, incorporating a phramacokinetics and pharmacodynamics study evaluates the protective role of sodium thiosulphate in cisplatin-induced hearing loss, its routine clinical use cannot be recommended. This is important in the Indian scenario as a large number of children with cancer are getting treatment in a resource-poor setting. Often these children have a poor nutritional reserve and poor compliance; and hearing assessment is not being done routinely. Persistent, subclinical and undiagnosed hearing loss can lead to impairment of cognition. Hence, a protective agent is needed against cisplatin-induced hearing loss, and sodium thiosulphate could be such an agent.

Conflicts of interest. None.

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BIVAS BISWAS
bivasbiswas@gmail.com

SANDIP GANGULY
JOYDEEP GHOSH
Department of Medical Oncology
Tata Medical Center
Kolkata
West Bengal

ATUL BATRA
Department of Medical Oncology
Dr B.R. Ambedkar Institute Rotary Cancer Hospital
All India Institute of Medical Sciences
New Delhi