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Original Article

Relationship of Type and Number of Chemotherapy Cycles with Acoustic Emission Disorder in Childhood Malignancy

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ABSTRACT

Chemotherapy is the primary therapy for several types of malignancies in children. Platinum-based chemotherapy could cause hearing loss due to its ototoxic properties (60-70%). Hearing loss could be detected through otoacoustic emission (OAE) examination. This study investigates the relationship between the type and number of chemotherapy cycles with acoustic emission disorder in childhood malignancy. A cross-sectional study was conducted at Dr. Kariadi Hospital Semarang. The inclusion criteria were patients, who had undergone a minimum of three cycles of chemotherapy, had type A tympanometry, and consent from patients or parents to be included in the study. Patients with a history of congenital abnormalities, speech delays, diabetes mellitus, hypertension, heart disease, kidney failure, long-term use of drugs (antibiotics, NSAIDs, and quinine), head and neck radiation, history of noise exposure, and patients who changed chemotherapy regimen in the middle of treatment were excluded. An acoustic emission disorder was established if OAE results showed pass ≤5 frequency and SNR point <6. Data analysis was done using *Chi-square* (X^2) and double logistic regression tests. A total of 89 pediatric patients in chemotherapy were included in the study, with 20 patients (52.6%) receiving platinum-based chemotherapy (p=0.0005), 23 (39.7%) patients with >3 cycles of chemotherapy (p=0.042), and 20 (51.3%) patients with non-systemic malignancy developed acoustic emission disorder. In conclusion, platinum-based chemotherapy has been shown to have the potential to cause hearing problems. Giving more than three chemotherapy cycles is associated with auditory emission disorder in children with malignancy.

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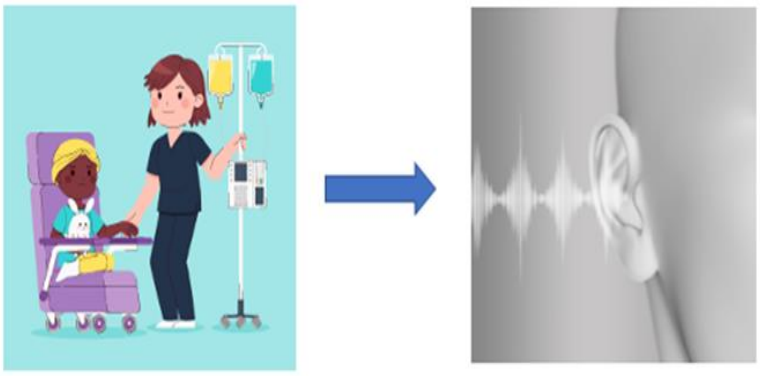
GRAPHICAL ABSTRACT



Introduction

Childhood malignancy consists of solid tumours and hematologic malignancies (leukemia). The incidence was approximately 5% of all malignancies. Chemotherapy is currently still an important modality of main therapy for cancer in children. According to The American Joint Committee on Cancer (AJCC), around 30-40% of stage I/II malignancies were treated with a single modality such as chemotherapy, whereas about 60% of advanced malignancies (stage III and IV) were treated with multi-modality therapy. Chemotherapy usually uses a combination of drugs (combination chemotherapy) to kill tumour cells most effectively and prevent resistance to develop. Chemotherapy is often repeated in cycles (1 cycle = 21 to 28 days, but this can vary) over varying periods of time, from months to years, with the goal of permanently eradicating the tumour is applied in chemotherapy protocols vary in duration, frequency, and number of cycles, depending on the type and extent of cancer, drug type and dose, expected toxicity, and how long it takes the patient to recover between rounds. The goal is to maximize the elimination of cancer cells while minimizing the adverse effects on normal and healthy cells [1-3].

The type of chemotherapy regiment administered could be platinum-based or non-platinum-based. Platinum-based chemotherapy carries an ototoxic property which may cause hearing loss with an average dose of 1500 mg/m^2. Ototoxic prevalence in pediatric patients with cisplatin induction is up by approximately 60-70%. A combination of platinum-based chemotherapy regimens which causes ototoxicity is up to 80-90% in prevalence [4, 5]. Platinum-based chemotherapy regimens may cause damage from basal cochlea bases extending to the apex area. Hearing impairment in children could cause disturbance regarding language development and verbal and communication abilities. Poor reading, writing, and counting skills were also reported in some studies. Problems that arise from this would decrease the life quality of children with malignancy receiving chemotherapy with ototoxic properties [6].

Several chemotherapy cycles were considered as the leading risk factor for chemotherapy-induced hearing loss, with an estimation of three to four chemotherapy cycles with adjustments of regimen doses and patient's body weight. Initially, the damage in the basal cochlea, associated with hearing in the high-frequency range, is affected, further affecting another area, and thus progressing to the lower frequencies. The chemotherapy cycle is related to the type of malignancy, the chemotherapy agent used, the therapy response, and its therapeutic goal. The number of chemotherapy cycles is based on the type of malignancy and the outcome of the chemotherapy evaluation. A study in Amsterdam (2005) reported that high-frequency hearing impairment (4 and 8 kHz) might occur with cisplatin with a dosage higher than 60 mg/m^2.

This occurrence is more distinct if the chemotherapy is given twice weekly [5-7].

Acoustic emission disorder (GEA) is a condition where damage occurs in the cochlea or vestibular apparatus caused by exposure to chemical substances, including medication. GEA could be detected through otoacoustic emission examination (OAE). OAE is an objective hearing assessment used to monitor drug ototoxicity effects or early detection of hearing function impairment. An abnormal OAE result indicates damage to the outer hair cell of the cochlea [8, 9]. The main impact of ototoxic drugs on the ear is causing loss of hair cells starting from the basal cochlea, cellular damage on stria vascularis, spiral limbus, and cochlear and vestibular hair cells [10].

This study investigates the relationship between the type and number of chemotherapy cycles with acoustic emission disorder in childhood malignancy.

Materials and Methods

This study was conducted in Kasuari Oncology Clinic Dr. Kariadi Hospital Semarang in mid-2020. It is a study with a cross-sectional design. Data were obtained using primary data from children with malignancy, consisting of history-taking, ear physical examination, tympanometry, and OAE examination.

Patients with a history of diabetes mellitus, hypertension, kidney failure, heart disease, congenital anomaly, long-term usage of medications (antibiotics, NSAID, and quinine), head and neck radiation, speech delay, noise exposure, and patients who had changes in chemotherapy regimen in the middle of treatment course were excluded. Data were obtained from subjects, a total of 89 patients, who were children of age ≤ 18 years old with malignancy that had undergone at least three chemotherapy cycles and showed a type of a tympanometry test result.

The GEA (-) criteria were established in the OAE examination, resulting in pass > 5 frequency and SNR > 6. In contrast, the GEA diagnosis was established if the OAE result showed a pass ≤ 5 frequency and SNR < 6. If one of the ears showed positive results, the patients were included in the study. Data were then analyzed with Chi-square and double logistic regression tests. The Research Ethical Committee of Kariadi Hospital Semarang approved this study with No. DP.02.01/I.II/4856/2020.

Results and Discussion

Acoustic emission disorder induced by platinum-based chemotherapy is a permanent sensorineural hearing loss, ranging from high to low frequencies, and usually on both ears. The damage in cochlear hair cells may be caused by ototoxic drugs that begin from the basal cochlea, which affects high-frequency hearing, increases dose accumulation, and may extend to another area, affecting low-frequency hearing. The impaired cochlear function could be temporary or permanent and, if not detected in early development, could cause hearing loss [10, 11].

Descriptive data of study subjects

The descriptive data study is presented in Table 1. A total of eighty-nine subjects were recruited, consisting of 56.2% males and 43.8% females. The average age was 6.62 ± 3.953 years old, and the most common type of systemic malignancy was Acute Lymphoblastic Leukemia (ALL) in 39 cases. In contrast, the most prevalent solid tumour is neuroblastoma at eight points.

Interferential analysis

The interferential analysis (Table 2) showed that a platinum-based chemotherapy regimen is associated with acoustic emission disorder (p = 0.0005). This was consistent with the study conducted by Emilia P., which reported that cisplatin chemotherapy is related to acoustic emission disorder (p = 0.001). Patients receiving cisplatin chemotherapy risk (58 times higher) developing auditory emission disorder [12].

This study showed a significant association between platinum-based chemotherapy cycles of > 3 times and acoustic emission disorder with p = 0.042. This is also in line with another study, a study carried out by Edward D., which proved that platinum-based chemotherapy is

significantly associated with acoustic emission disorder in patients who were given higher cumulative doses of chemotherapy of cisplatin >600 mg/m² (p = 0.022) and carboplatin >1800 mg/m² (p = 0.004). The chemotherapy cycle is related to the type of malignancy, the chemotherapy agent used, the therapeutic response, and the purpose of therapy itself [10].

The factor causing the occurrence of acoustic emission disorder

The type of malignancy in children is divided into non-systemic/solid tumour and systemic/haematology malignancy. Another factor that may cause acoustic emission disorder based on the analysis result (Table 3) is in the solid tumor group, which showed a significant association with auditory emission disorder in children with malignancy (p = 0.001).

Table 1: Descriptive data of study subjects

Variables	N	%
Age		
≤5 years old	38	42,7
>5 years old	51	57,3
Sex		
Male	50	56,2
Female	39	43,8
Type of malignancy		
Non-Systemic	39	43,8
Systemic	50	56,2
Chemotherapy		
Platinum	38	42,7
Non-platinum	51	57,3
Platinum-based		
Cisplatin	21	55,3
Carboplatin	17	44,7
Number of cycles		
>3 cycles	58	65,2
≤3 cycles	31	34,8
Anemia		
Transfusion +	69	77,5
Transfusion -	20	22,5
Acoustic emission disorder (GEA)		
GEA +	28	31,5
GEA -	61	68,5
Total	89	100

Table 2: Interferential analysis

Variables	Acoustic Emission Disorder				P-value	RP	CI 95%
	+		-				
	N	%	N	%			
Chemotherapy							
Platinum	20	52.6	18	47.4	0.0005*	5.972	2.225-16.031
Non-Platinum	8	15.7	43	84.3			
Number of cycles							
>3 cycles	23	39.7	35	61,3	0.042*	3.417	1.146-10.186
≤3 cycles	5	16,1	26	83.9			

Note: Chi-square p<0.05.

Table 3: The factor causing the occurrence of acoustic emission disorder

Variables	Acoustic Emission Disorder				*P*	RP	CI 95%
	+		-				
	n	%	n	%			
Type of malignancy							
Non Systemic	20	51,3	19	48,7	0,001*	5,526	2,068-14,766
Systemic	8	16	42	84			
History of transfusion							
Transfusion +	20	29	49	71	0,509	0,612	0,218-1,723
Transfusion -	8	40	12	60			

Note: Chi-square p<0.05.

Table 4: The dominant factor causing acoustic emission disorder

Variables	B	Wald	Sig.	Exp (B)	95% CI	
					Lower	Upper
Platinum-based chemotherapy >3x cycles	3	11,7	0,001	12,126	2,903	51
Platinum-based chemotherapy	2	0,62	0,430	5,981	0,07	509
Non-systemic malignancy	1	0,21	0,648	2,82	0,033	241

Note: Chi-square p<0.05.

This is also supported by a study survey by Emilia P, which proved that patients with Wilms's tumor risk developing acoustic emission disorder with a p-value=0.01 [12]. A non-systemic malignancy venom is most commonly treated with platinum-based chemotherapy, hence more prone to acoustic emission disorder [1].

There was no significant association between the variable of anaemia with acoustic auditory emission disorder in children with malignancy (p = 0.509) (Table 3). According to the World Health Organization (WHO) (2014), the anaemia incidence on malignancy is variable depending on the type of malignancy, staging, and period of the disease, therapeutic regimen used, and infection presence. More than 50% of patients with malignancy also suffer from anemia. Researchers found that anemic patients have a 2.4 times higher potential to develop mixed-type hearing loss (both conductive and sensorineural) than non-anemic patients [13-16]. Another study that was carried out by Prayuenyong P., explained that iron deficiency anemia might put an individual at risk for vascular damage, which may result in acoustic emission disorder [15]. This study's results showed that analysis of anemic subjects showed that only 29% developed acoustic emission disorder. In comparison, the other 71% did not, which resulted in no significant association between anaemia and auditory emission disorder in children with malignancy (p = 0.509). This may be explained by the fact that the anemic condition of the patients was already corrected with transfusion before the chemotherapy session, thus minimizing the occurrence of acoustic emission disorder.

The dominant factor causing acoustic emission disorder

The multivariate logistic regression analysis confirmed that more than three chemotherapy cycles were the dominant factor associated with acoustic emission disorder in children with malignancy (p=0,001; RP=12,126; CI 95%=2,903-50,645) (Table 4). This is consistent with the study conducted by Schwartz, that mentioned that a high-frequency auditory emission disorder (4 and 8 kHz) might be developed on the administration of three or more cycles of cisplatin regimen, where the amount of process would cause damage to basal cochlea extends up to the apex and increases along with subsequent cycle [10]. Therefore, each patient who gets chemotherapy with platinum-based should get regular monitoring hearing tests. It needs research with more subjects to ascertain the

relationship between dose and hearing damage caused.

Once again, managing cancer is a multi-modality, including managing side effects like these requires a comprehensive approach. Given that, the child is still in the growth and development phase, a psychological approach to the basic disease and its side effects, including nutritional problems, adherence to medication, and psychological management should be considered [17].

Conclusion

In conclusion, it should be noted that platinum-based chemotherapy has been shown to have the potential to cause hearing problems. Giving more than three chemotherapy cycles with platinum-based chemotherapy drugs is associated with acoustic emission disorder in children with malignancy. A further study is suggested to observe the difference between chemotherapy dose and hearing damage.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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