Prospective evaluation of cisplatin- and carboplatin-mediated ototoxicity in paediatric and adult soft tissue and osteosarcoma patients

ALEXANDRA NITZ[1], EVANGELOS KONTOPANTELIS[2], STEFAN BIELACK[3], EWA KOSCIELNIAK[4], THOMAS KLINGEBIEL[5], THORSTEN LANGER[1*] and MARIOS PAULIDES[1*]

[1]Department of Paediatric Oncology and Immunology, LESS Centre, University Hospital for Children and Adolescents, Erlangen D-91054, Germany; [2]Department of Community Based Medicine (Health Sciences Research Group - Primary Care), University of Manchester, Manchester, M13 9PL, UK; [3]Department of Oncology, Haematology, Immunology, General Pediatrics, Gastroenterology, Rheumatology (COSS Study), Klinikum Stuttgart - Olgahospital, Stuttgart D-70176; [4]Department of Oncology, Haematology, Immunology, General Pediatrics, Gastroenterology, and Rheumatology (CWS study), Klinikum Stuttgart - Olgahospital, Stuttgart D-70176; [5]Department of Paediatric Haematology, Oncology and Haemostaseology, Universitaetsklinikum Frankfurt - Johann-Wolfgang-Goethe-University, Frankfurt D-60596, Germany

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Abstract. Platinum-compound chemotherapy is known to have ototoxic side-effects. However, there is a paucity of literature examining hearing function prospectively and longitudinally in cohorts containing paediatric and adult patients treated within the same cisplatin- or carboplatin-containing treatment trial protocols. In Germany, Austria and Switzerland, late effects of treatment for osteosarcoma and soft tissue sarcoma have been prospectively and longitudinally registered by the Late Effects Surveillance System since 1998. The aim of this study was to analyse cisplatin- and carboplatin-induced ototoxity in a group of 129 osteosarcoma and soft tissue sarcoma patients treated within the COSS-96, CWS-96 and CWS-2002P treatment trials. The cohort consisted of 112 children and 17 adults. The median age at diagnosis was 13.56 (IQR, 10.26-16.27) years. Follow-up was 6.97 (IQR, 0.87-15.63) months. Hearing function was examined by audiometry before and after platinum treatment. A total of 108 patients were treated with cisplatin with a median cumulative dose of 360 mg/m^2. Thirteen patients received carboplatin with a median cumulative dose of 1500 mg/m^2 and 8 patients were treated with both platinum compounds (median cisplatin dose, 240 mg/m^2; IQR, 240-360 mg/m^2 and median carboplatin dose: 1200 mg/m^2; IQR, 600-3000 mg/m^2). Following cessation of therapy, 47.3% of the patients demonstrated a hearing impairment, namely 55 children (49.1%) and 6 adults (42.1%). Out of thirteen children treated with carboplatin with a cumulative dose of 1500 mg/m^2, six revealed a significant hearing impairment. Although ototoxicity caused by platinum compounds is considered irreversible, we identified hearing improvements over time in 11 children (9.8%) and 3 adults (17.6%). None of these patients received irradiation to the head. We conclude that hearing loss is frequent in children treated with protocols containing platinum compounds and recommend prospective testing via audiometry.

Correspondence to: Professor Thorsten Langer, Department of Paediatric Oncology and Immunology, LESS Centre, University Hospital for Children and Adolescents, Loschgestrasse 15, D-91054 Erlangen, Germany
E-mail: ki-less@uk-erlangen.de

*Contributed equally

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Introduction

Children receiving platinum-compound chemotherapy for the treatment of malignancies may be at risk of an early- or delayed-onset hearing impairment that may affect learning, development, communication, school performance, social interaction and overall quality of life (1-4).

Patients at risk include those receiving cisplatin and/or carboplatin for neuroblastoma, hepatoblastoma, osteosarcoma, soft-tissue sarcoma or germ-cell tumors (1). Cisplatin is known to cause permanent, sensorineural hearing loss, which is mostly bilateral, begins at high frequencies and progresses to involve mid-frequencies with continued exposure. The reported incidence varies widely from 11 to 97% (5). This may be explained by differences in the treatment modalities and in the populations under investigation. In addition, to date, there is no agreement regarding the definition of hearing impairment. This impedes comparisons between different studies (5). Cisplatin-induced hearing loss has been reported to be enhanced with increasing cumulative dose (6-10), bolus administration (11,12), prior cranial irradiation (10) and young age (5,8-10). In comparison,

the newer platinum compound carboplatin has been reported to be less ototoxic. In a number of studies no, or only low, ototoxicity was identified (13,14); although severe hearing loss may occur after high-dose therapy (2,15). The severity of hearing loss is often graded according to the Münster classification (17), but also according to the Brock grading system (7) and the ASHA criteria (www.asha.org). These late effects of cisplatin and carboplatin in the treatment of children have been well-described (7,10,14,16). The effects in adult patients, however, have not been adequately investigated. The aim of this prospective cohort study was to analyse platinum-induced ototoxicity in patients with similar treatment, within the same trial protocols for soft tissue sarcoma or osteosarcoma. This was possible using the Late Effects Surveillance System (LESS), which was founded in 1998 to register and multicentrally, prospectively and longitudinally assess the late effects of treatment for these groups of former cancer patients in Germany, Austria and Switzerland (16).

Patients and methods

Patients. Our study population consisted of 129 patients, including 112 children and 17 adults. The children group consisted of 93 osteosarcoma and 19 soft-tissue sarcoma patients. In the adult population, 16 patients were diagnosed with osteosarcoma and 1 patient had a soft-tissue tumour. Follow-up was conducted in local cooperating hospitals (n=21). Patients were excluded in the case of relapse, secondary malignancy or mortality and diagnosis younger than three years of age (audiometry not reasonable). Treatment for osteosarcoma and soft tissue sarcoma patients was performed according to the COSS-96 and CWS-96/2002P protocols (unpublished data). All studies were approved by the ethics committee of the University of Erlangen, and written informed consent was obtained from either from the patient. Cisplatin was administered intravenously (i.v.) via 72-h infusion with 120 mg/m^2 per course. Carboplatin was administered i.v. via 1-h infusion with 500 mg/m^2 per course. In the adult population, 15 patients received cisplatin and 2 patients received both platinum compounds. Thirteen children with soft tissue sarcoma were treated only with carboplatin. Fourteen children and one adult received additional radiotherapy. Five of these children received radiotherapy to the head with a median cumulative dose of 44.8 Gy.

Methods. Hearing function was analyzed using pure-tone audiometry. Air conduction in children, and additionally bone conduction in all adult patients, were measured at the stimulus frequencies of 0.125, 0.25, 0.5, 1, 2, 4, 6 and 8 kHz. According to the protocols of COSS, CWS and LESS, audiometry should be performed prior to platin application (T1), after platinum chemotherapy blocks (T2) and at least twice after cessation of therapy, namely at 4 weeks (T3) and 1 year (T4) after the end of treatment. In the study of the late effects, the difference between at least two audiograms was interpreted. The study only included patients in whom pre- and post-therapy audiograms were available. In 51 patients the audiogram at T1 was evaluated and compared with an audiogram after cessation of therapy (T3 or T4). One audiogram at T1, at T2 and only one audiogram (T3 or T4) after therapy were available in 60 patients. Audiograms at all four times were evaluated in 2 adult and 16 paediatric patients. All audiograms were interpreted by the same member of the LESS study group to eliminate interobserver variability. This individual was blinded to the patients' treatment. Cumulative radiochemotherapy doses for each patient were provided by the COSS and CWS trial centres. In our study, hearing impairment was classified by a modified Münster score (17) (Table I). The Münster score defines hearing thresholds ≤20 dB at 4 kHz as no considerable damage. Hearing impairment with moderate damage is defined as a hearing threshold >20 dB at 4 kHz and above. Our score defined hearing impairment as a hearing threshold ≥20 dB either at <4 kHz or ≥4 kHz or both, while the Münster score defines hearing impairment in more subgroups. We also registered hearing improvement over time in certain patients, which we defined as an improvement in the hearing threshold level to 20 dB or lower, if a pathological result (hearing threshold >20 dB) had been registered at the same frequency previously.

Table I. Hearing loss after platinum therapy expressed using our score (modified Münster score).

Ototoxicity score	Hearing loss
0	<20 dB at 4 kHz and above
1	≥20 dB at 4 kHz and above
2	≥20 dB below and above 4 kHz
3	≥20 dB below 4 kHz

Statistical analysis. In our main multivariate analysis we included 128 patients for which complete information was available, and used ordinal regression models to investigate ototoxicity in patients receiving either one or both drugs, controlled for patient age, gender, type of malignancy, follow-up time, chemotherapy regime (cisplatin, carboplatin or both) and radiotherapy regime.

As we were unable to control dosage, due to the different nature of the drugs, we conducted a sensitivity analysis on the most populous chemotherapy group; the 107 patients with complete information receiving cisplatin. This was also an ordinal regression in which we controlled all the factors described in the main analysis, except the non-applicable chemotherapy regimen, plus the cumulative dosage.

We also used ordinal regression models to estimate the effect of head irradiation on cisplatin and carboplatin induced ototoxicity. Stata v11.2 (StataCorp LP, College Station, TX, USA) and an α level of 0.05 was used for all analyses.

Results

Summary data. In total, our study included 129 patients, 66 males (51.2%) and 63 females (48.8%) (Table II). The median age at diagnosis was 13.56 (IQR, 10.26-16.27) years. A total of 108 patients received cisplatin with a median cumulative dose of 360 mg/m^2 (IQR, 360-480). Thirteen patients were treated with carboplatin at a median cumulative dose of 1500 mg/m^2 (IQR, 1500-1500 mg/m^2). Eight patients

Table II. Hearing status of children and adults.

	Total population		Children		Adults	
	No.	%	No.	%	No.	%
Hearing impairment	61	47.3	55	49.1	6	35.3
Male	30	49.2	27	49.1	3	50.0
Female	31	50.8	28	50.9	3	50.0
Hearing impairment without improvement	47	77.1	44	80.0	3	50.0
Improvement in hearing over time	14	23.0	11	20.0	3	50.0
No. hearing impairment	68	52.7	57	50.9	11	64.7
Male	36	52.9	30	52.6	6	54.5
Female	32	47.1	27	47.4	5	45.5
Improvement	14		11		3	
Male	7	50.0	6	54.5	1	40.0
Female	7	50.0	5	45.5	2	60.0
Hearing impairment (in dB)						
<4 kHz	2		2			
≥4 kHz	41	67.2	37	67.3	4	66.7
</≥4 kHz	18	29.5	16	29.1	2	33.3
Improvement						
<4 kHz	4	28.6	3	27.3	1	33.3
≥4 kHz	6	42.9	4	36.4	2	66.7
</≥4 kHz	4	28.6	4	36.4		
All patients	129	100.0	112	86.8	17	13.2

received both cisplatin (median dose, 240 mg/m^2; IQR, 240-360 mg/m^2) and carboplatin (median dose, 1200 mg/m^2; IQR, 600-3000 mg/m^2). The median interval from the end of the last cisplatin and carboplatin chemotherapy course to the first post-treatment audiometry was 6.97 months (IQR, 0.87-15.63 months). The study only included patients in whom pre- and post-therapy audiograms were available.

Hearing impairment. A hearing impairment was identified in 61 (47.3%) cases. In 55 (49.1%) children, of which 27 were male (49.1%) and 28 were female (50.9%), and 6 adults (42.1%), of which 3 were male (50%) and 3 were female (50%). In 21 cases only one side was affected, while in 40 cases hearing impairment was bilateral (58.8%). Classified by our modified Münster score, 41 patients developed a grade 1 hearing loss, 18 developed grade 2, and 2 cases developed grade 3. Four children required bilateral hearing aids.

Four adults and 37 children had a hearing impairment ≥20 dB in the main speech frequency of ≥4 kHz. In 16 children and two adults a hearing impairment of ≥20 dB at ≥4 kHz and in the frequencies lower than 4 kHz was detected. One of the adult patients had a significant hearing impairment at 0.25 kHz. Two children suffered from a hearing impairment at frequencies <4 kHz.

Hearing improvements. In 14 of 61 patients with a hearing impairment, an improvement in hearing was observed over time in the post-therapy audiograms, namely in 11 children and 3 adults.

Four children and two adults at first had hearing impairments ≥4 kHz and improved in the following audiograms. One adult and 3 children demonstrated hearing impairments in the frequency ranges <4 kHz and ≥4 kHz, but in the follow-up only the impairment at <4 kHz improved, with continous hearing impairment at ≥4 kHz. The final 4 children who had hearing impairments in both frequency ranges, <4 kHz and ≥4 kHz, also developed improvements in hearing in the higher and lower frequencies (Table II).

Main speech frequencies. In two female children significant hearing impairments developed in the main speech frequencies; in the first patient at a frequency of 0.125 kHz, while in the other at 2 kHz. Hearing impairments appeared in one male and one female patient at a cumulative cisplatin dose of 120 mg/m^2. One male who received a dose of 200 mg/m^2 developed a hearing impairment over time. Three other male patients who had received a cumulative dose of 240 mg/m^2 cisplatin developed a hearing impairment. In 68 patients no hearing impairment was identified (57 children and 11 adults).

Multivariate statistical analyses. Radiotherapy was not identified to be a significant predictor of ototoxicity in either the main or the sensitivity analysis. Ototoxicity was not significantly associated with age, gender, type of malignancy or follow-up time in either of the analysis. Chemotherapy regime and cumulative dosage were not significant ototoxicity predictors in the main and sensitivity analyses, respectively.

Discussion

In this study, we report on cisplatin- and carboplatin-induced ototoxicity in a cohort, including paediatric and adult patients, treated for osteosarcoma or soft tissue sarcoma.

Despite our study being conducted as a prospective, longitudinal, trinational, population-based study, a limited number of patients were included in this analysis. The cohort size was thus a severely limiting factor for statistical analysis. Higher data completeness is required in order to have sufficient patient numbers for meaningful multivariate analysis.

However, we are able to garner significant new results from our analysis. The patients treated with carboplatin demonstrated similar rates of ototoxicity compared with the patients treated with cisplatin.

A total of 41 patients revealed hearing impairments only in the higher frequencies. Eighteen patients developed hearing impairments at high frequencies at first, with subsequent involvement of lower frequencies in the following audiograms; an effect which has been described in previous studies (10,18).

We also observed hearing impairments after doses as low as 120 mg/m^2, a result which has also been described by Lanvers-Kaminsky *et al* (19), who identified hearing impairments in 6 out of 13 patients who had been treated with cumulative doses of 120-160 mg/m^2. Li *et al* (20) described hearing impairments only at doses > 400 mg/m^2 in accordance with other studies (1,6,7).

Our results reveal relevant levels of ototoxicity of cisplatin even at low doses, which may suggest a genetic predisposition. However, statistical analyses did not identify a statistically significant correlation between cumulative platinum dosage and hearing impairment, in contrast to other studies (6-8,10,21-23).

Patients <18 years old demonstrated hearing impairments in 55/112 (49.1%) cases. Previous studies have revealed hearing impairments mainly in patients <5 years old (20,24,25). In the adult group, hearing impairments were identified in 6/17 (35.3%) patients. Younger age as a risk factor has been observed in previous studies (1,8-10,26), but was not evident in our analysis. Aguilar-Markulis *et al* (27) suggested that adults receiving cisplatin may be vulnerable to additive damage from previous or concurrent use of other potentially ototoxic drugs, in accordance with other studies (28,29). Simon *et al* (30) also observed no association between age and risk of developing hearing impairment, similar to our results.

Six children and two adults received a combination of cisplatin and carboplatin. In our study population, no adult was treated with carboplatin only. Thirteen children received carboplatin at a median dose of 1500 mg/m^2. In this subgroup, 6 (46.2%) patients suffered from hearing impairments. In 4 patients, the hearing impairments had an impact on the main speech frequencies. Our results demonstrate an ototoxic effect of carboplatin similar to that of cisplatin. This is confirmed by Macdonald *et al* (13), who described that carboplatin may cause similar, but usually milder, toxicity. Parsons *et al* (15) also described cases of severe hearing impairment following high-dose carboplatin.

To date, cisplatin-induced ototoxicity has mostly been considered to be irreversible (2,7,9,10,31). However, Skinner *et al* (2) identified an improvement of 20 dB (at 8 kHz) in 2 out of 7 patients, after cessation of therapy. Laurell and Jungnelius (32) demonstrated certain improvement in 2 out of 6 patients; however, hearing thresholds remained increased. In our study, 14 patients in total (7 female and 7 male) demonstrated a significantly improved hearing threshold with ≥20 dB improvement in at least one frequency. None of these patients had received radiotherapy to the head.

In conclusion, our prospective study reveals that paediatric, as well as adult, sarcoma patients treated with platinum derivatives, suffer with over 40% ototoxic side-effects, irrespective of platinum compound and without modulation by age, gender or cumulative platinum compound dose. Patients may demonstrate improvement, but also deterioration, of hearing thresholds. Therefore, we recommend prospective testing via audiometry for patients treated with platinum derivative chemotherapy. Further studies are required to further elucidate the modulation of hearing threshold improvement by a potential toxic synergy between chemotherapy and radiotherapy and other ototoxic drugs, including ototoxic antibiotics.

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