암환자 및 암생존 환자에서 Cisplatin과 Vinca Alkaloid가 청력 장애에 미치는 부작용 연구

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Adverse Factors and the Role of Cisplatin and Vinca Alkaloids for Hearing Impairment in Childhood Cancer Patients and Survivors

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Background: Although combined chemotherapy has increased survival rates among children with cancer, such treatments can induce sensorineural hearing loss. Therefore, we aimed to identify risk factors for hearing impairments in patients with childhood cancer.

Methods: Audiograms were obtained from 115 patients with childhood cancer and survivors (age <20 years). Pure tone audiometry (PTA) was performed at octave intervals within the range of 250-8000 Hz. We evaluated clinical risk factors associated with hearing impairments. Hearing loss was evaluated based on the maximal decibel (dB) loss in any frequency for each ear (RA_{max} or LA_{max}) and weighted mean dB loss for specific frequencies (RA_{avg} or LA_{avg}).

Results: Forty percent of patients (N=46) exhibited hearing loss >20 dB based on the weighted mean value in either ear. Severe hearing impairments were observed in 56% of patients with brain tumors. Although cisplatin or vinca alkaloids were significant risk factors for hearing impairment, the use of both cisplatin and vinca alkaloids exhibited the highest odds ratio for hearing impairment (P<0.001, <0.001 for R/LA_{max}; P=0.099, 0.039 for R/LA_{avg}). Multivariate analysis revealed that the use of both cisplatin and vinca alkaloids was an independent risk factor for hearing impairment based on RA_{max}, LA_{max}, and LA_{avg} (P<0.001, <0.001, 0.039, respectively).

Conclusion: Our findings indicate that cisplatin and vinca alkaloids exert an additive effect on the risk of hearing impairment in survivors of childhood cancer. Further prospective studies are thus required to determine the most effective chemotherapeutic regimen for reducing ototoxicity.

Key Words: Survivors, Hearing loss, Neoplasms, Cisplatin, Vinca alkaloids

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Introduction

Over the past twenty years, survival rates for children with malignant tumors have increased due to the advance of more effective treatments such as combined chemotherapy, as well as improvements in diagnostic methods, surgical techniques, and radiation therapy [1]. However, children with malignant tumors are also exposed to various side effects of chemotherapeutic treatment — which vary based on the type of cancer, treatment modalities, chemotherapeutic agents, and age at diagnosis — with more than 60% of survivors experiencing late-onset effects [2,3]. Curative chemotherapeutic treatments for childhood cancer involving agents such as cisplatin induce sensorineural hearing loss following treatment in up to 85% of patients [1,4].

Hearing impairment is one of the most common adverse effects in patients with childhood cancer and survivors [5], and typically occurs due to ototoxic reactions affecting components of the auditory and vestibular system in the inner ear. Generally, hearing loss is bilateral, irreversible, associated with tinnitus, and begins with the loss of the ability to perceive high-frequency auditory stimuli [1,5]. Hearing loss affects various aspects of child development and may result in psychosocial problems as well as delayed development of speech and language; poor educational achievement; and impairments in communication, social interaction, and overall quality of life [2].

There are various risk factors for hearing impairments in survivors of cancer. Drugs such as antineoplastic agents, aminoglycosides, nonsteroidal anti-inflammatory drugs, antibiotics, diuretics, and anti-hypertensive agents have been associated with hearing impairments and ototoxicity leading to hearing loss [6]. Moreover, chemotherapeutic agents such as doxorubicin, vincristine, cyclophosphamide, gemcitabine, and oxaliplatin are ototoxic [5,6]. Platinum agents such as cisplatin and carboplatin generate the most severe auditory symptoms, including tinnitus and changes in auditory sensitivity [5-8]. Radiotherapy, which accelerates the destruction of tumor cells via ionizing radiation beams, can also damage the auditory organs and related brain structures. Hearing loss is most common during radiotherapy for tumors of the head and neck [9,10]. Previous studies have reported that, when cranial radiotherapy is utilized as the only treatment modality, ototoxicity occurs only when the dosage exceeds 32 Gray (Gy) in cochlear structures [2]. However, combined chemotherapy and radiation cause worse ototoxicity than either one alone. Nevertheless radiation therapy is limited to most of brain tumors.

In the present study, we aimed to investigate hearing impairments in patients with childhood cancer and survivors according to clinical risk factors such as the type of cancer, classes of chemotherapeutic agents, and other treatment modalities utilized, based on standard medical practices in Korea.

Materials and Methods

1) Study population

The present study included 115 patients with childhood cancer and survivors of childhood cancer (age under 20 years) who had been diagnosed and treated at the Yonsei Cancer Center of the Yonsei University Health System in Seoul, Korea from January of 1993 to December of 2014.

We established the Long-Term Follow-Up Clinic (LTFC) for survivors of childhood cancer in 2004, at which patients of the present study underwent follow-up assessment. Audiograms were recommended for the survivors based on treatment type and medical history. Follow-up procedures and schedules were developed in accordance with Korean standards and institutional guidelines, as described in previous reports [11,12]. Consent to perform an audiogram was obtained from 115 patients. All patients were regarded as survivors of childhood cancer, based on survival in the absence of disease for over 2 years following the completion of treatment. Among the study population, 79.1% (91/115) were survivors at the time of the audiogram, while the remaining patients underwent evaluation for 2 years following the completion of treatment. This study was approved by institutional review board of Severance Hospital, Yonsei University Health System (4-2017-6000).

2) Audiometry

Pure-tone audiometry (PTA) was performed at octave in-

tervals within the range of 250-8000 Hz, and the loss of hearing threshold was expressed in decibels (dB) at each frequency. Maximal dB loss at any frequency was defined in each ear (RA_{max} for right ear and LA_{max} for left ear). The weighted mean dB loss for audible frequencies was calculated and defined as RA_{avg} for the right ear and LA_{avg} for the left ear, as follows: [dB at 500 Hz+(dB at 1000 Hz×2)+(dB at 2000 Hz×2)+dB at 4000 Hz]/6.

We analyzed the association between hearing loss and clinical risk factors such as age, gender, diagnosis, class of chemotherapeutic agents, use of radiotherapy, hematopoietic stem cell transplantation, etc. The severity of impairment was defined as follows: mild, <20 dB loss; moderate: 20 to 40 dB loss; severe: 40 to 60 dB loss; and profound: >60 dB loss. The presence of hearing impairment was defined as >20 dB loss in maximal and weighted mean levels of hearing.

3) Statistical notes

To evaluate the effect of diagnosis on hearing loss, we classified diagnoses into three groups: brain tumors, hematologic malignancies, and other solid tumors. Chemotherapeutic agents were classified based on general cytotoxicity, with the exception of platinum agents. Categorical variables, including diagnoses and treatment types, were analyzed using chi-square tests. Continuous variables were compared using Student's *t*-tests for parametric analyses and Mann-Whitney U-tests for non-parametric analyses. Multivariate logistic regression analysis was performed to examine the association between clinical risk factors and hearing impairment: severe impairment based on maximal dB loss at any frequency in either ear (RA_{max} >60 dB and LA_{max} >60 dB) and weighted mean dB loss in audible frequencies for either ear (RA_{avg} >20 dB, and LA_{avg} >20 dB). SPSS version 23 for Windows (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis of each outcome measure.

Results

1) Characteristics of survivors

The present study included 63 male patients and 52 female patients, with a mean age at diagnosis of 5.8±4.6 years old. Median age at diagnosis was 4.9 years (interquartile range [IQR]: 2.1-8.5 years) (Table 1). Brain tumor (N=41, 35.7%) was the most common diagnosis.

Table 1. Characteristics of survivors of childhood cancer

Characteristics	Values (median, IQR)
Age at diagnosis (years)	4.9 (2.1-8.5)
Age at treatment completion (years)	6.4 (3.5-10.0)
Time since after completion (years)	10.1 (6.9-13.5)
Age at audiogram (years)	5.8 (4-10)
Time from completion to audiogram (years)	4.8 (2.3-8.3)
Gender (M:F)	63:52
Diagnosis	N (%)
Leukemia/lymphoma	28 (24.4%)
Brain tumor	41 (35.7%)
Neuroblastoma	14 (12.2%)
Wilms tumor	2 (1.7%)
Hepatoblastoma	7 (6.1%)
Germ cell tumor	6 (5.2%)
Sarcoma	12 (10.4%)
Others	5 (4.3%)
Treatment modalities	N (%)
Chemotherapy	114 (99.1%)
Radiotherapy	68 (59.1%)
Surgery	82 (71.3%)
Hematopoietic stem cell Transplantation	34 (29.6%)

2) Prevalence of hearing impairment

Among the 115 included patients, hearing impairment was observed in the right (RA_{max} >20 dB) and left ear (LA_{max} >20 dB) in 63.5% (N=73) and 67.8% (N=78) of patients, respectively. When hearing impairment was defined based on the weighed mean of dB loss, 32.2% (N=37) of patients exhibited hearing loss in the right ear (RA_{avg} >20 dB), while 40.0% (N=46) of patients exhibited hearing loss in the left ear (LA_{avg} >20 dB). Median RA_{max} was 40 dB (IQR: 15-75), while median LA_{max} was 35 dB (IQR: 15-80). Median RA_{avg} was 11.6 dB (IQR: 5.8-24.1), and median LA_{avg} was 12.5 dB (IQR: 6.6-26.6). Median age at diagnosis (ages 3, 7.5, and 10 years old) was not identified as a risk factor for hearing impairment based on either maximal or weighted mean dB loss >20 dB. Forty percent of patients (N=46) exhibited hearing loss >20 dB based on the weighted mean value in either ear. Severe hearing im-

Table 2. Hearing impairments according to chemotherapy agents and treatment modalities

		Use (N)	RAmax	*P*-value	LAmax	*P*-value	RAavg	*P*-value	LAavg	*P*-value
Treatment modality	HSCT	N (81)	55 (15-77.5)	0.886	45 (15-80)	0.581	12.5 (5.8-25)	0.259	13.3 (7.5-30)	0.313
		Y (34)	20 (10-76.2)		25 (10-75)		7.5 (5-21)		9.1 (3.9-17.9)	
	Cranial radiation >5,000 cGy	N (82)	25 (10-70)	0.011	30 (15-75)	0.088	9.5 (5-21)	0.125	11.6 (6.2-22.9)	0.215
		Y (33)	75 (30-87.5)		75 (15-85)		19.1 (6.6-37)		17.5 (7-45.4)	
Class of chemotherpeutic agents	Corticosteroid	N (70)	65 (15-80)	0.027	65 (15-80)	0.066	12.9 (5.6-26)	0.439	12.5 (6.6-27)	0.887
		Y (45)	20 (10-70)		25 (10-65)		10 (5-22.9)		11.6 (5.4-27.9)	
	Alkylating	N (20)	15 (10-65)	0.235	20 (11.2-68.7)	0.235	6.6 (4.3-19.9)	0.309	9.1 (4.1-16.4)	0.154
		Y (95)	60 (15-80)		55 (15-80)		12.5 (6.6-26.6)		13.3 (6.6-30.8)	
	Anthracyclines	N (69)	55 (15-88)	0.909	30 (15-80)	0.790	10.8 (5-24.1)	0.849	11.6 (6.6-28.3)	0.731
		Y (46)	37.5 (10-76.2)		42.5 (13.7-75)		11.6 (5.8-26)		13.3 (4.1-27.2)	
	Antibiotics	N (89)	65 (15-80)	<0.001	65 (17.5-80)	<0.001	14.1 (6.2-28.7)	0.028	15 (7.5-32)	0.035
		Y (26)	15 (10-26.2)		15 (10-26.2)		7.5 (4.1-12.7)		7.5 (2.5-13.3)	
	Antimetabolites	N (77)	65 (15-85)	0.012	65 (15-85)	0.012	14.1 (6.6-27.5)	0.024	13.3 (7-32)	0.184
		Y (38)	15 (10-60)		20 (10-60)		7 (4.1-17.9)		10.4 (3.9-16.6)	
	Vinca alkaloids	N (27)	15 (10-30)	0.002	20 (10-30)	0.002	7.5 (5-15)	0.133	7.5 (5-13.3)	0.065
		Y (88)	62.5 (15-80)		60 (15-80)		12.9 (6-30.4)		14.1 (7.5-32.9)	
	Heavymetals-cisplatin	N (52)	15 (10-25)	<0.001	15 (10-30)	<0.001	6.6 (4.1-11.4)	<0.001	7.5 (3.3-13.1)	<0.001
		Y (63)	75 (60-90)		75 (55-85)		17.5 (8.3-35.8)		17.5 (10.8-42.5)	
	Heavymetals-carboplatin	N (74)	55 (15-80)	0.478	42.5 (15-80)	0.749	12.5 (6.4-27.2)	0.411	14.1 (6.6-31.6)	0.283
		Y (41)	25 (10-75)		25 (10-75)		7.5 (5-20.4)		9.1 (6.2-21.2)	
	Epipodophylotoxins	N (45)	55 (15-82.5)	0.648	45 (20-77.5)	0.648	14.1 (6.6-25.4)	0.128	14.1 (7-31.2)	0.600
		Y (70)	30 (10-75)		25 (10-80)		8.7 (5-24.5)		11.6 (6.4-23.9)	
	Enzymes	N (99)	60 (15-80)	0.003	60 (15-80)	0.065	12.5 (5.8-26.6)	0.089	12.5 (6.6-30.8)	0.277
		Y (16)	17.5 (10-32.5)		17.5 (10-38.7)		8.7 (4.5-12.2)		9.5 (3.3-20.8)	

RAmax, maxium decibel on right side of ear; LAmax, maxium decibel on left side of ear; RAavg, weighted mean decibel on right side of ear; LAavg, weighted mean decibel on left side of ear; N, not used or not applied; Y, used or applied.

pairments were observed in 56% of patients with brain tumors.

3) Clinical risk factors for maximal dB loss

Cranial radiation >5,000 cGy was identified as a significant risk factor for RA_{max} but not for LA_{max} (P=0.011, 0.088, respectively) (Table 2). Although cisplatin was identified as a risk factor for both RA_{max} and LA_{max} (P<0.001, <0.001 respectively), carboplatin was not identified as a significant risk factor for either RA_{max} or LA_{max} (P=0.478, 0.749, respectively). Among cisplatin users, 63.5% and 67.8% exhibited hearing loss in the right and left ear, respectively (data not shown). The use of vinca alkaloids was identified as an adverse factor for both RA_{max} and LA_{max} (P=0.002, 0.002, respectively). Among cisplatin users, the odds ratio for severe hearing loss based on maximal dB loss in the right ear (RA_{max} >60 dB) was 32.9 (10.99-98.51) (P<0.001), while that based on maximal dB loss in the left ear (LA_{max} >60 dB) was 22.5 (8.1-62.61) (P<0.001), respectively.

4) Clinical risk factors for weighted mean dB loss

Among those who had received treatment with vinca alkaloids, RA_{avg} was 12.9 dB (IQR: 6.0-30.4), and LA_{avg} was 14.1 (IQR: 7.5-32.9), respectively (Table 2). In contrast, RA_{avg} and LA_{avg} values were 7.5 dB (IQR: 5.0-15.0) (P=0.133) and 7.5 dB (IQR 5.0-13.3) (P=0.065) for those who did not undergo treatment with vinca alkaloids, respectively. Patients treated with cisplatin exhibited RA_{avg} values of 17.5 dB (IQR 8.3-35.8) and LA_{avg} values of 17.5 dB (IQR 10.8-42.5), whereas, RA_{avg} and LA_{avg} values for patients who did not undergo treatment with cisplatin were 6.6 dB (IQR 4.1-11.4) (P<0.001) and 7.5 dB (IQR 3.3-13.1) (P<0.001), respectively.

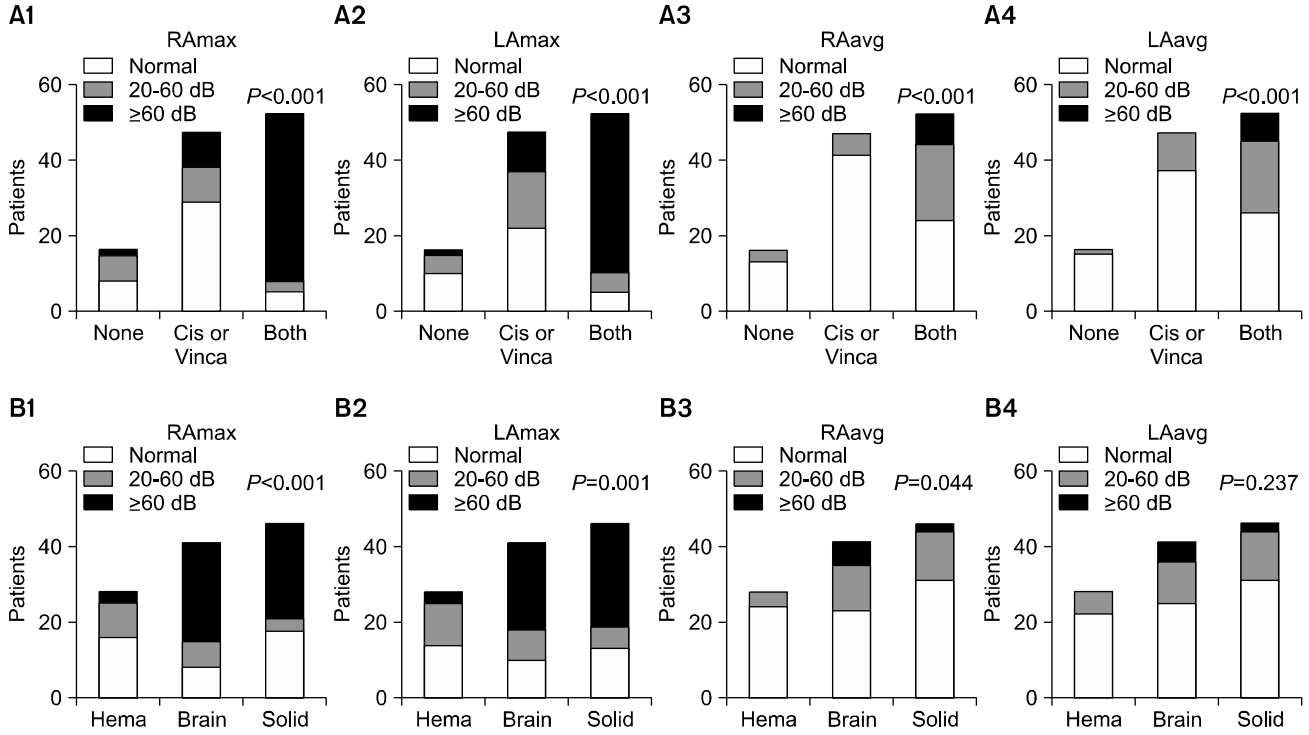

Fig. 1. Comparison of hearing impairments based on loss of decibels (dB) in hearing threshold according to clinical risk factors. (A1-4) Risk according to use of chemotherapeutic agents: none, either cisplatin or vinca alkaloids, and both use of cisplatin and vinca alkaloids. (B1-4) Risk according to diagnosis: hematologic malignancies, brain tumors, or other solid tumors. *P*-value means linear by linear association. cis, cisplatin; Vinca, vinca alkaloids; hema, hematologic malignancies; brain, brain tumors; solid, other solid tumors; RA_{max}, maximal dB loss of thresholds at any frequency in the right ear as determined via pure tone audiometry; LA_{max}, maximal dB loss in the left ear; RA_{avg}, weighted mean dB loss of thresholds in the right ear; LA_{avg}, weighted mean dB loss in the left ear.

5) Additive effect of cisplatin and vincristine on hearing impairment

Among those who had received combined treatment with cisplatin and vincristine, 84.6% and 80.8% exhibited hearing loss >60 dB for both RA_{max} and LA_{max}, respectively; however, normal audiometry results were observed in 50.0% and 62.5% of patients who did not receive treatment with either of these agents, for RA_{max} and LA_{max}, respectively ($P<0.001$ and <0.001, by linear by linear association, respectively; Fig. 1A-1 and 2). Among users of both cisplatin and vincristine, RA_{avg} and LA_{avg} >60 dB were observed in 15.4% and 13.5% of patients, respectively; however, normal audiometry results were observed 81.3% and 93.8% of patients who did not receive treatment with either of these agents ($P<0.001$ and 0.001 by linear by linear association, Fig. 1A-3 and 4).

6) Association between diagnosis and severity of hearing impairment

Maximal dB loss >60 dB was observed in more than 50% of patients with brain/other solid tumors (RA_{max}, $P<0.001$; LA_{max}, $P<0.001$, by linear by linear association, respectively; Fig. 1B-1 and 2).

7) Multivariate analysis

For RA_{max} >60 dB and LA_{max} >60 dB, the use of cisplatin and vinca alkaloids was a significant risk factor for hearing impairment, with odds ratios of 65.21 (P=0.001) and 147.4 (P=0.001), respectively (Table 3). For RA_{avg} >20 dB and LA_{avg} >20 dB, use of both cisplatin/vinca alkaloids exhibited odds ratios of 3.64 (P=0.099) and 10.06 (P=0.039), respectively. Antibiotic use was identified as a favorable factor for hearing impairment with regard to both RA_{max} > 60 dB and LA_{max} >60 dB (P=0.004, <0.001, respectively). Radiotherapy consisting of >5,000 cGy targeted toward the head region was not identified as an independent risk factor for hearing impairment (RA_{max} >60 dB, P=0.692; LA_{max} >60 dB, P=0.178).

Table 3. Multivariate analysis for hearing impairments according to clinical risk factors

	RAmax >60 dB		LAmax >60 dB		RAavg >20 dB		LAavg >20 dB	
	Odds ratio	*P*-value	Odds ratio	*P*-value	Odds ratio	*P*-value	Odds ratio	*P*-value
Diagnosis								
Hematologic Malignancies	Reference		Reference				Reference	
Brain tumors	0.317 (0.252-39.83)	0.372	3.84 (0.23-64.32)	0.349	0.79 (0.08-7.70)	0.839	0.35 (0.03-3.52)	0.370
Other solid tumors	4.69 (0.750-29.27)	0.098	11.39 (1.47-88.32)	0.020	0.12 (0.21-6.04)	0.892	0.67 (0.14-3.18)	0.616
Chemotherapy agents								
Cisplatin/vinca alkaloids								
None	Reference		Reference		Reference		Reference	
Cisplatin or vinca alkaloids	11.14 (0.85-146.55)	0.067	36.91 (1.67-814.80)	0.022	0.71 (0.14-3.70)	0.682	4.31 (0.44-41.88)	0.207
Both	65.21 (5.73-742.53)	0.001	147.40 (8.27-2628.31)	0.001	3.64 (0.78-16.87)	0.099	10.06 (1.12-90.51)	0.039
Antimetabolites	0.378 (0.067-2.12)	0.269	0.18 (0.015-2.01)	0.163	0.82 (0.20-3.34	0.787	0.39 (0.093-1.65)	0.202
Antibiotics	0.066 (0.011-0.414)	0.004	0.009 (0.001-0.13)	<0.001	0.39 (0.08-1.84)	0.233	0.32 (0.070-1.48)	0.146
Radiation treatment								
Radiotherapy on Head Region >50 Gy	0.658 (0.083–5.22)	0.692	0.178 (0.013-2.51)	0.178	1.57 (0.31-7.82)	0.586	1.73 (0.32-9.20)	0.522

Discussion

In the present study, we identified treatment regimens involving platinum agents or vinca alkaloids as significant risk factors for hearing impairment in survivors of childhood cancer. The poorest hearing outcomes were observed in patients who had undergone treatment with both cisplatin and vinca alkaloids, compared with those who had undergone treatment with one or none of these chemotherapeutic agents. According to a 2012 report by the World Health organization (WHO), approximately 16 million children worldwide (range: 12-26 million) live with hearing loss >35 dB, and the estimated global prevalence of hearing loss >35 dB in children 5 to 14 years of age is 1.4% [13,14]. However, the rate of hearing impairment in the present study was significantly higher, as hearing loss was observed in over 40% of included patients.

A previous study regarding cisplatin-induced hearing loss reported that 64% of the 55 included patients who had received cisplatin treatment developed hearing impairment, in accordance with rates of 63.5-67.8% observed in the present study [15]. However, Chang et al. reported that hearing loss occurred in 52.2% of included patients who had undergone treatment with cisplatin (N=35/67) [16], which is lower than those showed in present study. Nonetheless, our study included only 11 patients who had undergone treatment with cisplatin only, which may have resulted in this discrepancy. Among users of both cisplatin and vinca alkaloids, 90.4% exhibited hearing loss in each ear, which significantly affected the proportion of cisplatin users exhibiting hearing loss in our cohort. In addition, inconsistencies in the reported rates of hearing impairment among studies may be due to differences in the combination of treatment agents, age, diagnosis, use of radiotherapy, cumulative doses, and other factors [17].

Previous studies have further reported that the incidence of platinum-related hearing impairment increases along with increases in cumulative dose [17]. Different dosing formulas, such as dose per kilogram of bodyweight or body surface area, may thus influence these effects. Moreover, research has indicated that bolus injections of chemotherapeutic agents are more ototoxic than doses provided over a longer duration [17]. Cisplatin ototoxicity manifests as mild yet permanent bilateral hearing loss, affecting 10-25% of adults and 26-90% of children [18]. In our study, cisplatin and carboplatin induced severe hearing impairment in 54.7% and 35.6% of patients, respectively. Cochlear toxicity associated with platinum is due to interference with signal transduction in the cochlea [18]. The risk factors for ototoxicity in cisplatin include patient age at treatment, cumulative dose of cisplatin, prior hearing impairments, dosing schedule, concomitant use of aminoglycosides, and cranial irradiation [18]. Carboplatin is an analog of cisplatin, which was developed to reduce the dose-limiting toxicity of cisplatin. However, large doses of carboplatin can damage the outer hair cells after the destruction of all inner hair cells in the ear, thereby leading to hearing impairment [19].

Neuropathy is a well-known dose-limiting side effect of vincristine that can manifest as peripheral, cranial, or autonomic neuropathy. Peripheral neuropathy commonly presents as neuropathic pain, loss of deep tendon reflexes, wrist and foot drop, and paresthesia. Less commonly, cranial nerve palsies such as jaw pain, oculomotor nerve dysfunction, facial palsy, and laryngeal nerve paresis have been observed following treatment with vincristine [20]. In our study, vincristine was identified as a significant factor for hearing impairment. While use of either cisplatin or vincristine alone was a risk factor for hearing impairment, the use of both chemotherapeutic agents significantly increased the risk of hearing impairment. To our knowledge, the present study is the first to report an additive effect of cisplatin and vinca alkaloids on the risk for hearing impairment in survivors of childhood cancer. In our study, vincristine combined with cisplatin may potentiate neurologic damage in children with brain tumors or sarcoma.

Our findings also indicated that treatment with actinomycin or antimetabolite served as a favorable factor. However, such findings do not indicate that these agents exert protective effects against hearing damage, but instead reflect the close association between chemotherapeutic agents and the treatment regimen for specific diagnoses. Actinomycin is typically used in combination with vincristine, and cyclophosphamide. In contrast, cisplatin-contain-

ing regimens usually exclude actinomycin.

In our study, radiation therapy alone was not identified as a significance risk factor, although the risk of hearing loss increased with the addition of cisplatin or vinca alkaloids. Radiation to the cochlea can lead to sensorineural hearing impairment [1], as histopathologic changes due to radiation therapy often lead to inner ear damage [21]. To reduce late toxicity, treatment should aimed to reduce the volume of normal tissue exposed to radiation [22].

Diagnosis alone was also not identified as a significant risk factor, likely due to the application of specific treatment modalities and regimens for specific diagnoses. For example, cisplatin is more frequently used in the treatment of brain tumors, neuroblastoma, gynecological cancer, germ cell tumors, and sarcoma than in that for other tumor types [23]. Our findings suggest that the treatment regimen should be modified in patients at risk for severe ototoxicity. While our results indicate that simultaneous use of vincristine and cisplatin should be avoided, further studies are required to determine whether this approach effectively reduces ototoxicity without affecting mortality.

The present study possesses several limitations of note. First, this study was a retrospective analysis of a heterogeneous study population based on diagnosis and involved only a small number of survivors who had completed audiometry assessments. Moreover, we did not perform long-term follow-up assessments to determine whether further impairments or improvements in hearing loss had occurred. In addition, we were unable to examine the influence of age on hearing impairment due to the limited number of patients. Also, we did not examine the effect of cumulative doses of these agents on hearing impairment. Nonetheless, our findings indicate that cisplatin and vinca alkaloids exert an additive effect on the risk of hearing impairment when they were used in combination in survivors of childhood cancer. Further prospective studies are thus required to determine the most effective chemotherapeutic regimen for reducing ototoxicity.

References

1. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. Int J Radiat Oncol Biol Phys 2010;76:S50-7.
2. Grewal S, Merchant T, Reymond R, McInerney M, Hodge C, Shearer P. Auditory late effects of childhood cancer therapy: a report from the Children's Oncology Group. Pediatrics 2010;125:e938-50.
3. Park HJ, Nam BH, Yun YH, et al. Establishment of Korean childhood cancer survivor cohort and long-term follow-up system. Clin Pediatr Hematol Oncol 2007;14:1-42.
4. Hirose Y, Simon JA, Ou HC. Hair cell toxicity in anti-cancer drugs: evaluating an anti-cancer drug library for independent and synergistic toxic effects on hair cells using the zebrafish lateral line. J Assoc Res Otolaryngol 2011;12:719-28.
5. Brinkman TM, Bass JK, Li Z, et al. Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. Cancer 2015;121:4053-61.
6. Ding D, Allman BL, Salvi R. Review: ototoxic characteristics of platinum antitumor drugs. Anat Rec (Hoboken) 2012;295:1851-67.
7. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;309:2371-81.
8. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 2014;14:61-70.
9. Landier W. Ototoxicity and cancer therapy. Cancer 2016;122:1647-58.
10. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. Head Neck 2013;35:1662-8.
11. Han JW, Kim HS, Kim BS, et al. Increasing and worsening late effects in childhood cancer survivors during follow-up. J Korean Med Sci 2013;28:755-62.
12. Han JW, Kwon SY, Won SC, Shin YJ, Ko JH, Lyu CJ. Comprehensive clinical follow-up of late effects in childhood cancer survivors shows the need for early and well-timed intervention. Ann Oncol 2009;20:1170-7.
13. Stevens G, Flaxman S, Brunskill E, et al. Global and regional hearing impairment prevalence: an analysis of 42 studies in 29 countries. Eur J Public Health 2013;23:146-52.
14. Yun C, Wang Z, Gao J, et al. Prevalence and social risk factors for hearing impairment in chinese children-a national survey. Int J Environ Res Public Health 2017;14.
15. Yasui N, Adachi N, Kato M, et al. Cisplatin-induced hearing loss: the need for a long-term evaluating system. J Pediatr Hematol Oncol 2014;36:e241-5.
16. Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. J Clin Oncol 2010;28:1788-95.
17. van As JW, van den Berg H, van Dalen EC. Platinum-induced hearing loss after treatment for childhood cancer. Cochrane Database Syst Rev 2016:CD010181.

18. Lee JW, Pussegoda K, Rassekh SR, et al. Clinical practice recommendations for the management and prevention of cisplatin-induced hearing loss using pharmacogenetic markers. Ther Drug Monit 2016;38:423-31.
19. Ruggiero A, Trombatore G, Triarico S, et al. Platinum compounds in children with cancer: toxicity and clinical management. Anticancer Drugs 2013;24:1007-19.
20. Nazir HF, AlFutaisi A, Zacharia M, et al. Vincristine-induced neuropathy in pediatric patients with acute lymphoblastic leukemia in Oman: Frequent autonomic and more severe cranial nerve involvement. Pediatr Blood Cancer 2017;64.
21. Bass JK, Hua CH, Huang J, et al. Hearing loss in patients who received cranial radiation therapy for childhood cancer. J Clin Oncol 2016;34:1248-55.
22. Rowe LS, Krauze AV, Ning H, Camphausen KA, Kaushal A. Optimizing the benefit of CNS radiation therapy in the pediatric population-part 1: understanding and managing acute and late toxicities. Oncology (Williston Park) 2017;31:182-8.
23. Ho GY, Woodward N, Coward JI. Cisplatin versus carboplatin: comparative review of therapeutic management in solid malignancies. Crit Rev Oncol Hematol 2016;102:37-46.