Platinum-induced ototoxicity in pediatric cancer survivors
GSTP1 c.313A>G variant association

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Abstract
Hearing damage is one of the main toxic effects of platinum compounds, it derives from the irreversible degeneration of hair cells of the ear. Genetic association studies have suggested an association between GSTP1 c.313A>G variant and platinum-induced ototoxicity in childhood cancer survivors. We aimed to detect the frequency of ototoxicity and associated risk factors in survivors of childhood cancer receiving platinum-based chemotherapy and to detect the relation between GSTP1 c.313A>G (rs1695) polymorphisms and ototoxicity. We conducted a cross-sectional study on 64 cancer survivors who received platinum agents (cisplatin and/or carboplatin) at least 2 years after the end of chemotherapy. The patients underwent comprehensive audiological evaluations and genotyping to detect the presence of the GSTP1 c.313A>G polymorphisms. Hearing loss (HL) was identified in 16/64 patients (25%), including 62.5% treated with cisplatin and 37.5% treated with carboplatin. The greater incidence of ototoxicity was found in children treated for osteosarcoma (28.1%) followed by patients with germ cell tumors (25%) and neuroblastoma (21.9%). The AA, AG, and GG types of GSTP1 c.313A>G variant were detected in 84.4%, 9.4%, and 6.3%, respectively, of patients with HL with a significant association between mutant genotype of GSTP1 rs1695 and platinum-induced ototoxicity (P = .035). HL was not significantly associated with the total cumulative dose of cisplatin and carboplatin. GSTP1 c.313A>G variant may increase the risk of HL in pediatric oncology patients treated with cisplatin or carboplatin chemotherapy.

Abbreviations: EDTA = ethylene diamine tetra acetic acid, GCT = germ cell tumor, GST = glutathione-S-transferases, HL = hearing loss, PCR = polymerase chain reaction.

Keywords: cancer, carboplatin, cisplatin, ototoxicity

1. Introduction
Chemotherapy is a core component of treatment for pediatric cancer.[1] Unfortunately, the use of cisplatin and carboplatin can lead to serious side effects, such as nephrotoxicity, neurotoxicity, and ototoxicity.[2] Platinum-induced ototoxicity has been described as a bilateral, progressive, and irreversible sensorineural hearing loss (HL). It has also been observed that patients can develop HL years after completing their chemotherapy treatment and can also exhibit tinnitus.[3] HL, particularly in children, can be debilitating, as it can have a negative impact on their ability to learn, develop, and interact with their peers. As a result, it can lead to distressing consequences on the quality of life of childhood cancer survivors.[1]

Various risk factors have been described for platinum-induced ototoxicity. It is believed that age at treatment (patients less than 5 years old), high cumulative doses, preexisting renal insufficiency, preexisting HL, concomitant ototoxic medication use, and cranial irradiation play a role in its severity.[4]

One of the cisplatin cytotoxic mechanisms is to induce oxidant stress generating reactive oxygen species, from which cochlea cells are protected by a high expression of antioxidant enzymes, like glutathione-S-transferases (GST), or superoxide dismutase. A deletion of 3 nucleotides on the GSTM3 gene has been shown to have a protective role, whereas having GSTT1 and GSTMI and GSTP1 genes has been associated with HL.[5]

GSTs, phase II metabolic isoenzymes, play an important role in cell protection by scavenging free radicals caused by cisplatin and catalyzing cisplatin by conjugating it with glutathione.[6]

GSTs, a family of enzymes, the dominant member of which is the GSTP1 isoenzyme.[7] The GSTP1 c.313A>G single
nucleotide polymorphism leads to a substitution of isoleucine for valine (p. Ile105Val) that results in a hypoactive enzyme and thus a reduced ability of the synthesized enzyme to detoxify and reduce the rate of its biological effect.\textsuperscript{[9]}

Elucidation of associations between genetic variants and ototoxicity risk is crucial for better management of cancer treatment in pediatric patients. This study hypothesizes that a genetic variant of the GSTP1 (rs1695) gene may contribute to the susceptibility of cisplatin- and carboplatin-induced HL in children treated for a variety of malignancies.

2. Material and methods

This cross-sectional study was conducted in 2 tertiary care pediatric oncology centers, Hematology and Oncology Department of Children Hospital—Zagazig University and the Pediatric Department of Tanta Cancer Center, on 64 cancer survivors from January 2019 to February 2020.

This study was approved by the Institutional Review Board of the Faculty of Medicine Zagazig University and each participant or legal guardian signed informed written consent before enrollment in the study.

Were included all survivors of pediatric solid tumors who received platinum agents (cisplatin and/or carboplatin) as osteosarcoma, neuroblastoma, germ cell tumor (GCT), and medullo-blastoma at least 2 years after the end of chemotherapy, were below the age of 18 years at the time of diagnosis of having cancer who had a normal hearing before starting of chemotherapy as assessed by medical records or hearing tests. Patients were excluded if the age at diagnosis was greater than 18 years if having renal and hearing impairment before the start of the chemotherapy, patients who had undergone facial, cerebral, or total body irradiation, had a familial risk of hearing impairment and if baseline hearing evaluation was abnormal or audiogram was not done before starting chemotherapy.

Clinical data and audiological evaluation were extracted from electronic and paper medical records. Data collected included age at treatment initiation, type, and staging of the primary tumor, time elapsed between the end of the treatment and the last audiogram test, treatments received (cisplatin and/or carboplatin), cumulative dose of cisplatin or carboplatin (mg/m\(^2\)), ototoxic antibiotics as aminoglycoside and ototoxic diuretics as furosemide, past history or family history of hearing affection and complete physical examination including chest, heart, abdominal and neurological examination. The main parameter to assess ototoxicity was the audiogram. Tympanometry and pure tone audiometry were done for all eligible patients before treatment and at least 2 years after the end of the treatment. HL was assessed using the Brock criteria (Clemens et al, 2019), one of the classifications specifically designed for platinum compounds related ototoxicity. Patients that developed moderate to severe HL (Grades 2, 3, or 4) were defined as cases. Patients who exhibited normal hearing function (Grade 0) were defined as controls.

Brock classification\textsuperscript{[9]} is defined as follows; Grade 0: < 40 dB at all frequencies, Grade 1: ≥ 40 dB at 8 kHz, Grade 2: ≥ 40 dB at 4 kHz and above, Grade 3: ≥ 40 dB at 2 kHz and above, and Grade 4: ≥ 40 dB at 1 kHz and above.

3. Laboratory data

Peripheral blood samples have been tested for GSTP1 gene mutation.

Collection of blood samples. Blood was collected from the peripheral venous blood of each participant into ethylene diamine tetra acetate acid (EDTA K2) tube (2 cm) under complete aseptic condition.

DNA extraction and storage. All the reagents were highly purified analytical polymerase chain reaction (PCR) materials.

All the tubes and tip pipettes used for DNA extraction were DNase, RNase-free tubes to avoid contamination. They were purchased from Gentra (Minneapolis). Genomic DNA was extracted from whole blood using QiAamp DNA Blood Mini kit (Qiagen, Valencia, CA).

Protocol used for DNA extraction from whole blood.

1. 200 µL EDTA blood was added to a 1.5-ML microcentrifuge tube containing 20 µL proteinase K and 5 µL of RNase A solutions. The tube was gently mixed.
2. 200 µL of Buffer BL were added into the tube and mixed thoroughly by a gentle mix. The mixture was incubated at 56°C for 10 minutes. Mixing 3 or 4 times during incubation by inverting tube was performed after which the red color of lysate became dark green. The tube was centrifuged to remove drops from inside of the rim.
3. 200 µL ethanol (96-100%) was added to the sample and mixed by gentle inverting 5 to 6 times. Then, the tube was briefly centrifuged to remove drops from the inside of the lid.
4. The mixture was poured into the spin column (in a 2-ML collection tube) without wetting the rim. The cap was closed, and the column was centrifuged at 13,000 rounds per minute (rpm) for 1 minute.
5. The filtrate was discarded, and the spin column was placed in a collection tube.
6. 700 µL of buffer washing buffer were added to the spin column without wetting the rim. The column was centrifuged at 13,000 rpm for 1 minute. The flow-through was discarded and the collection tube was reused.
7. 700 µL of buffer washing buffer were added to the spin column without wetting the rim. The column was centrifuged at 13,000 rpm for 1 minute. The filtrate was discarded, and the collection tube was reused.
8. The spin column was centrifuged at 13,000 rpm for 1 minute to dry the membrane then the filtrate and collection tube was discarded.
9. The spin column was placed in a new 1.5-ML tube. 100 µL of buffer CE (elusion buffer) was directly added to the membrane, incubated for 1 minute at room temperature, and then centrifuged for 1 minute at 13000 rpm to elute the DNA.
10. The column was discarded and the microcentrifuge tube containing the DNA sample was stored at −20°C till further analysis.

Quantification and purity of DNA. It was performed for the determination of DNA concentration and the evaluation of DNA purity. This is done by the determination of the A260/A280 ratio. This ratio for pure double-stranded DNA was taken between 1.7 and 1.9. The procedure included 20 µL of each extracted DNA sample added to 1 mL of deionized water, and absorbance was measured at 260 and 280 nm wavelengths using Milton Roy Spectro Nic 3000 Array. DNA has a maximum absorbance at 260 nm as the resonance structures of pyrimidine and purine bases are responsible for the absorbance. An absorbance of 1.0 at 260 nm gives a DNA concentration of 50 µL/mL. Proteins absorb maximally at 280 nm due to the presence of tyrosine, phenylalanine, and tryptophan, and absorption at this wavelength is used for the detection of protein in DNA samples.

Alu26l (BsmAI) (10 µU/µL). The Alw26l (BsmAI) (Catalog number: ER0031), restriction enzyme recognizes GTCTC (1/5)\textsuperscript{a} sites and cuts best at 37°C in Tango buffer (isoschizomers: BsmAI, BstMAI).

GSTP1 Genotype Analysis. The exon 5 polymorphic site in the GSTP1 locus (Ile1053Val) was detected by restriction fragment length polymorphism of PCR-amplified fragments. The primers used were:
P105 forward, 5′-ACC CCA GGG GCTC TAT GGG AA-3′
P105 reverse, 5′-TGA GGG CAC AAG CCC CT-3′.

PCR Protocol. PCR reactions were carried out in a 30-µL volume containing about 50 ng of genomic DNA template, 200
µM each dNTP, 200 ng each primer, 1.5 mM MgCl₂, 1× PCR buffer [50 mM KCl, 10 mM Tris–HCl (pH 8.3)] and 1-unit Taq DNA polymerase (Promega, Southampton, UK). After an initial denaturation step of 10 minutes at 95 °C, the samples were processed through 30 temperature cycles of 30 seconds at 94°C, 30 seconds at 55°C, and 30 seconds at 72°C. A final extension step of 72°C for 10 minutes was performed. The 176-bp PCR products (20 µL) were digested for 2 hours at 37°C with 2 units of Alw26I (Fermentas Inc, Vilnius, Lithuania). The detection of the different alleles was carried out by horizontal ethidium bromide 4% agarose gel electrophoresis, along with a 100-bp DNA ladder.

3.1. Statistical analysis

Collected data were tabulated and analyzed using IBM SPSS version 24 software (IBM Corp. Released 2016. Armonk, NY: IBM Corp). Categorical data were presented as frequencies and percentages while quantitative data were described as mean ± standard deviation, median, and range. Chi-square test (χ²) or Fisher’s exact test was used to analyze categorical variables. Quantitative data were tested for normality using Kolmogorov–Smirnov test, assuming normality at P > .05. Student “t” test was used to analyze normally distributed variables among 2 independent groups. While nonparametric variables were analyzed using Mann–Whitney U test. The significance level was set at 5%.

4. Results

This study included 64 cancer survivors: 24 were females (37.5%) and 40 were males (62.5%). The mean age at the time of the study was (12.17 ± 5.79 yr), the age at the start of treatment was (9.25 ± 5.79 yr) and the mean time between the end of treatment and the last audiometry was (2.98 ± 1.84 yr). Thirty-six (56.3%) patients received cisplatin and 28 (43.8%) patients received carboplatin. Only 4 (6.3%) patients received amikacin antibiotic (6.3%) none received ototoxic diuretics.

The majority of patients who received cisplatin-based chemotherapy had neuroblastoma (28.1%), GCT (25%), or osteosarcoma (21.9%; Figure 1).

The characteristics of patients with and without HL (any grade) are displayed in Table 1 and Figure 2. Overall, 25% (16/64) exhibited HL of Brock grade > 1.

The mean number of doses of cisplatin our patients received was not statistically significant different from that of carboplatin (14.06 ± 9.72 vs 20.29 ± 18.42, respectively, P = .227), while there was a statistically significant decrease in total cumulative dose among cisplatin than carboplatin (1086.78 ± 1456.22 vs 5174.70 ± 2873.01, respectively, P < 10⁻⁴).

Regarding gene mutation, the percentage of AA (wild type no mutation) was 84.4%, versus 9.4% for AG (heterozygous mutated), and 6.3% for GG (homozygous mutated).

Patients with older age at the time of the study, older age at the start of treatment, more time between the end of treatment and last audiometry and those who received ototoxic antibiotics had significantly more HL. Among the 16 patients with HL, 10 (62.5%) received cisplatin and 6 (37.5%) received carboplatin chemotherapy. Notably, no significant difference between average dosages was recorded for patients with HL and without HL within each of the 2 drug groups. However, slightly higher dosage means were recorded for patients with HL than for those without HL (Table 2).

Among HL cases, ten patients (62.5%) were found to have AA (wild type no mutation), while 2 patients (12.5%) had AG (heterozygous mutated) and 4 patients (25%) had GG (homozygous mutated). Moreover, there was a significant association between the mutant genotype of GSTP1 rs1695 and platinum-induced ototoxicity with 6 of the 16 patients with HL (N = 6, 37.5%) having at least one c.313A>G allele (AG or GG). (P = .035), Table 3.

There was no statistically significant association between HL and cumulative dose of cisplatin (P = .648), but 8 out of 10 patients developed cisplatin-induced ototoxicity at the cumulative dose ≥ 400 mg/m² (Table 4).

There was a significant positive correlation between HL and age at the start of treatment and time between the end of treatment and last audiometry (P = .037 and P < 10⁻⁴ respectively, Figure 3), while there was no significant correlation between HL and the cumulative dose of cisplatin and carboplatin (P = .467 and P = .445 respectively).
5. Discussion

Platinum-induced ototoxicity has been described as a bilateral, progressive, and irreversible sensorineural HL. [10] Various risk factors have been described for platinum-induced ototoxicity. Because not all children with risk factors develop HL, and because the same chemotherapy treatment can lead to different levels of severity, it has been suggested that there is a genetic susceptibility for this condition. [11]

The current study showed that sensory neural HL of various degrees was detected in 25% (16/64) of patients, which affected both ears nearly with the same degree. No cases of conductive or mixed HL were found. This is in agreement with Esfahani et al. [12] who observed an overall incidence of HL of 25.8% after cisplatin administration in Iranian patients, versus 31% as reported by Lui et al. [5] However, a higher percentage (44%) was reported by Turan et al. [13] and reached 50.8% in Liberman et al. [14] This may be related to the fact that there is no consensus about how to define HL, leading to variability in the assessment and grading of ototoxicity. [4]

The incidence rates for platinum-induced ototoxicity depend on the distribution of risk factors in the patients such as age, dose of cisplatin, treatment schedules, hearing grading, and coadministration of concurrent ototoxic agents and cranial radiotherapy. [4]

This research examining predictors of cisplatin ototoxicity has not reported a difference in HL between genders. Many studies have reported the same finding. [1,15,16] However, in other studies, male gender is defined as a risk factor for cisplatin ototoxicity. [17,18] Olgun et al. [19] also reported that the male gender was associated with cisplatin ototoxicity. Moreover, it was associated with the occurrence of moderate to severe ototoxicity according to the Muenster classification. This may be due to the possible otoprotective effect of estrogen. [20]

In some studies, age is the determining factor for cisplatin-induced ototoxicity, especially in pediatric and elderly patients. [21,22] In our study, HL was seen predominately in children older than 5 years at the time of cancer diagnosis. However, several studies reported that young children are at more risk...
that head and neck irradiation and aminoglycoside use were not
radiotherapy. Therefore, we could not assess their association
neither received ototoxic antibiotics, ototoxic diuretics nor
for medulloblastoma and osteosarcoma.

reported a greater incidence of ototoxicity in children treated
P = .002). Waissbluth et al [3] found that 7 of the 8 patients
less HL as compared to all other tumor types in the cohort
HL across specific tumor types. Germ cell tumor patients had
50% of children treated for osteosarcoma and in 25% of those
treatment, 44% of patients were found to have Grade ≥ 2 HL,
the grade of hearing loss and time at the start of treatment. (B) Scatter graph
showing a significant positive correlation between the grade of hearing loss
and time between the end of treatment and last audiometry.

Figure 3. (A) Scatter graph showing a significant positive correlation between
the grade of hearing loss and age at the start of treatment. (B) Scatter graph
showing a significant positive correlation between the grade of hearing loss
and time between the end of treatment and last audiometry.

of developing moderate to severe HL from cisplatin than their
adult counterparts.[23,24]

Although the ototoxicity experienced by older patients is
often reported as less severe in terms of grading scales, HL may
progress in all patients over time independently of or synergis-
tically with exposure to other hearing insults.[17] Bertolini et al[11]
reported a HL of Grade ≥ 2 in 11% of patients within 2 years
of the end of therapy. In evaluations greater than 2 years off
therapy, 44% of patients were found to have Grade ≥ 2 HL,
supporting the possibility of progression of HL with time. In
the present study, HL was significantly higher over time, which is
compliant with the findings of Waissbluth et al,[3] who observed a
tendency to worsening hearing levels as time progressed.
The type of malignancy being treated is also an important
factor as different cancers affect pediatric patients at different
dates. Determining the type of chemotherapy, dosage, and use
of concomitant radiotherapy are also important. This study
showed that a greater incidence of ototoxicity was found in
50% of children treated for osteosarcoma and in 25% of those
treated for neuroblastoma and in 25% of whom had GCT.

Chang and Chinosornvatana[21] examined the incidence of HL
across specific tumor types. Germ cell tumor patients had
less HL as compared to all other tumor types in the cohort
(P = .002). Waissbluth et al[11] found that 7 of the 8 patients
that developed HL were being treated for medulloblastoma
and received cranial irradiation. Knight and Neuwelt[26]
also reported a greater incidence of ototoxicity in children treated
for medulloblastoma and osteosarcoma.

Our work revealed that the 16 children who developed HL
neither received ototoxic antibiotics, ototoxic diuretics nor
radiotherapy. Therefore, we could not assess their association
with platinum-induced ototoxicity. While Turan et al[13] found
that head and neck irradiation and aminoglycoside use were not
associated with cisplatin ototoxicity.

Co-treatment with other ototoxic drugs was found to be
associated with cisplatin ototoxicity in some studies[27,28]. Also,
Olgun et al[19] revealed that cotreatment with aminoglycosides
increased the risk of ototoxicity. Moreover, patients co-treated
with aminoglycosides tended to develop severe to moderate ototo-
xicity. In the study of Waissbluth et al,[3] all of the patients
who developed HL received cranial irradiation.

In the current work, we found the percentage of HL among
cisplatin cases was 62.5% while the percentage of HL among
carboplatin cases was 37.5%. This agrees with Clemens et al[29]
where the percentage of HL among cisplatin cases was 78%.
Also, Qaddoumi et al,[10] revealed that the percentage of HL
among carboplatin cases was 25%.

This work showed that there was no statistically significant
difference between HL and no HL groups regarding the cumu-
lative dose of cisplatin. However, 8 out of 10 patients developed
cisplatin-induced ototoxicity at the cumulative dose > 400 mg.
This agrees with Turan et al[13] who found that HL was not asso-
ciated with the cumulative dose of cisplatin. While the study of
Clemen et al,[29] confirmed the effect of a cumulative cisplatin
dose on the risk of ototoxicity, as the patients who received a
cumulative cisplatin dose of > 450 mg/m² had 2.4 higher odds
(P < .01) of developing platinum-associated HL than patients
treated with low cumulative cisplatin doses (≤300 mg/m²).

Yancey et al[17] showed an association between ototoxicity and
cumulative doses of cisplatin and to a lesser extent of carbopla-
tin. The latter was suggested to be associated with a much lower
risk of ototoxicity than cisplatin.[5] This agrees with Esfahani
Monfared et al[12] who found that patients who received a higher
individual dose of cisplatin (>75 mg/m² in each chemotherapy
cycle) showed more tinnitus significantly. Therefore, the
cumulative cisplatin dose was found to be associated with ototoxicity
development. In addition, several studies confirmed that cispla-
tin cumulative dosages are considered to be the most important
predictor of cisplatin-induced ototoxicity.[3,17,13]

Although our study revealed a significant increase in the
total cumulative dose of carboplatin among no HL than the
HL group, the mean cumulative dose in patients who developed
ototoxicity was 3596 ± 413 mg.

We also noticed that there was a significant increase in the
total cumulative dose of carboplatin than that of cisplatin
among the children who developed ototoxicity. (mean dose was
3596 ± 413 mg versus 704 ± 338 mg, respectively)

Despite the results of Rabico-Costa et al[23] being statistically
not significant, the findings appear to agree with the abovemention-
tioned results, as the median cumulative dose was higher (cis-
platin: 560 mg/m², carboplatin: 4400 mg/m²) in patients with
HL compared with those who did not have auditory changes
(cisplatin: 280 mg/m²; carboplatin: 3000 mg/m²).

GSTs are antioxidant enzymes protecting the cell by scaveng-
ing free radicals.[6] Regarding GSTP1 c.313A>G (rs1695) pleo-
morphism, among HL cases, 5 patients (62.5%) were found to
have AA (wild type no mutation). While one patient (12.5%)
with the GSTP1 c.313A>G (rs1695) polymorphism.

Oldenburg et al[33] found a protective effect against ototox-
icity of homozygosity of the wild-type GSTP1 allele relative to
carriers of the GSTP1 c.313A>G variant. In a study of patients
received cisplatin and radiotherapy for central nervous sys-
tem tumors, Rednam et al[34] found that GSTP1 c.313A>G vari-
 carriers had a higher risk of severe HL than patients with
wild-type genotype.

Also, our results matched with the study by Olgun et al[19]
that revealed that the mutant genotype of GSTP1 rs1695 is
related to cisplatin ototoxicity in univariate analyses (P < .05). However, this relationship was not significant in multivariable analyses but very close to statistical significance. Also, Drogemoller et al[11] mentioned that the variant rs1695 in GSTP1 is associated with cisplatin ototoxicity in adult survivors of testicular cancer.

Recently Lui et al[11] found the A/A genotype at rs1695 in GSTP1 was also associated with hearing impairment, and patients with A/G or G/G genotypes were less likely to develop ototoxicity suggesting a protective role of the variant. Liberman et al[12] added that GSTP1 c.313A>G was a common variant, being detected (heterozygous AG or homozygous GG) in 31/61 (50.8%) of the patients. However, there was no significant association between HL and the presence of the variant GSTP1 c.313A>G (AG or GG), with roughly half of the 31 patients with HL (n = 16; 51.6%) having at least one c.313A>G allele. Conversely, Peters n = 16; GG), with roughly half of the 31 patients with HL (n = 16; 51.6%) having at least one c.313A>G allele. Conversely, Peters et al[12] and Jurajda et al[12] did not find any relation between the variant of the GSTP1 gene and cisplatin ototoxicity.

6. Conclusions

Ototoxicity is one of the most serious complications of platinum compounds. A cumulative dose especially of cisplatin and the progress in the follow-up time may be considered risk factors for the occurrence of platinum ototoxicity. The mutant genotype of GSTP1 rs1695 was associated with platinum-induced ototoxicity. The present findings should be confirmed in larger cohorts, including groups of patients with different genetic backgrounds. Our data opened a window to further investigations directed to validate this association and associations with other factors before including it in the clinical pediatric oncologic practice. Future research should focus on the investigation of the combined effects of variants, and the examination of gene-level associations. The early identification of a high-risk group can serve as a basis for a better definition of individualized treatment and the targeted use of new ototoxic drugs.

Author contributions

All authors contributed substantially to writing the manuscript, reviewing the literature, the concept and design, acquisition, and interpretation of data; drafting the article, revising it critically for important intellectual content; and final approval of the version to be published. LS submitted the work.

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