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Ototoxicity after platinum-based chemotherapy in the treatment of melanotic neuroectodermal tumour of infancy

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Abstract. Melanotic neuroectodermal tumor of infancy (MNTI) is a rare infantile tumor that originates from mesenchymal-neuroectodermal cells, the treatment of which uses platinum derivatives that can affect hearing loss. The present study evaluated the long-term effects of ototoxicity following chemotherapy with cisplatin, vincristine, cyclophosphamide, teniposide and adriamycin in a 10-year-old patient after surgical removal of a MNTI tumor at the age of 8 months. Audiometric tests (high-frequency tonal audiometry, speech audiometry, speech acoustics, tympanometry and absorbance measurements) were performed during a 10-year follow-up after receiving chemotherapy. Hearing disorders in the high-frequency range (6,000 to 16,000 Hz range) were demonstrated for both ears, indicating that these may be the long-term effects of chemotherapy with use of platinum compounds during the treatment of infants.

Introduction

Melanotic neuroectodermal tumor of infancy (MNTI) is a mixed mesenchymal-neuroectodermal tumor characterized by the presence of pigment cells containing melanin, which usually appears in the first year of life (1). The tumor is benign, but due to its rapid growth, it can damage the surrounding structures, which makes it dangerous (2). Most commonly, the tumor is located in the anterior part of the alveolar process; less frequently in the skull, brain or mandible (3). The treatment of choice is surgical excision of the tumor and chemotherapy (4). Chemotherapy is one of the primary methods of treatment in cancer therapy, but it may be associated with specific side effects (5). The most commonly used anti-cancer drug is cisplatin, which has a nephrotoxic and ototoxic impact (6). Chemotherapy based on platinum compounds is very useful in the treatment of neuroectodermal neoplasms in children. Unfortunately, their use can lead to morbid infections (7,8) as well as irreversible hearing loss (9). Literature data show that between 40 and 80% of cisplatin-treated patients experience permanent hearing loss (10,11). Some authors report that cisplatin-induced ototoxicity has been observed in 7 and 90% of cases at standard doses (12), as well as at different doses and in various age groups (13), including children (14). Clinically, ototoxicity manifests itself as bilateral hearing loss accompanied by tinnitus (15). Hearing loss begins in the high-frequency range and progresses towards lower frequencies (16,17).

As a consequence, ototoxicity can lead to delayed speech development, learning difficulties, and even a deterioration in psychosocial, emotional and general psychological well-being (16). Also, ototoxicity has been shown to have a progressive nature (11,15). Hearing impairment or delayed hearing loss can appear a few years after the end of treatment. Therefore, long-term specialist monitoring of the condition of the auditory system for a minimum of 10 years is recommended. Ototoxicity risk factors include the cumulative dose, impaired renal function, route of administration, cranial irradiation, previous sensorineural hearing loss, age under five years, concomitant use of ototoxic drugs, genetic susceptibility, and tumor localization (16). The study aimed to evaluate ototoxicity after MNTI chemotherapy from a long-term perspective.

Case study

This case study presents a long-term ototoxic effects after chemotherapy with cisplatin, vincristine, cyclophosphamide, teniposide and adriamycin in a 10-year-old female patient, who was administered this combination of drugs before and after surgical removal of MNTI at the age of 8 months. A female patient aged three months was admitted to the Department of Haematology and Paediatric Oncology of the Karol Jonscher Clinical Hospital in Poznan with a mixed mesenchymal-neuroectodermal MNTI, a solid tumor within the alveolar ridge. Histopathological examination

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Key words: melanotic neuroectodermal tumor of infancy, hearing impairment, cisplatin, oncological treatment, oncology

Table I. Results of otoacoustic emissions tests for the right and left ear before chemotherapy.

l1 (dB) R/L	l2 (dB) R/L	F1 (Hz) R/L	F2 (Hz) R/L	GM (Hz) R/L	DP (dB) R/L	NF (dB) R/L	DP-NF(dB) R/L	Result
64.8/65.6	55.0/53.8	4170/4170	5014/5014	4573/4573	13.3/7.1	4.4/-1.5	8.9/8.9	Pass
65.1/66.2	55.1/55.6	3514/3514	4217/4217	3850/3850	16.7/13.1	-7.8/3.4	24.5/9.8	Pass
65.3/64.6	55.7/55.9	2905/2905	3514/3514	3195/3195	15.1/12.9	-13.5/ 4.7	28.6/8.2	Pass
65.1/67.9	55.5/56.0	2296/2296	2765/2765	2519/2519	16.1/10.4	3.4/1.4	12.7/9.0	Pass
65.7/67.3	55.3/56.5	1687/1687	2015/2015	1844/1844	16.4/13.4	4.7/2.7	11.7/10,7	Pass

R, right ear; L, left ear; l, levels; F, frequency; GM, geometric mean; DP, distortion product level; NF, noise floor.

Table II. Results of otoacoustic emissions tests for the right and left ear one year after chemotherapy.

l1 (dB) R/L	l2 (dB) R/L	F1 (Hz) R/L	F2 (Hz) R/L	GM (Hz) R/L	DP (dB) R/L	NF (dB) R/L	DP-NF(dB) R/L	Result
67.3/64.4	56.3/53.2	4077/4170	4873/5014	4457/4573	6.7/-3.9	-3.9/-12.4	10.6/8.5	Pass
67.1/66.3	57.4/54.9	3514/3514	4217/4217	3850/3850	9.1/6.1	-6.7/-4.5	15.8/10.6	Pass
64.0/64.8	55.6/54.4	2905/2905	3514/3514	3195/3195	8.8/-0.7	-7.5/-17.3	16.3/16.6	Pass
64.4/65.3	52.2/54.8	2296/2296	2765/2765	2519/2519	14.9/7.6	-16.8/-6.1	31.7/13.7	Pass
64.2/64.8	54.1/55.3	1687/1687	2015/2015	1844/1844	13.7/15.5	-3.7/-10.4	17.4/25.9	Pass

R, right ear; L, left ear; l, levels; F, frequency; GM, geometric mean; DP, distortion product level; NF, noise floor.

confirmed MNTI. General tests were performed: Morphology, biochemistry, and immunochemistry, which did not show any abnormalities. Diagnostic imaging examinations, which consisted of a chest X-ray and abdominal ultrasound, were also standard. A computed tomography head scan showed lytic and osteogenic bone lesions on the left side. The lytic lesion was 26x15 mm in size and was located within the alveolar ridge of the maxilla. The osteogenic lesions were found in the body of the maxilla near the nasal wings. 'Floating teeth' (incisors) were visible within the soft tissues of the alveolar ridge. It was decided to administer chemotherapy before tumor resection. Chemotherapy according to the CWS protocol for standard risk rhabdomyosarcoma, which consisted of 7 treatments with vincristine and dactinomycin, was distributed. Before the introduction of chemotherapy, the patient underwent a hearing examination. Due to the patient's age and her apparent lack of cooperation, a non-invasive, objective hearing test was performed, namely a 3/5 otoacoustic emissions (OAEs) screening test. This test makes it possible to detect hearing loss of cochlear origin and to assess the function of external hair cells. It involves the recording of a very quiet acoustic signal that arises in the cochlea due to the contraction of outer auditory cells. For both ears, responses for all the frequencies were recorded, which means that the acoustic cell responded to the two-tone stimuli (Table I).

At the age of 8 months, the patient underwent surgical removal of the tumor in the Department of Oncological Surgery for Children at the Institute of Mother and Child in Warsaw. The removed fragment of the maxillary bone was 2.5x1.4x1.5 cm in size, was covered by overlying mucosa, and contained pieces of tooth structure. Next, multidrug chemotherapy was introduced with 23.5 mg cisplatin, 95 mg cyclophosphamide, 9.5 mg adriamycin, and 23.5 mg teniposide injected intravenously. One year after the completion of chemotherapy, another 3/5 otoacoustic emissions (OAEs) screening test was performed. The results for the left and right ears were normal (Table II).

Figure 1. Panoramic radiograph of the patient at 8 years of age 8 at the beginning of orthodontic treatment.

At the age of 8 years (Fig. 1) the girl came for consultation to the Clinic of Maxillofacial Orthopaedics and Orthodontics at the University of Medical Sciences in Poznań, of which she has been a patient ever since. To improve the aesthetics and function of the masticatory apparatus after the resection procedure, orthodontic treatment was planned and implemented. There were no changes in the structures of soft and bone tissues other than those connected with post-operative healing. After two years, as part of the orthodontic treatment, the patient was referred to the Department of Hearing Healthcare Profession, Chair of Biophysics Poznan University of Medical Sciences, Poland for a hearing test. Otoscopic examination revealed no contraindications for performing

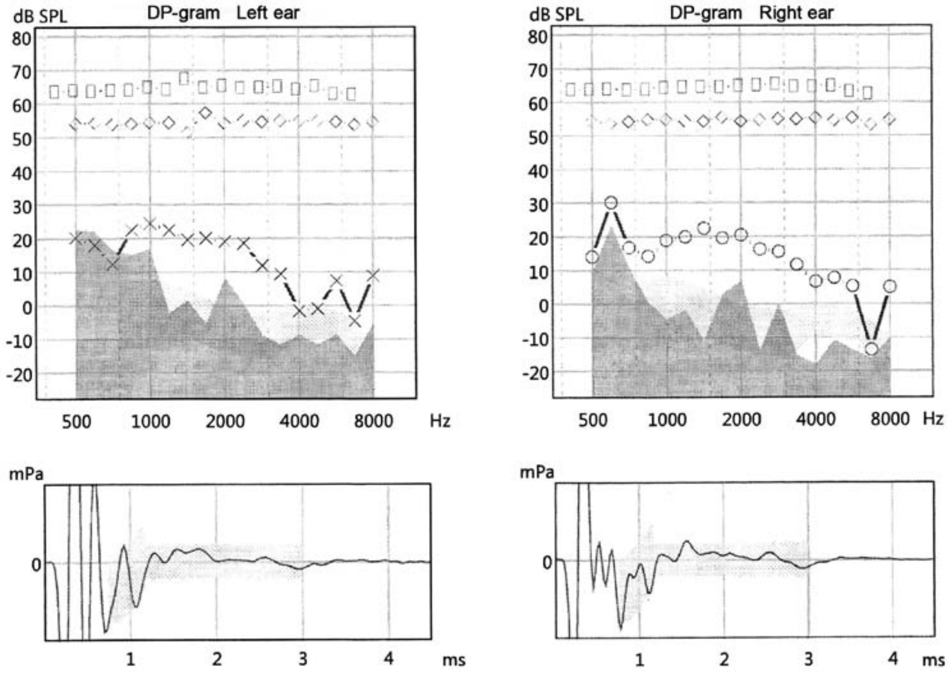

Figure 2. Results of the distortion product otoacoustic emissions test for both ears and the DP-grams 10 years after chemotherapy DB SPL, dB of sound pressure level.

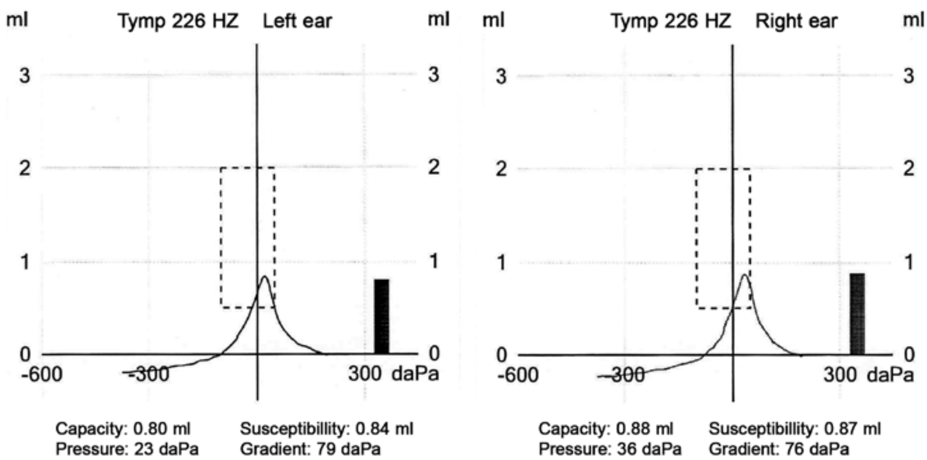

Figure 3. Results of classic tympanometry at 226 Hz for each ear, 10 years after chemotherapy.

the audiological evaluation. Subjective tests were conducted using a Madsen Itera II diagnostic audiometer and included pure-tone audiometry for the extended frequency range from 125 Hz to 16 kHz and speech audiometry. In accordance with the cross-check principle, objective tests were also performed: Classic tympanometry for the 226 Hz frequency; wideband tympanometry for the frequency range 226-8,000 Hz; stapedial reflex assessment with a Titan tympanometer (Interacoustic); and a Distortion Product Otoacoustic Emissions (DPOAE) test using a Madsen Capella 2 device (Medicus). Otoacoustic emissions evaluation makes it possible to measure the activity of external auditory cells; in particular, the DPOAE test indicates the frequency ranges in which external auditory cells are affected by platinum compounds.

The tests yielded the following results: Otoacoustic emissions were correct in both ears, normal tympanograms were obtained for both the right and left ear (type A), with correct stapedial muscle reflexes for all frequencies (Figs. 2 and 3; Table III). Absorbance measurements for both ears revealed characteristic peaks at around 1,000 and 3,000 Hz. The hearing threshold determined for the frequencies of 500, 1,000, 2,000, and 4,000 Hz was five dBHL for the right ear, and ten dBHL for the left ear (Fig. 4). Speech audiometry results were consistent with the results of pure-tone audiometry: The Speech Reception Threshold (SRT) was 35 dBSPL for both ears. However, a significant increase in the hearing threshold of both ears was recorded for the frequency range between 6,000 and 16,000 Hz. The results obtained reveal substantial abnormalities.

The present study was reviewed and approved by the institutional ethics committee of Poznan University of Medical Sciences. All the procedures performed in studies

Table III. Results of distortion product otoacoustic emissions tests for the right and left ear, 10 years after chemotherapy.

F2 (Hz) R/L	GM (dB) R/L	l1/l2 R/L	DP1 (dB) R/L	NF (dB) R/L	SNR (dB) R/L	Result R/L
498/498	452/452	64/55/64/55	14/20	9/23	5/-2	Rejected/Rejected
596/596	539/539	64/54/64/54	30/18	24/22	7/-4	Pass/Rejected
703/703	636/636	64/54/64/54	17/12	11/16	6/-4	Rejected/Rejected
840/840	763/763	64/55/64/54	14/23	0/15	14/7	Pass/Pass
996/996	904/904	64/55/64/54	19/23	-5/17	23/7	Pass/Pass
1191/1191	1079/1079	64/54/64/54	20/22	-2/-2	22/25	Pass/Pass
1416/1416	1283/1283	65/55/64/51	22/20	-11/2	33/18	Pass/Pass
1680/1680	1521/1521	65/55/68/57	20/20	7/-5	14/26	Pass/Pass
2002/2002	1812/1812	65/54/65/54	20/19	7/8	14/11	Pass/Pass
2383/2383	2157/2157	65/55/65/55	16/19	-14/1	30/18	Pass/Pass
2832/2832	2560/2560	65/55/65/55	16/12	0/-9	15/21	Pass/Pass
3359/3359	3042/3042	65/55/65/55	12/9	-15/-12	27/21	Pass/Pass
4004/4004	3625/3625	65/55/65/55	7/-2	-18/-9	25/7	Pass/Pass
4756/4756	4305/4305	65/5464/55	8/-1	-11/-12	18/11	Pass/Pass
5654/5654	5121/5121	65/55/65/55	5/7	-14/-9	19/16	Pass/Pass
6729/6729	6093/6093	63/53/63/54	-14/-5	-16/-15	3/10	Rejected/Pass
7998/7998	7239/7239	63/55/63/55	5/9	-10/-5	15/15	Pass/Pass

R, right ear; L, left ear; F, frequency; GM, geometric mean; l, level; DP, distortion product; NF, noise floor; SNR, signal to noise ratio.

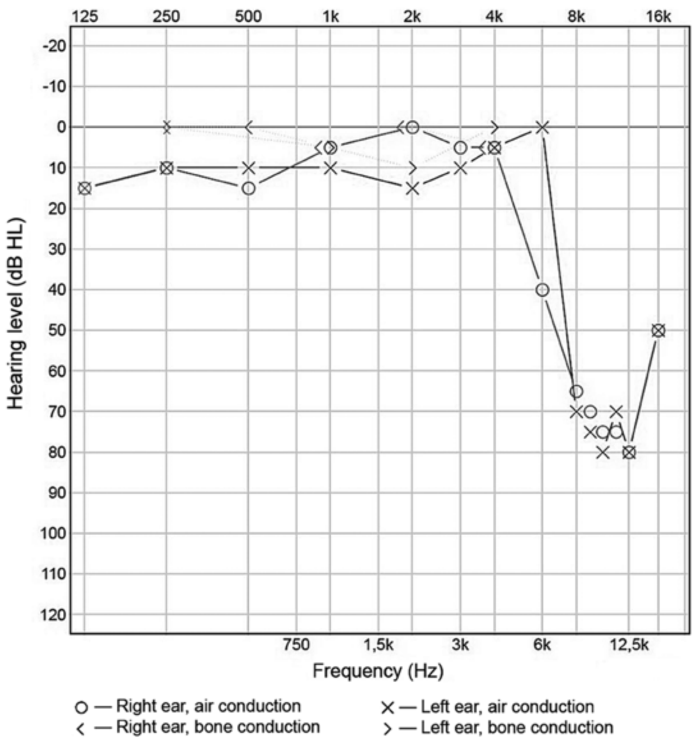

Figure 4. Results of pure-tone audiometry for each ear, 10 years after chemotherapy.

involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (no. 645/16). Written informed consent was obtained from all parents prior to enrollment.

Discussion

Platinum compounds are used in the standard treatment of mesenchymal-neuroectodermal tumors in pediatric oncology. The use of cisplatin is one of the most common causes of drug-induced hearing loss because its ototoxicity has a destructive effect on external auditory cells, which are not capable of regeneration (18). The means that the hearing loss after cisplatin-based treatment is irreversible (19). In this study, a patient with a mesenchymal-neuroectodermal tumor who had been treated with cisplatin was diagnosed with bilateral high-frequency hearing loss, which is consistent with literature reports (10-13). The damage associated with chemotherapy begins in the first row of the external auditory cells, at the base of the cochlea, where high-frequency sounds are processed. As a result, chemotherapy using cisplatin causes bilateral high-frequency sensorineural hearing loss, which is consistent with our findings (20). High frequencies are not crucial for the understanding of speech; however, with higher doses and the passage of time after the completion of the treatment, hearing loss may in some cases also affect lower frequencies (21).

As a consequence, cisplatin-induced ototoxicity can impair a child's development, learning, and behavior (12,22). Unfortunately, in our case no previous pure-tone audiometry tests were performed, which makes it impossible to determine whether the hearing loss is progressive or whether it has remained at the same level since the end of chemotherapy. In the literature, reports are stating that after the completion of treating hearing loss is permanent and stable (19,23). However, many authors have observed progressive hearing loss following chemotherapy with platinum compounds in children treated for solid tumors (15,21,22).

It is worth noting the research of Liberman *et al*, conducted on a group of 200 patients to assess hearing loss caused by cancer treatment in childhood. The types of cancer from which the studied patients suffered included solid tumors. All the patients were seen at least eight years after the cancer treatment, which consisted of a combination of radiotherapy and chemotherapy with or without the use of cisplatin (CDDP). The audiological evaluation included pure-tone audiometry, speech audiometry, and impedance audiometry. The assessment of hearing loss was made according to the criteria adopted by the International Office for Audiophonology, where a hearing loss means the presence of pure tones >20 dBHL for the frequency range 500-4,000 Hz. The authors found symmetric, bilateral hearing loss at the 4, 6 and 8 kHz frequencies in patients who had undergone chemotherapy with CDDP, and in those after radiotherapy combined with chemotherapy using CDDP. Hearing loss was not observed in patients who had experienced only radiotherapy or chemotherapy without CDDP. It was found that the risk factors for hearing loss are the use of CDDP in cancer therapy and the patient's age at the time of cancer diagnosis (24). Evaluation of the patient discussed in this paper conducted ten years after the completion of chemotherapy clearly shows a high-frequency hearing loss, which is consistent with the foregoing study. Cooperation with the child's parents/guardians is essential. Their consent and help in the multi-faceted therapy of the child (regardless of the disease entity) is a prerequisite for the implementation of treatment and rehabilitation procedures, which was emphasized in many items cited, including the study, references.

Most of the available literature does not contain reports on the possibility of complications resulting from the administration of cisplatin-based chemotherapy in the treatment of MNTI. One of the possible side effects of cisplatin is ototoxicity, which developed in the patient discussed in this paper, an occurrence which is confirmed by literature reports. Cisplatin-induced hearing loss develops in patients in the long-term and initially affects only the high-frequency range. In the presented case, hearing loss was observed ten years after the completion of chemotherapy, and it concerned high frequencies in the 6,000 to 16,000 Hz range for both ears. Thus, it is essential to inform the parents or legal guardians of a child patient in advance about the possibility of ototoxicity and to acquaint them with the possible consequences of hearing the loss in children. It is also crucial to ensure multidisciplinary cooperation between doctors and hearing care professionals monitor the auditory system during and after chemotherapy.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

DHJ conceived the current study, developed the methodology, supervised the experiments and critically revised the manuscript. ACh and ACz analyzed and interpreted orthodontic treatment data, and analyzed orthodontics literature. ACh edited the figures and wrote the manuscript. MMK carried out orthodontic treatment, collected data, was responsible for patient approval and secured intellectual property from the patient and parents. AM and MUO analyzed and interpreted hearing system data. AM analyzed ototoxity literature. MUO carried out audiological examination and wrote the manuscript. TMB conceived and scheduled the experiments, interpreted results, edited and revised the manuscript, and approved the final version of the manuscript for publication. All authors read and approved the final manuscript.

Ethics and consent to participate

The present study was reviewed and approved by the Institutional Ethics Committee of Poznan University of Medical Sciences. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (no. 645/16). Written informed consent was obtained from all parents prior to enrollment.

Patient consent for publication

Parents provided written informed consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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