The incidence of ototoxicity in child malignancy cases that received carboplatin therapy with otoacoustic emission (OAE) examination

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Abstract. Malignancy is a significant public health problem, both globally and in Indonesia. Chemotherapy is one of the modalities in malignancy cases. Carboplatin (cis-diammine-cyclobutanediacarboxylato platinum) is a second-generation platinum compound that has often been used in the management of cases of malignancies. On the other hand, side effects of cytotoxic drugs need to be considered, especially ototoxic effects. Ototoxicity is dysfunction and damage to the structure of the inner ear that has been caused by drugs or other certain chemicals. The aim of this study is to assess ototoxic effects due to the influence of carboplatin in the cases of children with malignancy. This study uses a serial cross-sectional design to evaluate otoacoustic emission (OAE) signal-to-noise ratio (SNR) change as a result of ototoxic effects and risk factors due to the use of ototoxic carboplatin in the Division of Hematology-Oncology of the Department of Pediatrics at Cipto Mangunkusumo General Hospital in Jakarta, where two of 52 studies’ subjects experienced ototoxicity. In the group were receiving chemotherapy, two (5%) of the 40 subjects has experienced ototoxic events characterized by SNR values less than six, whereas SNR values were not less than six in the group that had not received chemotherapy. Risk factors such as gender, age, carboplatin dose, and cycles of chemotherapy did not have a statistically significant relationship to ototoxicity.

1. Introduction
Cases of malignancy are one of the leading causes to death of children in the United States. In 2007 as many as 10,400 children were diagnosed with malignancy, and 1,545 (14.85%) of those cases ended with death [1-2]. Chemotherapy is one of the treatment modalities of malignant cases. Carboplatin (cis-diammine-cyclobutenedicarboxylato platinum) is a second-generation platinum compound commonly used in malignant cases [3,4]. In children, carboplatin is routinely used to treat tumors such as neuroblastoma, retinoblastoma, hepatoblastoma, brain tumors, and germ cell tumors [3,5]. Cytotoxic drugs such as carboplatin need to be considered for their side effects, especially effects on hearing, known as ototoxicity. Ototoxicity can be defined as interference infunction of and damage to the inner ear structure caused by certain drugs or chemicals; symptoms include hearing loss, impaired balance function, or both. Carboplatin may damage the outer cochlear hair cells temporarily or permanently; however, no studies exist concerning the occurrence of damage to cochlear outer hair cells due to carboplatin administration in humans. Ototoxic effects should be considered in determining the carboplatin dose, so that ototoxic effects can be prevented or reduced [6,7].
Some studies have suggested that there is a risk for impaired cochlear function due to carboplatin usage. Qaddoumi et al. [8] reported that of 60 cases of retinoblastoma in children receiving carboplatin therapy, 10 (16.7%) of them suffered ototoxicity. Nitz et al. [7] reported that in a study of 13 children with various malignancies who received carboplatin, 6 (46.2%) of the subjects suffered hearing loss with an average dose of 1500 mg/m². Based on the data described, monitoring and evaluation of cochlear function and hearing function in study’s subjects with malignancy who received carboplatin therapy is necessary. Cochlear integrity assessment, especially the assessment of outer hair cells function can be done by otoacoustic emission (OAE) examination [9]. Damage to cochlear hair cells due to the administration of ototoxic drugs begins from the cochlear basal section of high frequency, but with a cumulative increase in dose, the disturbance may progress to other sections of low frequency [3]. Impaired cochlear function may be temporary or permanent; if the disorder is not detected early, hearing function may be impaired. Therefore, impaired cochlear function should be detected early to avoid hearing function disorders in children with malignancy who received carboplatin therapy.

Until now, there has been no exact data about the incidence of impaired cochlear function in subjects who received carboplatin in Hematology Oncology, Department of Pediatric at Cipto Mangunkusumo Hospital, Jakarta. The use of carboplatin in this division from January to July 2015 reached ±48 cases. The Community Division of the Department of Ear, Nose, Throat, Head, and Neck at Cipto Mangunkusumo General Hospital has been identified hat 35 (72.9%) of those cases involved malignancies, and OAE examination revealed that 14 of the 35 cases of malignancy (40%) demonstrated cochlear function disorders. The aim of this research is: 1, to identify ototoxic effects on cochlea resulting from carboplatin use, based on changes in the signal-to-noise ratio (SNR) value in OAE between groups who have and have not received carboplatin therapy, and 2, to observe the risk factors of that ototoxicity as the result of carboplatin therapy in cases of children with malignancy at the Cipto Mangunkusumo General Hospital Department of Pediatrics Division of Oncology-Hematology-Oncology.

2. Materials and Methods

This study uses a serial cross-sectional design to assess children with malignancy who have carboplatin administration in the Division of Hematology-Oncology division, Department of Pediatrics at Cipto Mangunkusumo General Hospital, Jakarta. Subjects have divided into five groups based on cumulative doses of carboplatin administered, assuming that they had no complaints regarding hearing problems before receiving carboplatin. This study is a preliminary study which designed to have 10 research subjects for each group, where all subjects underwent OAE and tympanometry examination. Data was analysed statistically using SPSS 20 software.

Due to the limited number of study subjects and short research retrieval time (six months), this study used a serial cross-sectional research design as an alternative to prospective cohort design, which would have enabled better monitoring of study subjects with pre- and post-therapeutic examination of carboplatin. This study meets total sampling requirements for the total number of research subjects (52), but the required number of research subjects per group according to dose of chemotherapy has not met. Each dose group of carboplatin should have a total of 10 research subjects, but an imbalance occurred in which the carboplatin dose group of more than 2000-3000 mg/m² had only five research subjects, whereas other dose groups ranged from 10 to 14 subjects.

3. Results and Discussion

3.1 Results

There were 52 subjects, 28 (53.85%) female, and retinoblastoma was the most frequent malignancy (78.84%). 42 (80.77%) subjects were less than 5 years old, age were ranging from 8 to 200 months with the median age of 39 months. OAE examination was performed on both ears for a total of 51 subjects; one study subject was only examined on one ear due to perforation of the tympanic
membrane on the other ear. All subjects received chemotherapy, with a median of four cycles and a range of 0-21 cycles (Table 1).

Table 1. Characteristics of study subjects (n=52)

| Characteristics          | N  | %   |
|-------------------------|----|-----|
| **Gender**              |    |     |
| Male                    | 24 | 46.15 |
| Female                  | 28 | 53.85 |
| **Age (months), median (min-max)** |    |     |
| ≤5 year                 | 42 | 80.77 |
| >5 year                 | 10 | 19.23 |
| **Laterality**          |    |     |
| Unilateral              | 1  | 1.92 |
| Bilateral               | 51 | 98.08 |
| **Malignancy Type**     |    |     |
| Neuroblastoma           | 6  | 11.54 |
| Retinoblastoma          | 41 | 78.85 |
| Tumor yolk sac          | 4  | 7.69 |
| Tumor Wilm’s            | 1  | 1.92 |
| **Chemotherapy cycles, median (min-max)** |    |     |
|                         | 4  | (0–21) |

Table 2. OAE results based on ear side and carboplatin dosage

| OAE Examination Results | Carboplatin Dosage (mg/m²) | Total |
|-------------------------|---------------------------|-------|
|                         | Pre | ≤1000 | ≤2000 | ≤3000 | >3000 |
| **Level 1453**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 1734**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 2063**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 2531**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 3000**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 3563**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 4219**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 5016**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 0     |
| **Level 6000**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 0     |
| Left side               | 0   | 0     | 0     | 0     | 1     |
| **Level 7031**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 1     |
| Left side               | 0   | 0     | 0     | 0     | 1     |
| **Level 8391**          |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 1     |
| Left side               | 0   | 0     | 0     | 0     | 1     |
| **Level 10031**         |     |       |       |       |       |
| Right side              | 0   | 0     | 0     | 0     | 1     |
| Left side               | 0   | 0     | 1     | 0     | 1     | 2     |
Two research subjects experienced impaired emission of cochlear outer hair cells characterized by changes in SNR (Table 2). One subject, a 39-month-old, with a yolk sac tumor malignancy type had undergone 11 cycles of chemotherapy with a total carboplatin dose of 3505 mg/m². In this case, OAE examination showed disruption of cochlear outer hair cells emission characterized by changes in SNR at the frequency range of 7031-10031 Hz in the right ear and 5016-10031 Hz in the left ear. The other subject was 41 months old with a retinoblastoma malignancy type and had undergone four cycles of chemotherapy with a total dose of carboplatin of 1500 mg/m². His OAE examination results showed a disturbance of the cochlear outer hair cell emission at a frequency of 10031 Hz in the left ear (Table 3).

Table 3. Ototoxic events (n=2)

| Description                  | Bilateral | Unilateral |
|------------------------------|-----------|------------|
| Gender                       | Male      | Male       |
| Age                          | 39 months | 41 months  |
| Malignancy type              | Yolk sac tumor | Retinoblastoma |
| Chemotherapy cycles          | 11        | 4          |
| Carboplatin dosage accumulation (mg/m²) | 3505 | 1500       |
| Frequency                    | 7031-10031 Hz | 10031 Hz   |

No significant relationship (p>0.05) was found between the occurrence of ototoxic events and various risk factors such as gender, age, dosage and cycles of chemotherapy (Table 4).

Table 4. Correlation between risk factors and ototoxic events

| Risk Factor       | Ototoxic | Non-Ototoxic | p   |
|-------------------|----------|--------------|-----|
| Gender            | Male     | Female       |     |
|                   | 2        | 22           | 0.2851|
| Age Group         | ≤5 years | ≥5 years     |     |
|                   | 2        | 40           | 0.6493|
| Dosage            | ≤3000 mg/m² | >3000 mg/m² |     |
|                   | 1        | 10           | 0.4231|
| Cycles            | ≤4 cycles| >4 cycles    |     |
|                   | 1        | 21           | 0.8462|

3.2 Discussion
In this study, most subjects were female (53.85%). The gender ratio varies across related studies: Bertolini et al. [10] has a male-to-female ratio of 61:59, Qaddoumi et al. [8] has a ratio of 34:26, the ratio in Dean et al. [11] is 58:41, while Nitz et al. [7] has a ratio of 30:31. Research showed that the incidence of malignancies found in this study, such as retinoblastoma, neuroblastoma, and Wilms tumors, are not influenced by gender, except for yolk sac tumors. Imbach et al. [12] and Herzog et al. [13] stated that in malignant cases of yolk sac tumors, there was a 6:1 incidence of males to females. Because of the low prevalence of yolk sac tumor cases in this study (only 4 cases, or 7.69%), the gender ratio was not significant. The median age in this study was 39 months, with a range of 8-200 months. Ototoxic effects occurred in two study subjects, aged 39 months and 41 months. Dean et al. [11] reported that in various malignancies treated with carboplatin, the median age was 5 years old, with a range of 0.02 to 14 years. The age factor is closely related to the type of malignancy studied, since malignancy type is associated with age at first diagnosis and therapy administered. Retinoblastoma, neuroblastoma, and Wilms' tumor types of malignancy can be diagnosed at less than
five years of age, whereas, according to Imbach et al. [12] and Herzog et al. [13] the yolk sac tumor is diagnosed at less than 16 years of age [14-18]. Qaddoumi et al. [8] reported that study subjects with retinoblastoma had a median age of 8.6 months, with a range of 0.4 to 163.3 months. Landier et al. [19] neuroblastoma study subjects had a median age of 5.6 years with a range of 1.01 to 29.56 years.

The most common type of malignancy found in this study was retinoblastoma (78.84%), which is the second most malignant after; thus carboplatin therapy was the most used chemotherapy agent. This is in contrast to the Dean et al. [11] study of hearing loss in malignancies that are treated with carboplatin, in which brain tumors are the most common malignancy (36%). This is supported by Cancer Research UK [20], which states that intracranial tumors are the most common malignancy managed with carboplatin, followed by kidney tumors, germ cell tumors, and retinoblastoma, while 2016 data from Cancer National Institute [21] (CNI) identify brain tumors and neuroblastoma malignancy in children as most common in management with platinum analogues. The chemotherapy cycle is related to the type of malignancy that occurs, the chemotherapy agent used, the therapeutic response, and the purpose of the therapy itself. The number of chemotherapy cycles depends on the type of malignancy and the outcome of chemotherapy treatment evaluation. In this study, the median value of chemotherapy cycles is four, with a range of 0 to 21 times. Qaddoumi et al. [8] reported a median cycle of chemotherapy of eight times, with a range of 5-8 times. Previous study reported six cycles for the subject of their study [22].

The ototoxic characteristics induced by platinum analogues are permanent sensorineural hearing loss, ranging from high frequencies to low frequencies, usually on both ears. In this study high-frequency outer hair cell emission disturbances with different characteristics were identified in two research subjects. One study subject in the carboplatin dosage group of more than 3000 mg/m² had outer hair cell emission disturbances in both cochlea, i.e. the left ear in the frequency range of 5016-10031 Hz and the right ear in the frequency range of 7031-10031 Hz. The second subject was classified in the carboplatin dosage group of 2000-3000 mg/m² and had impaired cochlear function only in the left ear, which occurred at a frequency of 10031 Hz. Brock et al. [23] reported that platinum analogue induced events may involve several factors, such as damage to cochlear hair cells, the stria vascularis, or marginal and complementary cells. Damage that occurs in the cochlear hair cells starts from the basal cochlea and then extends to the apex area, increasing with platinum analogue dose accumulation. This explains the disruption that occurs in research subjects, especially starting at high frequency (>2 KHz).

There are several potential risk factors for the occurrence of ototoxic events, including gender, age, chemotherapy dosage and cycles, among others. Both subjects who experienced ototoxic events in this study are male. There is still a crossover of opinions about gender as a risk factor for the occurrence of ototoxic events. Langer et al. [24] says that gender is one of the risk factors for the occurrence of ototoxic events due to platinum analogues and that they are four times more likely in men than in women. However, Gratton et al. [3] declared that gender is not a risk factor for the occurrence of ototoxicity. In this study, both subjects with ototoxic events are nearly the same age; one study subject was 39 months old, while the other was 41 months old. Gratton et al. [3], Qaddoumi et al. [8], and Langer et al. [24] all stated that age is one of the risk factors for ototoxic events. Langer et al. [24] stated that children younger than five years old have a 20 times greater risk of hearing loss than individuals aged 15 to 20; according to Moore et al. [25] this is associated with neuro development that occurs in the early years of life. Qaddoumi et al [8] reported that children younger than six months have a risk of permanent hearing loss 21 times greater than children older than six months.

In this study, the subject who experienced bilateral ototoxicity had undergone 11 cycles of chemotherapy with a total dose of carboplatin reaching 3505 mg/m², whereas the unilateral ototoxic case occurred in the fourth cycle with a total dose of carboplatin of 1500 mg/m². The type of malignancy determines the management of carboplatin combinations to be administered, influencing the chemotherapy cycle that will ultimately affect the total dose of carboplatin. Jehanne et al. [22] and Dean et al. [11] conclude that carboplatin chemotherapy doses of more than 3000 mg/m² may lead to ototoxic events, whereas Bright et al. [26] concluded hearing impairment with an average dose of
carboplatin of 2131 mg/m$^2$. Nitz et al. [7] reported that hearing loss occurred with an average dose of carboplatin of 1500 mg/m$^2$, whereas Brock et al. [23] and Gratton et al. [3] stated that the maximum accumulated dose of carboplatin that could be tolerated to avoid ototoxic occurrence is less than 1600 mg/m$^2$. Gratton et al. [3] also stated that use of carboplatin alone has a 1% ototoxic risk, but the combination of carboplatin with other drugs increases muscular toxicity risk to 33%. Qaddoumi et al.[8] found that of 60 subjects in retinoblastoma studies, there were 10 subjects with ototoxicity; 7 of these ototoxic events started after the eighth cycle, with a median dose of 3576 mg/m$^2$ and doses ranging from 2580 to 4480 mg/m$^2$. Jehanne et al. [22] reported that of 176 study subjects with retinoblastoma, there were eight study subjects (5.6%) who were ototoxic due to chemotherapy, with a median age of four months and age range spanning1 to 41 months. The ototoxic effect began at the fifth cycle, with a median dose of 3120 mg/m$^2$ and a dose range of 1200-5830 mg/m$^2$.

Some experts state that there are risk factors for the occurrence of ototoxic events. Gratton et al. [3] says that the dosage, duration of administration, age, radiation management, history of hearing loss, kidney disease, and other ototoxic drug use may increase the risk of ototoxic events. The same is also said by Langer et al. [24], who also include gender as a risk factor for the occurrence of ototoxic events. This study showed no significant correlation between the various risk factors and the occurrence of ototoxic events. This may be because only two of 52 subjects were found with ototoxic events.

4. Conclusion
Two (5%) of 40 subjects in the group receiving chemotherapy had an ototoxic event characterized by less than six SNR value, while no study subjects in the group not treated with chemotherapy were found to exhibit SNR values less than six. This indicates that OAE examination is still needed as a modality in the monitoring of ototoxic events. Risk factors in the form of gender, age, chemotherapy cycle, and dose of carboplatin did not have a statistically significant relationship (p>0.05) with ototoxic occurrence, potentially because in this study the number of patients who had ototoxic events was very small, 3.8% of 52 total study subjects. The research suggests that periodic ototoxicity checks each cycle of carboplatin therapy, particularly when the cumulative dose of carboplatin reaches 1500 mg/m$^2$, until completion of carboplatin administration, may be useful to reduce the effects of ototoxicity. Due to the limitations in this study, further research is required using a cohort study method with more subjects in order to obtain certainty regarding the occurrence of ototoxic events, which could be identified through a change in SNR values each cycle. This study’s results can be used as a common reference on the ototoxic events caused by carboplatin. The researchers recommend providing an understanding to the clinician, the community, and especially the patient's family, that the use of carboplatin as a treatment for malignancy is relatively safe, but regular monitoring should be undertaken to reduce risk of ototoxic effects.

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